The DEFINE-FLOW study

combined CFR and FFR assessment

Dr. Nils Johnson

on behalf of the DEFINE-FLOW investigators

Associate Professor of Medicine

Weatherhead Distinguished Chair of Heart Disease

Division of Cardiology, Department of Medicine

and the Weatherhead PET Imaging Center

McGovern Medical School at UTHealth (Houston)

Memorial Hermann Hospital – Texas Medical Center

United States of America

UTHealth® The University of Texas Health Science Center at Houston | McGovern Medical School

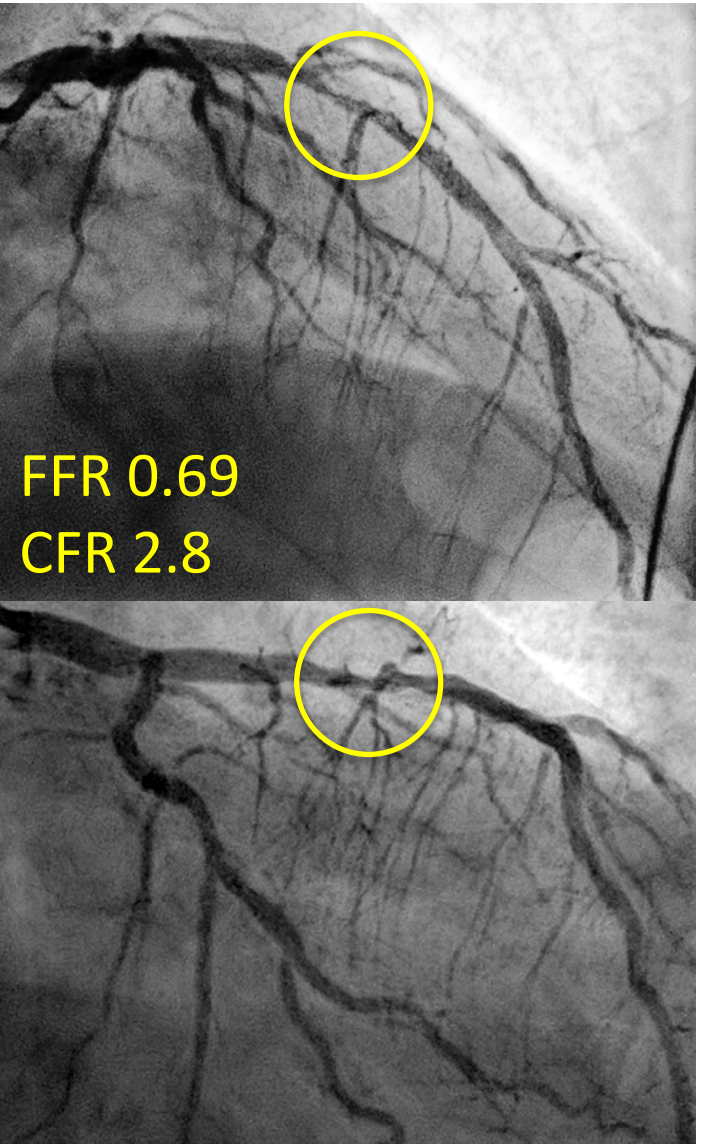
Weatherhead PET Imaging Center

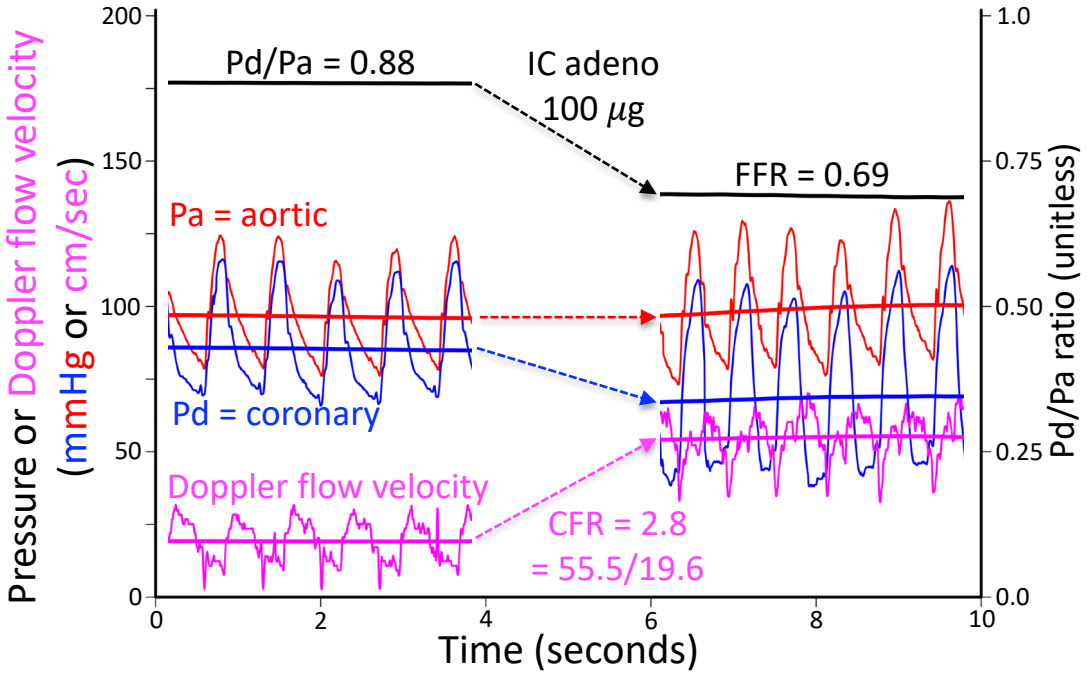
Disclosure Statement of Financial Interest

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

How to treat CFR/FFR discordance?





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

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

Hypothesis

Vessels with

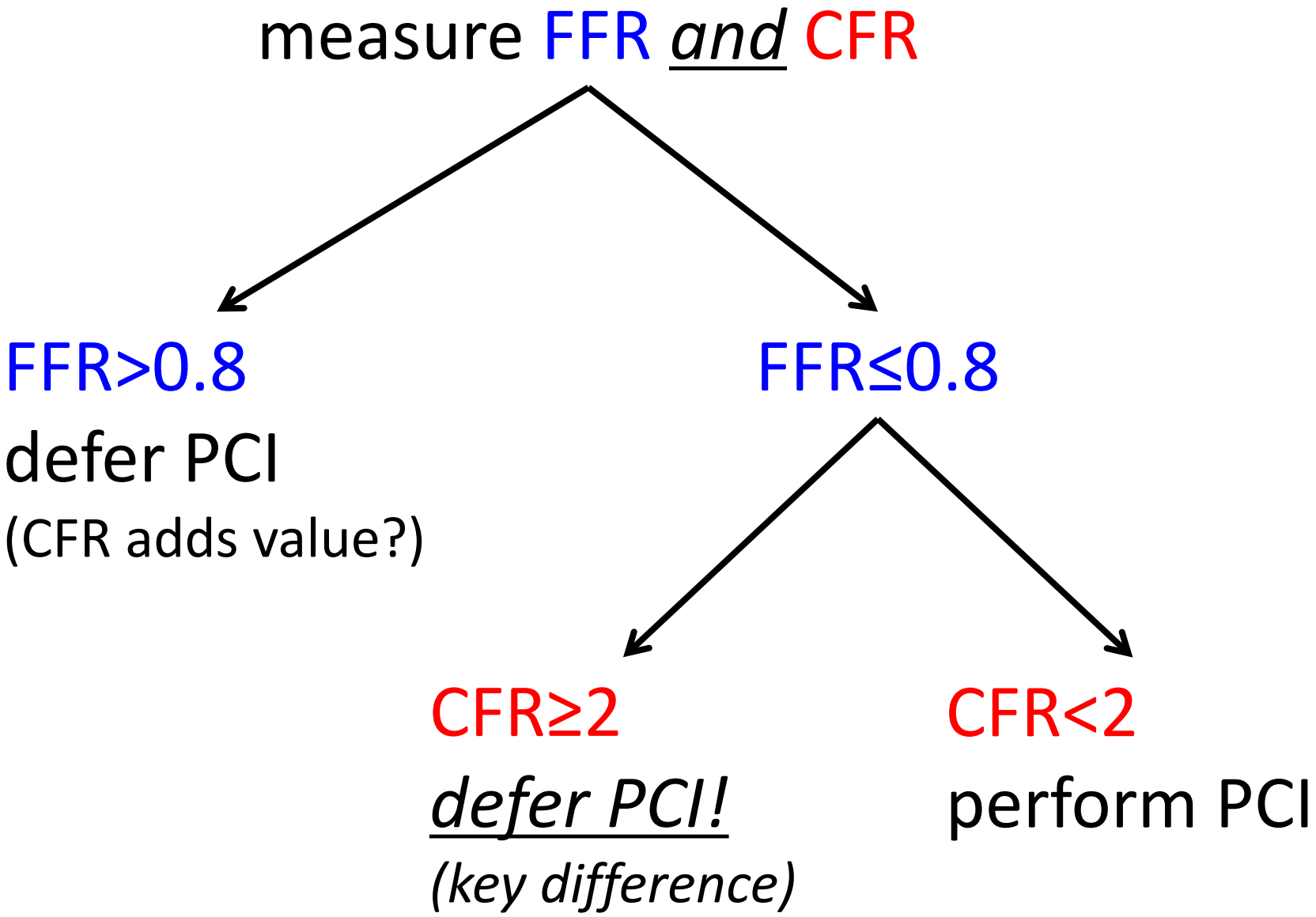
- *abnormal FFR≤0.8 but intact CFR≥2*
- will show *non-inferior* outcomes
- versus FFR>0.8 and CFR≥2
- when *treated medically*.

Primary endpoint:

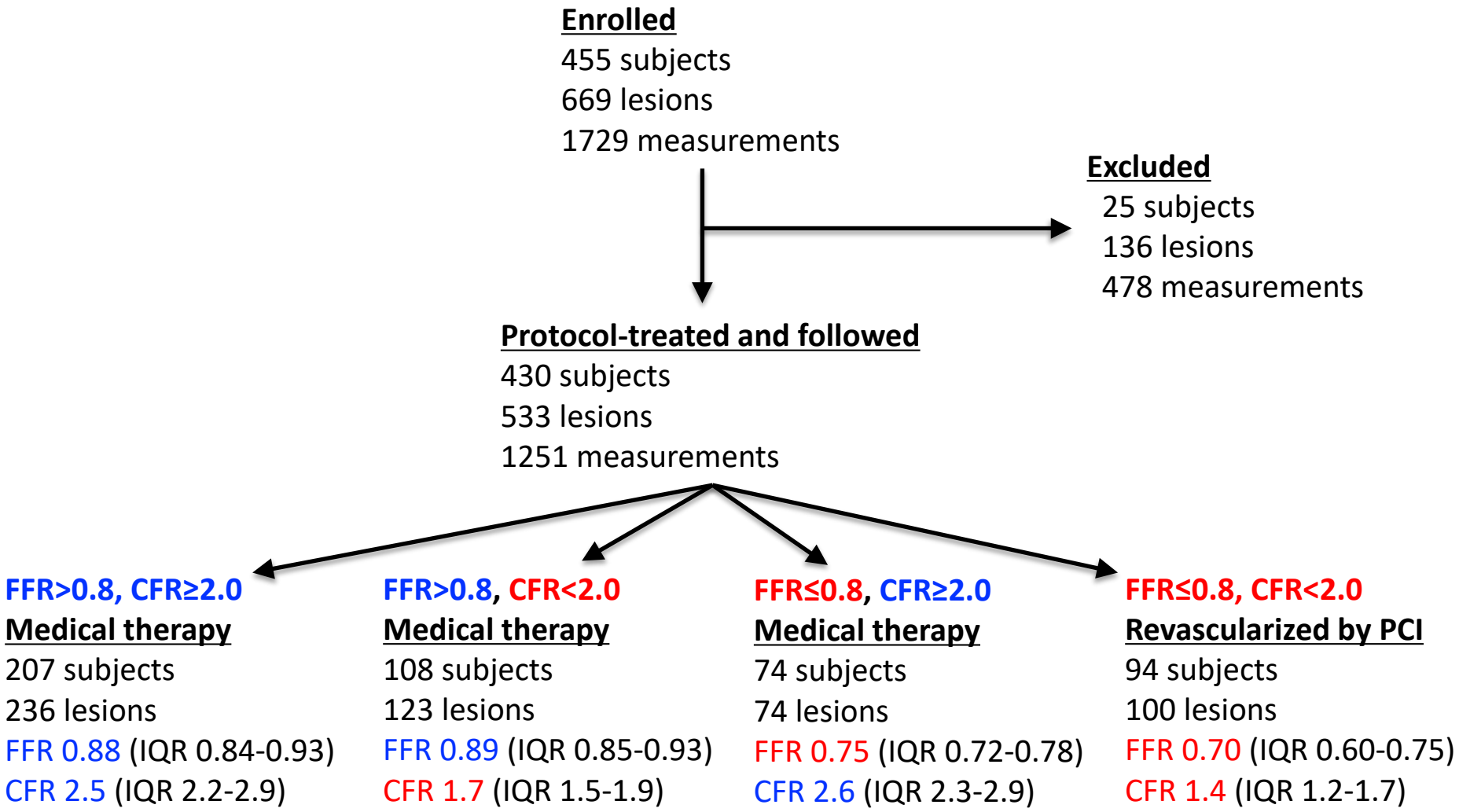
- composite of *all-cause death, MI, PCI/CABG*
- assessed after *2 years*
- central adjudication by events committee
- non-inferiority margin of 10%

Stegehuis VE, *Am Heart J*. 2020 Apr;222:139-146.

Treatment protocol



Study flow diagram

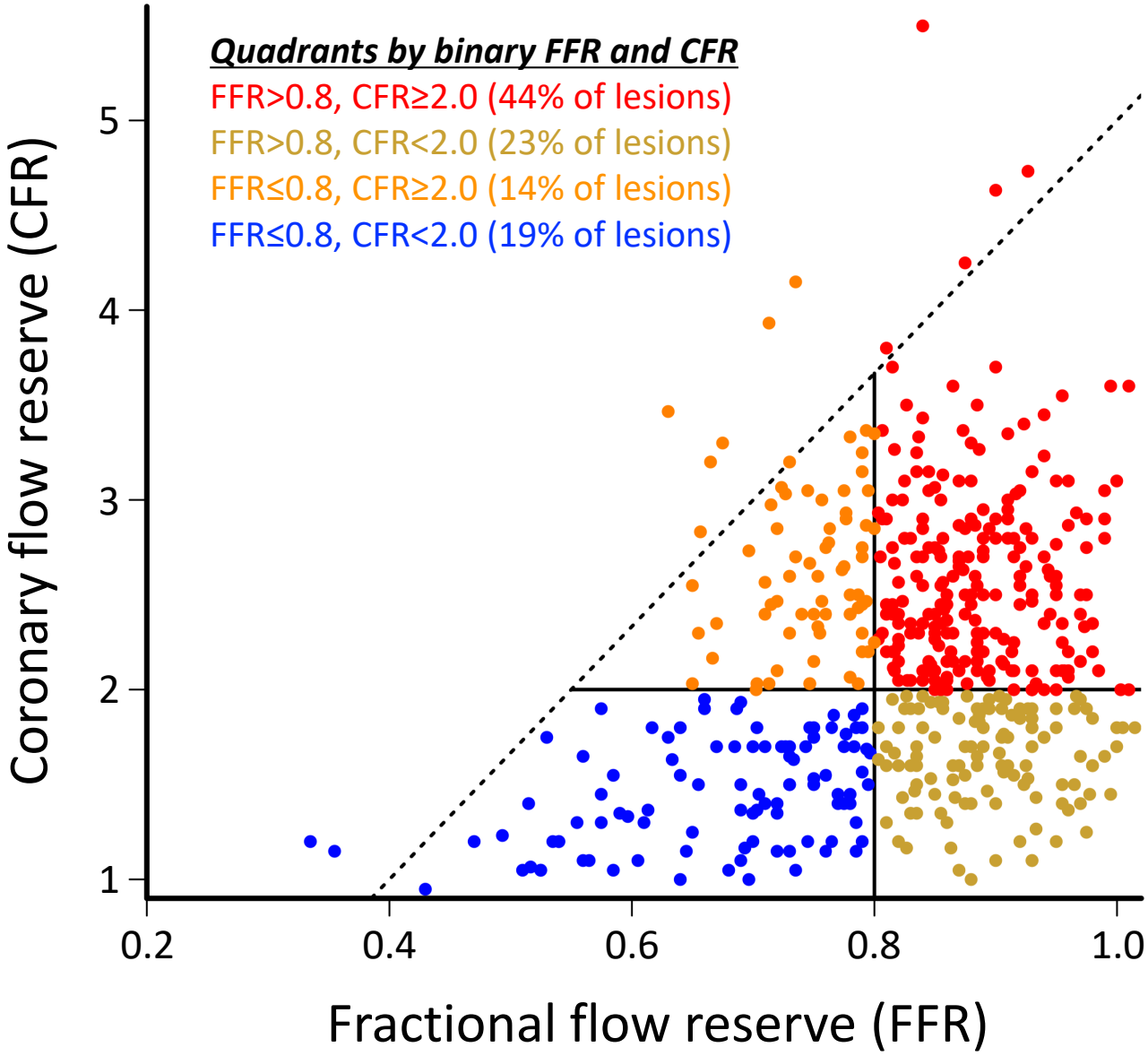


Baseline characteristics

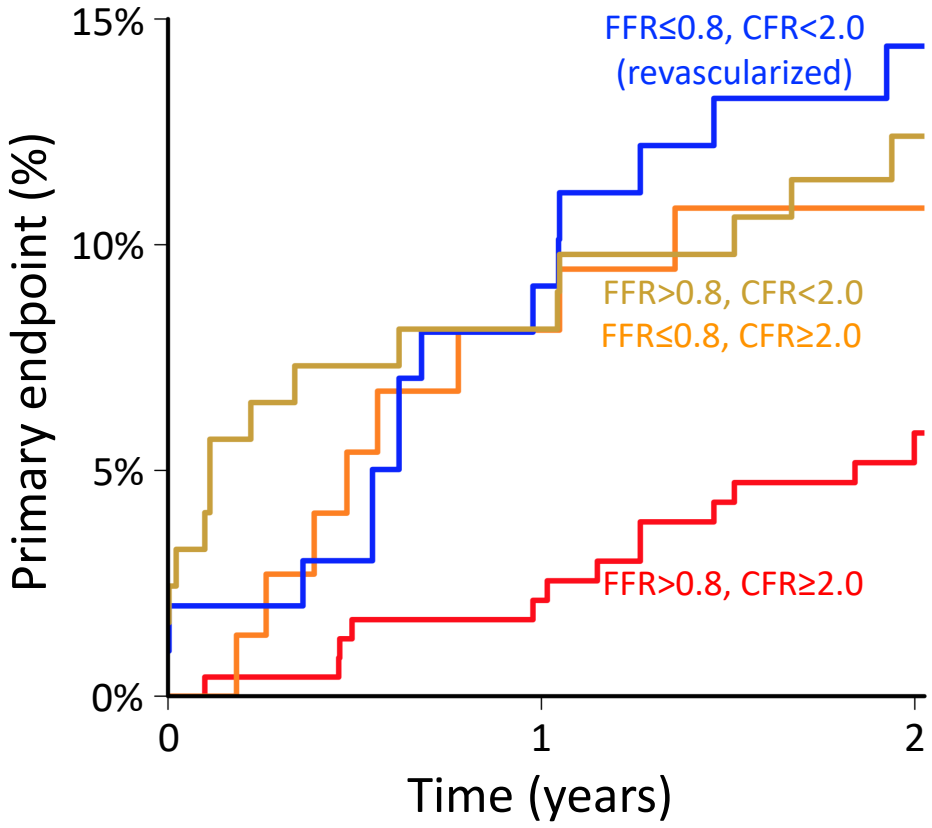
	N = 430 subjects		N = 533 lesions
Age (years)	67 ± 10	LAD	59%
Male	74%	LCx	23%
Diabetes	27%	RCA	18%
Active tobacco	22%	Prior PCI of vessel	14%
Prior MI	27%	FFR≤0.80	33%
Prior PCI	40%	CFR<2.0	42%
Stable presentation	80%		
Aspirin	89%		
Statin	80%		
≥2 anti-anginals*	50%		

* = includes beta blockers, calcium blockers, nitrates, ranolazine, ivabradine, trimetazidine, and nicorandil

CFR/FFR discordance



Primary endpoint



2-year MACE (death, MI, any PCI/CABG)
(from Kaplan-Meier estimates,
using site-reported FFR and CFR)

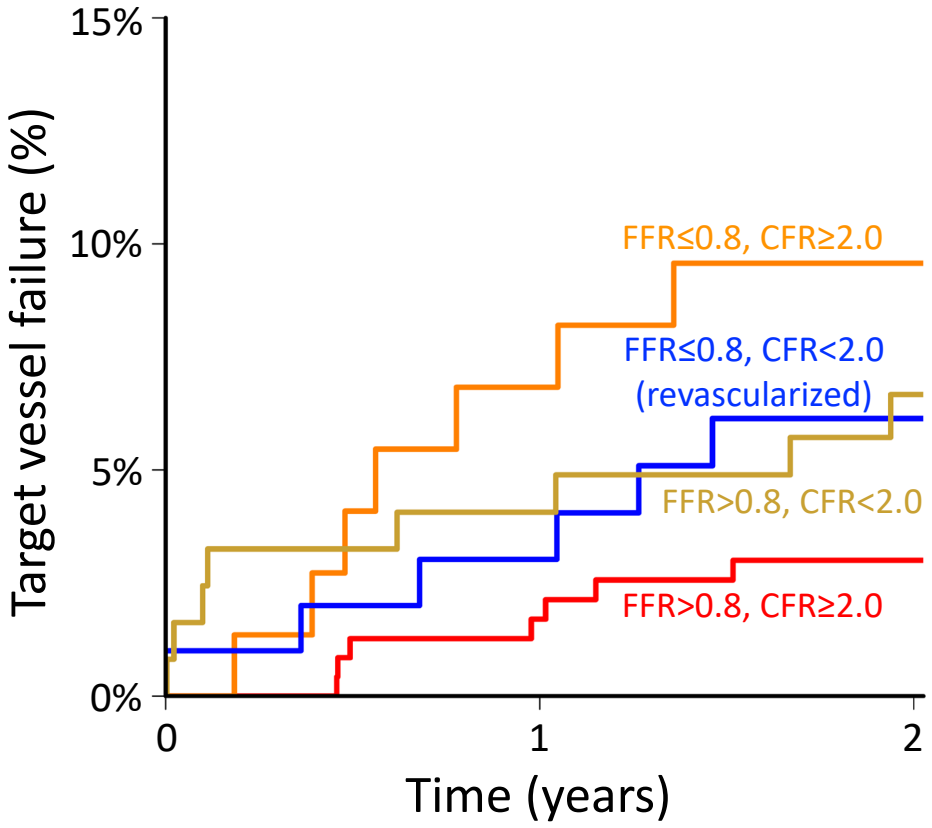
- FFR-/CFR- = 5.8%
- FFR+/CFR- = 10.8%
- FFR-/CFR+ = 12.4%
- FFR+/CFR+ = 14.4% (after PCI)

FFR+/CFR- vs FFR-/CFR-

- Δ = +5.0% (95%CI -1.5% to +11.5%)
- p-value 0.065 for non-inferiority

natural history *NOT non-inferior*
for FFR+/CFR- and FFR-/CFR-

Secondary data: **T**arget **V**essel **F**ailure



2-year TVF (MI or PCI/CABG of target)
(from Kaplan-Meier estimates,
using site-reported FFR and CFR)

- FFR-/CFR- = 3.0%
- FFR+/CFR- = 9.6%
- FFR-/CFR+ = 6.7%
- FFR+/CFR+ = 6.1% (after PCI)

Continuous predictors

- natural history (no FFR+/CFR+)
- 351 subjects, 433 lesions
- time-to-failure Cox mixed effects
- FFR hazard ratio <0.01, p=0.0067
- CFR hazard ratio 0.74, p=0.44

Secondary data: core lab

Measurements

- 69.8% of measurements accepted
- Δ FFR = 0.008 ± 0.026 (site<core lab)
- Δ CFR = 0.02 ± 0.23 (site>core lab)

→ core lab reduces sample size by 30%

→ but no change in FFR, CFR

TVF using continuous FFR, CFR

- natural history (no FFR+/CFR+)
- 286 subjects, 337 lesions
- time-to-failure Cox mixed effects
- FFR hazard ratio <0.01, p=0.038
- CFR hazard ratio 0.78, p=0.64

→ core lab analysis supports site analysis

Limitations

- Lack of randomization excludes causality
  (no comparison arm for FFR+/CFR- quadrant)
- Modest sample size with slow enrollment
  (took 3 years to enroll 455 subjects from 12 centers)
- Modest event rate with few “hard” endpoints
  (only 2 deaths [both non-cardiac], 5 infarcts)
- Unblinded subjects and physicians
  (might have biased the 32 TVR/TLR)
- Few lesions with severe FFR/CFR
  (FFR<0.75 in 20%, CFR≤1.7 in 27%)
- Therefore, a hypothesis-generating study

Primary conclusion

Natural history of FFR≤0.8 / CFR≥2

is NOT non-inferior

to lesions with FFR>0.8 / CFR≥2