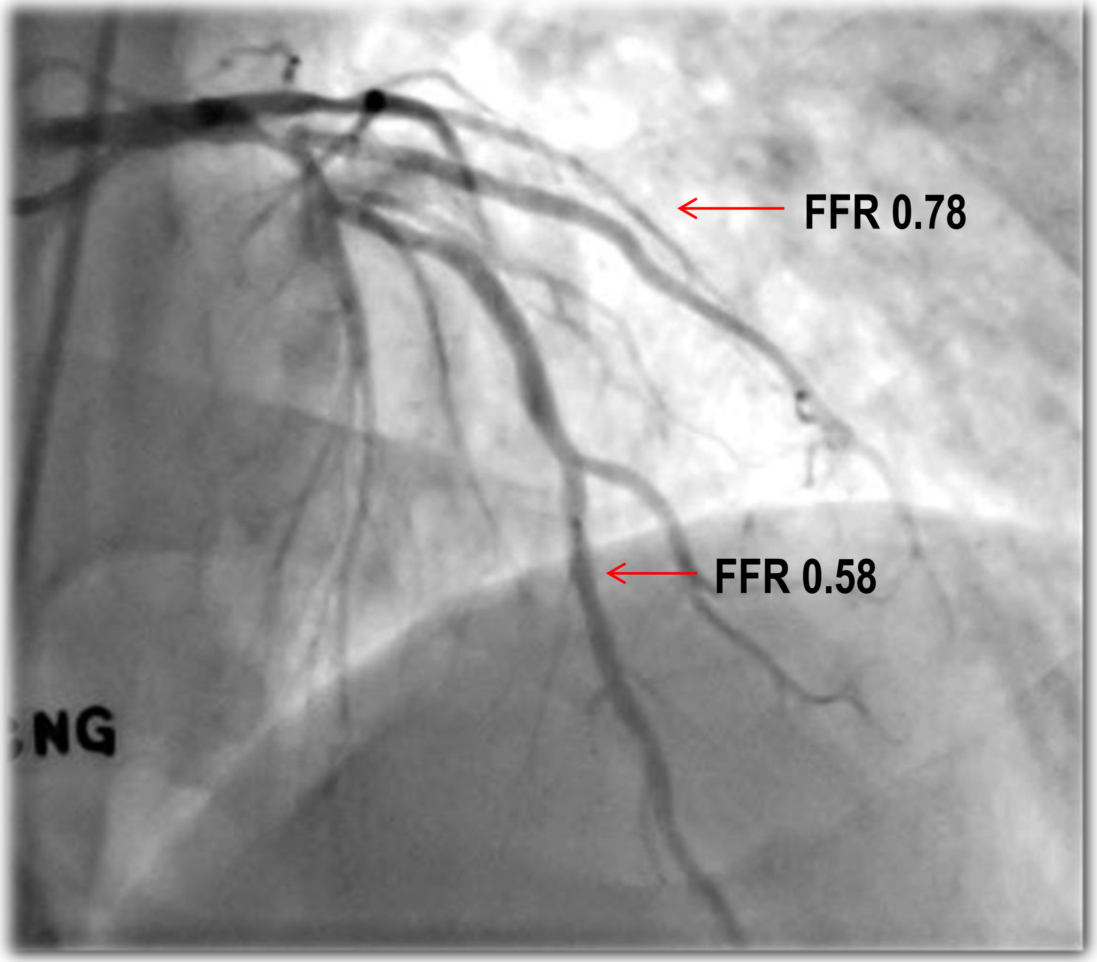
Imaging Based Coronary Physiology in the Clinical Practice: CT_{FFR} and $Angio_{FFR}$

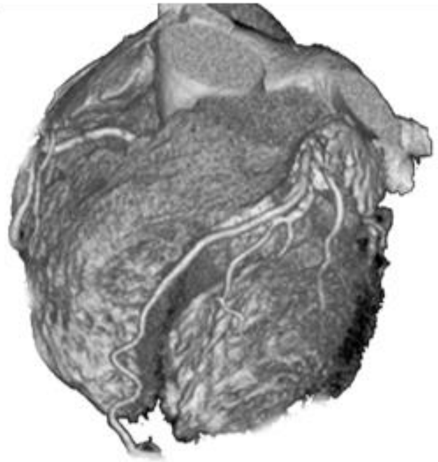
Bon-Kwon Koo, MD, PhD

Seoul National University Hospital, Seoul, Korea

15 years ago, in the cath lab…..

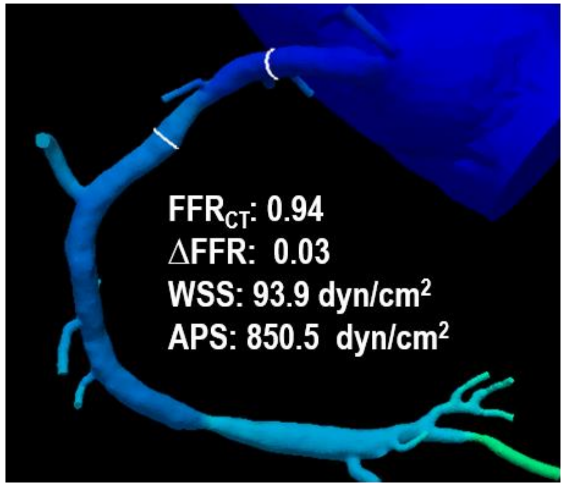


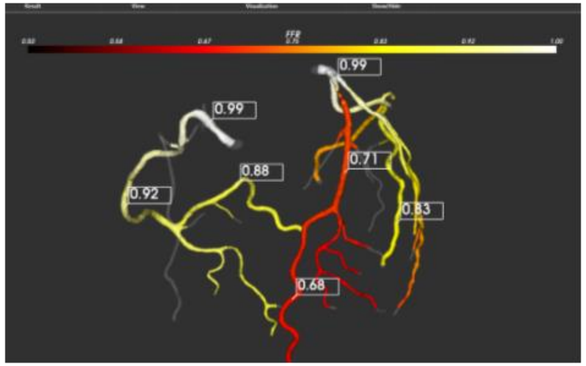
Is it possible to assess hemodynamics from images ?

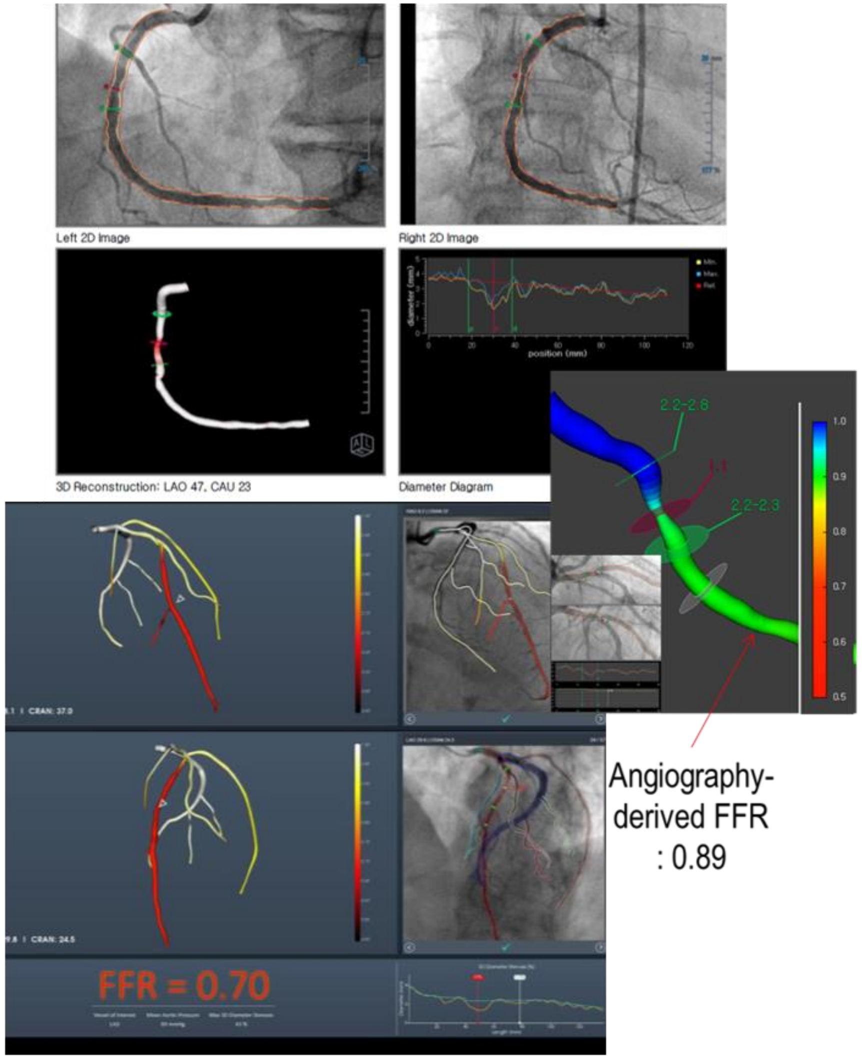


FFR, without invasive procedure
without pressure wire, without adenosine

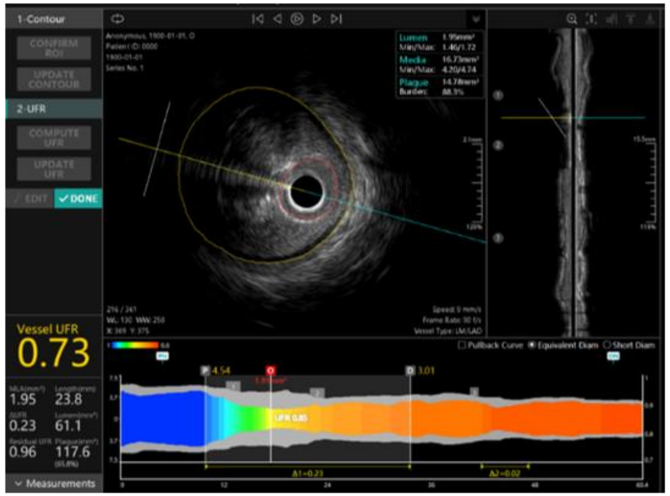
Image-based physiologic assessment

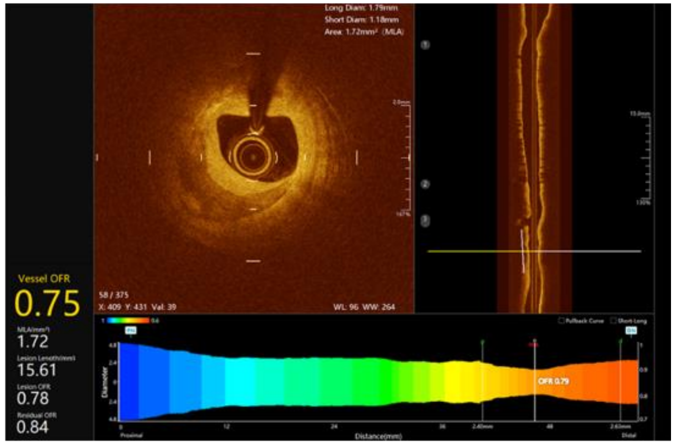






Angiography-derived FFR : 0.89



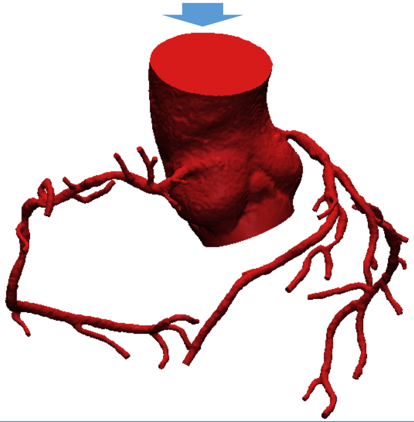


Patient-specific non-invasive FFR using CT & CFD

Computational Model based on CCTA

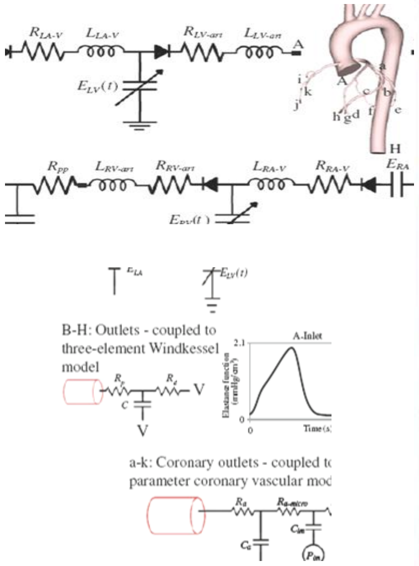
3-D anatomic model from CCTA

No additional imaging
No additional medications



Blood Flow Solution

Blood flow equations solved on supercomputer

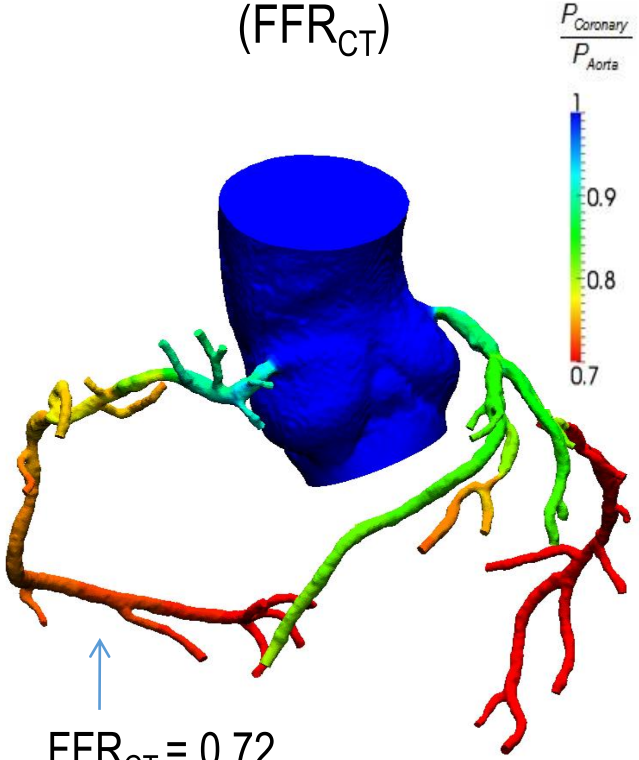


$$\rho\bar{v}_{,t} + \rho\bar{v}\cdot\nabla\bar{v} = -\nabla p + \nabla\cdot\underline{\tau}$$
$$\nabla\cdot\bar{v} = 0$$

Physiologic models

-Myocardial demand
-Morphometry-based boundary condition
-Effect of adenosine on microcirculation

CT-derived computed FFR (FFR_{CT})



FFR_{CT} = 0.72
(can select any point on model)

Koo BK. EuroPCR 2011

Guideline-directed pathway

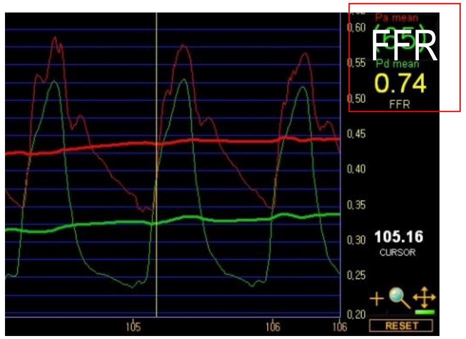
CCTA

>50% diameter stenosis

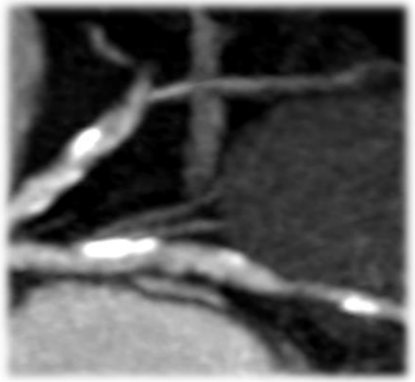
Invasive angiography

>50% diameter stenosis

FFR

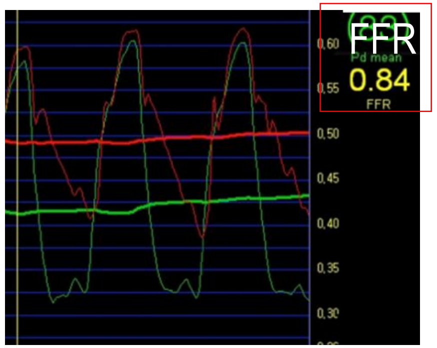


FFR 0.74 → PCI



>50% diameter stenosis

>50% diameter stenosis



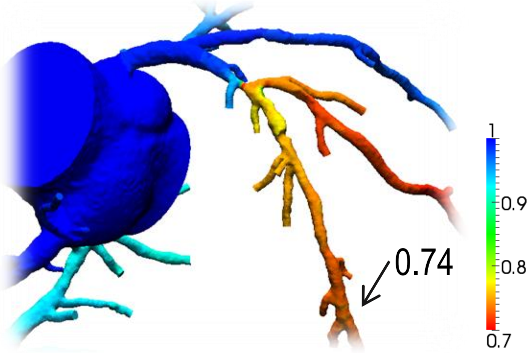
FFR 0.84
→ Medical treatment

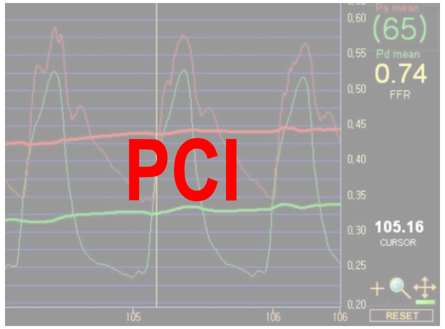
Risk-(almost) free, non-invasive, cost-saving pathway

CCTA

FFR$_{CT}$

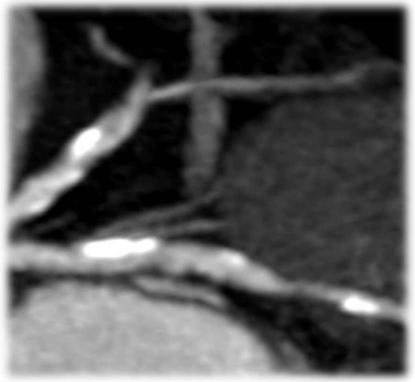
Invasive angiography and PCI

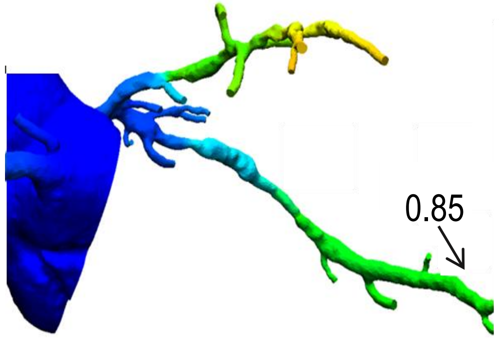


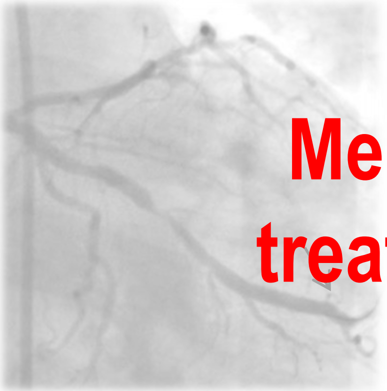


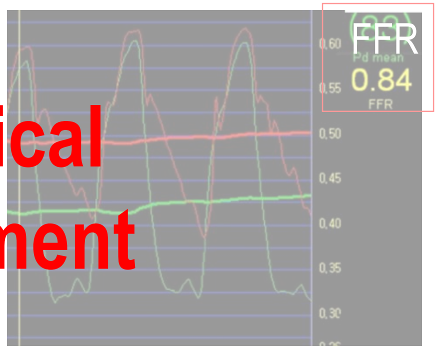
>50% diameter stenosis

FFR$_{CT}$ 0.74 → Invasive procedures









>50% diameter stenosis

>50% diameter stenosis

FFR 0.84 → no ischemia

This technology can be a gate keeper….

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Cardiac Imaging

Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms

Results From the Prospective Multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) Study

Bon-Kwon Koo, MD, PHD,* Andrejs Erglis, MD, PHD,† Joon-Hyung Doh, MD, PHD,‡ David V. Daniels, MD,§ Sanda Jegere, MD,‖ Hyo-Soo Kim, MD, PHD,* Allison Dunning, MD,¶ Tony DeFrance, MD,# Alexandra Lansky, MD,** Jonathan Leipsic, BSc, MD,†† James K. Min, MD‡‡

Seoul and Goyang, South Korea; Riga, Latvia; Palo Alto, San Francisco, and Los Angeles, California; New York, New York; New Haven, Connecticut; and Vancouver, British Columbia, Canada

	Sens	Specif	PPV	NPV	Accuracy
DISCOVER-FLOW	93%	82%	85%	91%	87%
DeFACTO	90%	54%	67%	84%	73%
NXT	86%	79%	65%	92%	81%
	90%	**72%**	**72%**	**89%**	**80%**

First author	Year	design	study population	number of evaluable patients	number of vessels	Time period between FFR and FFRCT	CFD software	threshold of ischemia: FFR	threshold of ischemia: FFRCT
Yang[9]	2019	retrospective, single-center	underwent CCTA for evaluation of CAD and FFR measurement	100	125	<30 days	Auto vessel	≤0.80	≤0.80
Wang[10]	2015	retrospective, single-center	suspected CAD	32	32	≤3 months	Siemens cFFR	<0.80	≤0.80
Tesche[11]	2016	retrospective, single-center	suspected or known CAD	37	37	<3 months	Siemens cFFR	≤0.80	≤0.80
Tang[12]	2019	retrospective, multicenter	suspected CAD	338	422	<3 months	United-Imaging	≤0.80	≤0.80
Tang[13]	2019	retrospective, multicenter	suspected or known CAD	136	183	<60 days	Siemens cFFR	≤0.80	≤0.80
Shi[14]	2017	retrospective, single-center	suspected CAD	29	36	4.3 days (0-14 days)	COMSOL Multiphysics	≤0.80	≤0.80
Sand[15]	2018	Prospective, single-center	patients with stable chest pain	143		ND	Heart Flow	≤0.80	≤0.80
Renker[16]	2014	retrospective, single-center	suspected or known CAD	53	67	<3 months	Siemens cFFR	<0.80	<0.80
Osawa[17]	2017	Prospective, single-center	suspected CAD	18	26	<60 days	Heart Flow	<0.80	<0.80
Nørgaard[18]	2014	Prospective, milticenter	suspected CAD	254	484	18 (1-55)days	Heart Flow	≤0.80	≤0.80
Miyajima[19]	2020	retrospective, single-center	suspected CAD	97	105	<3 months	W.I.P.	≤0.80	≤0.80
Min[20]	2012	Prospective, milticenter	suspected or known CAD	252	407	15.5 (5-33)days	Heart Flow	≤0.80	≤0.80
Kurata[21]	2017	Prospective, single-center	suspected or known CAD	21	29	55 (19-120)days	Siemens cFFR	≤0.80	≤0.80
Kruk[22]	2016	Prospective, single-center	suspected CAD	90	96	<6 months	Siemens cFFR	≤0.80	≤0.80
Koo[23]	2011	Prospective, milticenter	suspected or known CAD	103	159	2.3 (0-26)days	Heart Flow	≤0.80	≤0.80
Ko[24]	2019	Prospective, single-center	no known CAD	49	91	ND	Heart Flow	≤0.80	≤0.80
Ko[25]	2017	Prospective, single-center	Symptomatic patients with no known CAD	30	58	ND	Toshiba Medical Systems Corp	≤0.80	≤0.80
Kim[26]	2014	retrospective, multicenter	significant coronary stenoses	44	48	12 (2-40)days	Heart Flow	≤0.80	≤0.80
Kawaji[27]	2017	Prospective, single-center	suspected significant CAD	48	70	<60 days (23.6 ± 15.5)	Heart Flow	≤0.80	≤0.80
Gaur[28]	2017	Prospective, single-center	STEMI Patients	60	124	mean 1 day	Heart Flow	≤0.80	≤0.80
De Geer[29]	2015	retrospective, single-center	underwent CCTA and FFR measurement	21	23	49 (4-106 days)	Siemens cFFR	≤0.80	≤0.80
Coenen[30]	2015	retrospective, single-center	suspected or known CAD	106	189	<50 days	Siemens cFFR	≤0.80	≤0.80
Chung[31]	2017	retrospective, multicenter	suspected or known CAD	117	218	<30 days	Toshiba Medical	≤0.80	≤0.80

CAD= coronary artery disease; CCTA= coronary computed tomography angiography; CFD= computational fluid dynamics; FFR= fractional flow reserve; FFRCT= computed tomography-based fraction flow reserve; ND= not defined.

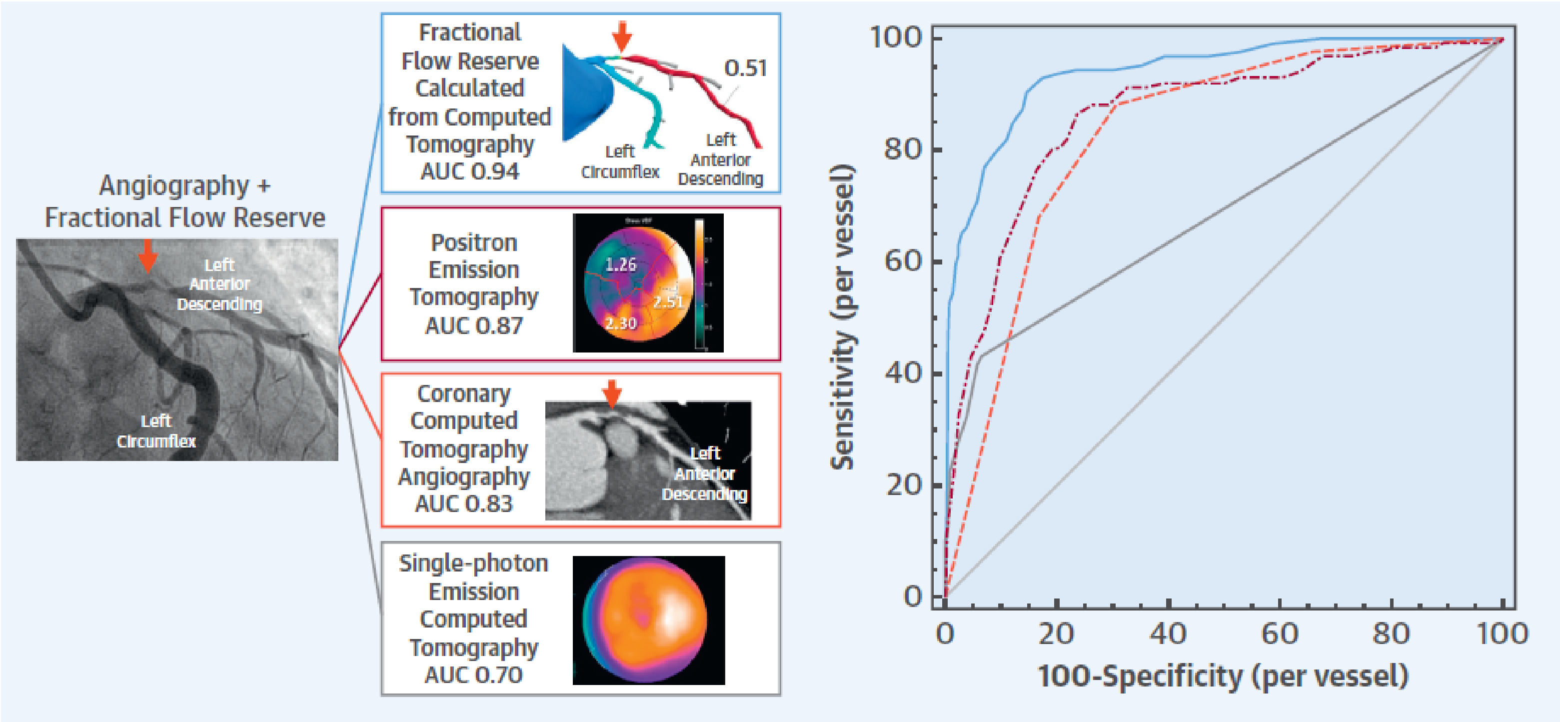
Perpatient and pervessel pooled analysis results

Level	Number of studies	Sensitivity (95%CI)	Specificity (95%CI)	AUC
Per-patient	13	0.88 (0.85-0.90)	0.79 (0.71-0.85)	0.89
Per-vessel	22	0.85 (0.82-0.87)	0.81 (0.76-0.85)	0.87

Luo Y, et al. Hellenic J Cardiol 2022

Diagnostic performance among non-invasive tests

CENTRAL ILLUSTRATION Discriminative Ability of Imaging Modalities for the Detection of Per-Vessel Fractional Flow Reserve-Defined Ischemia



Driessen, R.S. et al. J Am Coll Cardiol. 2019;73(2):161-73.

Significance of stable coronary artery disease, as defined by invasive FFR, was prospectively tested with several noninvasive imaging modalities. Each patient underwent FFR_{CT}, PET, coronary CTA, SPECT, and ICA with FFR, regardless of imaging results as illustrated by the typical imaging findings of a severe left anterior descending artery stenosis in the **colored boxes. Curves with corresponding colors** indicate that FFR_{CT} demonstrated the greatest AUC for the detection of per-vessel ischemia. CTA = coronary computed tomography angiography; FFR = fractional flow reserve; FFR_{CT} = fractional flow reserve calculated from computed tomography; ICA = invasive coronary angiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

10-year outcomes of DISCOVER FLOW study

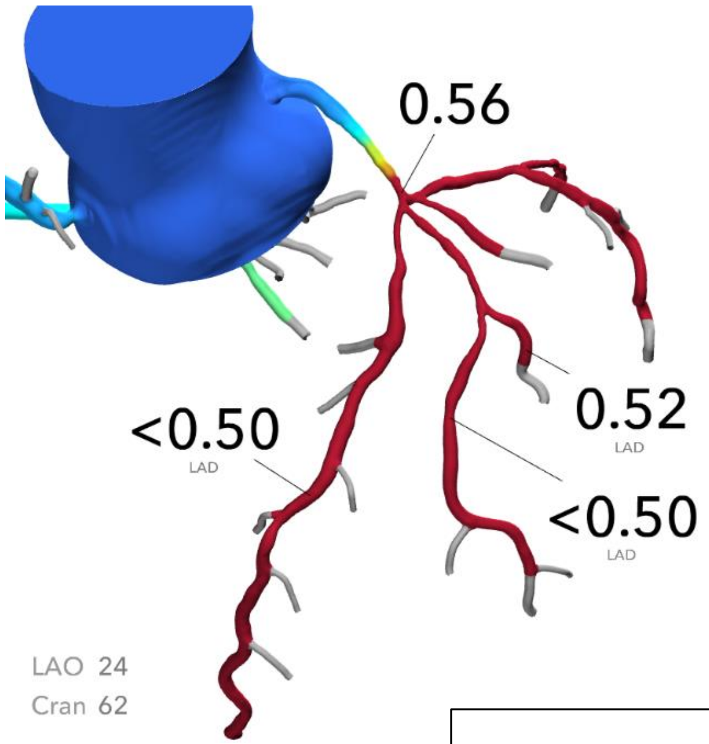
Predictors of 10-Year TVF

	Unadjusted HR (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Age	0.99 (0.92 – 1.06)	0.696	-	-
Male	1.88 (0.38 – 9.40)	0.440	-	-
Diabetes mellitus	0.99 (0.20 – 4.81)	0.988	-	-
Hypertension	0.55 (0.16 – 1.84)	0.328	-	-
Hyperlipidemia	1.43 (0.42 – 4.92)	0.568	-	-
Coronary CT stenosis (%)				
0-49%	1 (ref)	NA	1 (ref)	NA
50-69%	1.02 (0.27 – 3.89)	0.971	1.26 (0.29 – 5.41)	0.759
70-99%	2.27 (0.51 – 10.14)	0.282	2.40 (0.51 – 11.19)	0.265
FFR_{CT} (per 0.1 increase)	0.62 (0.44 – 0.88)	0.005	0.61 (0.43 – 0.86)	0.005

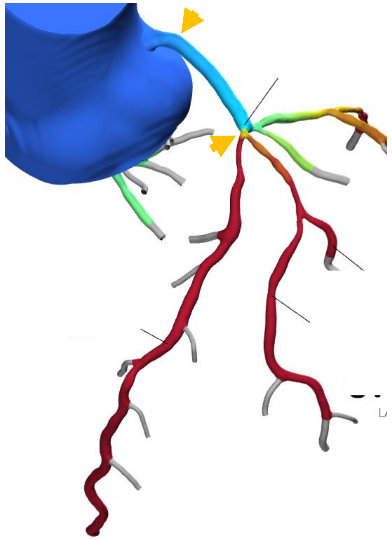
Koo BK. EuroPCR 2021

Treatment planning using CT-FFR technology

Before | Baseline

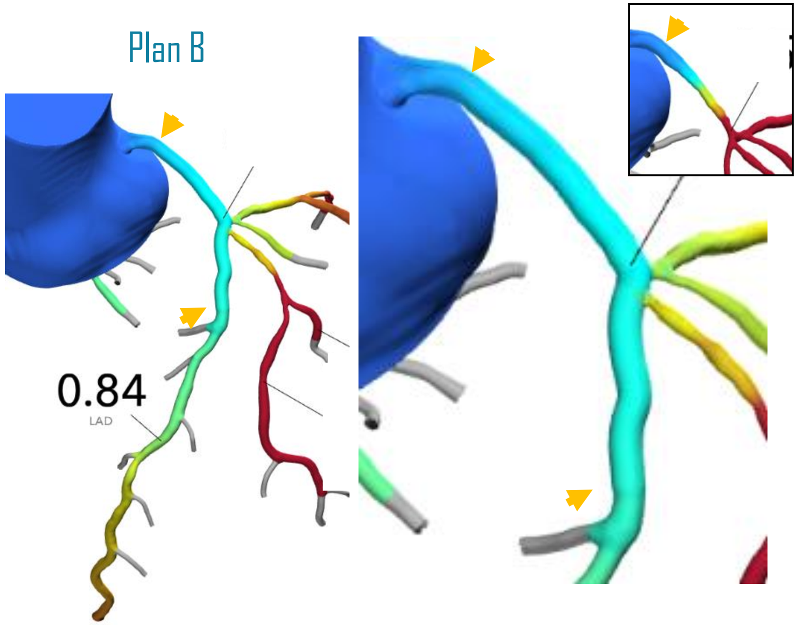


Plan A



Stent Length: **24mm**

Plan B

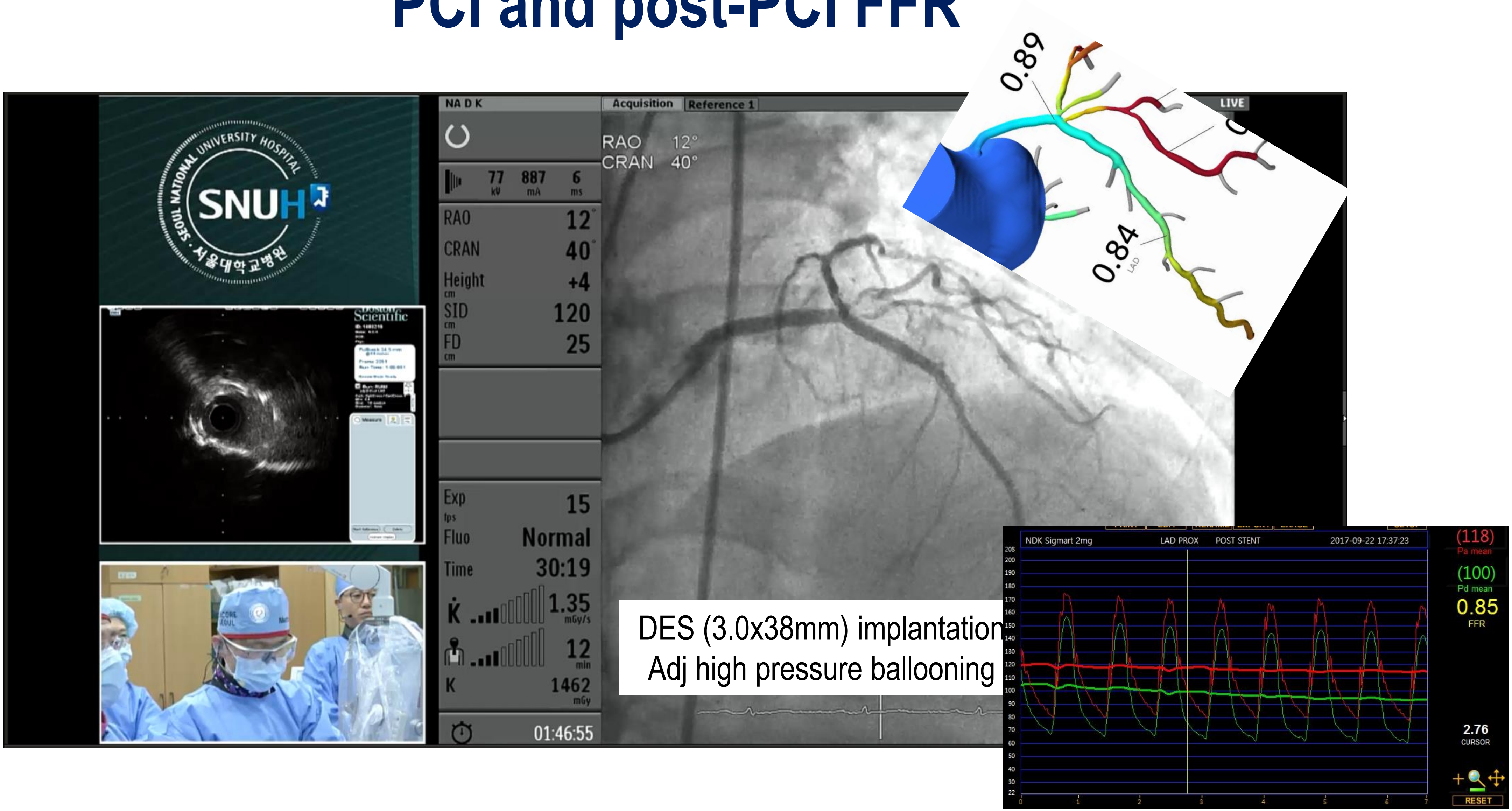


Stent Length: **40mm**

My Treatment Plan

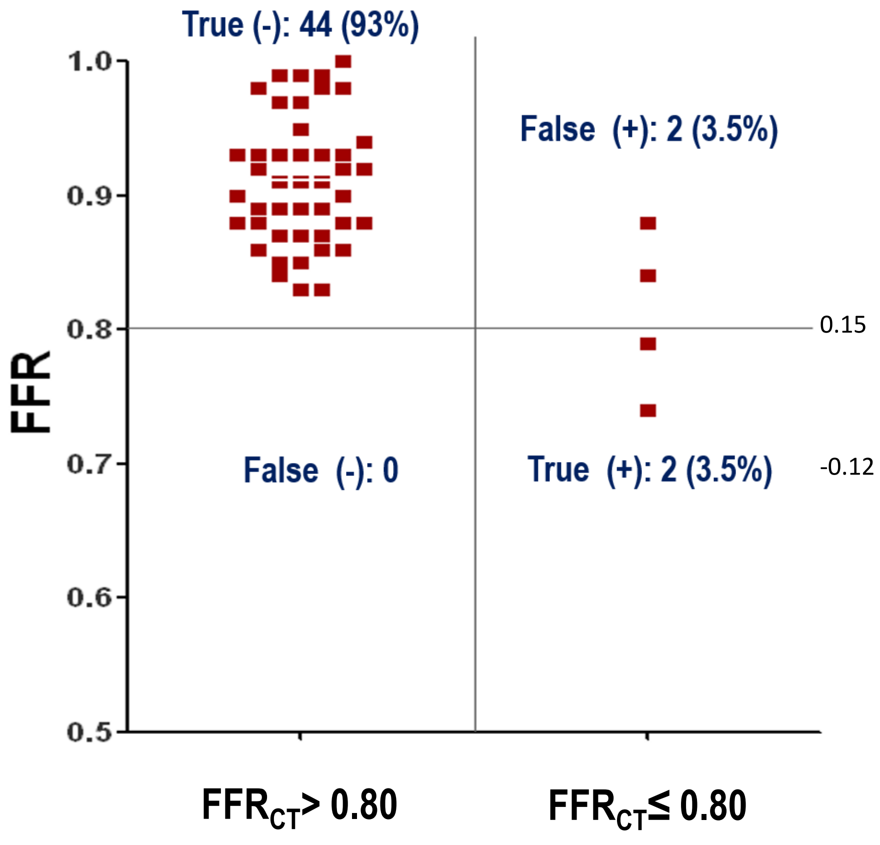
- LM to LAD stenting, stent diameter 3.0, stent length 38-40mm
- Adjunctive balloon inflation for LM
- Leaving the diagonal ischemia alone due to long diffuse disease

PCI and post-PCI FFR



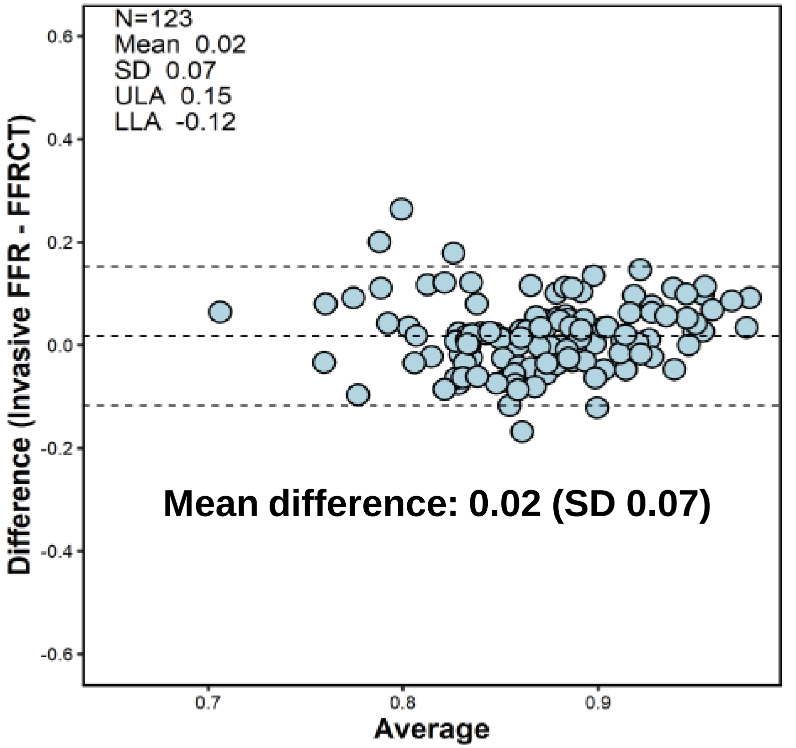
DES (3.0x38mm) implantation
Adj high pressure ballooning

Clinical Studies for Treatment Planner



Kim KH, Koo BK, et al. JACC interv 2014

Post-PCI invasive FFR vs FFR_{CT}



	Invasive FFR	FFR_{CT}
Post-PCI FFR (mean (SD))	0.88 (0.06)	0.86 (0.06)
Functional gain (mean (SD))	0.22 (0.14)	0.22 (0.12)

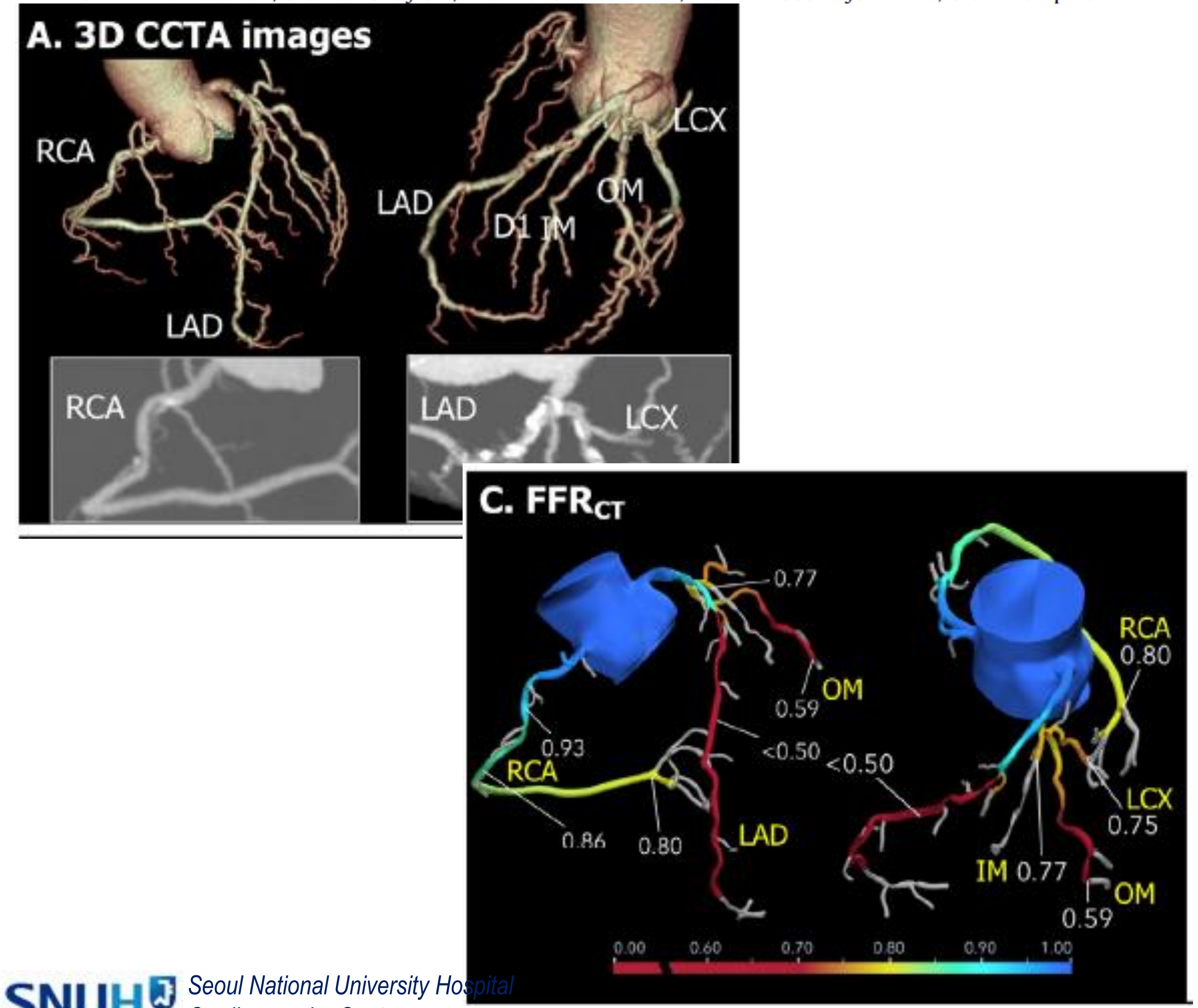
JACC imaging 2022 in press

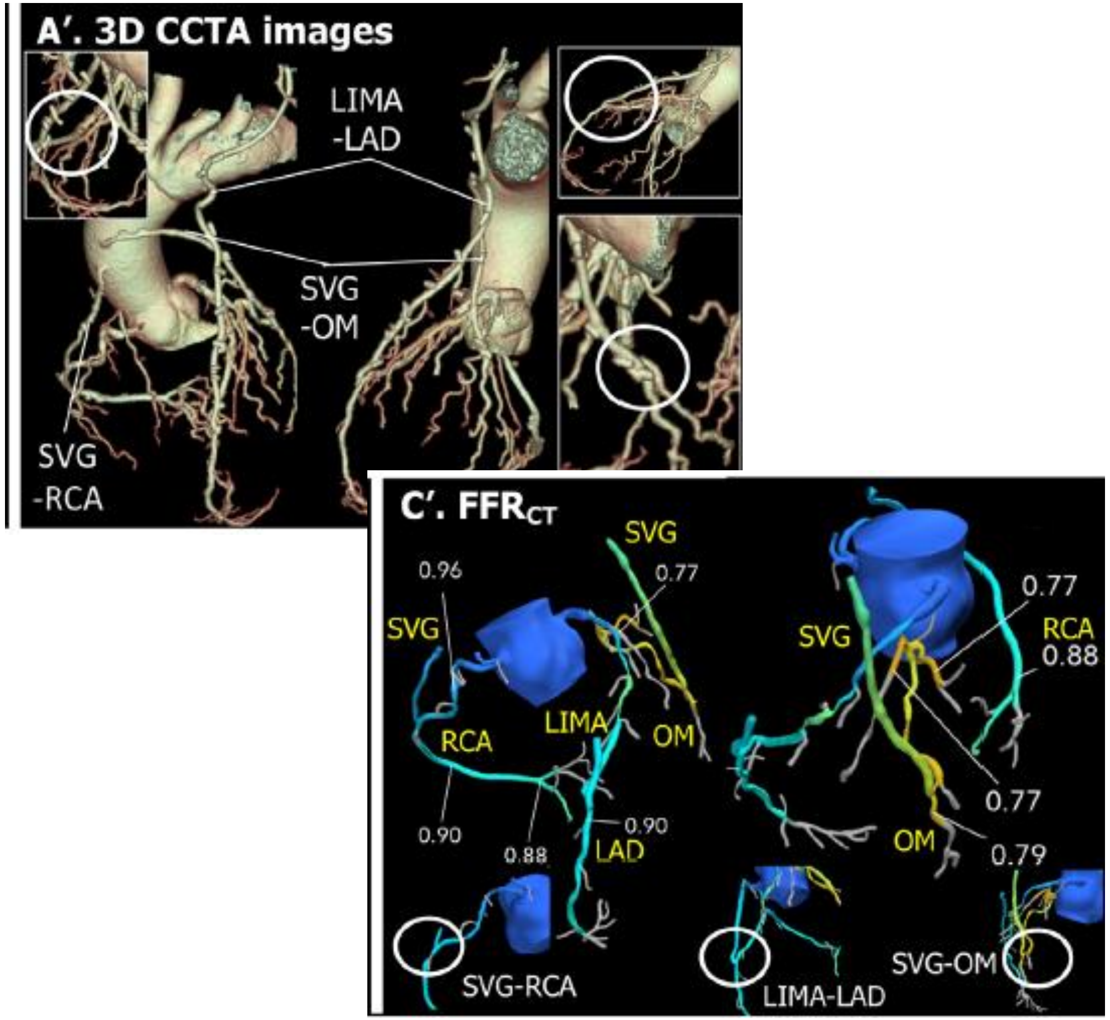
Contents lists available at ScienceDirect
Cardiovascular Revascularization Medicine

Successful coronary artery bypass grafting based solely on non-invasive coronary computed tomography angiography

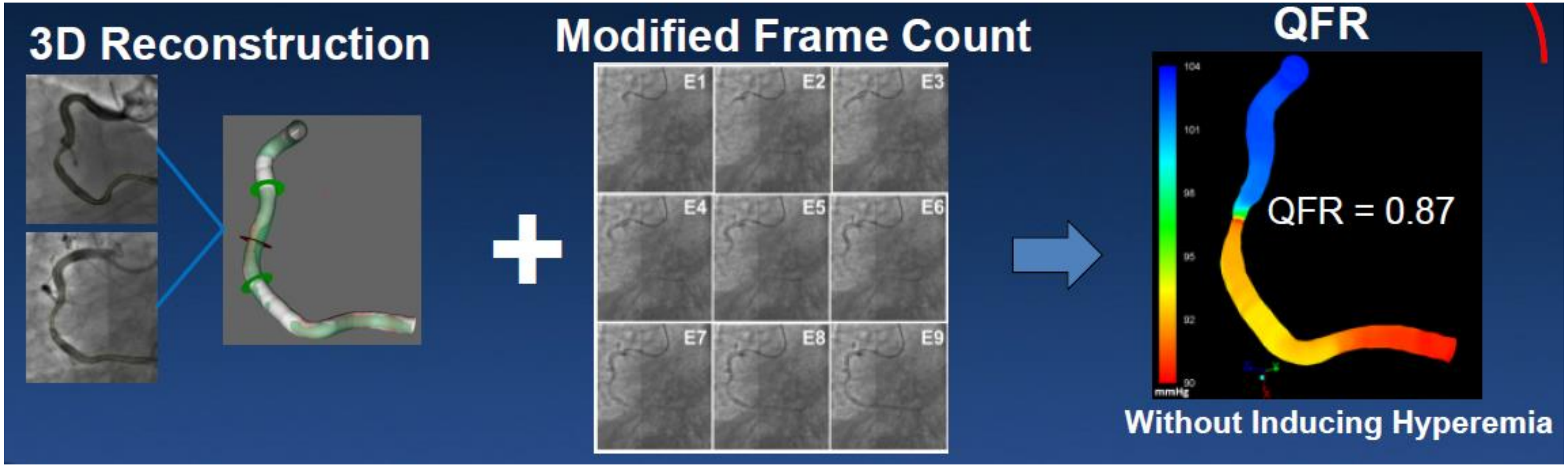
Hideyuki Kawashima [a,b], Yoshinobu Onuma [a,c], Daniele Andreini [d,e], Saima Mushtaq [d], Marie-angèle Morel [a], Shinichiro Masuda [a], Charles A. Taylor [f], Antonio L. Bartorelli [d,g], Patrick W. Serruys [a,c,h,*,**], Giulio Pompilio [d,i]

This case illustrates that in a patient with 3VD, planning and execution of CABG were successfully performed based solely on CCTA combined with FFR$_{CT}$. Repeat imaging assessment with non-invasive CCTA and FFR$_{CT}$ at 30-day follow-up confirmed the safety of this approach.

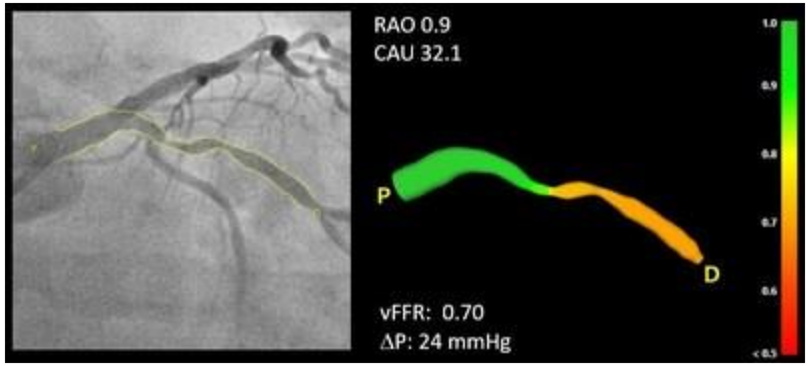


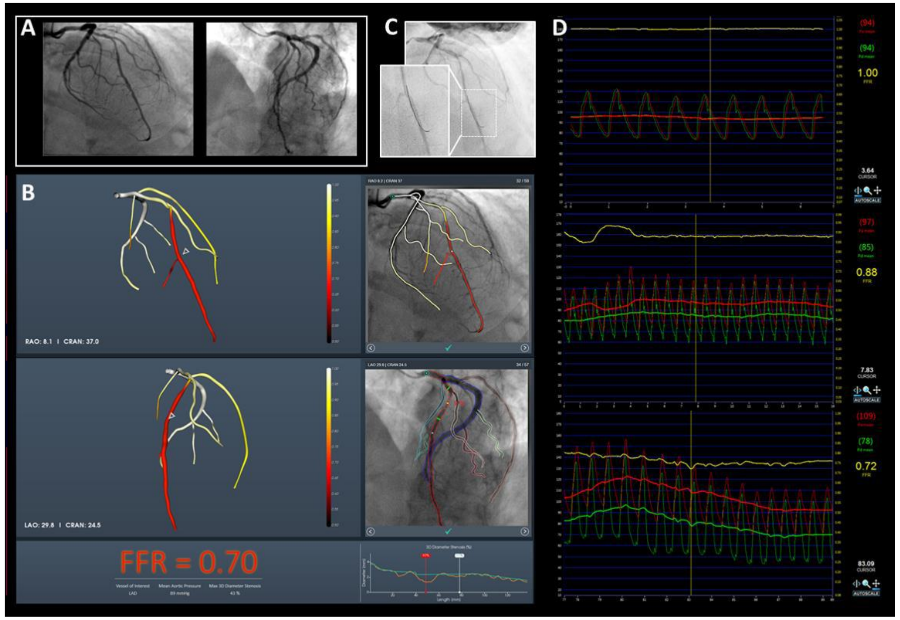


Angiography-derived FFR



- **QFR**
- **FFRangio**
- **vFFR**

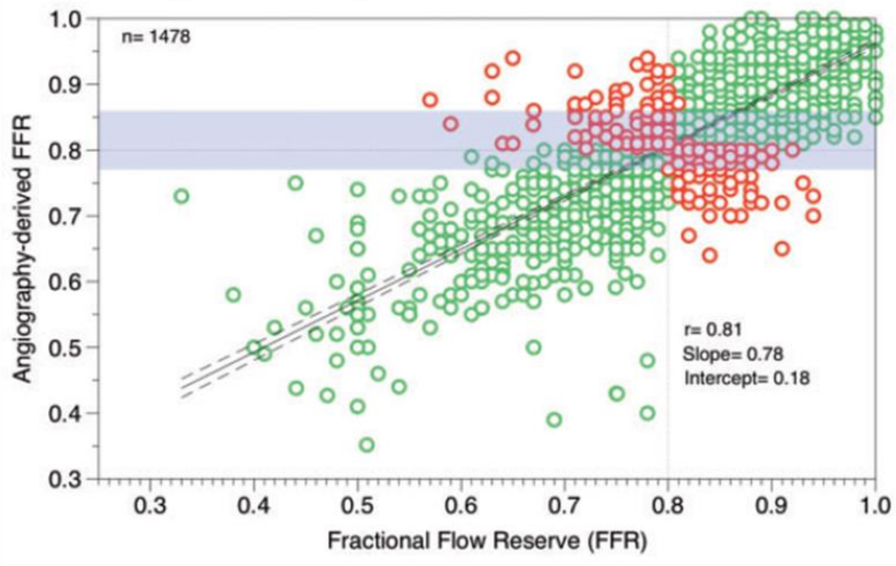




Angiography-derived FFR

Study-level meta-analysis for diagnostic performance

Study	Year	No. Lesion	Technology	Process
WIFI II	2017	240	**QFR**	Math. Formula
FAVOR II Europe Japan	2017	317	**QFR**	Math. Formula
Tar et al.	2017	68	**3D QCA**	Math. Formula
Yazaki et al.	2017	151	**QFR**	Math. Formula
FAVOR II China	2017	328	**QFR**	Math. Formula
FAVOR Pilot	2016	84	**QFR**	Math. Formula
Morris et al.	2013	35	**Virtual FFR**	CFD
Pellicano et al.	2017	203	**FFR_{angio}**	Rapid Flow
Tu et al.	2014	77	**FFR_{QCA}**	CFD
Kornowski et al.	2016	101	**FFR_{angio}**	Rapid Flow
Trobs et al.	2015	100	**IZ3D**	CFD
Van Rosendael et al.	2017	15	**QFR**	Math. Formula
Legutko et al.	2017	123	**QFR**	Math. Formula



Overall Sensitivity 89% (95% CI 83-94%)

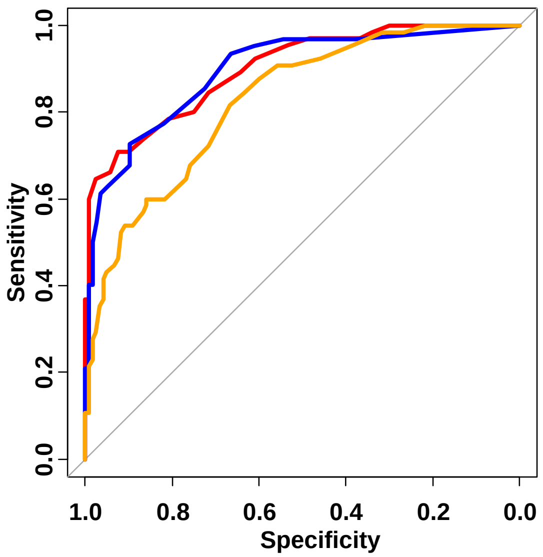
Overall Specificity 90% (95% CI 88-92%)

No difference according to different software and different computational methods

Collet et al. Eur Heart J 2018

Angiography-derived FFR vs. FFR/iFR by PET

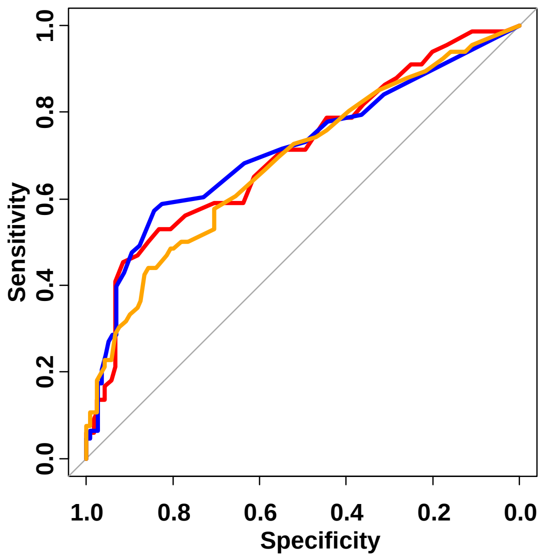
RFR as a reference



	AUC	95% CI
For FFR	0.899	0.853-0.946
For iFR	0.895	0.846-0.945
For QFR	0.826	0.766-0.886

p value for comparison	
For FFR vs. iFR	0.911
For QFR vs. iFR	0.082
For QFR vs. FFR	0.002

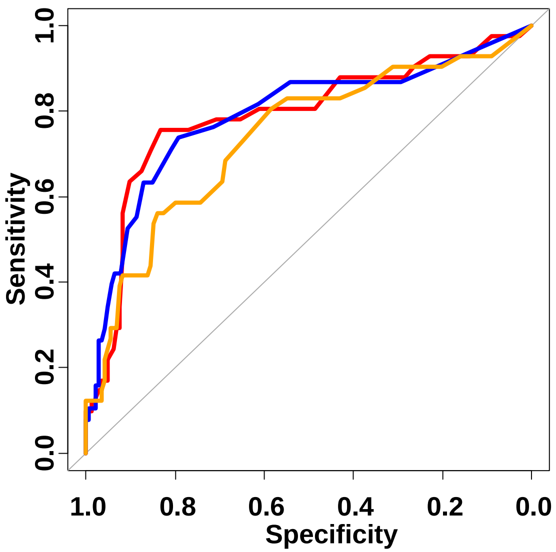
CFR as a reference



	AUC	95% CI
For FFR	0.706	0.625-0.787
For iFR	0.713	0.628-0.797
For QFR	0.685	0.603-0.768

p value for comparison	
For FFR vs. iFR	0.912
For QFR vs. iFR	0.650
For QFR vs. FFR	0.419

CFC as a reference



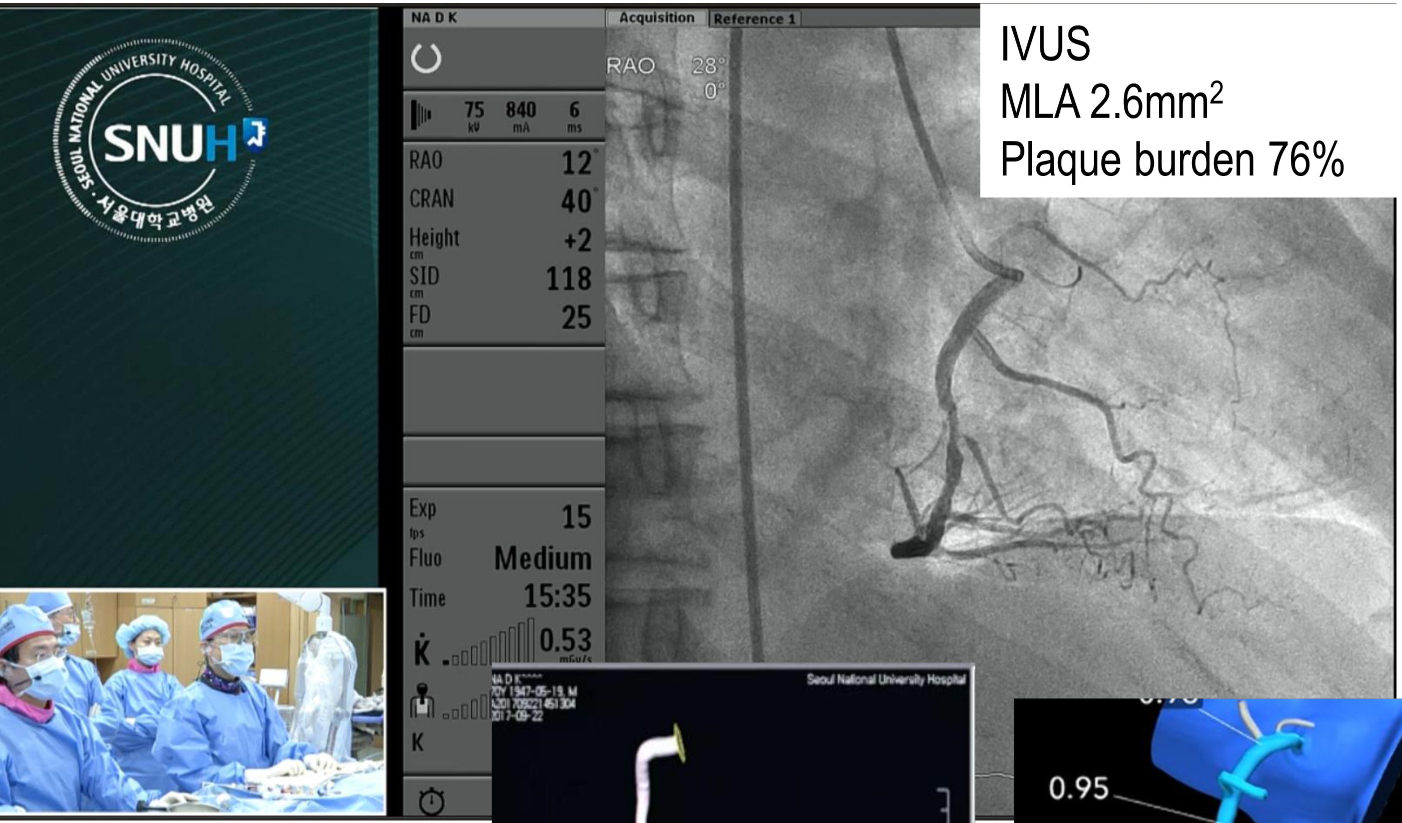
	AUC	95% CI
For FFR	0.788	0.697-0.879
For iFR	0.789	0.696-0.882
For QFR	0.737	0.643-0.831

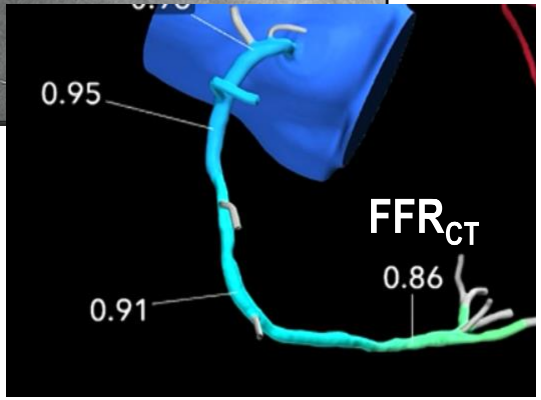
p value for comparison	
For FFR vs. iFR	0.986
For QFR vs. iFR	0.439
For QFR vs. FFR	0.044

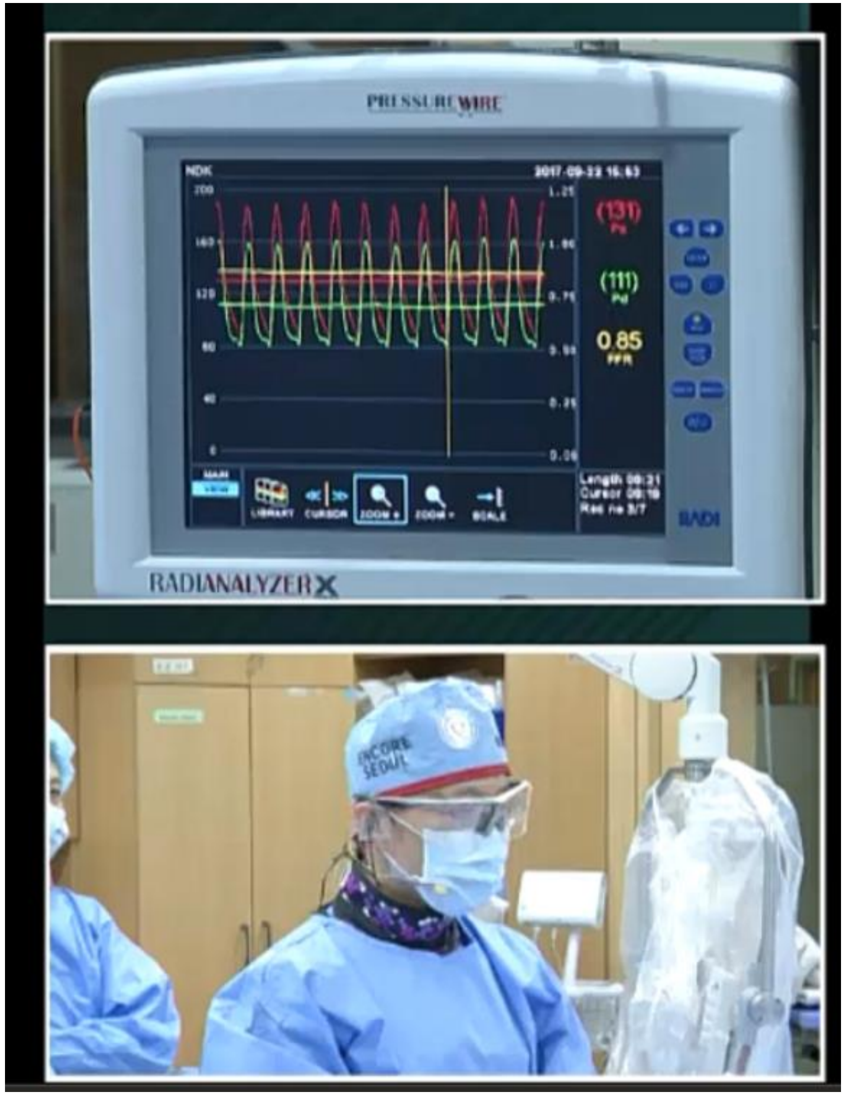
Dai N, Koo BK, et al. Korean Circ J2021

Functional significance? CT-FFR vs. Angio-FFR

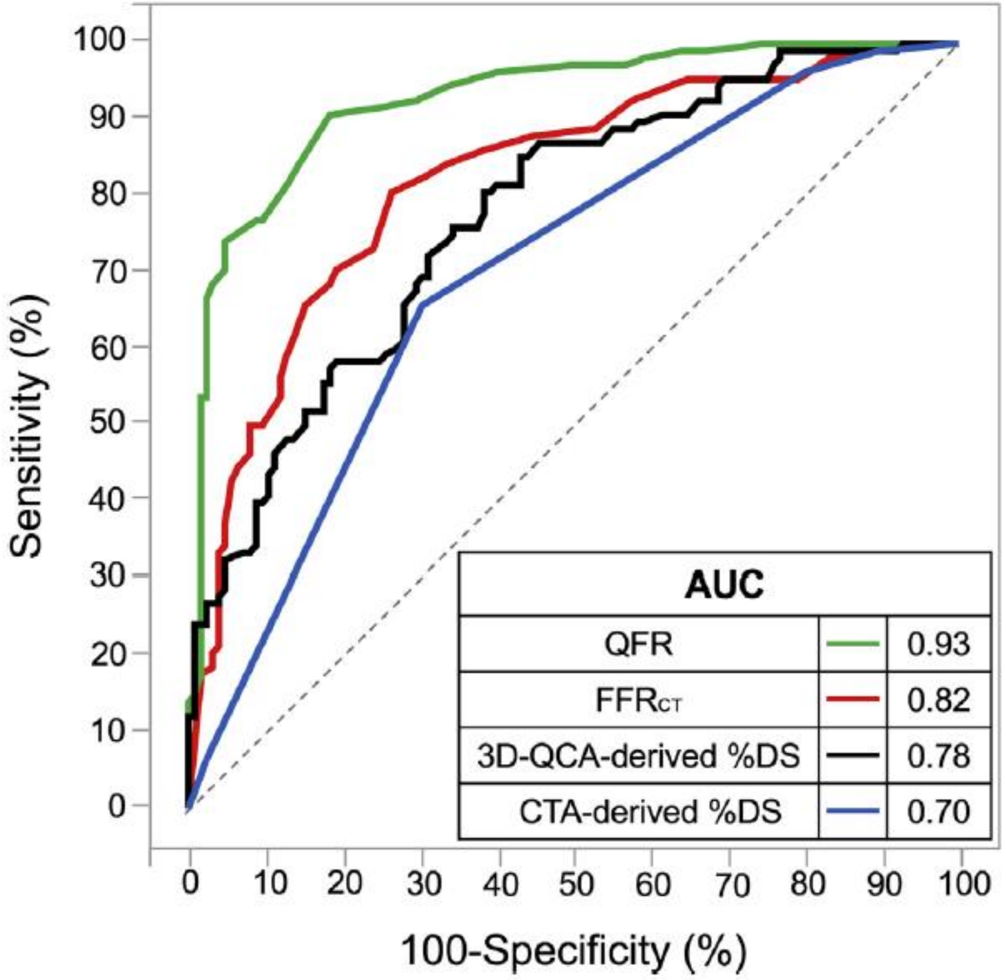
IVUS
MLA 2.6mm^2
Plaque burden 76%







Functional significance? CT-FFR vs. Angio-FFR



	QFR ≤0.80	FFR_{CT} ≤0.80
True positive	97 (41)	89 (39)
True negative	102 (44)	87 (37)
False positive	23 (10)	38 (16)
False negative	11 (5)	19 (8)
Accuracy, %	85 (81-89)	76 (70-80)
Sensitivity, %	90 (85-94)	82 (76-88)
Specificity, %	82 (77-85)	70 (64-74)
Positive predictive value, %	81 (76-84)	70 (65-74)
Negative predictive value, %	90 (85-94)	82 (76-87)
Positive likelihood ratio	4.9 (3.7-6.2)	2.7 (2.1-3.4)
Negative likelihood ratio	0.1 (0.1-0.2)	0.3 (0.2-0.4)

Tanigaki T, et al. JACC intervention 2019

FAVOR III China

Investigator-Initiated, Multicenter, Sham-Controlled Blinded Randomized Trial

Patients with coronary artery disease scheduled for coronary angiography

Meet all general inclusion and not meet any exclusion criteria

Inclusions: age ≥ 18 years; stable, unstable angina, or post-AMI (≥72 hours). Exclusions: moderate or severe chronic kidney disease (defined as creatinine >150 μmol/L or estimated glomerular filtration rate (GFR) <45 ml/kg/1.73 m^2).

Informed consent

Coronary angiography

Meet all angiographic inclusion and not meet any exclusion criteria

Inclusions: patients must have at least one lesion with a percent diameter stenosis between **50% and 90%** in a coronary artery with a **≥2.5 mm** reference vessel diameter by visual assessment. Exclusions: patients had only one lesion with DS%>90% and TIMI flow <3; interrogated lesions are related with AMI.

Randomization Stratifications

- Diabetes Mellitus
- Multivessel Disease
- Presence of any vessel with DS% >90% and TIMI flow <3
- Center

Identify target vessels intended to be treated with standard angiography guidance

N=3830 (1:1 randomization)

QFR-guided strategy
N=1915

QFR was measured in all coronary arteries containing any lesion with visually-assessed DS% ≥50% and ≤90% and RVD ≥2.5 mm

- QFR ≤0.80: PCI
- QFR >0.80: deferral
- All measured vessel QFR >0.80: OMT alone

Angiography-guided strategy
N=1915

PCI was performed based on visual angiographic assessment per local standard of practice

Independent Organizations

- Core Lab
- CEC
- DSMB
- Data Management
- Statistical Analysis

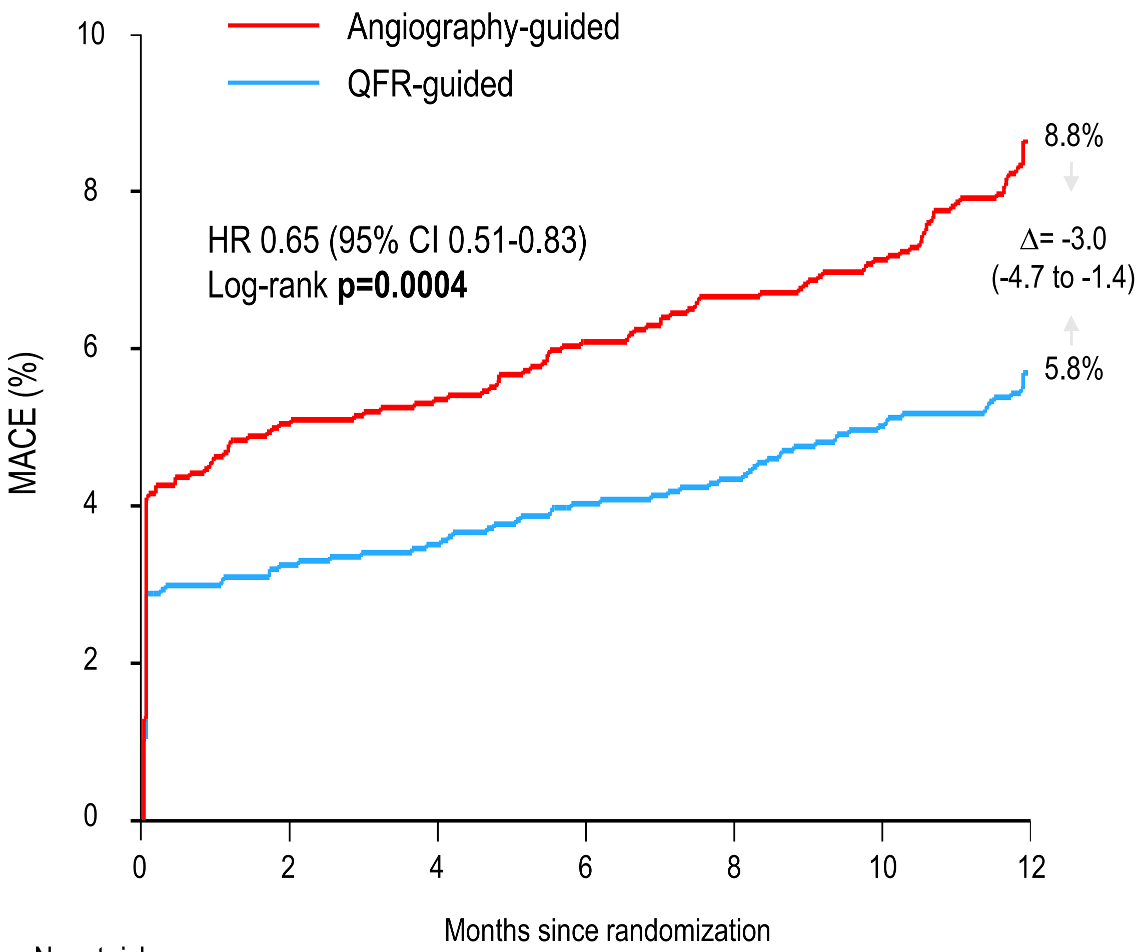
Xu B, et al. Lancet 2021

Key Procedural Results

	QFR-guided group (N=1913)	Angiography-guided group (N=1912)	p value
PCI performed	90.5%	99.1%	<0.0001
Number of stents placed per patient	1.45 ± 1.02	1.58 ± 0.97	<0.0001
Use of intravascular imaging	6.2%	6.3%	0.89
Contrast medium used per patient, ml	163.0 ± 75.6	169.7 ± 74.2	0.0060
Fluoroscopy time, min	14.1 ± 8.0	14.9 ± 7.4	0.0013
Adjusted procedure time, min	44.6 ± 28.8	49.5 ± 30.2	<0.0001
PCI lesion success	99.0%	99.3%	0.38
Residual anatomic SYNTAX score	2.4 ± 3.6	2.4 ± 4.0	0.49
Residual functional SYNTAX score	0.7 ± 2.3	1.0 ± 2.8	<0.0001

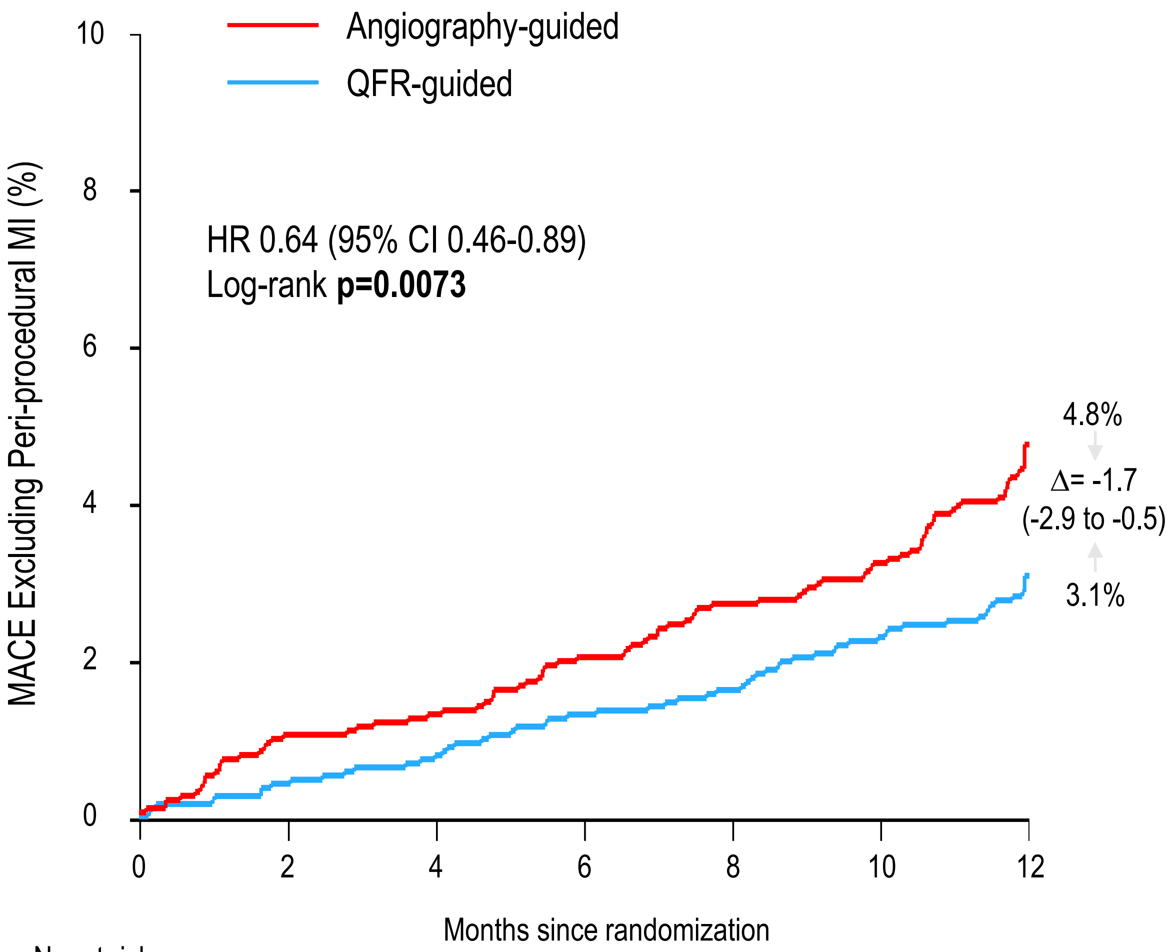
Xu B, et al. Lancet 2021

Primary and Major Secondary Endpoints



No. at risk

QFR-guided	1913	1845	1840	1828	1821	1809	1795
Angiography-guided	1912	1804	1798	1783	1770	1762	1732



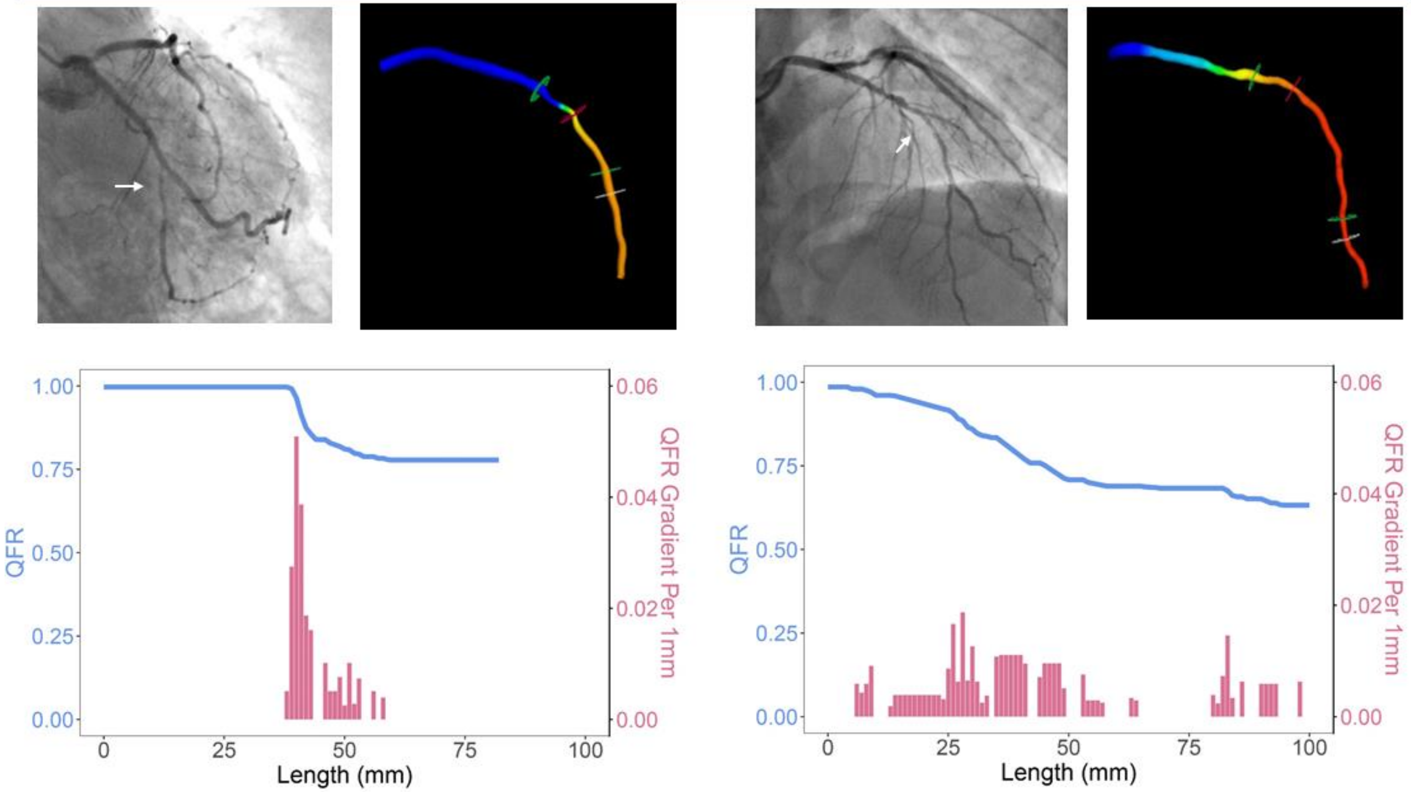
No. at risk

QFR-guided	1913	1900	1894	1881	1874	1862	1846
Angiography-guided	1912	1883	1877	1862	1847	1839	1808

Xu B, et al. Lancet 2021

Focal vs. Diffuse disease: Physiological discrimination

Focal pattern	Diffuse pattern



QFR derived PPG Index

$$\frac{MaxPPG_{20mm}/\triangle QFR_{vessel} + (1\text{-Length with functional disease(mm))/ Total vessel length (mm)}}{2}$$

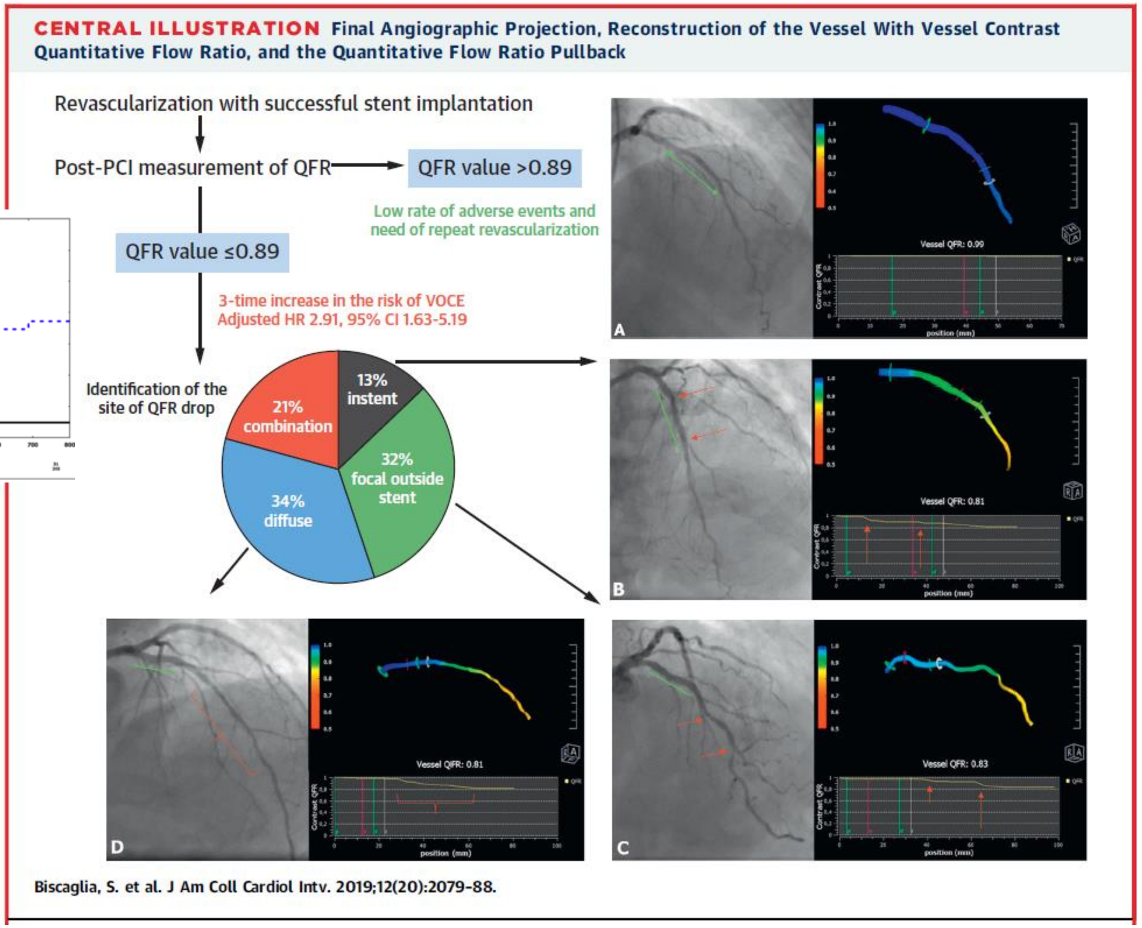
PPG Index = 0.907

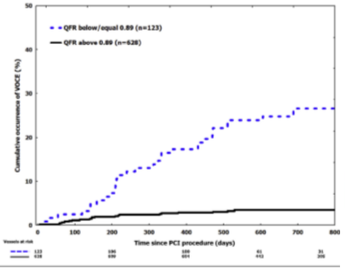
PPG Index = 0.466

Dai N, Koo BK, et al. JACC intervention 2021

Prognosis after PCI

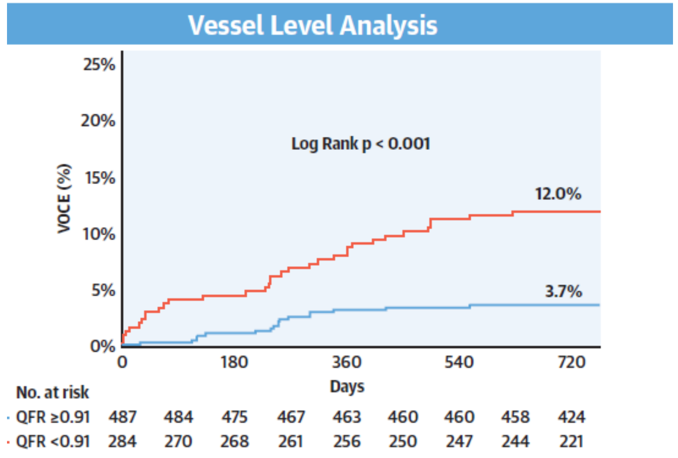
Prospective HAWKEYE Study

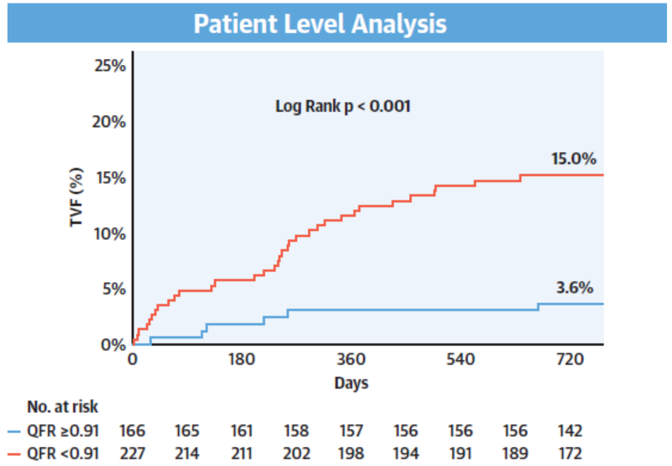




Biscaglia S, et al. JACC intervention 2019

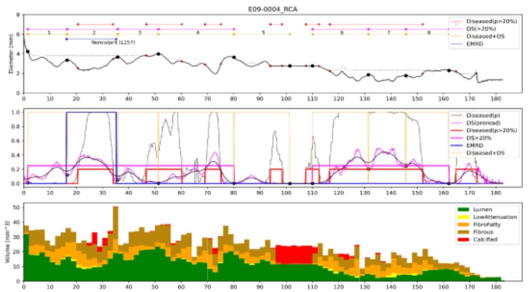
SYNTAX II study: Retrospective analysis



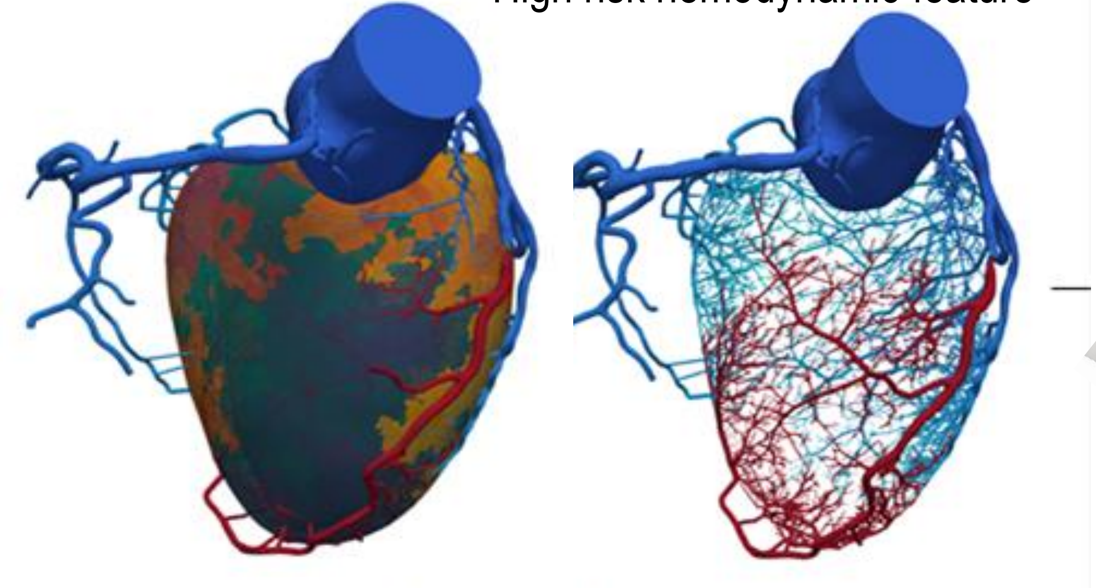


Kogame, et al. JACC intervention 2019

Future of image based hemodynamic assessment

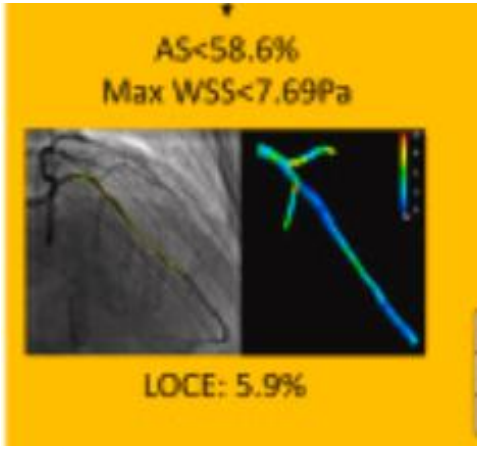


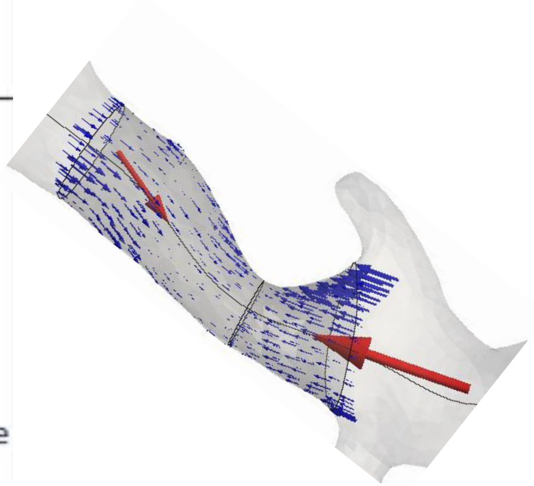
- Territory
- Flow
- Microcirculation
- New lesion definition
- Co-registration
- Plaque stress
- High risk plaque feature
- High risk hemodynamic feature



Simulation of MBF

Extension of segmented vasculature





1 mins **Clinical version**

2021 µQFR

- No need of adenosine
- Analysis time: 1 minute
- Only need 1 good angio view
- Short learning curve
- Analysis of all types of bifurcation l esions and side branches
- Analysis of myocardium bridge
- Analysis of angio strain (RWS)
- Analysis of angiography-based mic rocirculatory resistance (AMR)