The DEFINE-FLOW study

combined CFR and FFR assessment

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on behalf of the DEFINE-FLOW investigators

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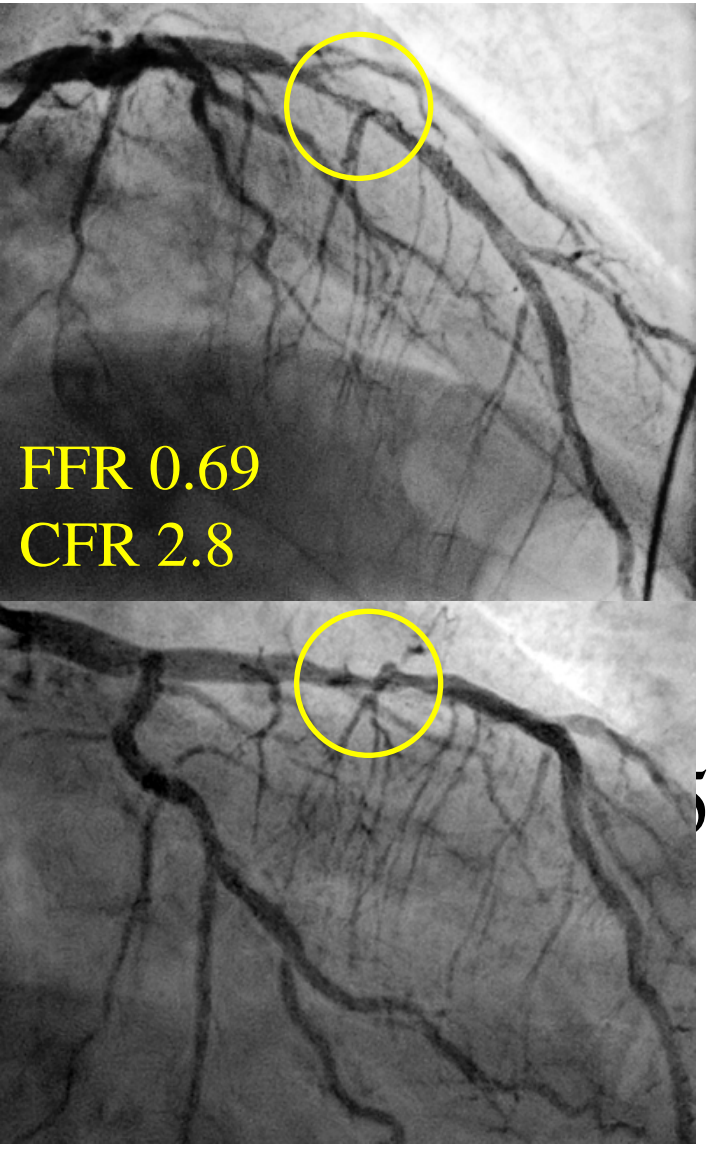
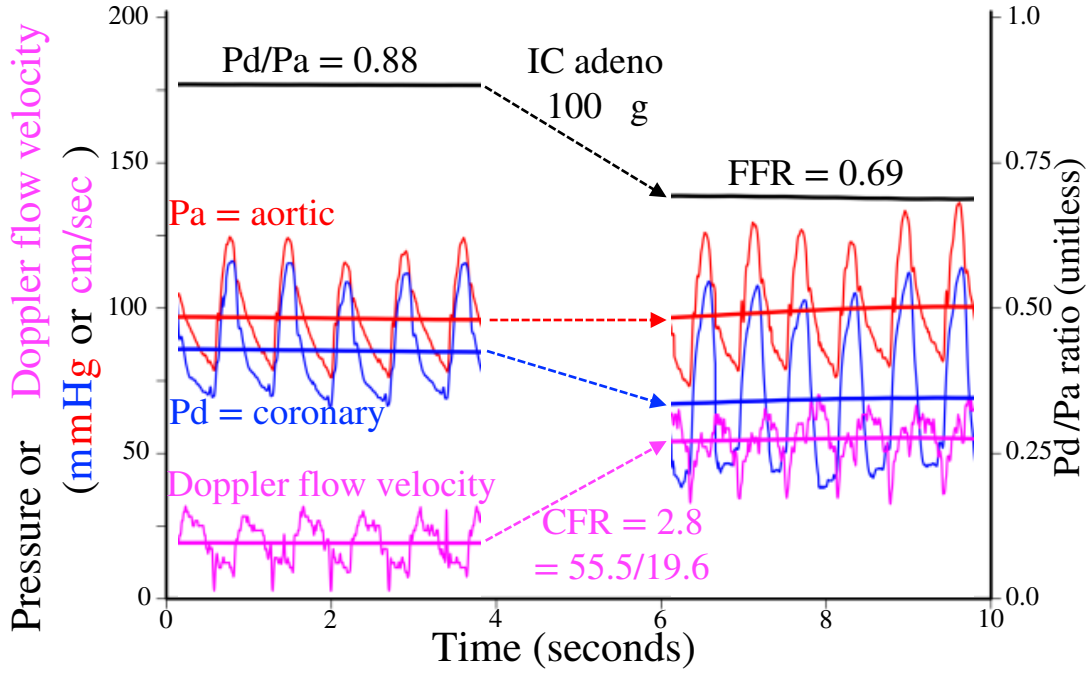
Disclosure Statement of Financial Interest

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

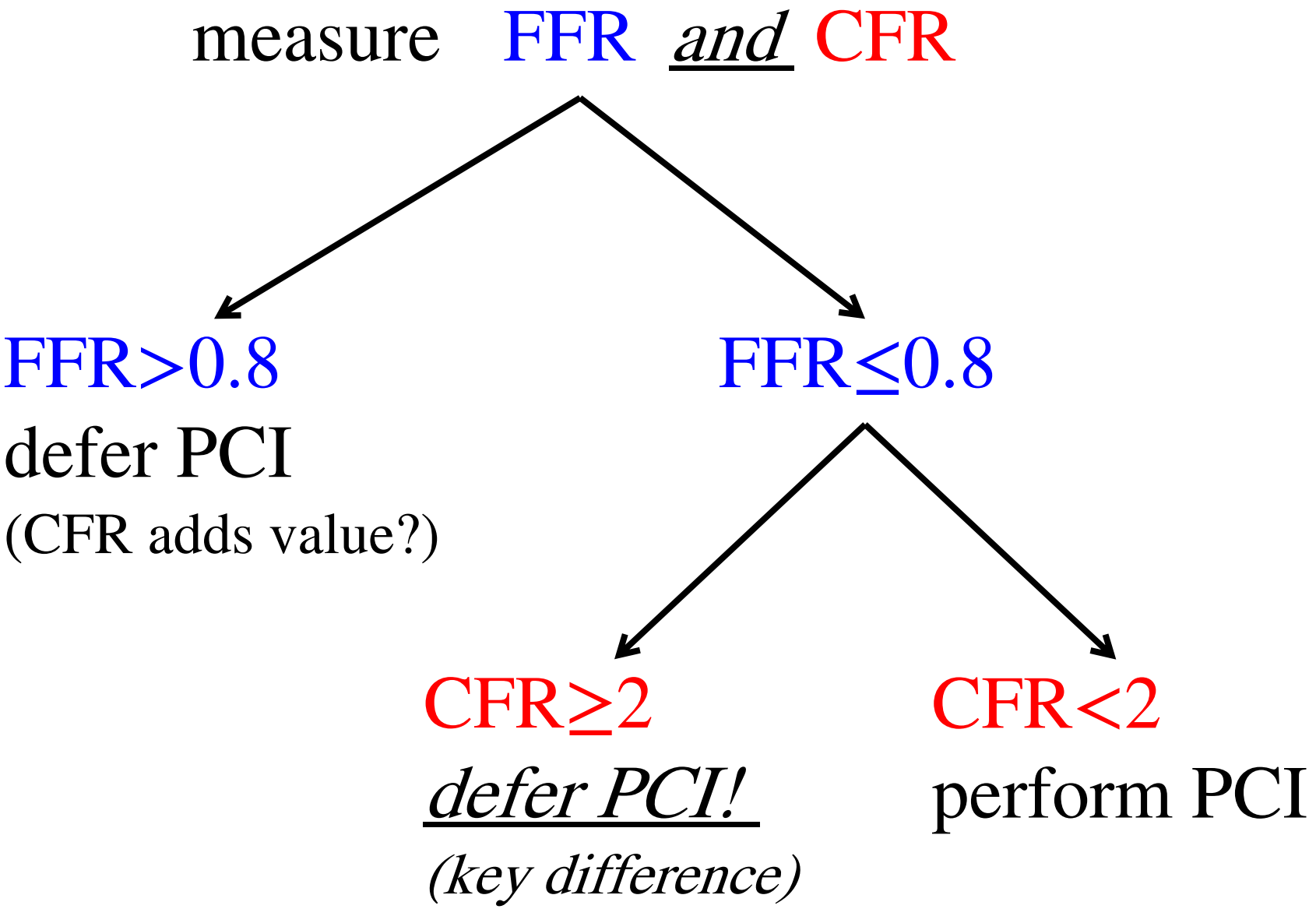
- *abnormal FFR≤0.8 but intact CFR≥2*
- will show *non-inferior* outcomes
- versus FFR>0.8 and CFR≥2
- when *treated medically* .

Primary endpoint:

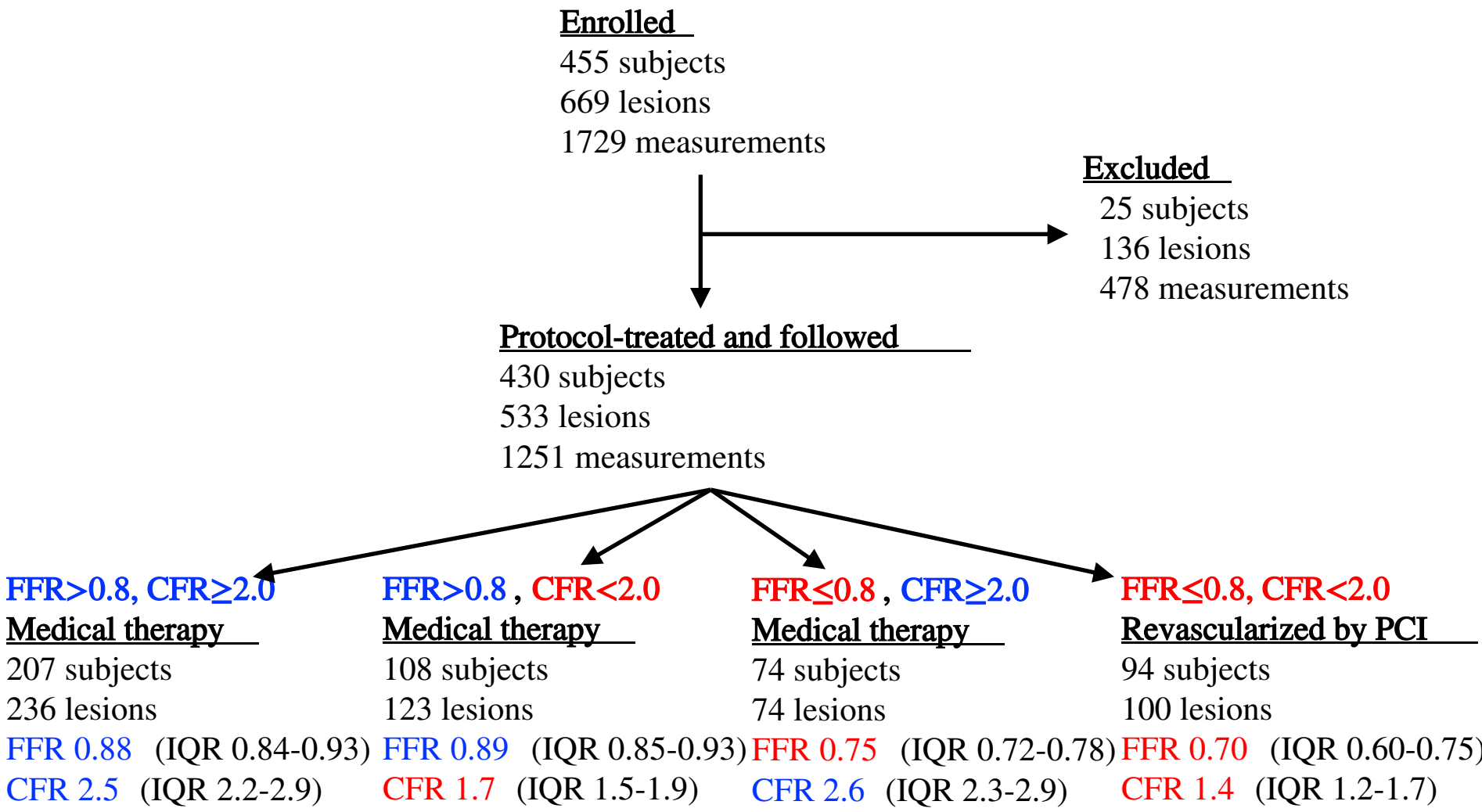
- composite of *all-cause death, MI, PCI/CABG*
- assessed after *2 years*
- central adjudication by events committee
- non-inferiority margin of 10%

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

Treatment protocol



Study flow diagram

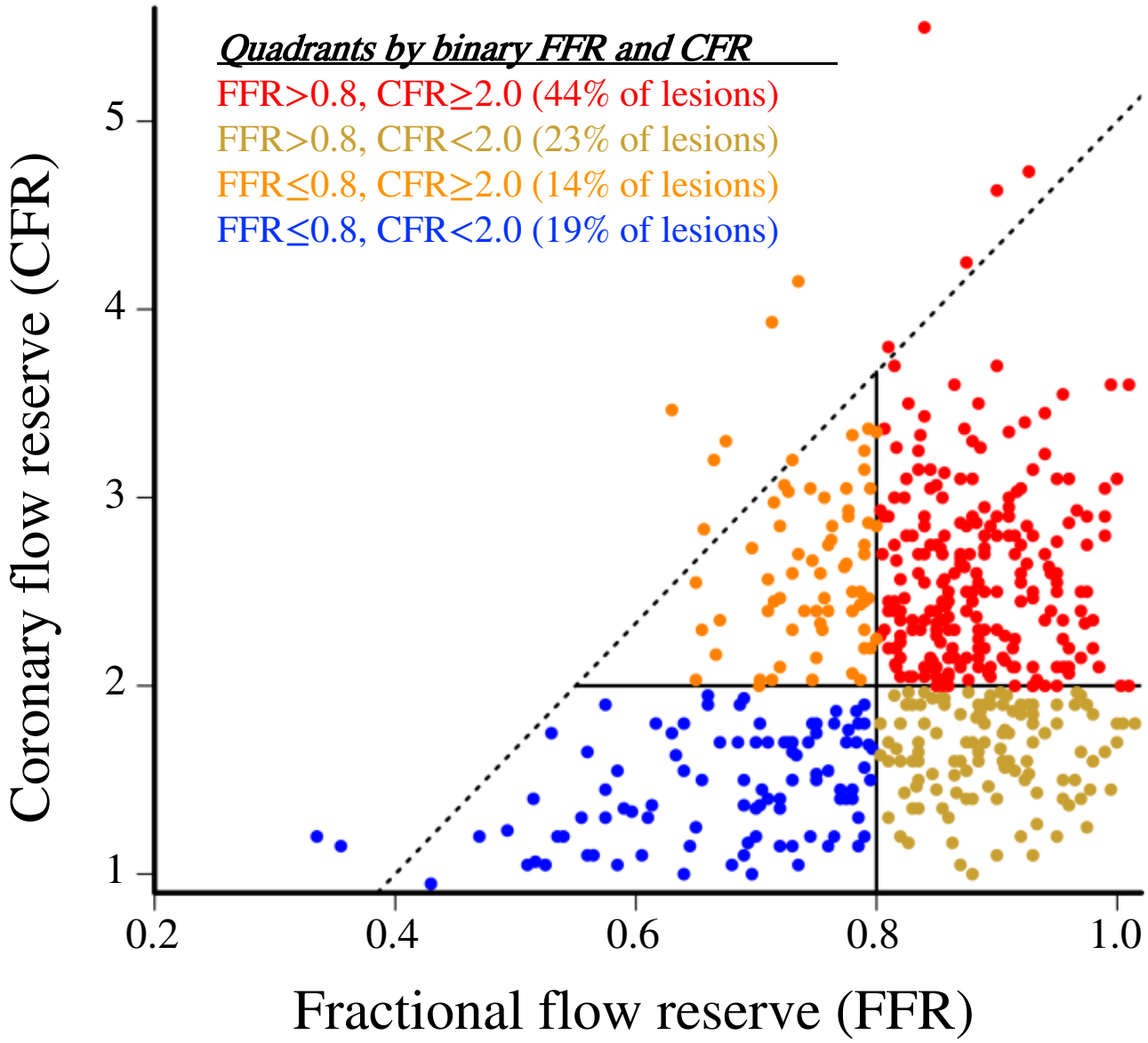


Baseline characteristics

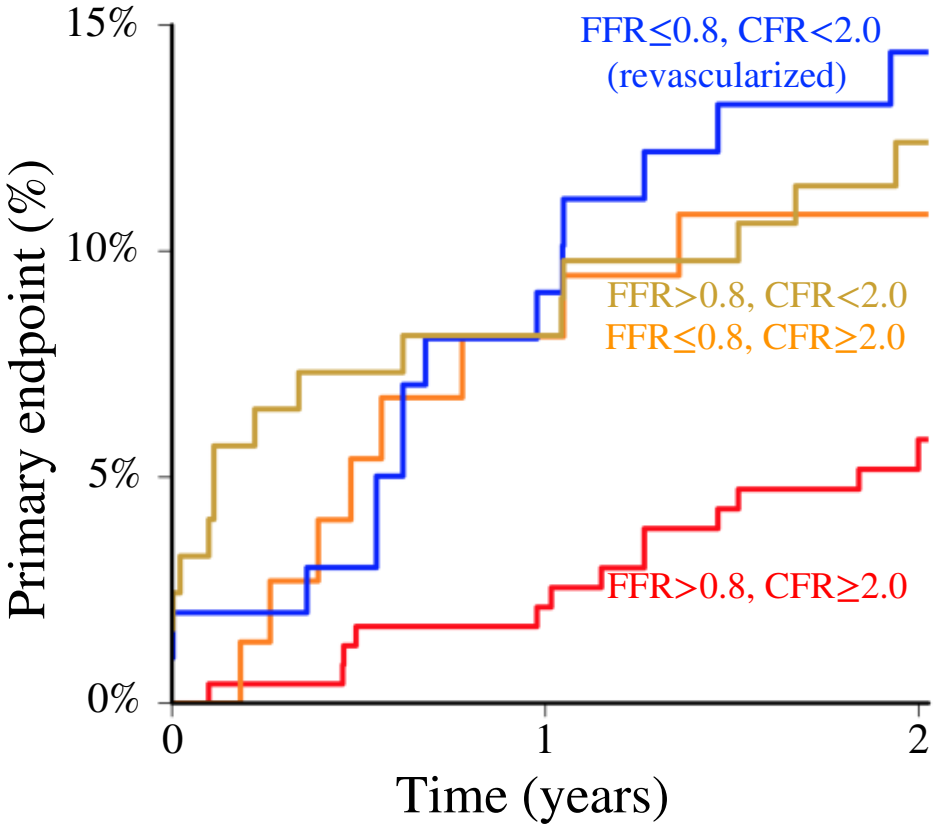
	N = 430 subjects		N = 533 lesions
Age (years)	67 ± 10	LAD	59%
Male	74%	LCx	23%
Diabetes	27%	RCA	18%
Active tobacco	22%	Prior PCI of vessel	14%
Prior MI	27%	FFR≤0.80	33%
Prior PCI	40%	CFR<2.0	42%
Stable presentation	80%		
Aspirin	89%		
Statin	80%		
≥2 anti-anginals*	50%		

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

CFR/FFR discordance



Primary endpoint



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

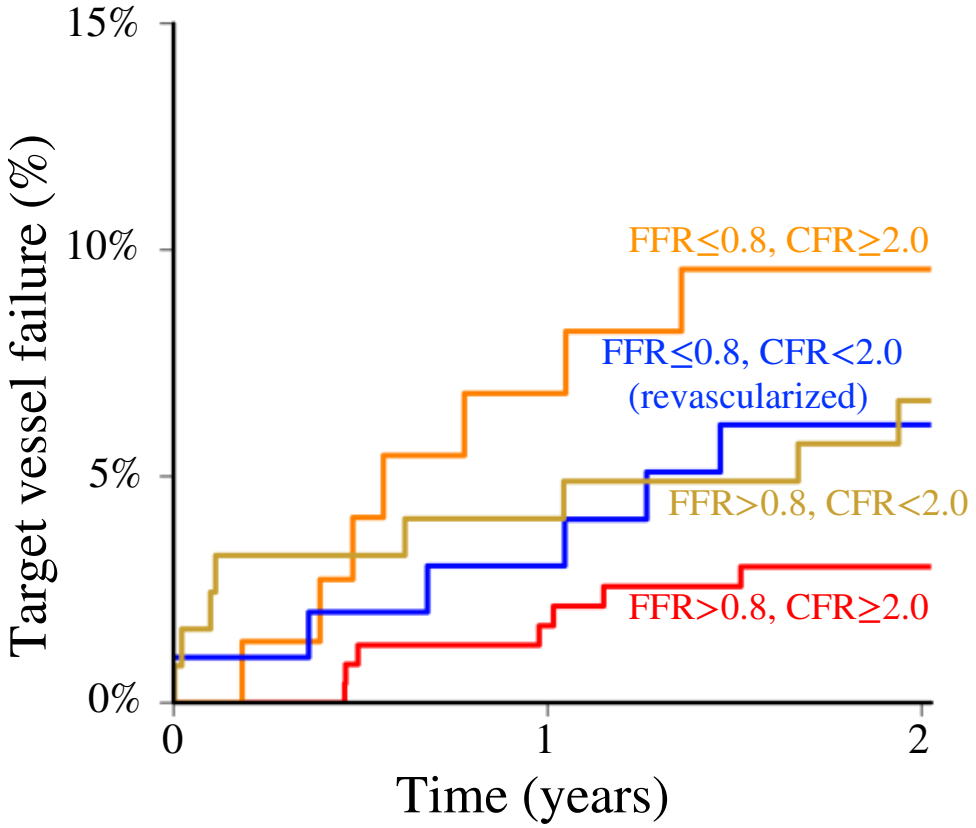
- FFR-/CFR- = 5.8%
- FFR+/CFR- = 10.8%
- FFR-/CFR+ = 12.4%
- FFR+/CFR+ = 14.4% (after PCI)

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: Target Vessel Failure



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 $\pm$ 0.026 (site<core lab)
- Δ CFR = 0.02 $\pm$ 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