The DEFINE-FLOW study

combined CFR and FFR assessment

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United States of America

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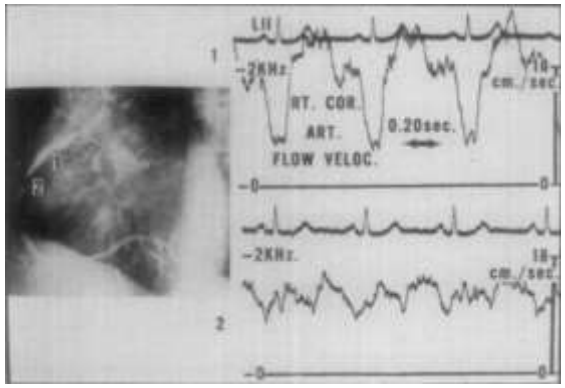
Weatherhead PET Imaging Center

Disclosure Statement of Financial Interest

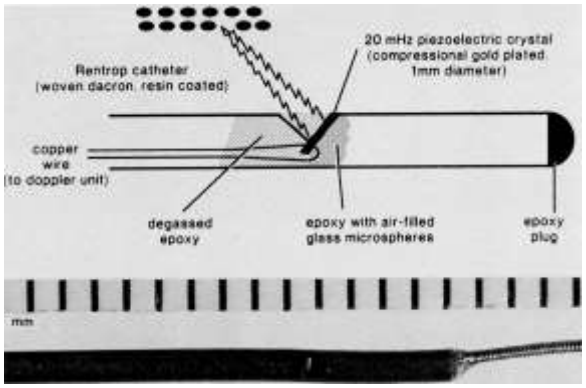
Within the past 12+ months, Nils Johnson has had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Organizations (alphabetical)
• Grant/research support (to *institution*)	• St Jude Medical (for CONTRAST study) • ***Volcano/Philips (for DEFINE-FLOW study)***
• Licensing and associated consulting (to *institution*)	• Boston Scientific (for smart-minimum FFR algorithm)
• Support for educational meetings/training (honoraria/fees donated to *institution*)	• Various, including academic and industry
• PET software 510(k) from FDA (application by Lance Gould, to *institution*)	• K113754 (cfrQuant, 2011) • K143664 (HeartSee, 2014) • K171303 (HeartSee update, 2017)
• Patents filed (USPTO serial numbers 62/597,134 and 62/907,174)	• SAVI and ΔP/Q methods • Correction of fluid-filled catheter signal

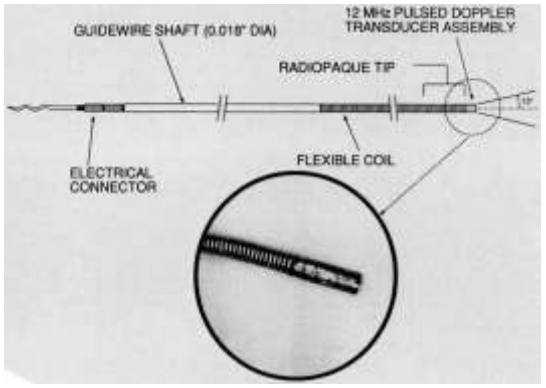
50 years of Doppler and thermo flow



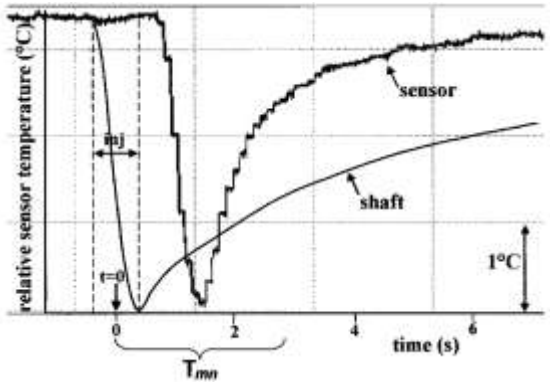
1971 = artery



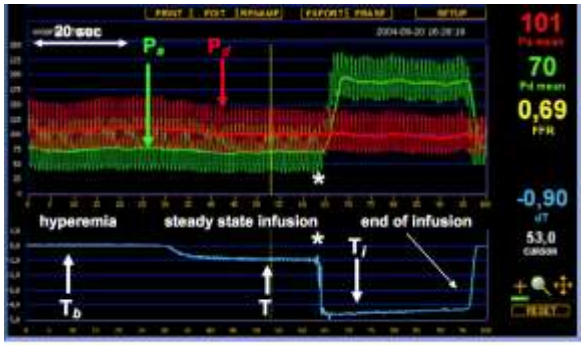
1985 = selective



1992 = 0.018”



2002 = bolus

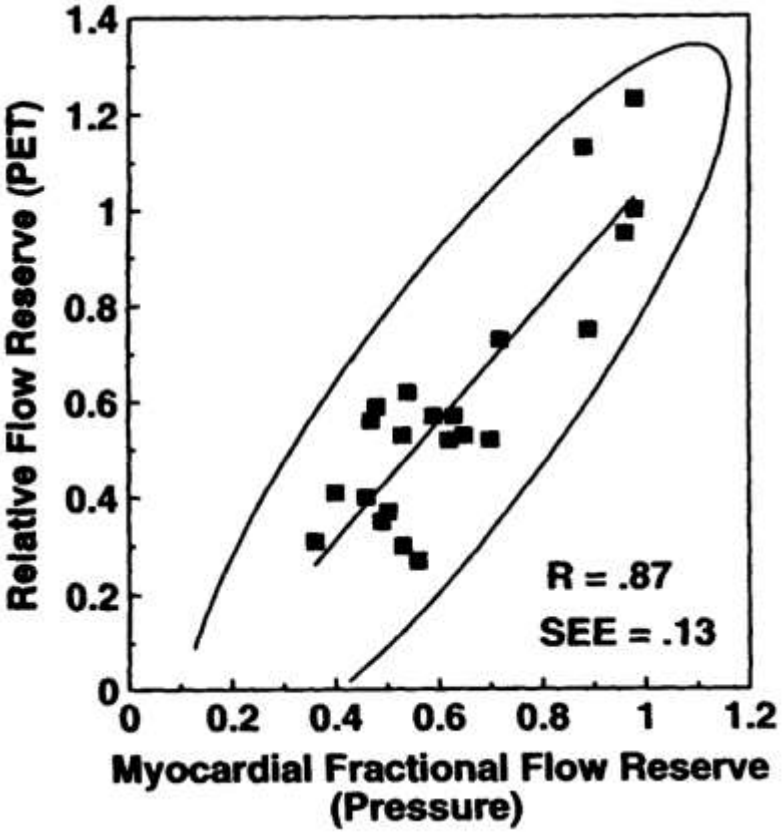


$Q_b = 15 \times (-4.5 / -0.9) \times 1.08 = 81$ ml/min

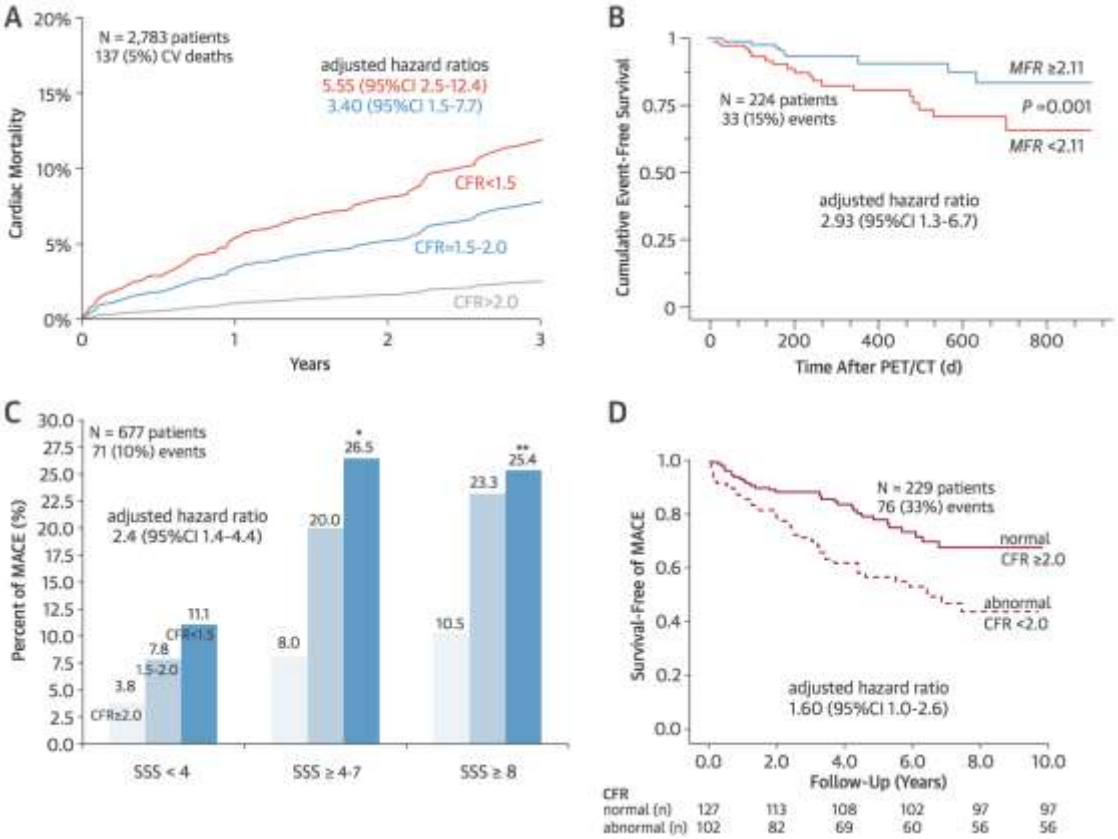
2007 = continuous

artery = Benchimol A, *Am Heart J* 1971;81:93-101. (Figure 4)
selective = Wilson RF, *Circulation* 1985;72:82-92. (Figure 1)
0.018” = Doucette JW, *Circulation* 1992;85:1899-911. (Figure 1)
bolus = Pijls NH, *Circulation* 2002;105:2482-6. (Figure 2)
continuous = Aarnoudse W, *JACC* 2007; 50:2294-304. (Figure 7)

CFR = coronary flow reserve



Relative CFR by PET vs invasive FFR



Prognostic gradient for CFR by cardiac PET

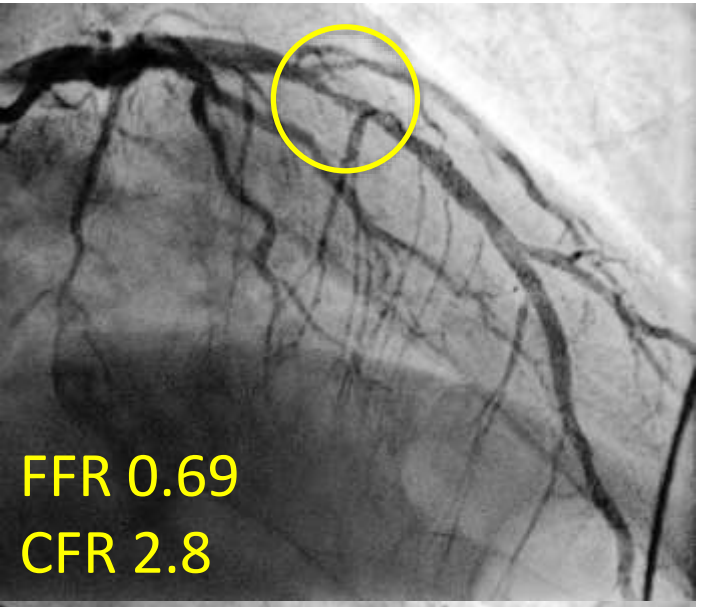
left = De Bruyne B, *Circulation*. 1994 Mar;89(3):1013-22. (Figure 4A)
right = Johnson NP, *JACC*. 2016 Jun 14;67(23):2772-88. (Figure 3 that compiles a broad literature)

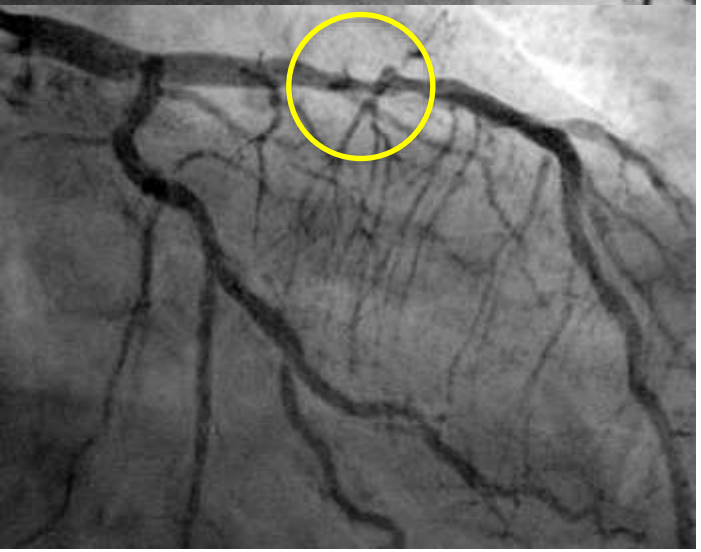
Complementary?

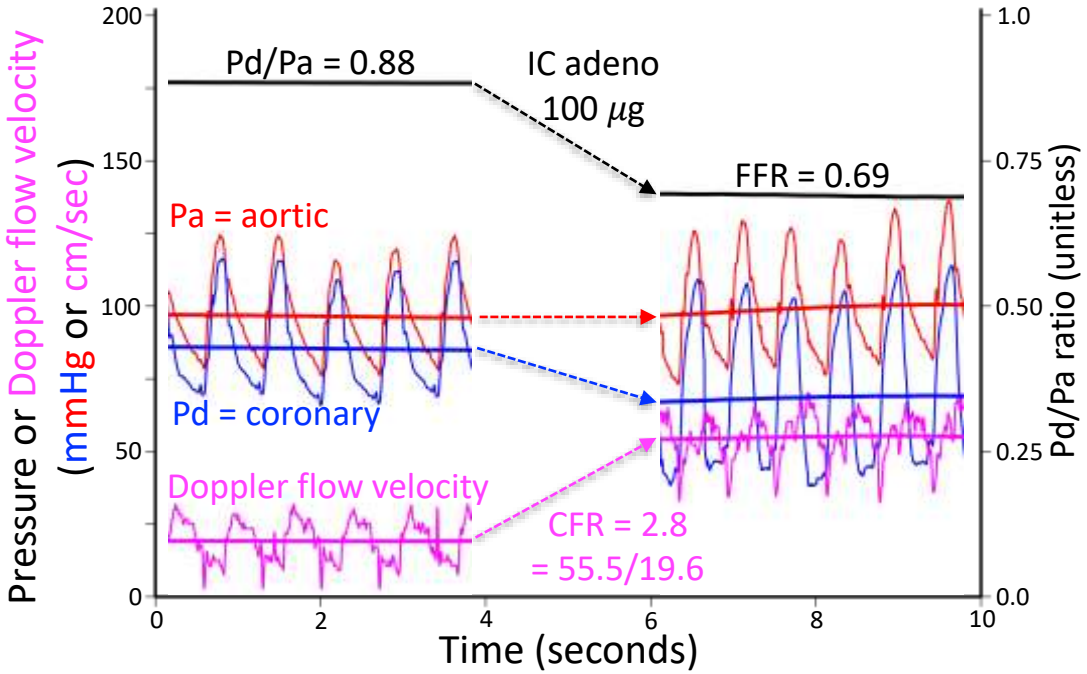
"… pressure and flow represent the
two sides of the same coin …
from the physiologic point of view,
both techniques are highly complementary."

Kern MJ, De Bruyne B, Pijls NH, *JACC*. 1997 Sep;30(3):613-20.

… or confusing?







57 year-old man with diabetes and CCS class I angina

Subject FLOW196 from DEFINE-FLOW (clinicaltrials.gov NCT02328820)

Mechanisms of FFR/CFR discordance

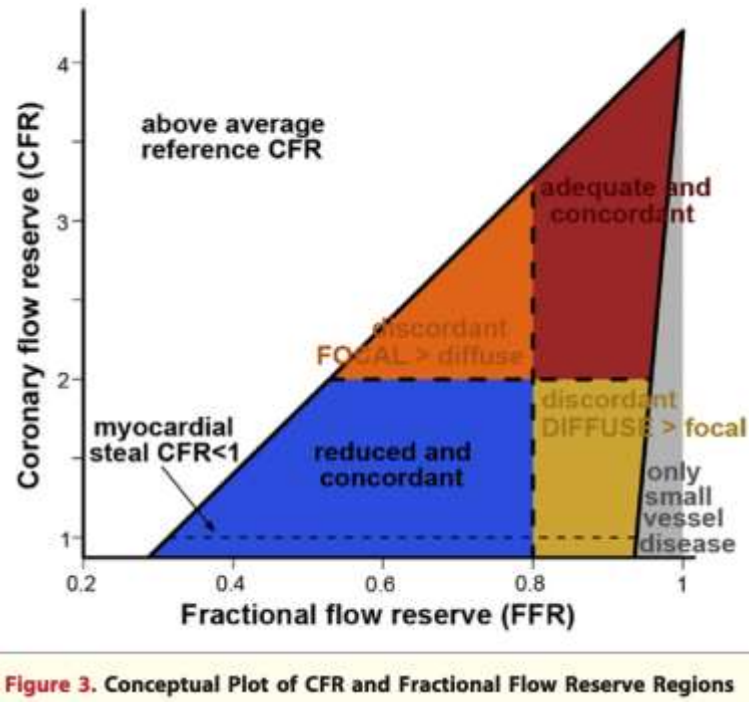
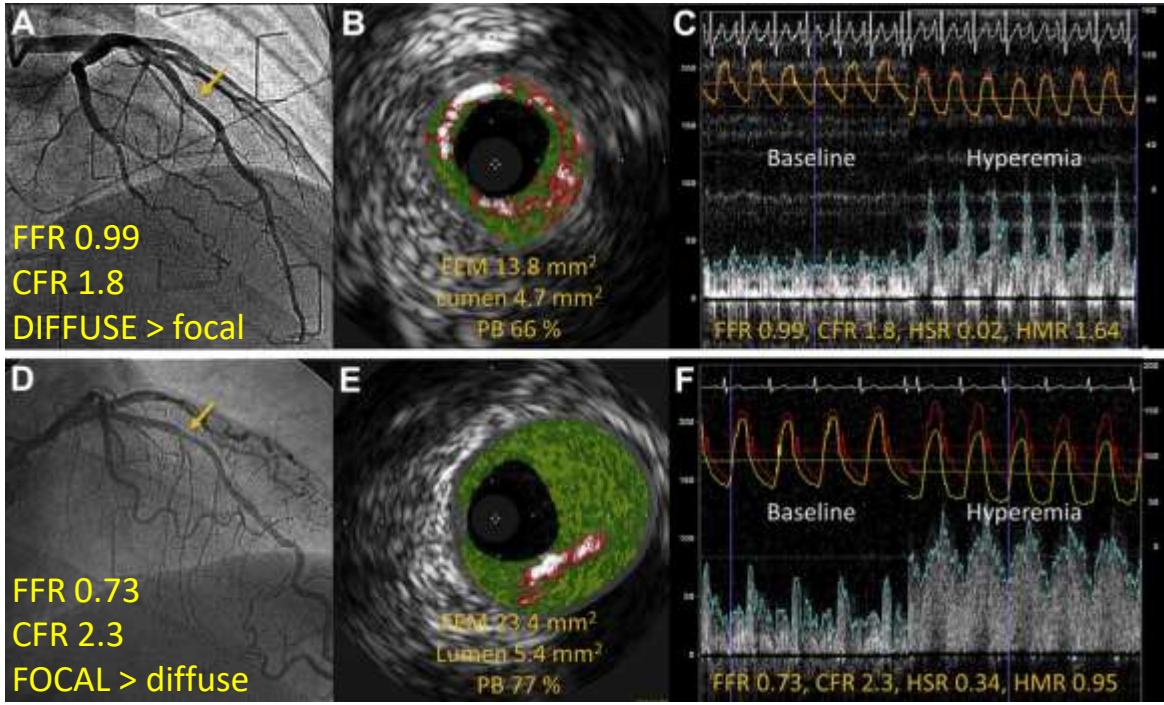
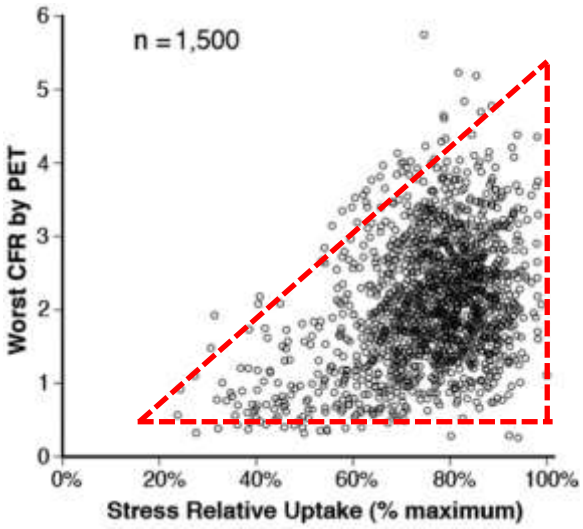


Figure 3. Conceptual Plot of CFR and Fractional Flow Reserve Regions



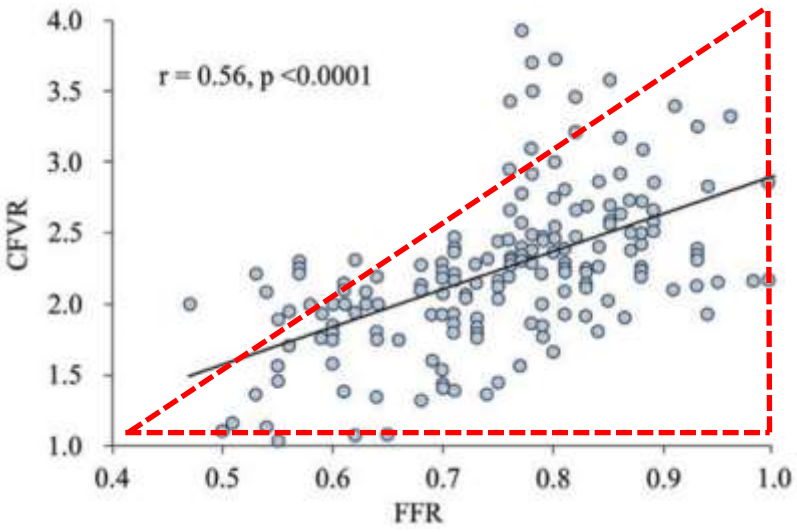
left = Johnson NP, *JACC Cardiovasc Imaging*. 5(2):193, 2012. (Figure 3)
right = Ahn SG, *JACC Cardiovasc Interv*. 2017 May 22;10(10):999-1007. (Figure 2 with *annotations)*

40% *discordance* and universal *triangle*



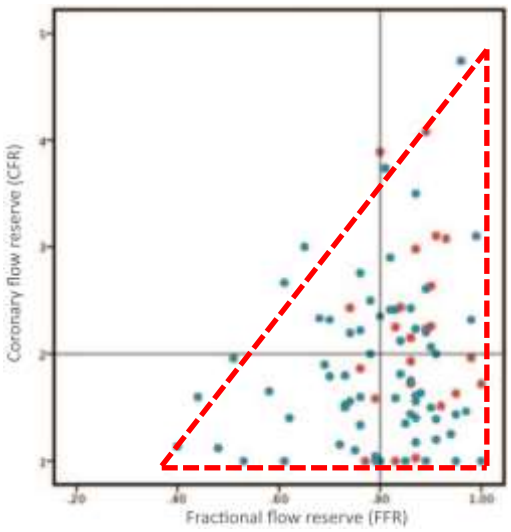
CFR by **PET**
Texas (2012)

43% discordance



CFR by **thoracic echo**
Japan (2014)

35% discordance

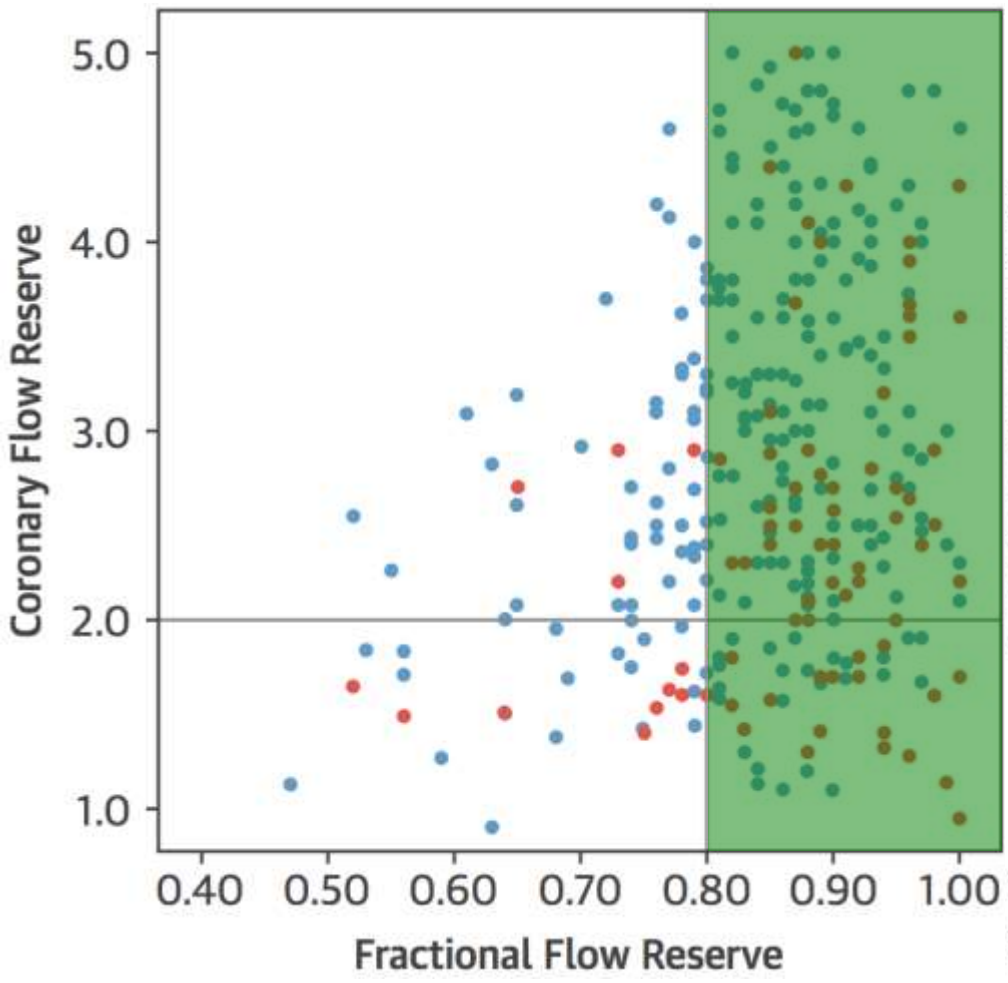


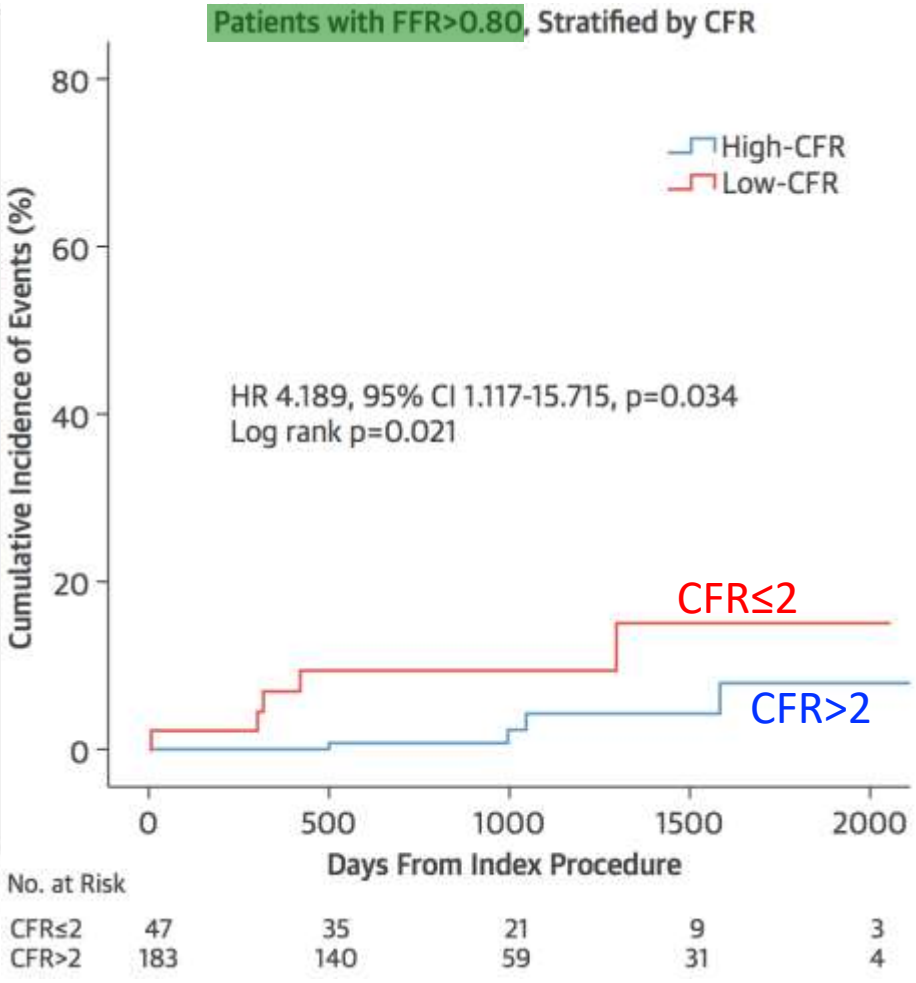
CFR by **thermo**
Madrid (2013)

44% discordance

left = Johnson NP, *JACC Cardiovasc Imaging*. 5(2):193, 2012. (Figure 1B)
middle = Wada T, *Eur Heart J Cardiovasc Imaging*. 15(4):399, 2014. (Figure 6)
right = Echavarria-Pinto M, *Circulation*. 128(24):2557, 2013. (Figure 1B)

Does FFR/CFR discordance matter?

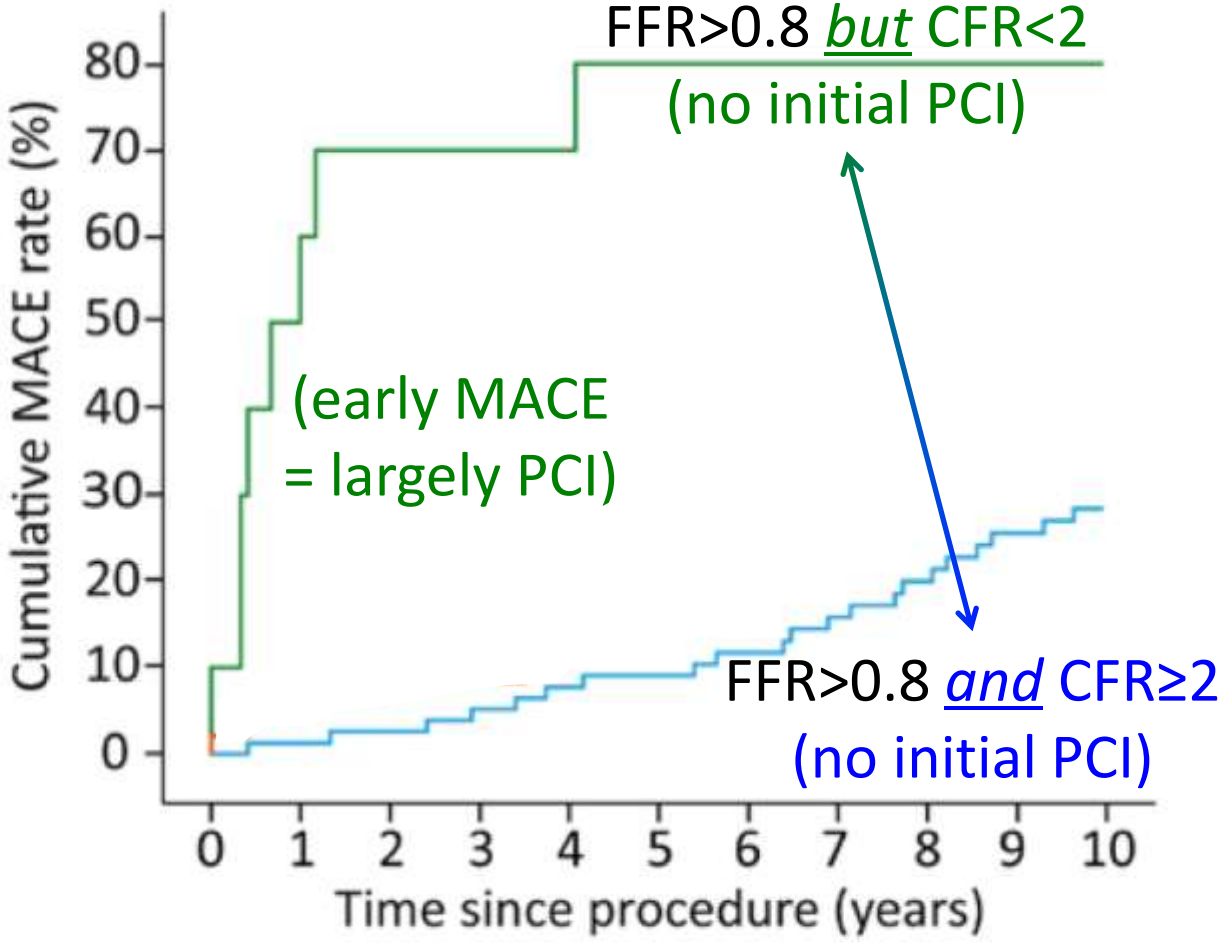




Lee JM, *JACC*. 2016 Mar 15;67(10):1158-1169. (Figures 1A and 2A with highlights and annotations)

For FFR>0.8, does CFR matter?

MACE = death, MI, or PCI/CABG



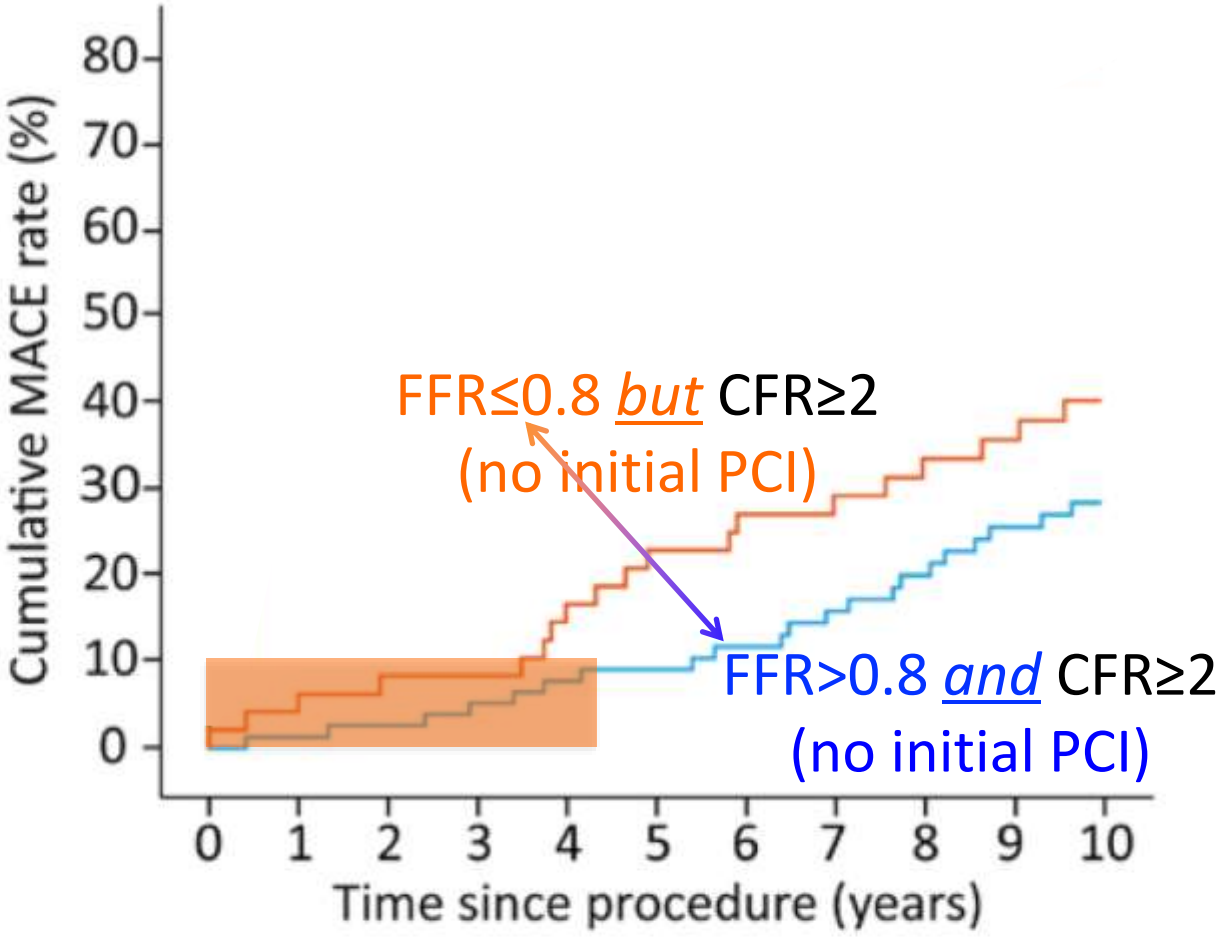
No. at risk:

FFR>0.80 / CFVR≥2.0	78	75	71	66	57	48
FFR>0.80 / CFVR<2.0	10	3	3	2	2	2

van de Hoef TP, *Circ Cardiovasc Interv*. 2014 Jun;7(3):301-311. (Figure 4B modified and annotated)

For CFR≥2, does FFR matter?

MACE = death, MI, or PCI/CABG

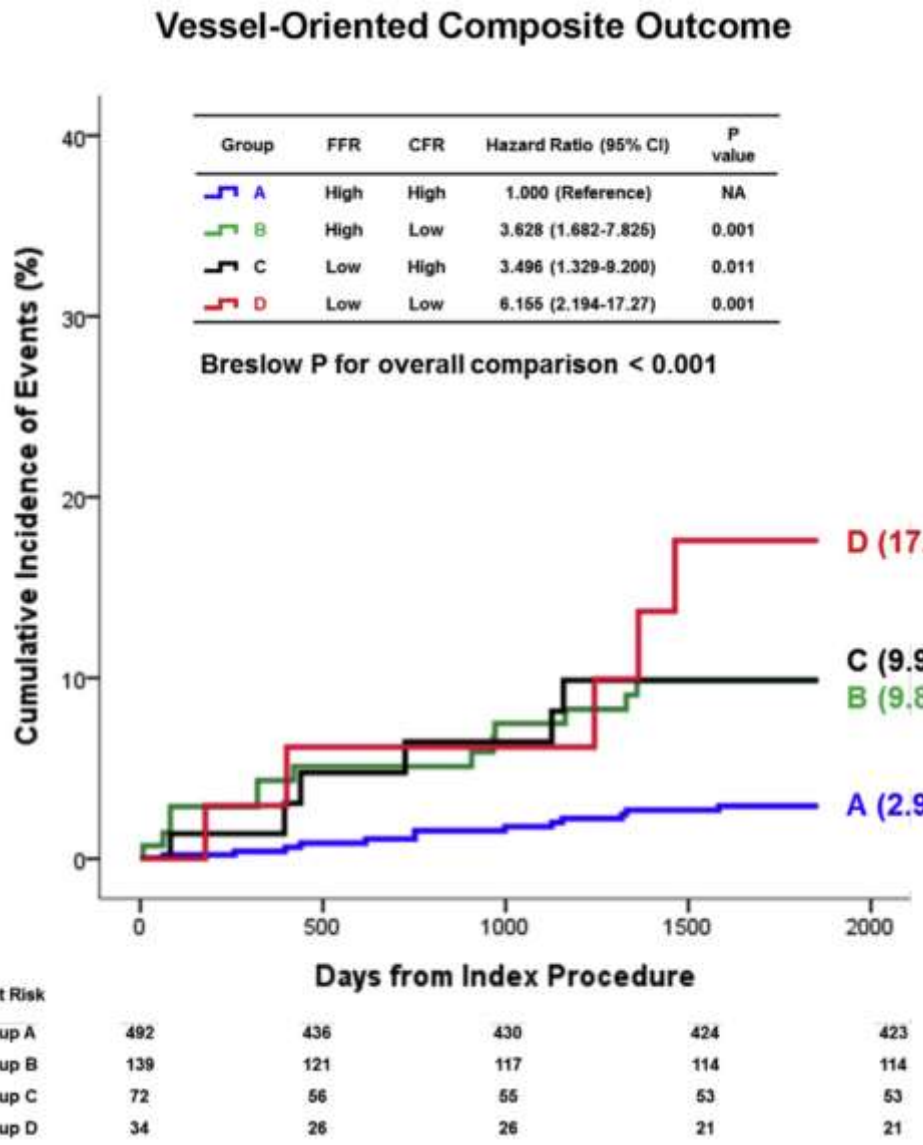


No. at risk:

FFR>0.80 / CFVR≥2.0	78	75	71	66	57	48
FFR>0.80 / CFVR<2.0	10	3	3	2	2	2
FFR≤0.80 / CFVR≥2.0	48	44	40	35	31	24

van de Hoef TP, *Circ Cardiovasc Interv*. 2014 Jun;7(3):301-311. (Figure 4B modified and annotated)

Medical treatment after CFR/FFR



D (17.6%) both CFR/FFR low

C (9.9%)
B (9.8%) mixed CFR/FFR

A (2.9%) both CFR/FFR high

Lee JM, *JACC Cardiovasc Interv*. 2018 Aug 13;11(15):1423-1433. (Figure 4A)

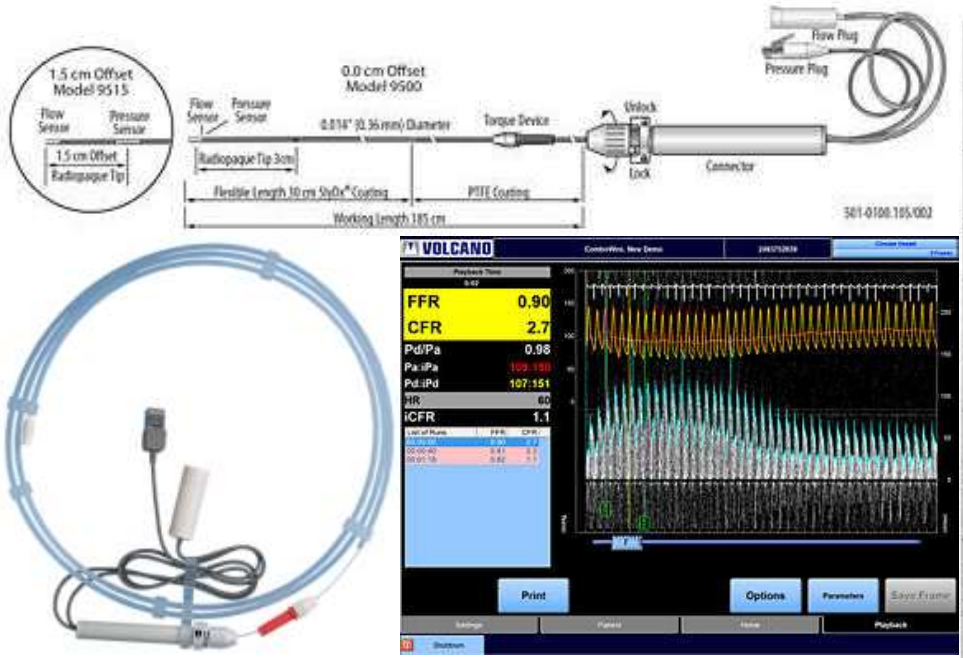
Limitations to existing literature

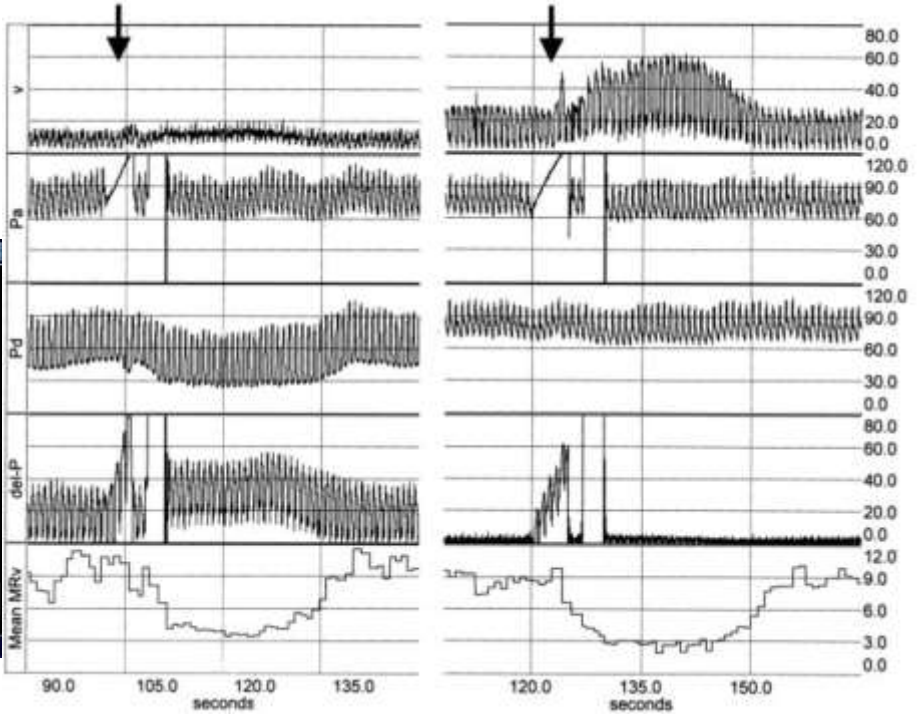
1. Single center/country
   - Amsterdam AMC
   - Korean collaboration (n=5)
2. Modest size of patients/lesions
   - n=157/157 from AMC
   - n=519/737 from Korea
3. **Treatment arbitrary**
   - **Why no PCI if FFR≤0.8?**
   - **Why PCI for FFR>0.8?**
4. Core lab
   - Partial for Korean collaboration
   - No for Amsterdam
5. Event committee for outcomes
   - Yes for Korean collaboration
   - No for Amsterdam

Treatment protocol

measure FFR *and* CFR

ComboWire XT: pressure and Doppler



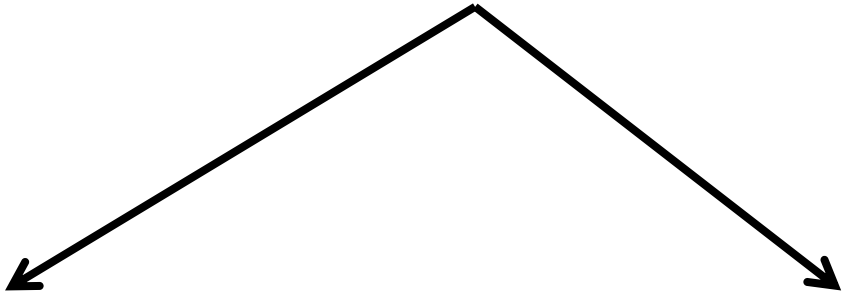


before PCI *after* PCI

left = https://www.usa.philips.com/healthcare/product/HCIGTD9500/combowire-xt-guide-wire/overview, accessed June 25, 2020
right = Siebes M, *Circulation*. 2004 Feb 17;109(6):756-62. (Figure 2)

Treatment protocol

measure FFR *and* CFR

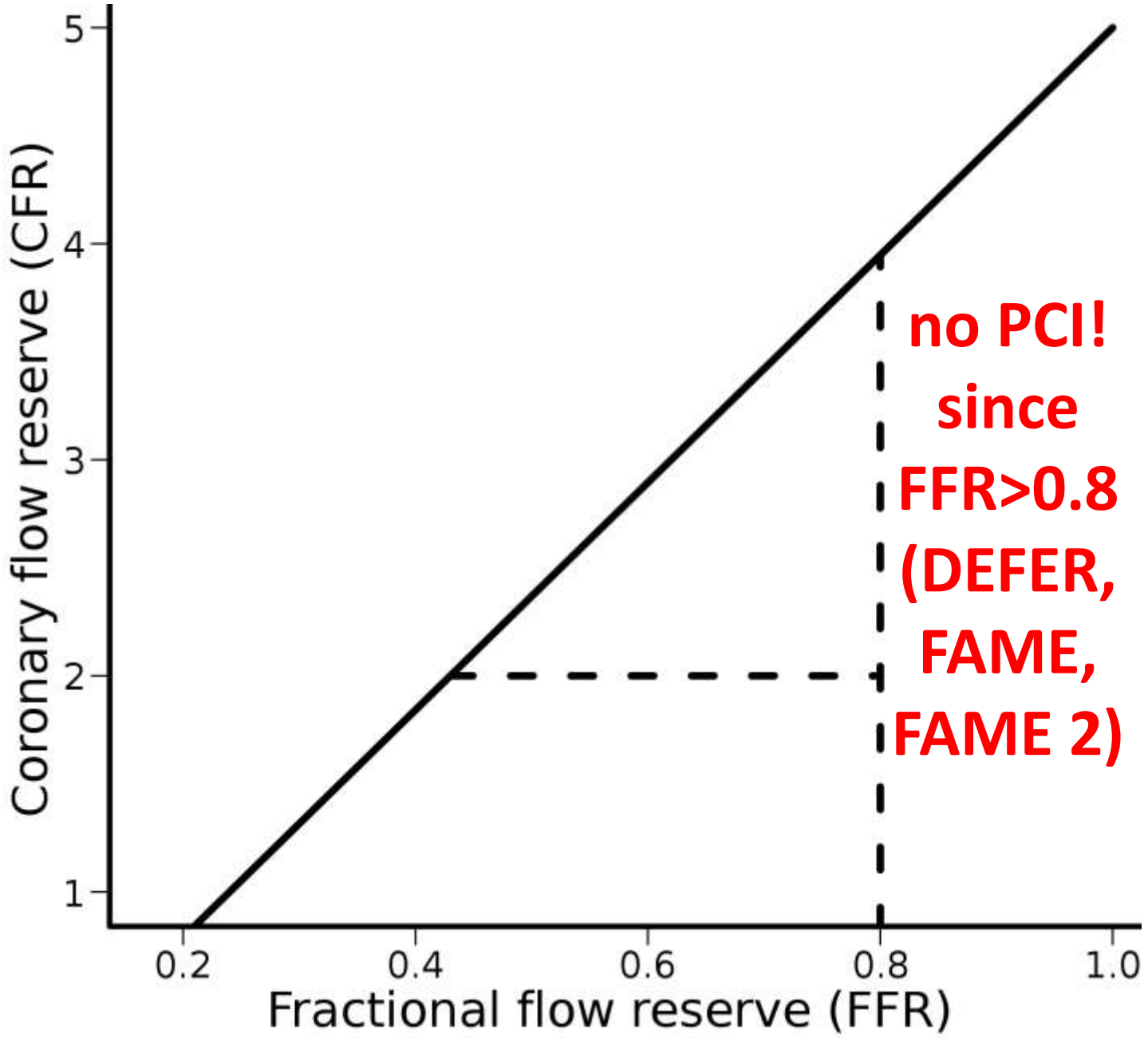


FFR>0.8

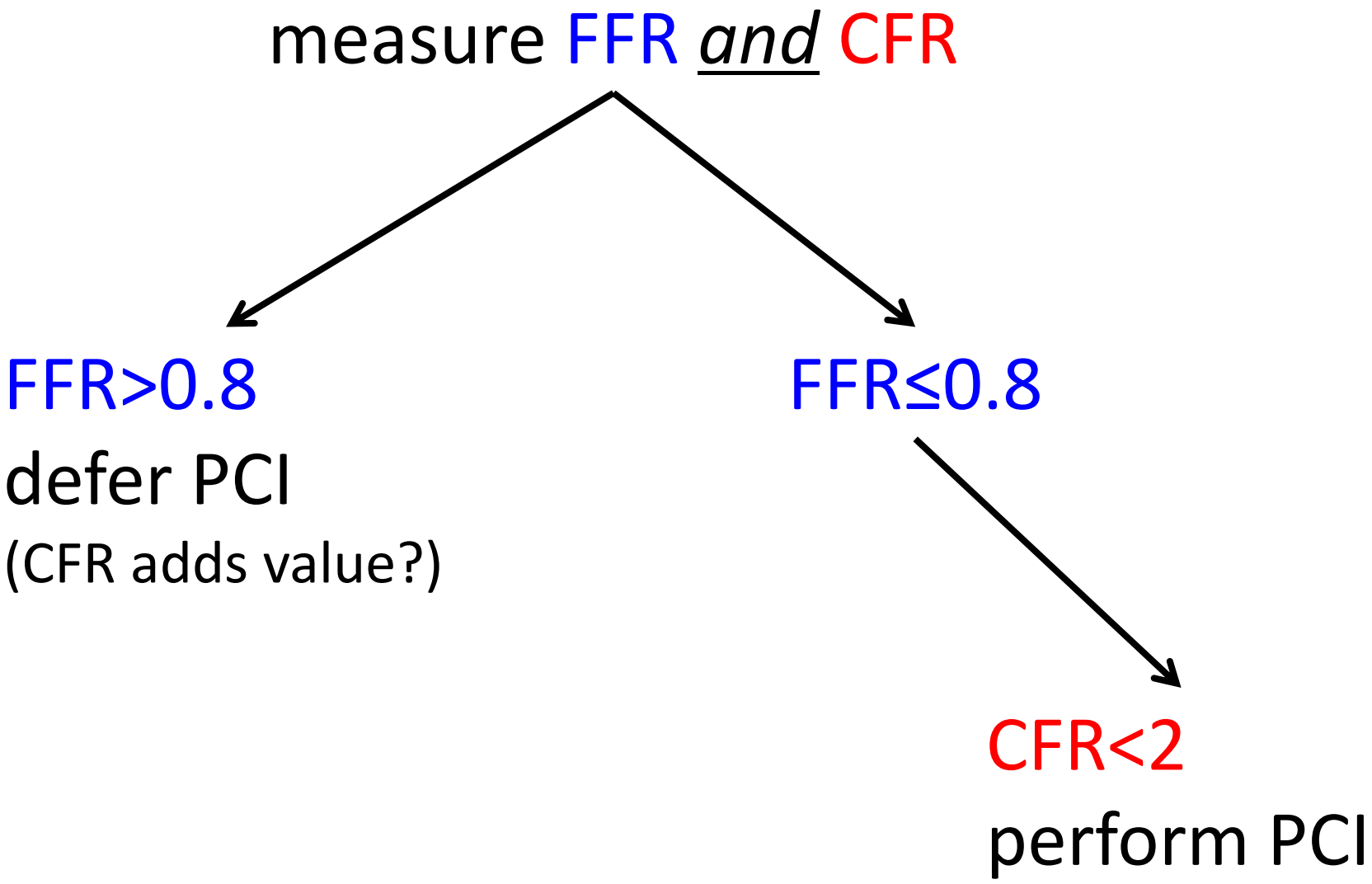
defer PCI

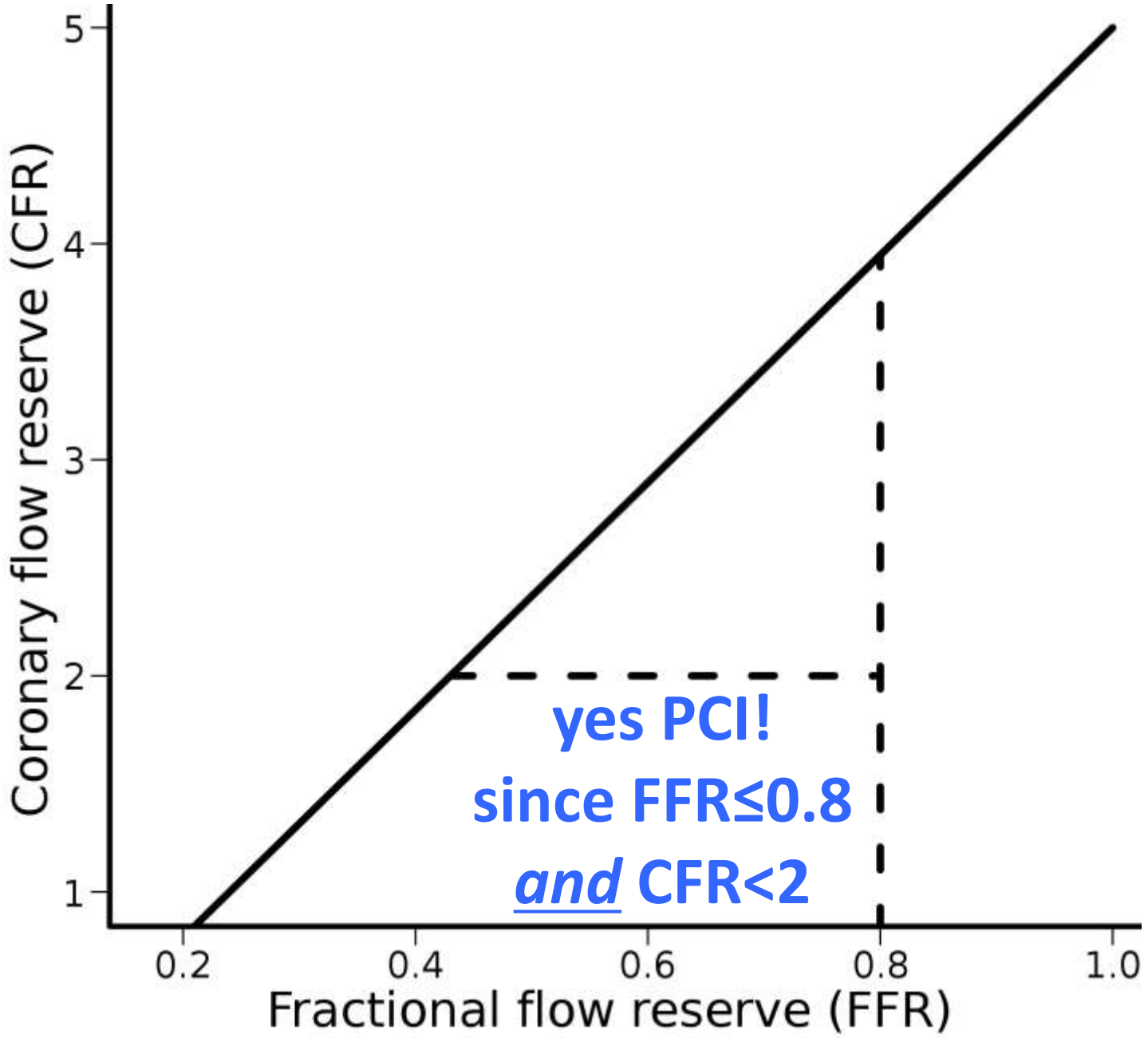
(CFR adds value?)

FFR≤0.8

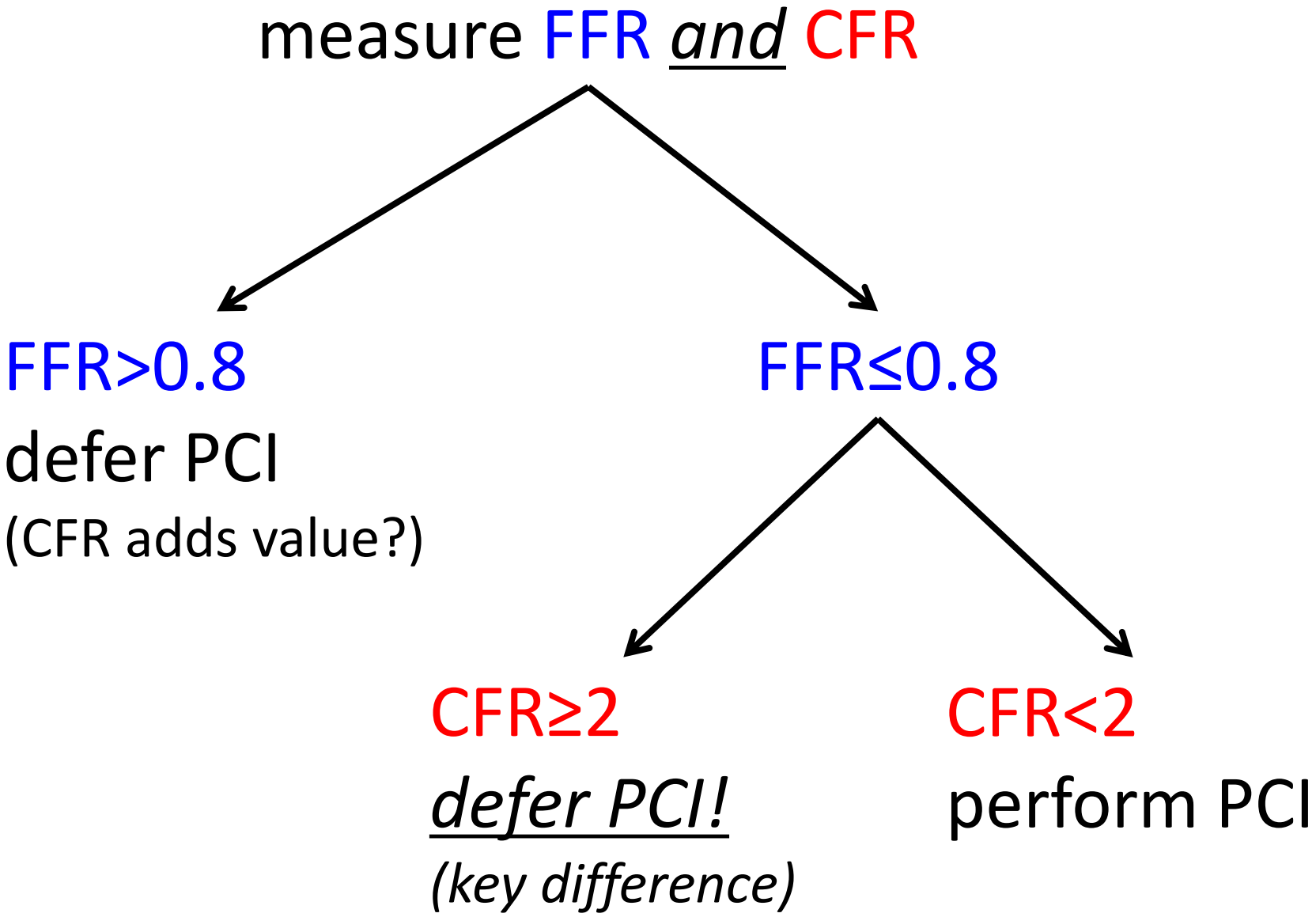

Coronary flow reserve (CFR)
5
4
3
2
1
0.2
0.4
0.6
0.8
1.0
Fractional flow reserve (FFR)
no PCI!
since
FFR>0.8
(DEFER,
FAME,
FAME 2)

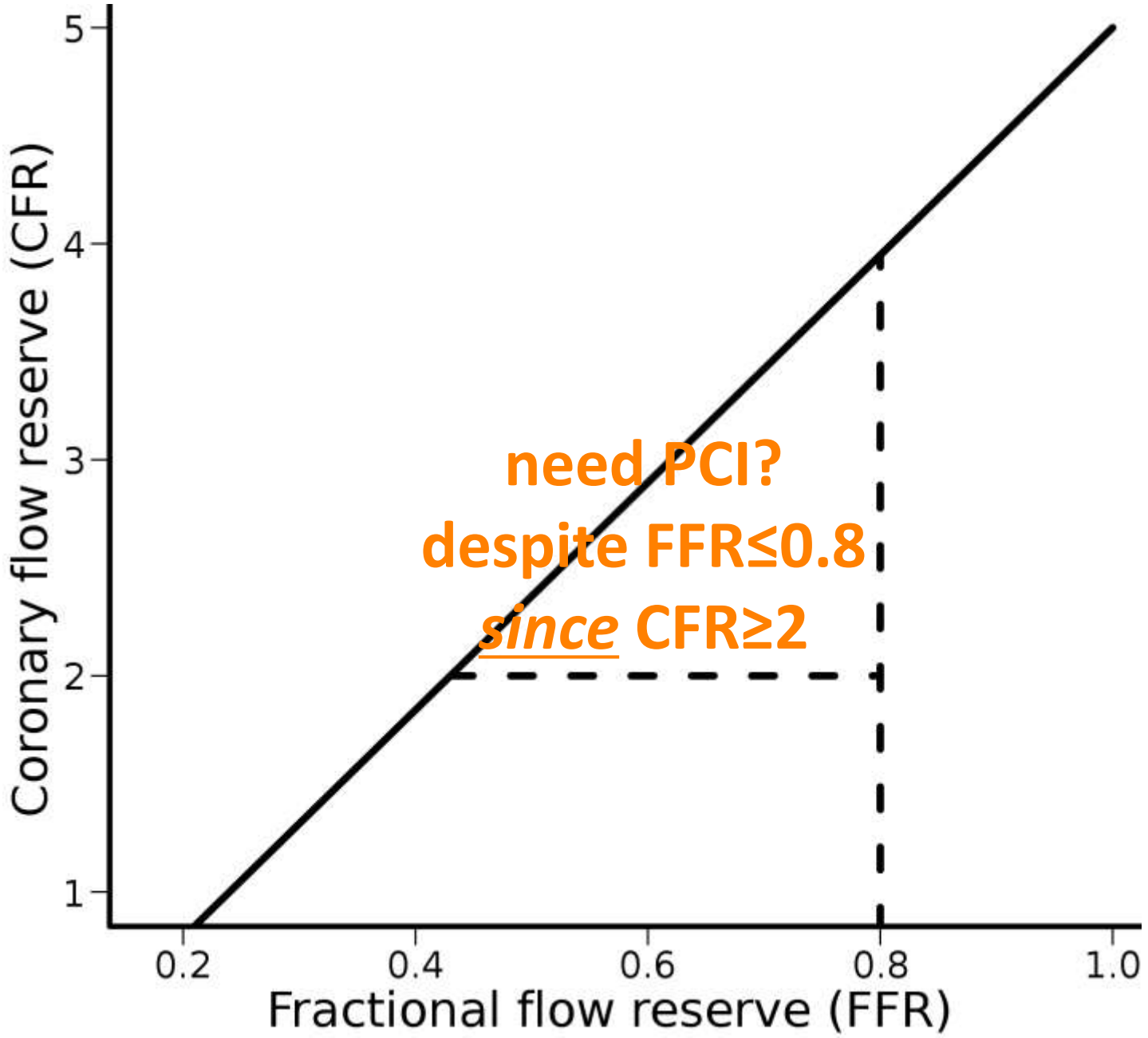
Treatment protocol

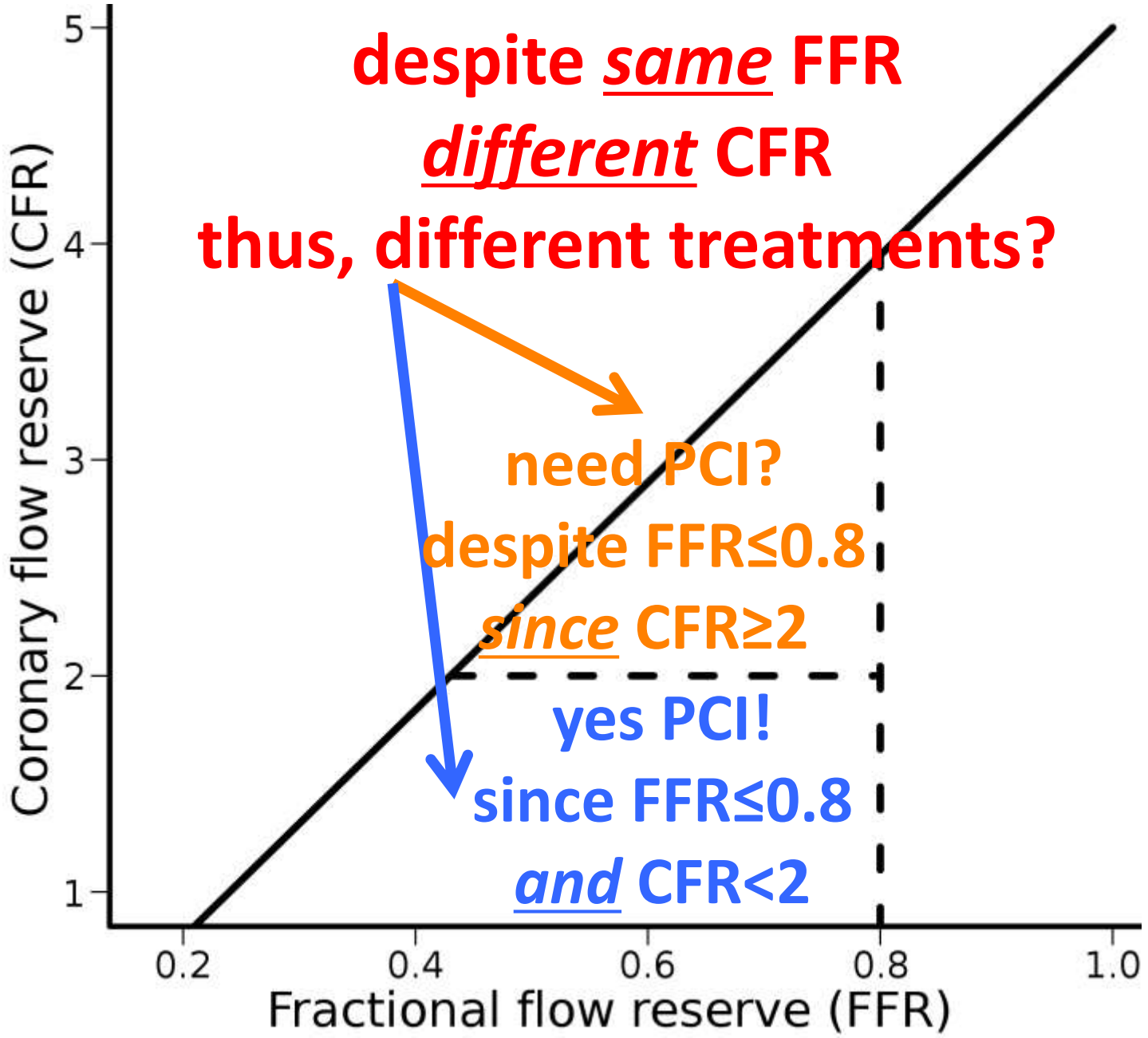



Coronary flow reserve (CFR)
5
4
3
2
1
0.2
0.4
0.6
0.8
1.0
Fractional flow reserve (FFR)
yes PCI!
since FFR≤0.8
and CFR<2

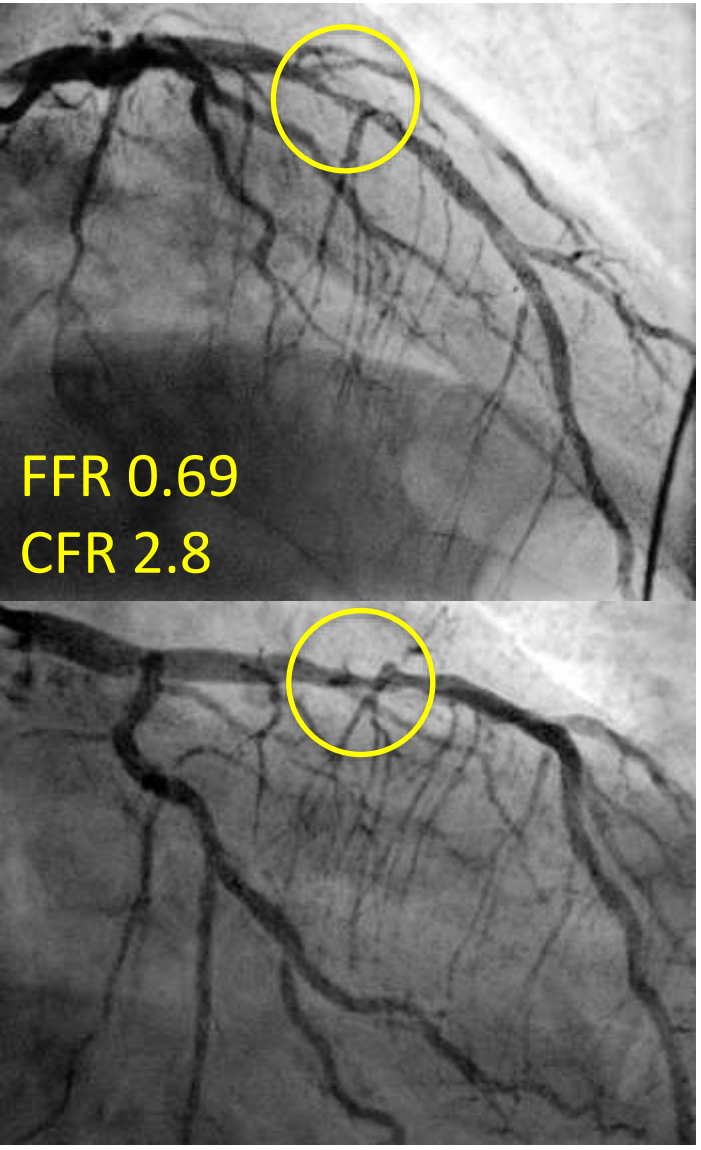
Treatment protocol

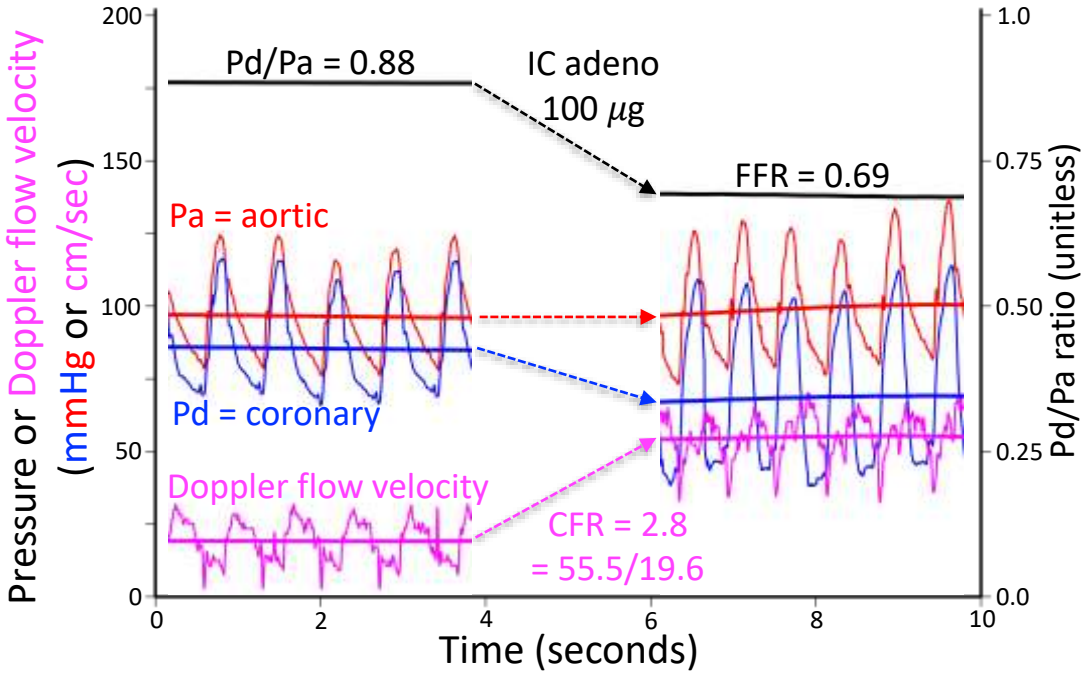



Coronary flow reserve (CFR)
5
4
3
2
1
0.2
0.4
0.6
0.8
1.0
Fractional flow reserve (FFR)
need PCI?
despite FFR≤0.8
since CFR≥2


despite same FFR
different CFR
thus, different treatments?
need PCI?
despite FFR≤0.8
since CFR≥2
yes PCI!
since FFR≤0.8
and CFR<2
Coronary flow reserve (CFR)
Fractional flow reserve (FFR)
1
2
3
4
5
0.2
0.4
0.6
0.8
1.0

No PCI/CABG, *event free @ 2 years*





57 year-old man with diabetes and CCS class I angina

Subject FLOW196 from DEFINE-FLOW (clinicaltrials.gov NCT02328820)

12 sites in 6 countries

- Denmark
  - ✓ Aarhus (University Hospital Skejby, Dr. Evald Christiansen)
- England
  - ✓ London (Royal Free, Dr. Tim Lockie)
- Italy
  - ✓ Rome (Sacred Heart, Drs. Filippo Crea and Giampaolo Niccoli)
- Japan
  - ✓ Gifu (Heart Center, Drs. Hitoshi Matsuo and Yoshiaki Kawase)
  - ✓ Toda City (Central General Hospital, Dr. Masafumi Nakayama)
  - ✓ Tokyo (Medical University, Dr. Nobuhiro Tanaka)
  - ✓ Tsuchiura (Kyodo, Dr. Tsunekazu Kakuta)
- Netherlands
  - ✓ Amsterdam (AMC, Dr. Jan Piek)
  - ✓ Amsterdam (VUmc, Dr. Niels van Royen)
  - ✓ Blaricum (Tergooi, Dr. Maribel Madera-Cambero)
  - ✓ Breda (Amphia, Dr. Martijn Meuwissen)
- Spain
  - ✓ Madrid (Hospital Clinico San Carlos, Dr. Javier Escaned)

Clinical characteristics, n=455

Age (years)	67 ± 10
Male	74%
Diabetes	21%
Prior MI	27%
Prior PCI	41%
Angina or heart failure	71%
Anti-anginal medication	84%
Aspirin	89%
Statin	80%

Stegehuis VE, *Am Heart J*. 2020 Apr;222:139-146. (Table 2 excerpts)

Table III. Baseline angiographic and physiologic data on lesion level (n = 670)

	Mean (range) or n	% of total
LV ejection fraction (%)	60 (56-65)	
Visual diameter stenosis (%)	60 (50-80)	
Guide catheter size		
5F	62	10%
6F	576	90%
7F	5	1%
Prior MI	32	5%
Prior PCI	88	13%
In-stent lesion	19	3%
Reference vessel	28	4%
Noninvasive results*†**		
None available	480	72%
Equivocal	28	4%
Negative	35	5%
Positive	127	19%
Coronary distribution		
Left anterior descending	361	54%
Left circumflex	163	24%
Right coronary artery	144	21%
Left main	2	0%
Treatment decision		
Medical therapy	469	70%
Balloon angioplasty	3	0%
Drug-coated balloon	10	1%
Bioresorbable scaffold	17	3%
Drug-eluting stent	171	26%
Physiologic lesion evaluation	540	81%
Site-reported median FFR†	0.84 (0.76-0.90)	
Site-reported median CFR†	2.1 (1.6-2.6)	

Stegehuis VE, *Am Heart J*. 2020 Apr;222:139-146. (Table 3 with *highlights*)

DEFINE-FLOW *overcomes* limitations

1. Single center/country
   - Amsterdam AMC
   - Korean collaboration (n=5)

   12 centers, 6 countries
2. Modest size of patients/lesions
   - n=157/157 from AMC
   - n=519/737 from Korea

   455/670 subjects/lesions
3. Treatment arbitrary
   - Why no PCI if FFR≤0.8?
   - Why PCI for FFR>0.8?

   PCI only if FFR≤0.8 *and* CFR<2
4. Core lab
   - Partial for Korean collaboration
   - No for Amsterdam

   Blinded analysis of pressure / flow
5. Event committee for outcomes
   - Yes for Korean collaboration
   - No for Amsterdam

   Central adjudication blinded to CFR/FFR