



Cardiovascular Center
OLV Aalst

Non-invasive physiologic assessment of coronary artery disease

Jeroen Sonck MD

Anatomy to functional evaluation: From COURAGE to FAME 2

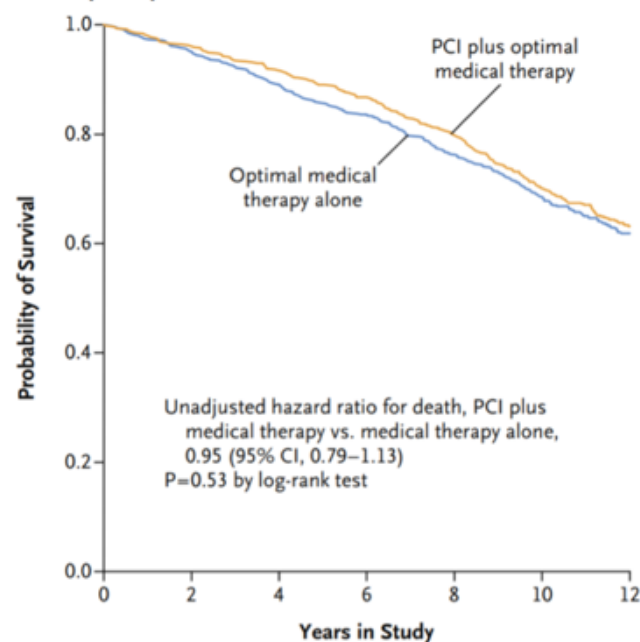
The current understanding of the pathophysiology of coronary artery disease relies on the potential adverse effect of myocardial ischemia.

Even though the ischemia hypothesis has been placed at the core of the evaluation of patients with stable coronary artery disease, no clear evidence supports the benefit of revascularization in terms of hard clinical endpoints namely myocardial infarction and death.

Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease

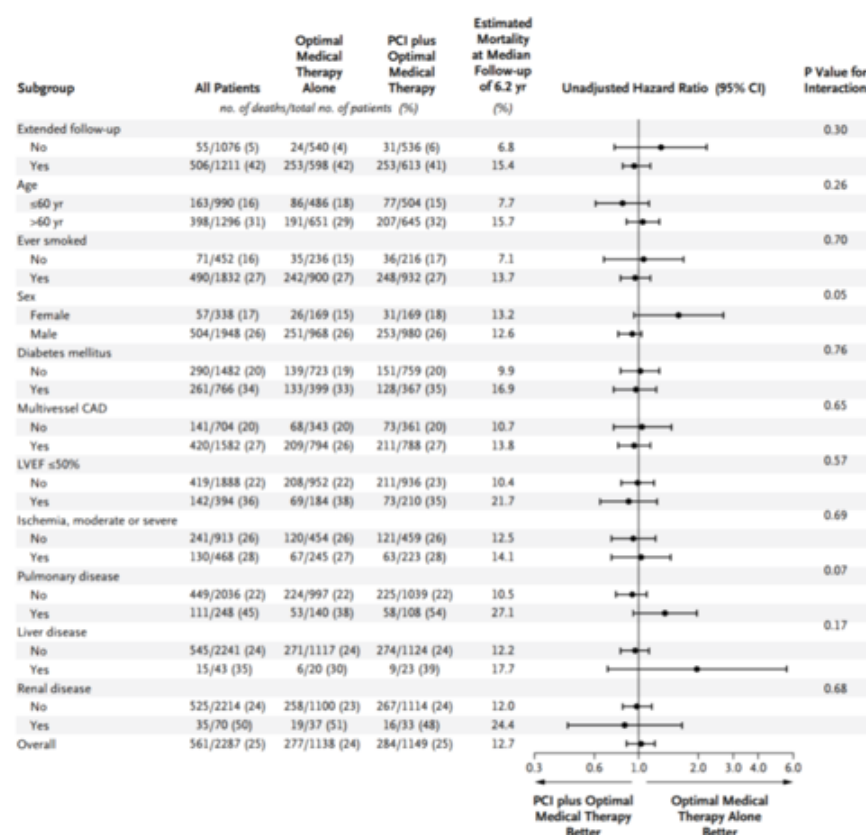
Steven P. Sedlis, M.D., Pamela M. Hartigan, Ph.D., Koon K. Teo, M.B., B.Ch., Ph.D., David J. Maron, M.D., John A. Spertus, M.D., M.P.H., G.B. John Mancini, M.D., William Kostuk, M.D., Bernard R. Chaitman, M.D., Daniel Berman, M.D., Jeffrey D. Lorin, M.D., Marcin Dada, M.D., William S. Weintraub, M.D., and William E. Boden, M.D., for the COURAGE Trial Investigators*

B Extended Follow-up Study Cohort



No. at Risk

Optimal medical therapy	598	569	533	500	455	403	280
PCI plus optimal medical therapy	613	589	561	529	486	416	302



The current understanding of the pathophysiology of coronary artery disease relies on the potential adverse effect of myocardial ischemia.

Even though the ischemia hypothesis has been placed at the core of the evaluation of patients with stable coronary artery disease, no clear evidence supports the benefit of revascularization in terms of hard clinical endpoints namely myocardial infarction and death.

Patients selection based on functional non-invasive methods was unable to identify which patients may benefit from revascularization using percutaneous based therapies.

FAME

**Defer PCI for
lesions with
FFR>0.8**

The NEW ENGLAND JOURNAL of MEDICINE

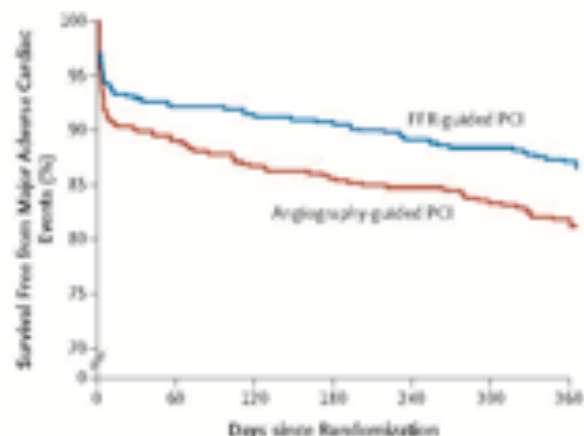
ESTABLISHED IN 1812 JANUARY 15, 2009 VOL. 360 NO. 2

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

CONCLUSIONS

Routine measurement of FFR in patients with multivessel coronary artery disease who are undergoing PCI with drug-eluting stents significantly reduces the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. (ClinicalTrials.gov number, NCT00267774.)

Tonino et al. NEJM 2009, 360: 213



THE NEW ENGLAND JOURNAL of MEDICINE

FAME-2

ORIGINAL ARTICLE

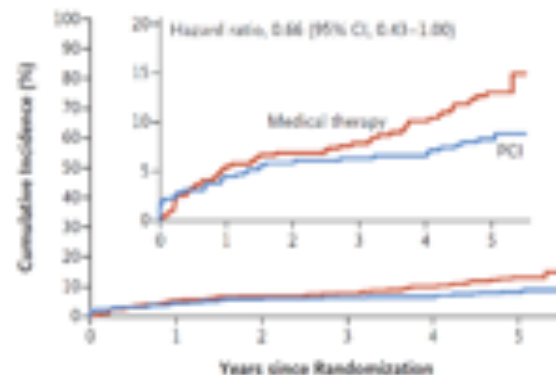
Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

CONCLUSIONS

In patients with stable coronary artery disease, an initial FFR-guided PCI strategy was associated with a significantly lower rate of the primary composite end point of death, myocardial infarction, or urgent revascularization at 5 years than medical therapy alone. Patients without hemodynamically significant stenoses had a favorable long-term outcome with medical therapy alone. (Funded by St. Jude Medical and others; FAME 2 ClinicalTrials.gov number, NCT01132495.)

Xaplanteris et al. NEJM 2018

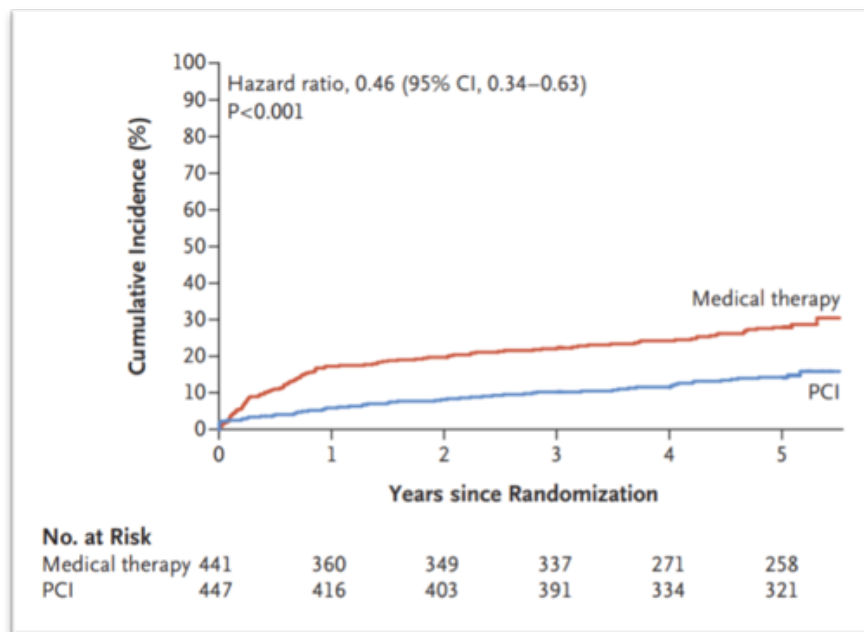
B Myocardial Infarction



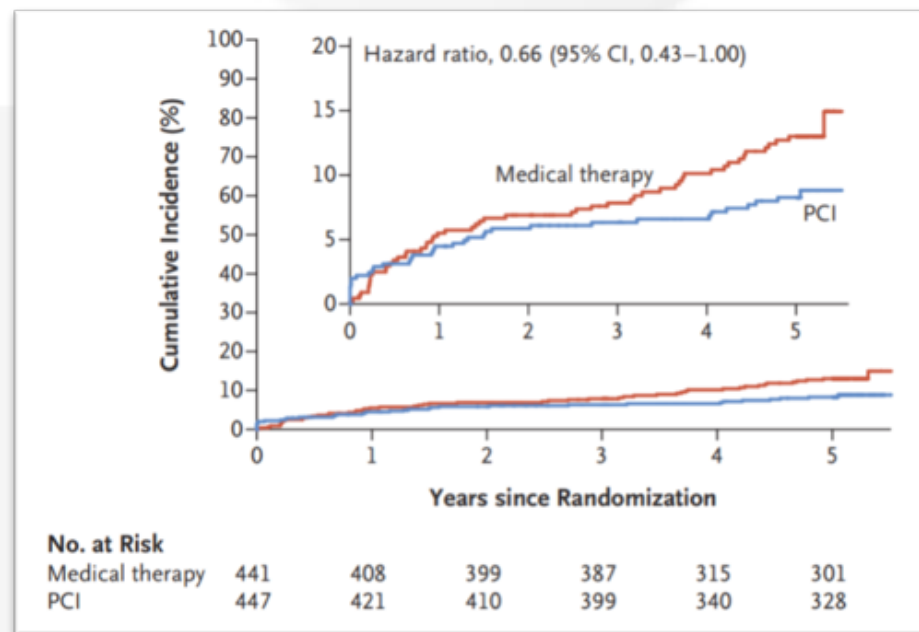
No. at Risk						
Medical therapy	441	408	399	387	315	301
PCI	447	421	410	399	340	328

**Perform PCI
for lesions
with FFR≤0.8**

MACE



Myocardial infarction

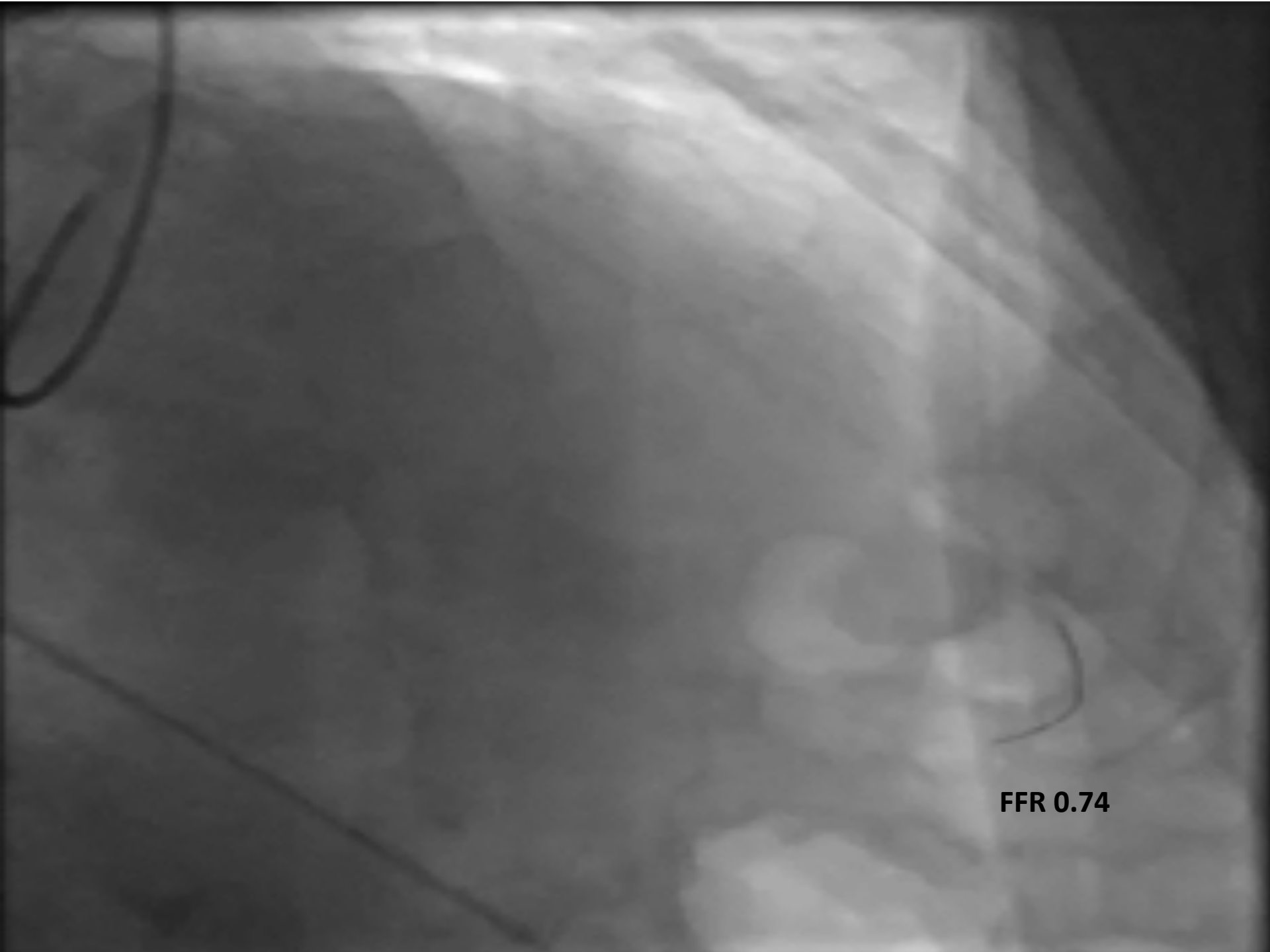


The current understanding of the pathophysiology of coronary artery disease relies on the potential adverse effect of myocardial ischemia.

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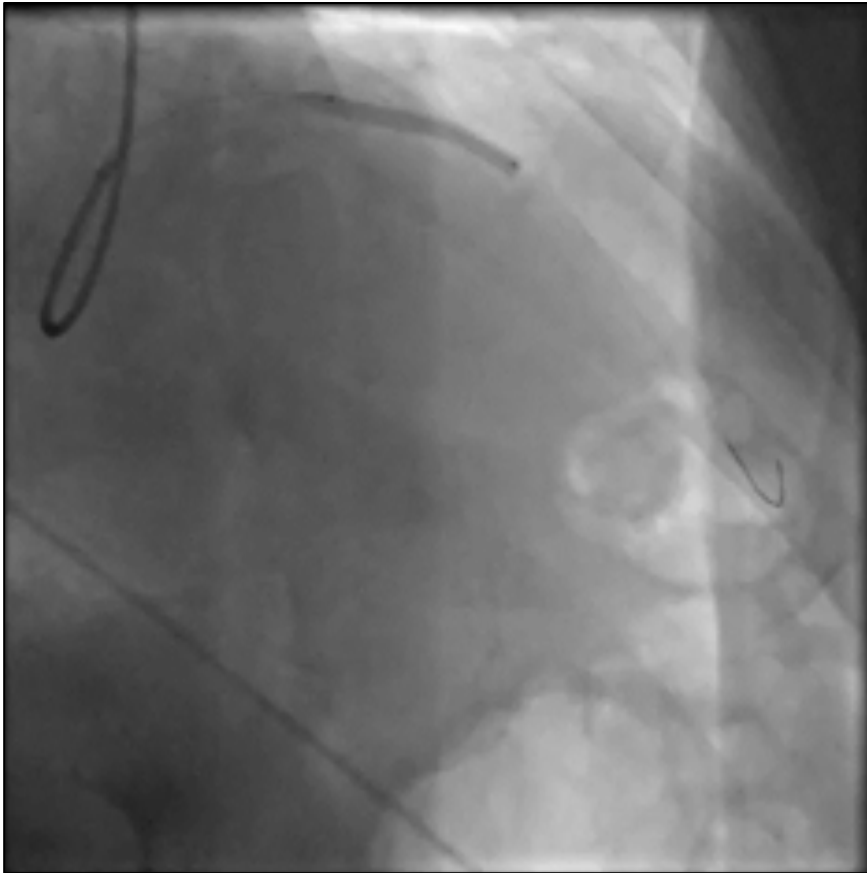
Patients selection based on functional non-invasive methods was unable to identify patients that may benefit from revascularization using percutaneous based therapies.

Patient selection using FFR *at the vessel level* is associated with improved clinical outcomes.

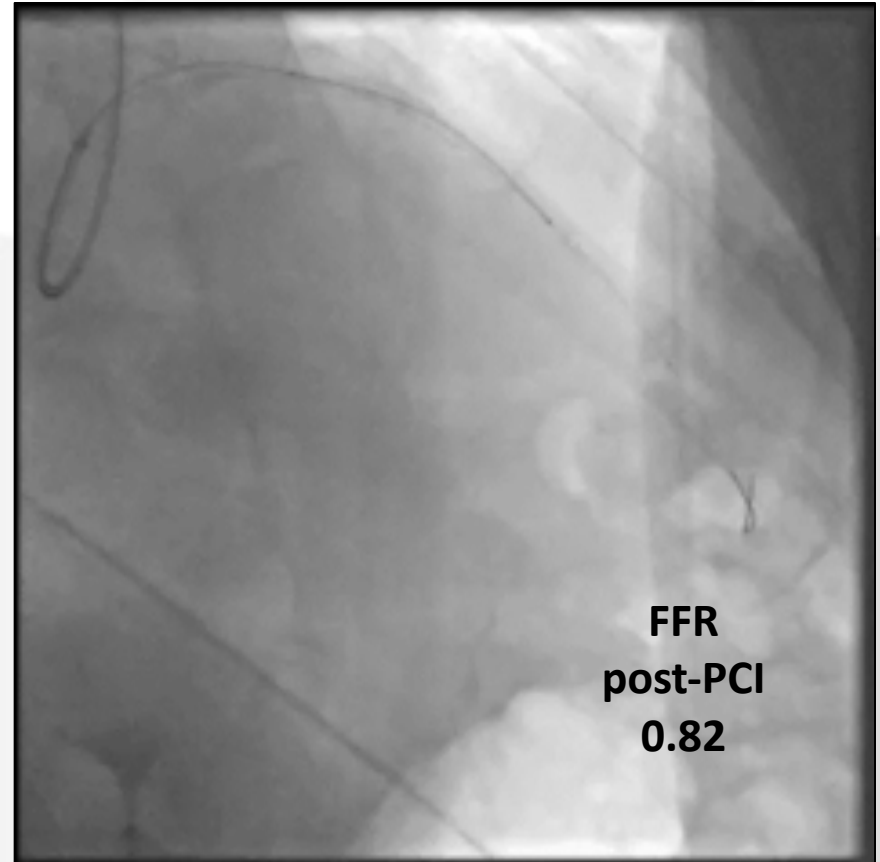


FFR 0.74

FFR post-PCI: the higher the better



Xience Alpine®
3.5/33 mm

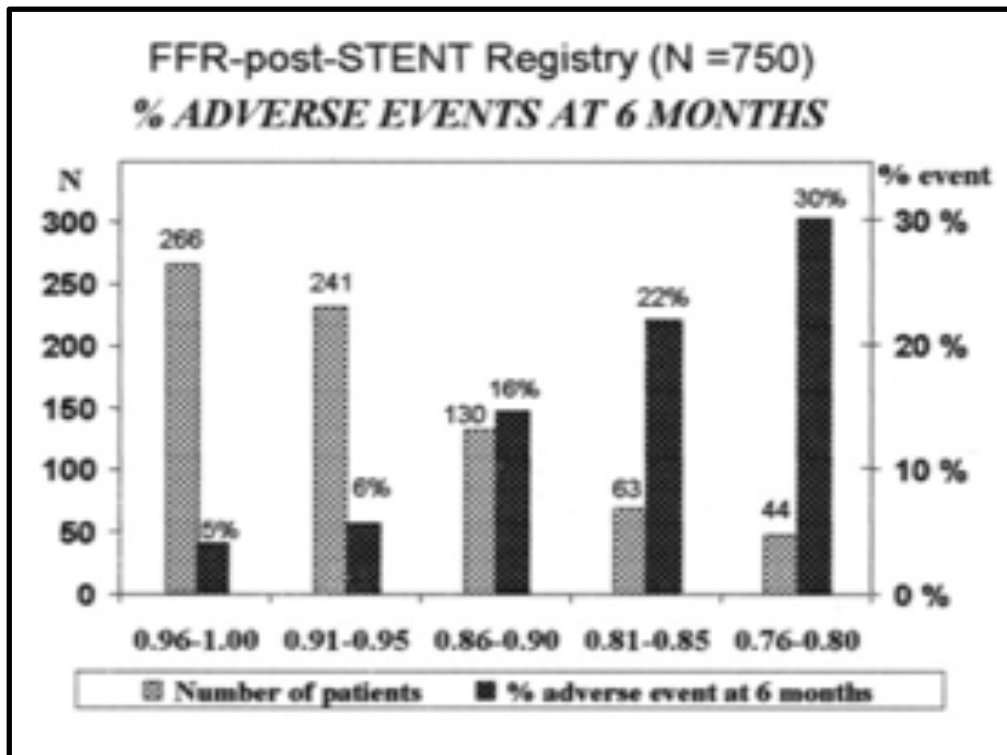


Post PCI

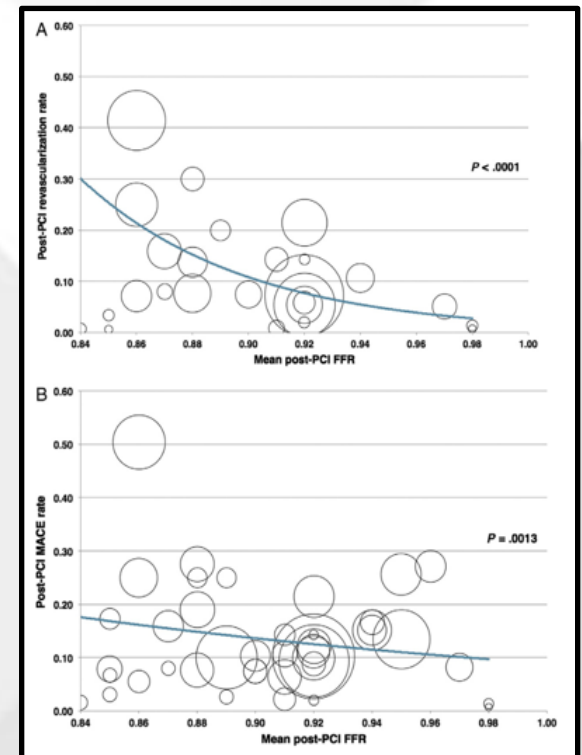
Imaging-guided PCI for all?



Why do we need more physiologic information?

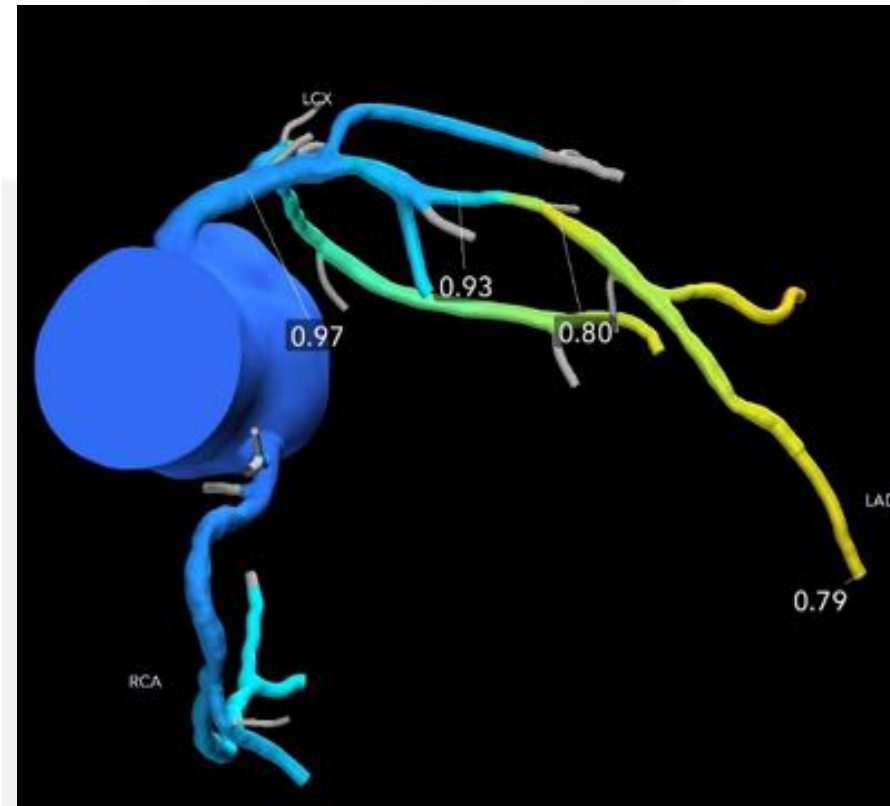


Pijls et al. Circulation. 2002;105: 2950-4



Rimac et al. Am Heart J 2017;183:1-9

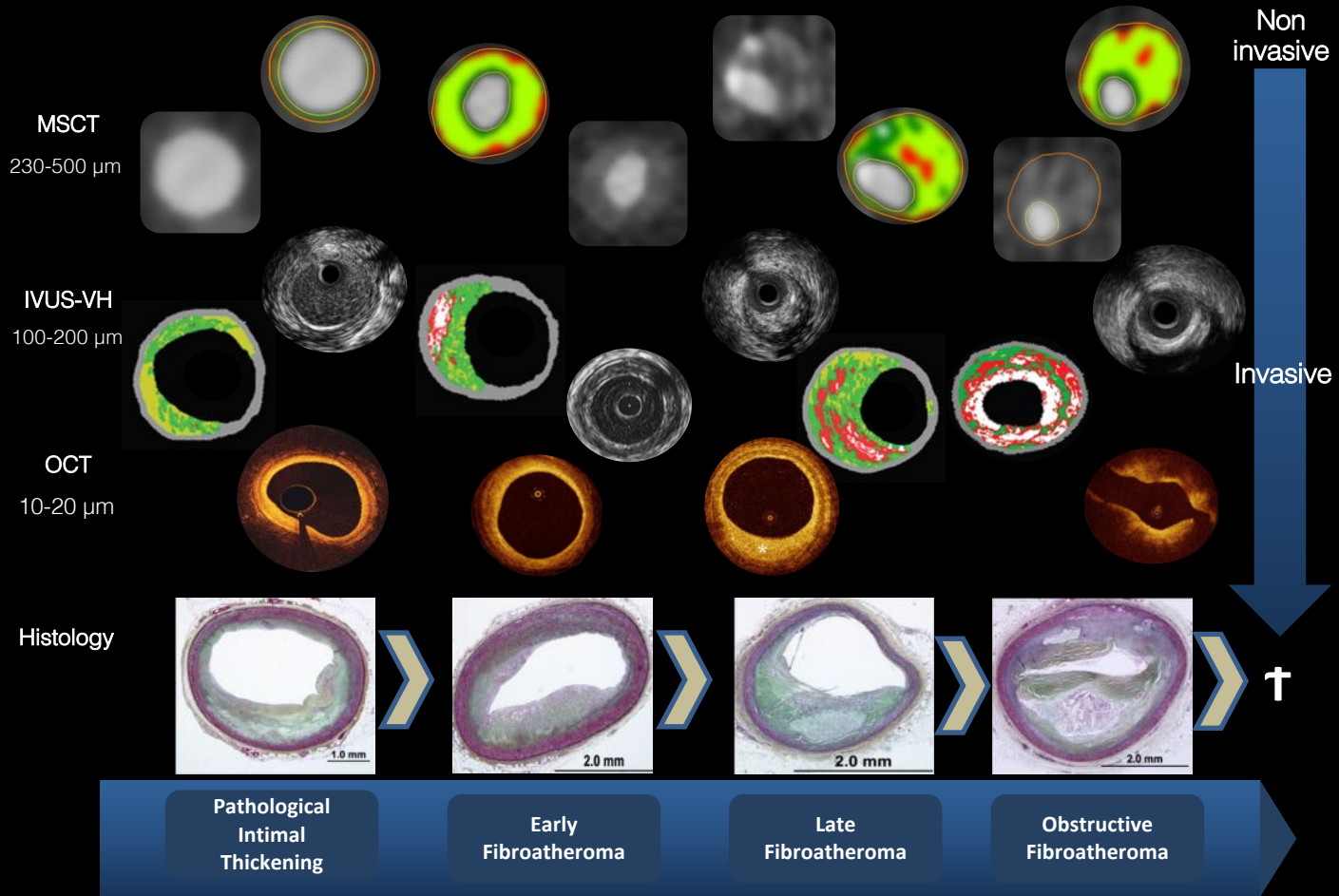
Improve PCI results and potentially patient outcome using imaging, physiology or hybrid planning tools?



What is the role of CT and FFR_{CT} ?

Non-invasive coronary physiology: The HeartFlow FFR_{CT} analysis

MSCT Coronary Imaging



Otsuka et al. Atherosclerosis 2015

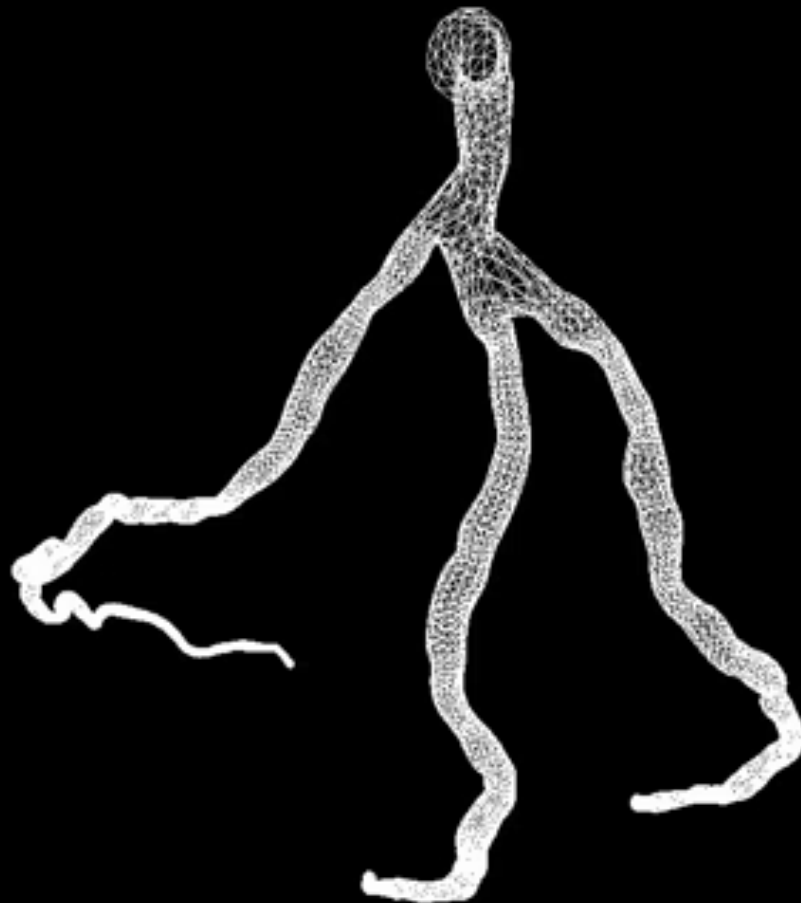
Cheng et al ATHEROREMO-IVUS EHJ 2014

Serruys et al. JACC 2015



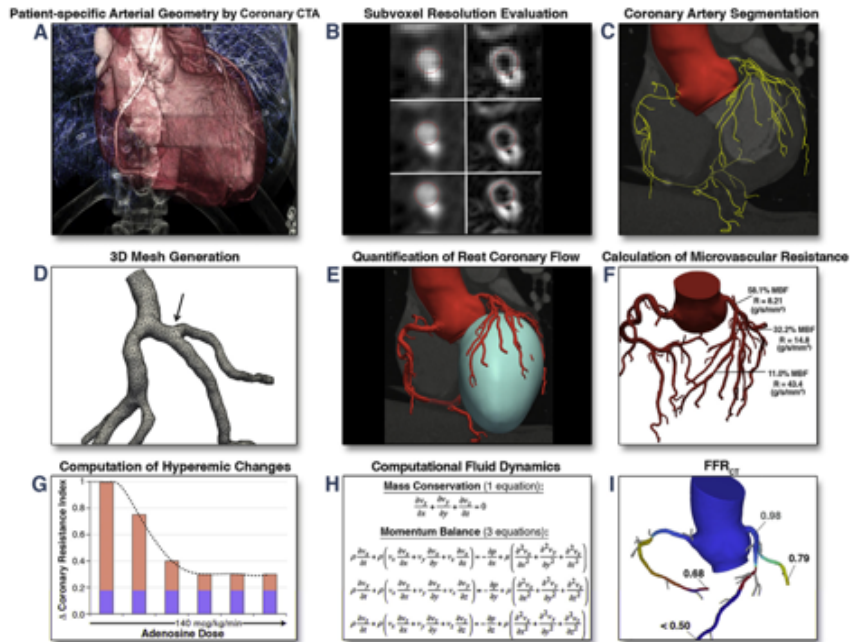
*Cardiovascular
Center
Aalst*

From 3D Patient Specific Geometry to FFR_{CT}

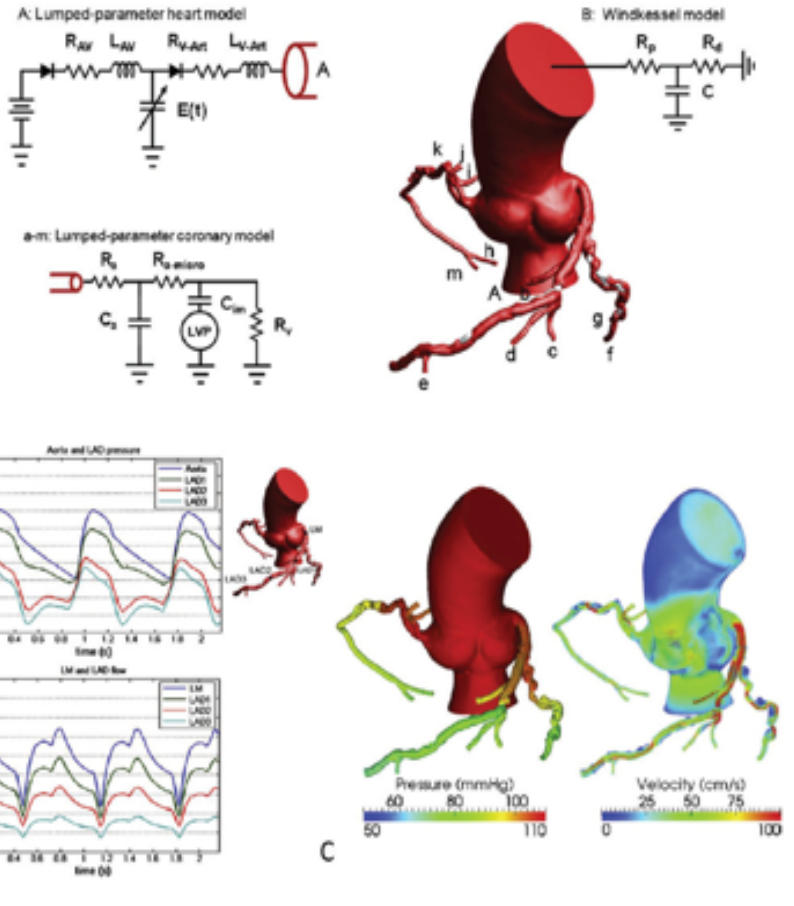


FFR_{CT}: The white box

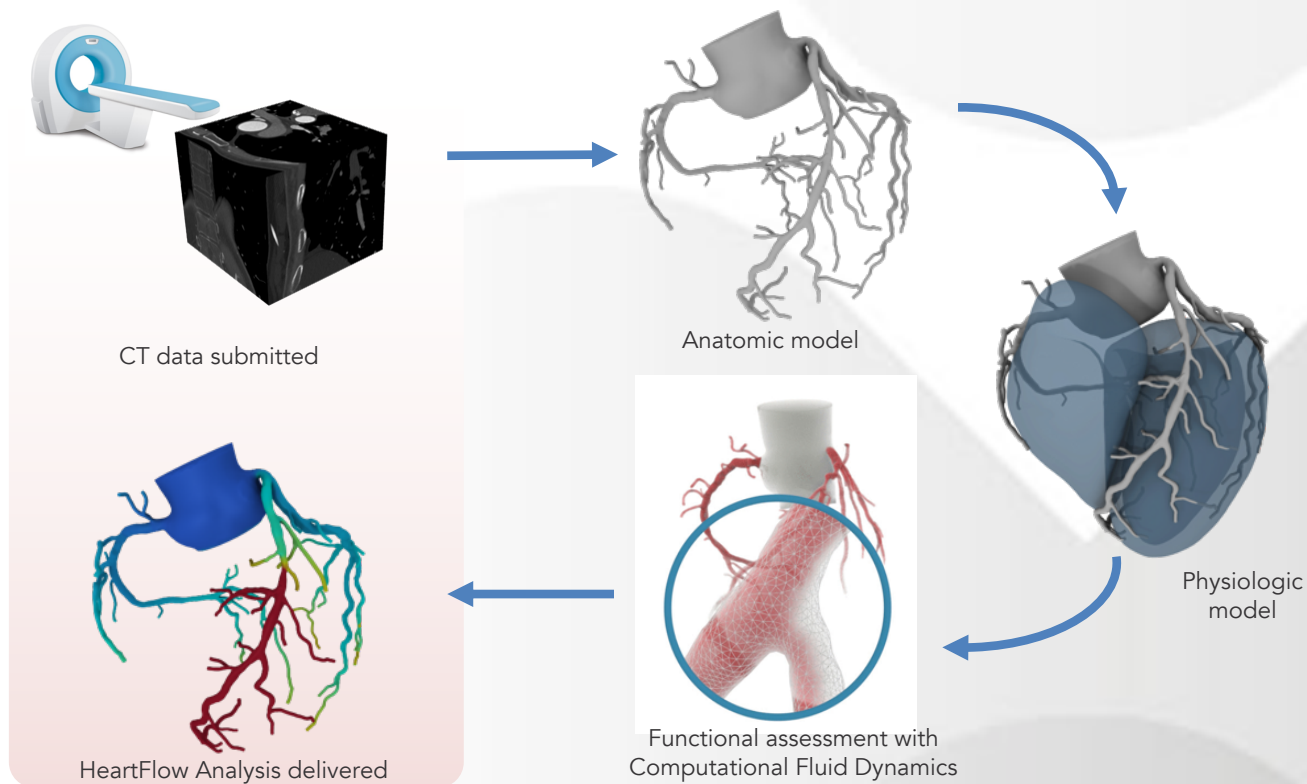
FIGURE 1 Step-by-Step Method for Calculation of FFR_{CT}



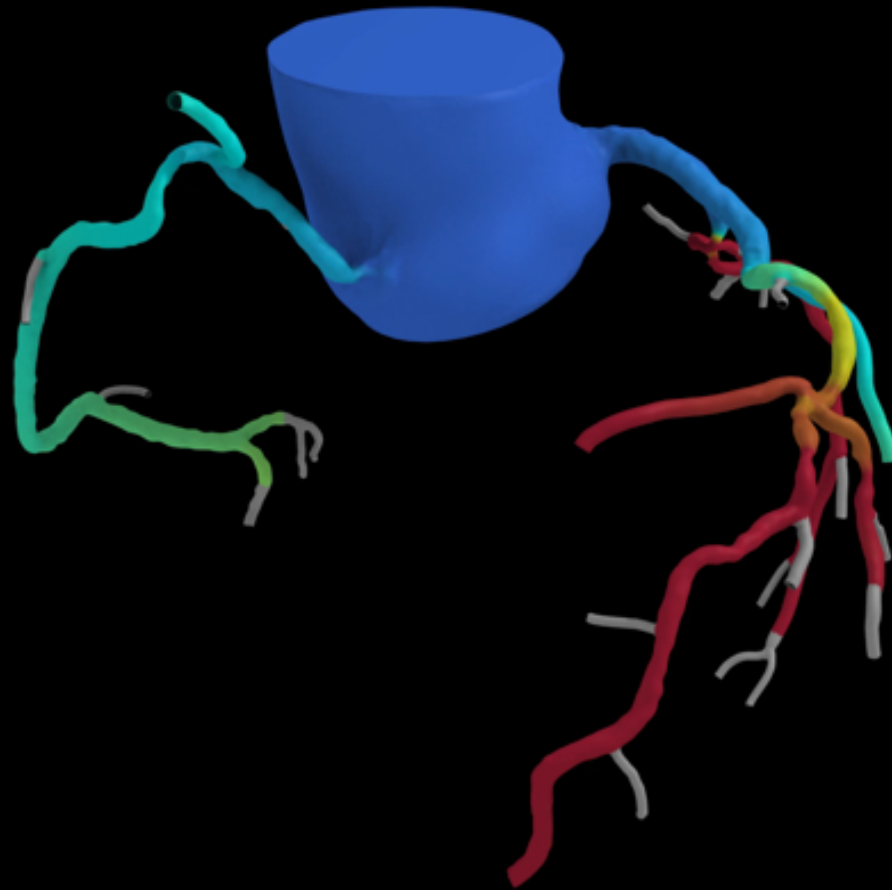
(A) Acquisition of coronary computed tomography angiography (CTA); (B) coronary artery segmentation to second- and third-order vessels; and (C) application of subvoxel resolution techniques. In this example, a cross-section of a coronary artery shown with image intensity data (left) and image-gradient data (right) illustrates typical coronary CTA reconstruction with increasingly improved image resolution (middle and bottom) demonstrating subvoxel resolution techniques. (D) Discretization of mesh elements for calculation of computational fluid dynamics (CFD) at millions of points in the coronary vascular bed. Note that the tetrahedral vertices are reconstructed in 3 dimensions and are continuous even at the branch points to accurately calculate coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) at these areas commonly affected by plaque. Reduced order methods that do not use 3-dimensional analyses are less accurate at these points. (E) Relationship of the location and size of coronary arteries to the left ventricular mass they subtend; (F) relationship of coronary vessel caliber and flow and resistance; (G) demonstration of reduced coronary resistance index at an adenosine dose of 140 µg/kg/min (Wilson et al., [25]); (H) Navier-Stokes equations that govern the fluid dynamics of blood (nonlinear partial differential equations related to mass conservation and momentum balance are solved); and (I) example of a patient-specific FFR_{CT}.



The FFR_{CT} Analysis Process



FFR_{CT} 3D patient specific model



FFR_{CT} studies

		Sites	Regions	Study Design	Population	PE Published	FFR _{CT} version used	Primary Endpoint / Objective
DISCOVER-FLOW	103 pts (159 vessels)	4	US, Korea, Latvia	Prospective	Pts with suspected or known CAD	Nov 2011 JACC	pre-1.x	To determine the diagnostic performance of noninvasively derived FFR _{CT} using invasive FFR as the gold standard
DEFACTO	252 pts (407 vessels)	17	US, Canada, Korea, Europe	Prospective	Pts with suspected or known CAD	Aug 2012 JAMA	pre-1.x	To determine the diagnostic performance of noninvasively derived FFR _{CT} using invasive FFR as the gold standard
NXT	254 pts (484 vessels)	10	Europe, Korea, Japan, Australia	Prospective	Pts with suspected stable CAD	Apr 2014 JACC	1.x	To determine the diagnostic performance of noninvasively derived FFR _{CT} using invasive FFR as the gold standard
PLATFORM	584 pts	11	Europe	Prospective consecutive cohort	Pts with stable chest pain, primary endpoint required planned ICA	Aug 2015 EHJ	1.x	To determine the impact of using a pathway of CTA ± FFR _{CT} instead of usual care on ICA showing no obstructive disease
RIPCORD FFR _{CT}	200 pts	11	Europe, Korea, Japan, Australia	Retrospective analysis of NXT study	Pts with suspected stable CAD	Oct 2016 JACC Imaging	1.x	To determine during a case review how management plan changes using cCTA alone compared to cCTA + FFR _{CT}
PROMISE FFR _{CT} sub study	181 analyzable cases	Analyzable cases came from 69 sites	US, Canada	Retrospective case review	Pts from the PROMISE study referred for ICA w/in 90 days of cCTA	Apr 2017 JACC Imaging	1.x	To determine if FFR _{CT} predicts revasc and outcomes and if its addition improves efficiency of referral to ICA
Syntax II sub study	77 pts	22	Europe	Subgroup analysis of a prospective study	Pts with 3 vessel disease by ICA	May 2018 JACC	1.x	To assess the feasibility of and validate the noninvasive functional SYNTAX score (FSS) derived from cCTA with FFR _{CT}
ADVANCE	5083 pts	38	US, Canada, Europe, Japan	Prospective registry	Pts with suspected stable CAD	Aug 2018 EHJ	1.x & 2.x	To determine if treatment plan changes using cCTA alone compared to cCTA + FFR _{CT} , as assessed by a core lab
Syntax III	223 pts	6	Europe	Prospective RCT	Pts with left main or 3 vessel disease by ICA	Sep 2018 EHJ	1.x & 2.x	To determine, in blinded fashion, the agreement of revascularization strategy based either on cCTA + FFR _{CT} or conventional angiography
PACIFIC FFR _{CT} sub study	208 pts	1	Europe	Retrospective analysis of a prospective study	Pts with suspected stable CAD	Jan 2019 JACC	2.x	To evaluate diagnostic performance of FFR _{CT} using invasive FFR as the gold standard, and compare to cCTA, SPECT, and [¹⁵ O]H ₂ O PET.

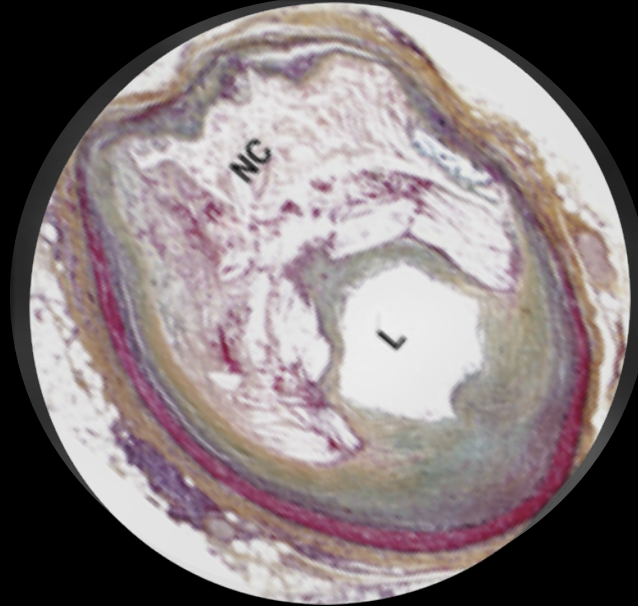
Non-invasive coronary physiology on top of plaque evaluation

Plaque Assessment



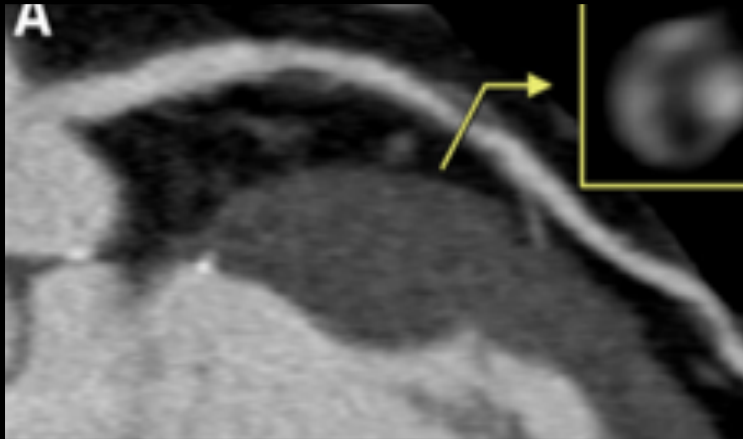
Low Attenuation Plaques

Voxel with HU < 30

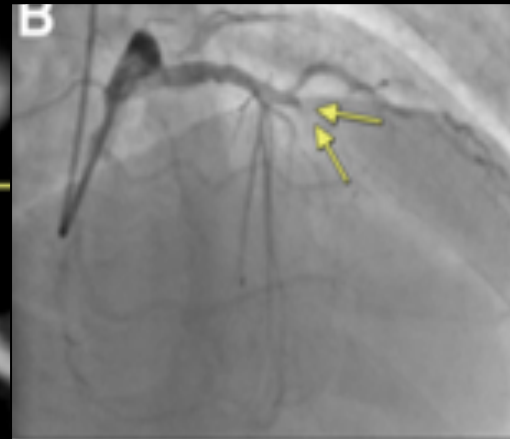


Hecht et al. JACC Imaging 2015
Otsuka et al. JACC imaging 2015

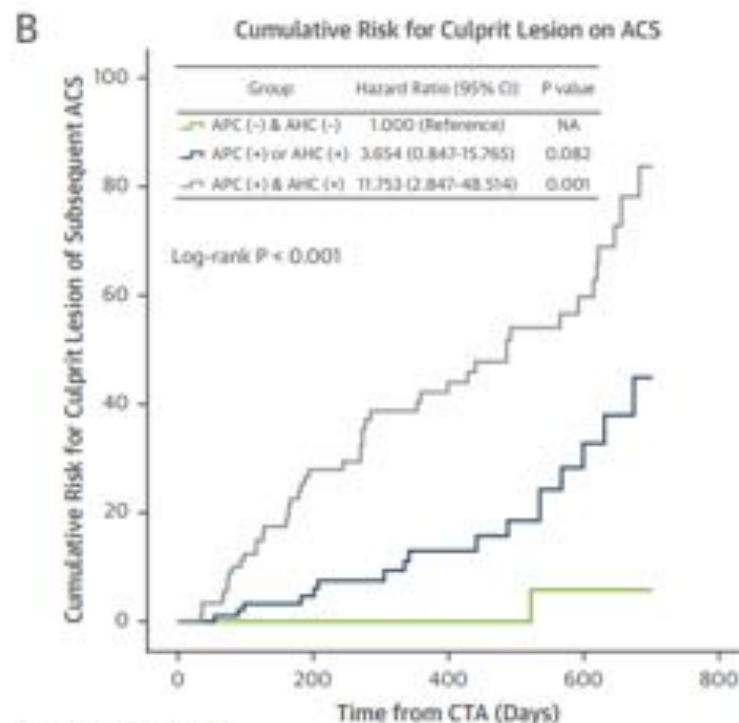
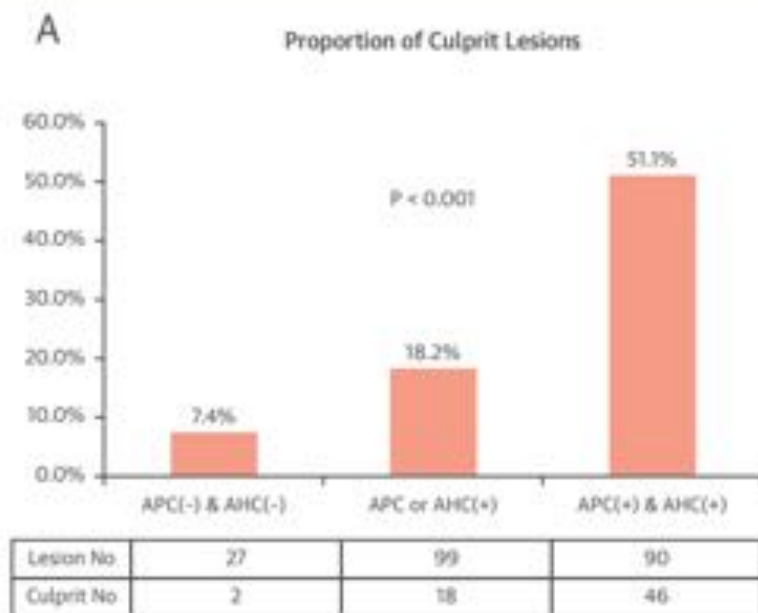
Baseline



10 months



Identification of High Risk Plaques



Adverse Hemodynamic characteristics (AHC) defined as lesions that have **low FFR_{CT}** (<0.80), **high ΔFFR_{CT}** (>0.06), **high WSS** (≥154.7 dyn/cm²), or **high axial plaque stress** (≥ 1,606.6 dyn/cm²).

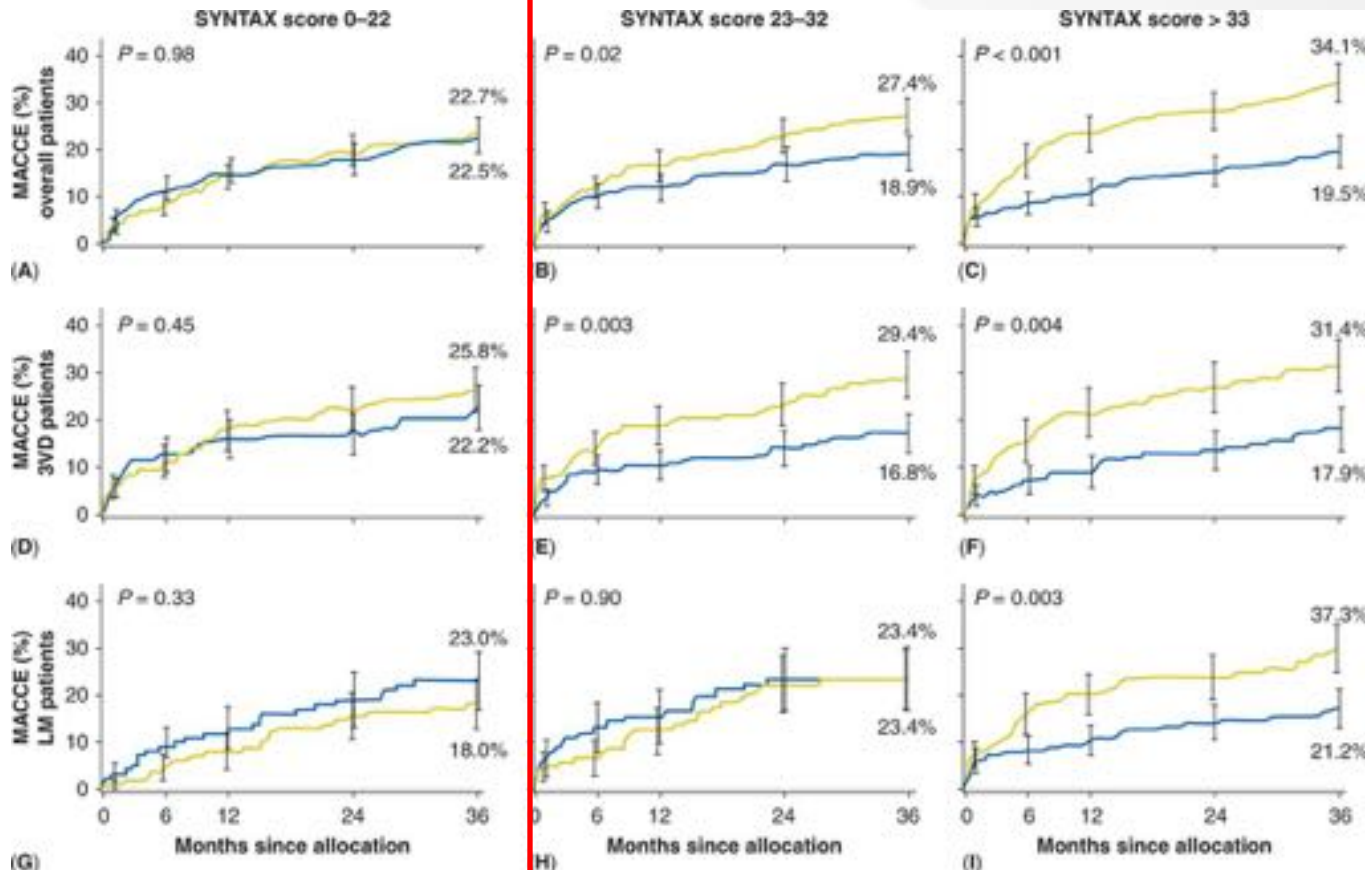
Non-invasive coronary physiology for clinical decision making in complex CAD



- **SYNTAX score** is purely an anatomic score of the extent of CAD (>50%) in a pt
- Each lesion is assigned a numerical number and then sum of all lesions score for a patient is calculated to come up with the final numerical SYNTAX score
- Pt are divided in 3 groups:
 - Low <22
 - Intermediate 23-32
 - High >32

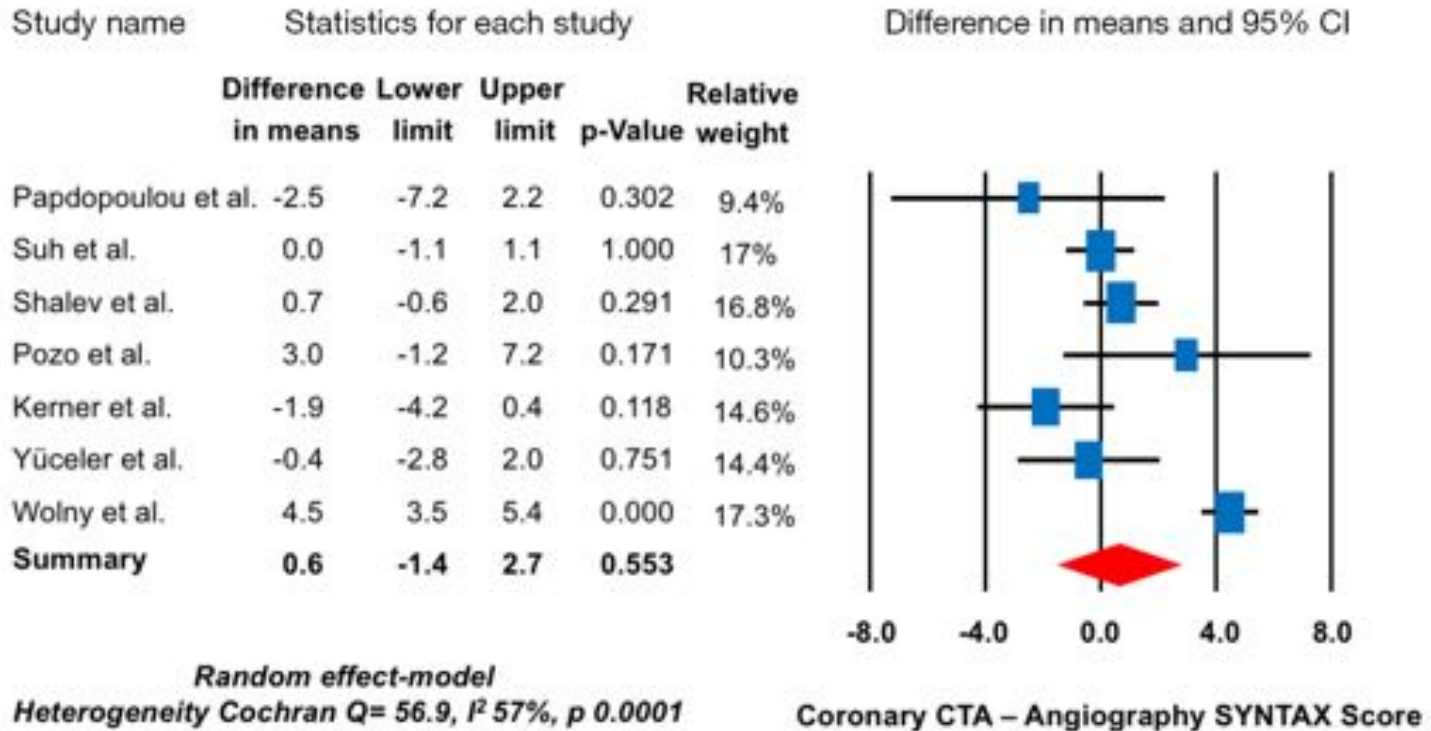
SYNTAX Score and Clinical Outcomes

— PCI
— CABG

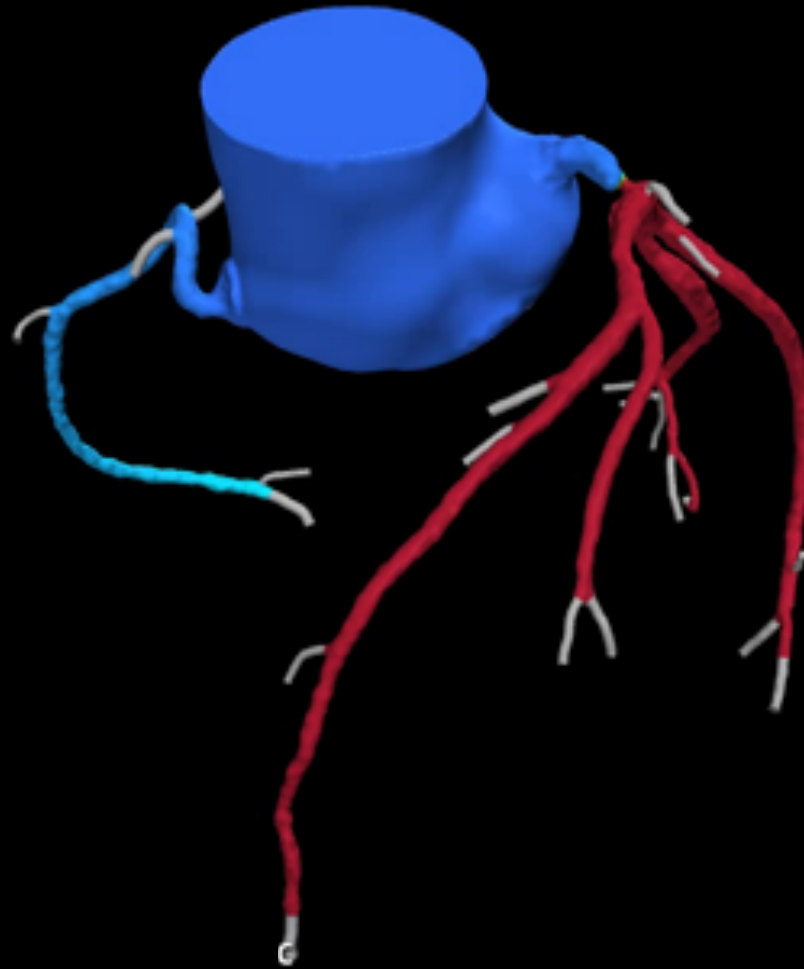


CTA vs. Angiography: SYNTAX Score Calculation

Meta-analysis comparing CTA vs. invasive angiography derived SYNTAX Score



Non-Invasive FFR_{CT}



**Presence of 3- vessel disease with/without LM on
conventional angiography (223 patients)**

CCTA (GE Revolution)

2 Heart Teams

*** Each Heart Team was randomized
to one of 2 diagnostic algorithms**

Heart Team A Angio first



Centro Cardiologico Monzino

- Antonio Bartorelli (Cardiologist)
- Daniele Andreini (Radiologist)
- Giulio Pompilio (Surgeon)
- Saima Mushtaq (Cardiologist)
- Gianluca Pontone (Radiologist)
- Stefano De Martini (Cardiologist)
- Francesco Alemanni (Surgeon)

University Hospital Zurich

- Oliver Gaemperli (Cardiologist)
- Philipp Kaufmann (Radiologist)
- Andre Plass (Surgeon)
- Ronny Buchel (Radiologist)
- Thomas Luscher (Cardiologist)
- Andre Plass (Surgeon)

Centre Cardiologique du Nord

- Philippe Guyon (Cardiologist)
- Laurent Macron (Radiologist)
- Nicolas Bonnet (Surgeon)
- Jean-Louis Sablayrolles (Radiologist)
- Philippe Guyon (Cardiologist)
- Patrick Mesnildrey (Surgeon)

Heart Team B CCTA first



University of Brussels

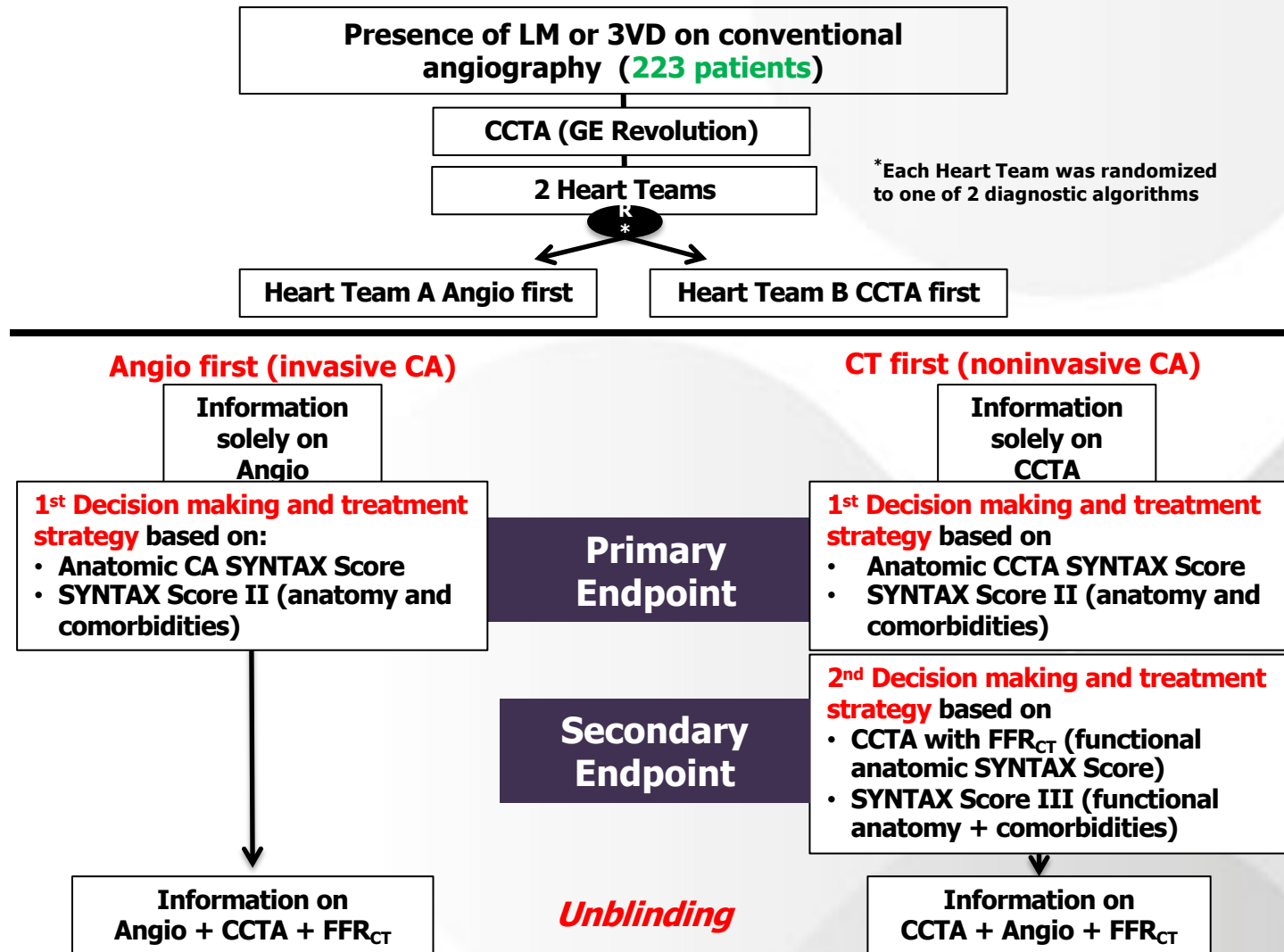
- Jeroen Sonck (Cardiologist)
- Johan De Mey Radiologist
- Mark La Meir (Surgeon)
- Dries Belsack (Radiologist)
- Dani Schoors (Cardiologist)
- Jens Czaplá (Surgeon)

University Hospital Nancy

- Edoardo Camezind (Cardiologist)
- Damien Mandry (Radiologist)
- Juan Pablo Moureira (Surgeon)
- Xavier Orry (Radiologist)
- PA Metzdorf (Cardiologist)
- Thierry Folliquet (Surgeon)

University Hospital Jena

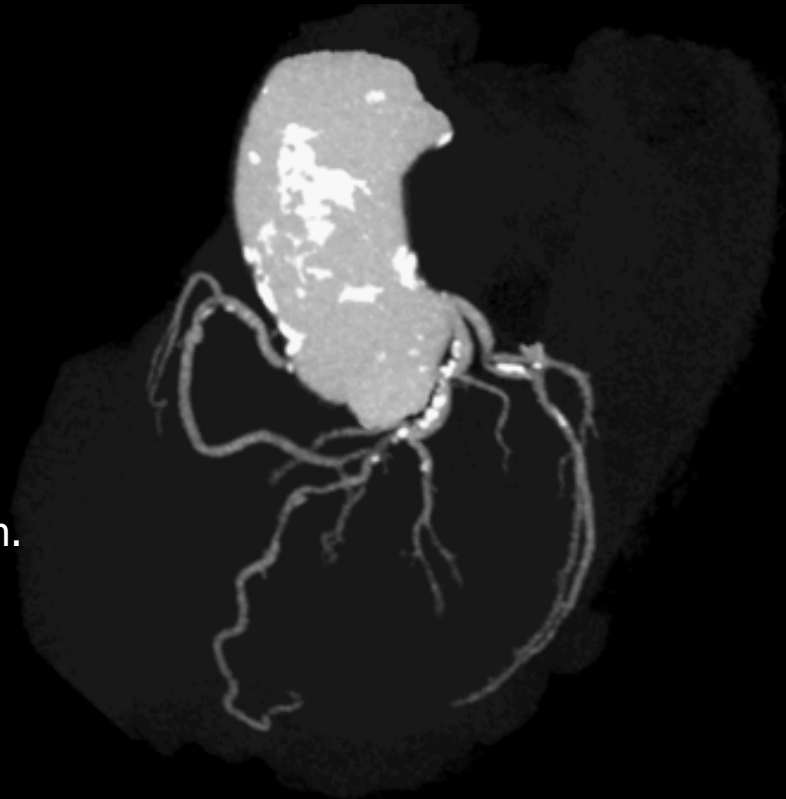
- Holger Sigusch (Cardiologist)
- Ulf Teichgraber (Radiologist)
- Tosten Doenst (Surgeon)
- Ioannis Diamantis (Radiologist)
- Marc Schonweil (Cardiologist)
- Gloria Farber (Surgeon)



MSCT Assessment

3D - Maximum Intensity Projection (MIP)

- ✓ Calcification of the Aorta.
- ✓ Calcified plaque in the LAD.
- ✓ Mid LAD obstructive lesion.
- ✓ LCX/OM bifurcation lesion.
- ✓ Proximal RCA obstructive lesion.
- ✓ Ostial lesion RCA (?)

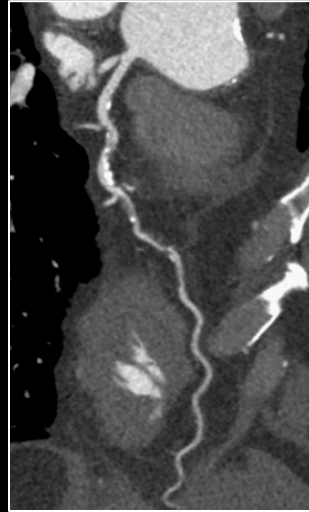


CT-derived SYNTAX score

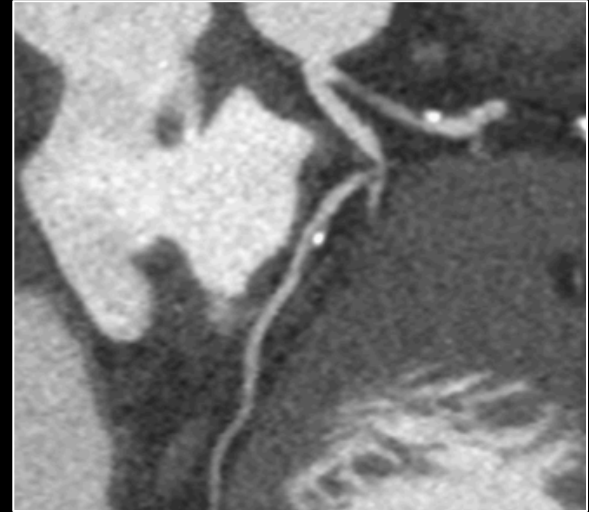
RCA



LAD



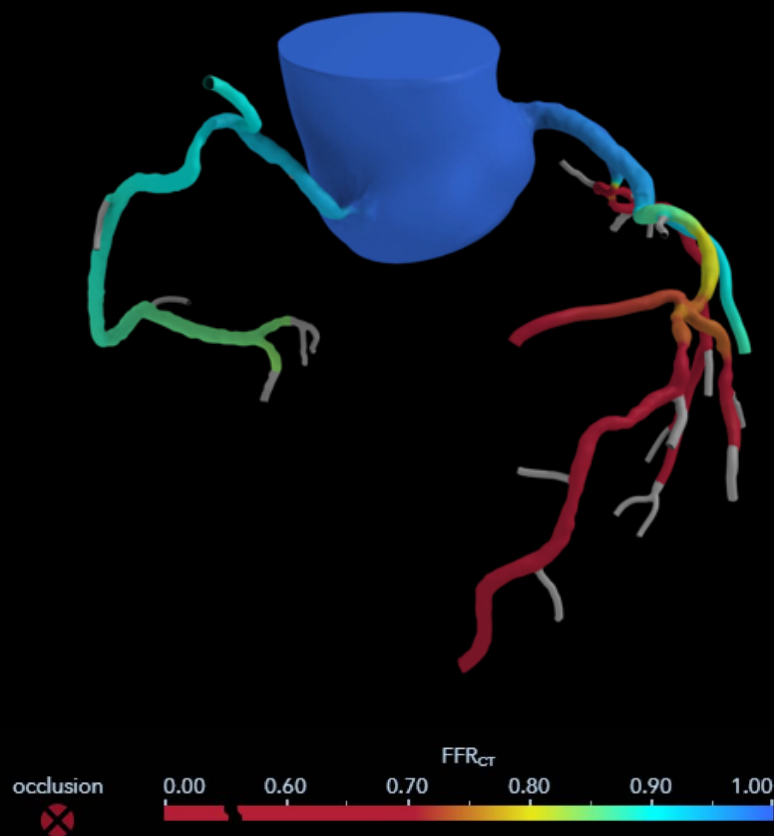
LCx



Lesion number	Detail of the lesion	SYNTAX score
RCA ostial (Seg 1)	aorto ostial	3 Points
RCA proximal (Seg 1)		2 Points
LAD mid (Seg 7)		5 Points
LAD mid (Seg 7)	long lesion	6 Points
LCX / OM (Seg 11/12a)	Bifurcation (1,1,1)	8 Points

Total Syntax score 24 points

Functional SYNTAX Score FFR_{CT}

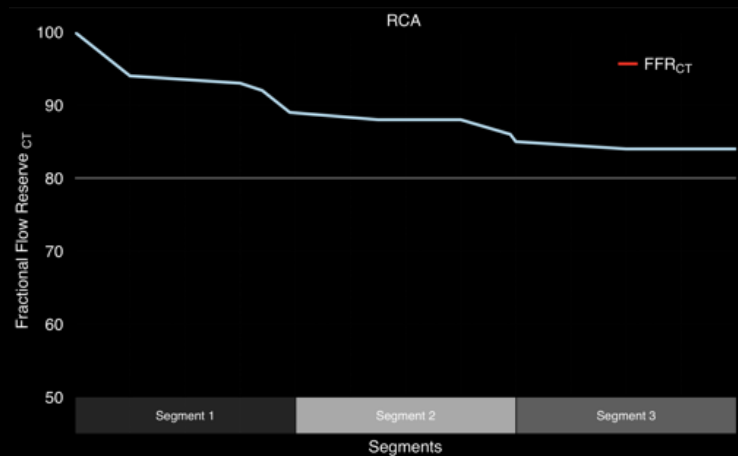
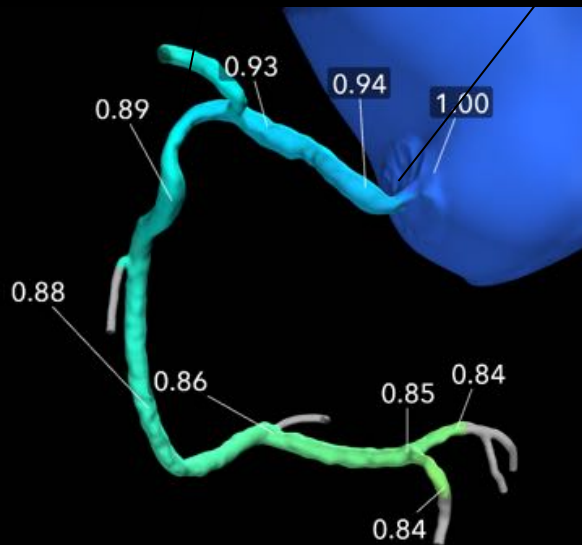


SYNTAX III
REVOLUTION

Functional SYNTAX Score FFR_{CT}

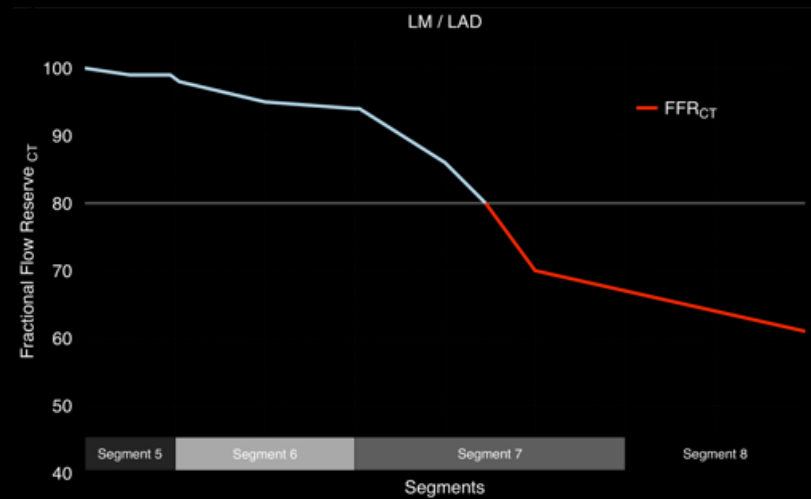
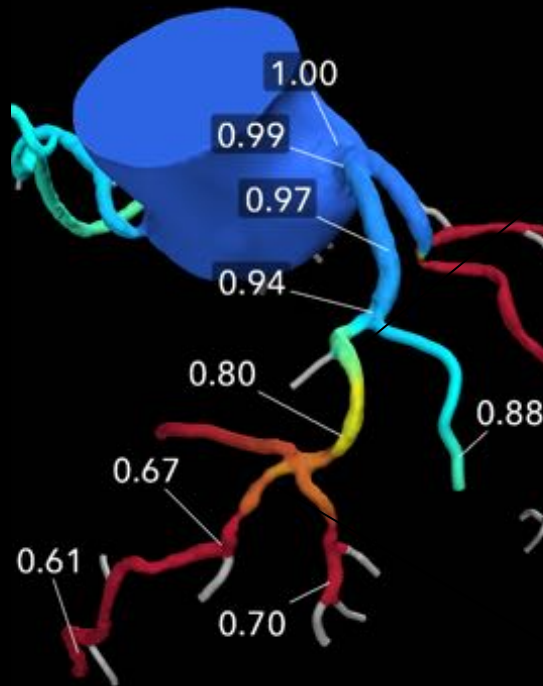
Segment 1 = 2 → 0 points

Segment 1 ostial = 3 → 0 points



Functional SYNTAX Score FFR_{CT}

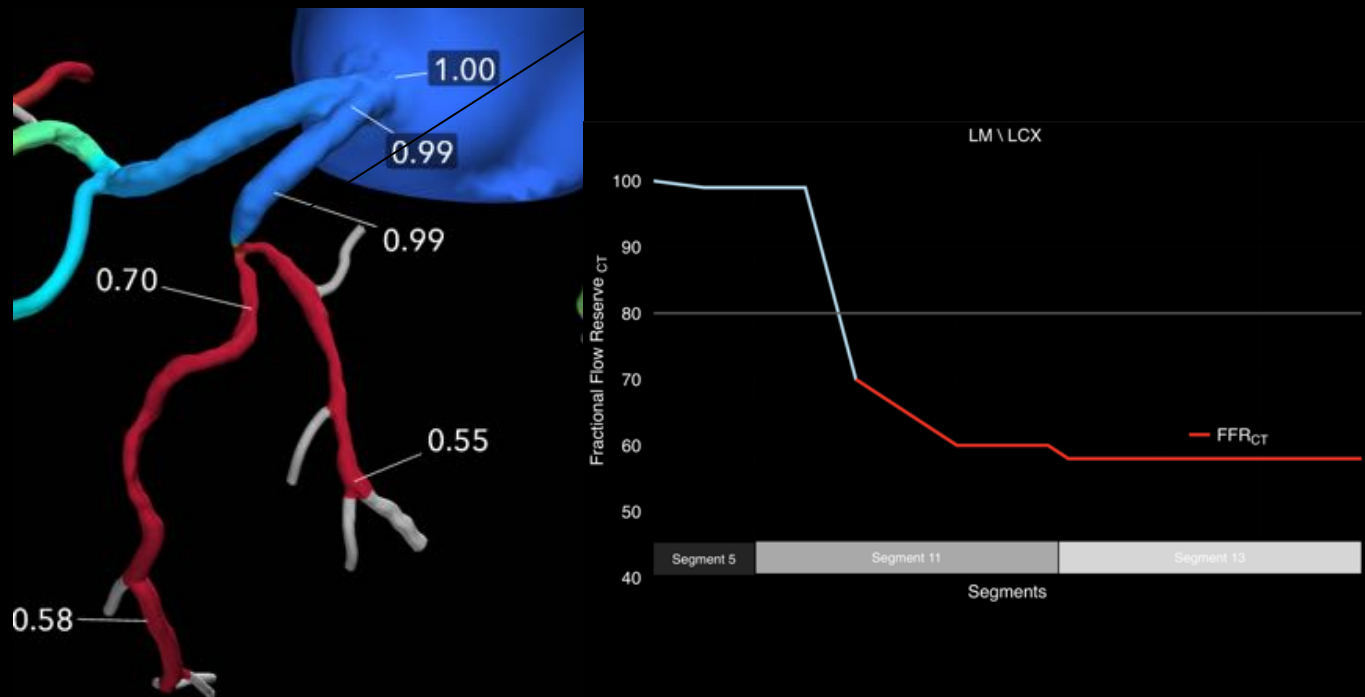
Segment 7, >20 mm = 5 points



Segment 7 = 6 pts

Functional SYNTAX Score FFR_{CT}

Segment 11, 12a 1.1.1 <70° = 8 points



Functional SYNTAX Score

Lesion number	Detail of the lesion	SYNTAX score	Functional SYNTAX score
RCA ostial (Seg 1)	Aorto ostial	3 Points	→ 0 Points
RCA proximal (Seg 1)		2 Points	→ 0 Points
LAD mid (Seg 7)		5 Points	5 Points
LAD mid (Seg 7)	Long lesion	6 Points	6 Points
LCX / OM (Seg 11/12a)	Bifurcation (1,1,1)	8 Points	8 Points

Total functional SYNTAX score 19 points

SYNTAX score II and Treatment Recommendation

Variables	Input
Functional CT SYNTAX Score I	19
Age	74
CrCl ml/min	38
LVEF(%)	50
Left Main	No
Gender	Male
COPD	No
PVD	No

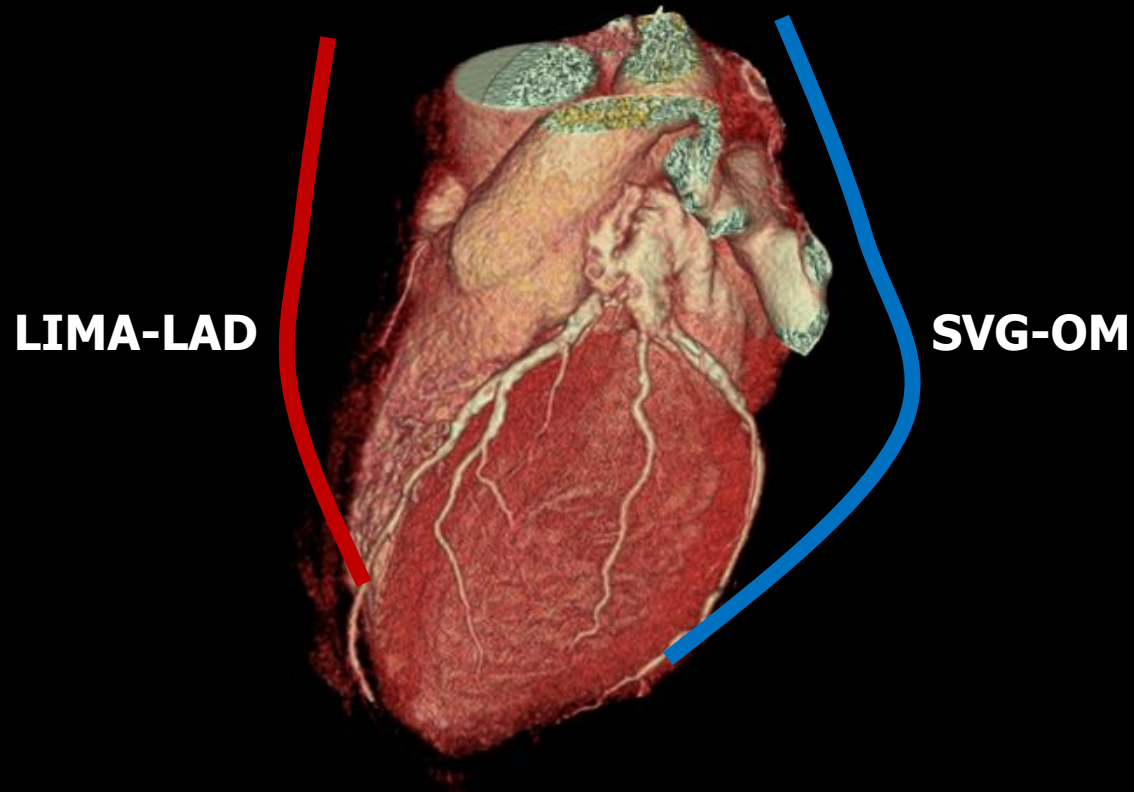
PCI	
SYNTAX Score II	38.7
PCI 4 Year Mortality	13.6%
CABG	
SYNTAX Score II	36.7
CABG 4 Year Mortality	11.6%

Recommendation
CABG or PCI

www.syntaxscore.com

Decision Monzino

CABG



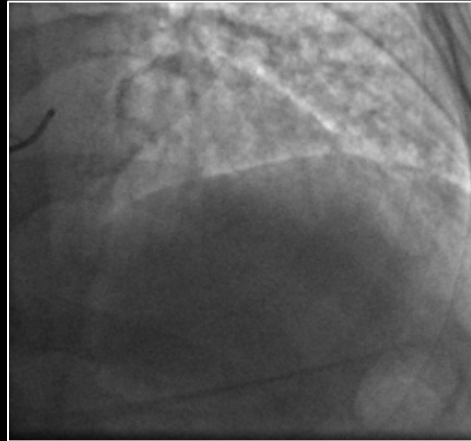
Angiogram Assessment

Angio-derived SYNTAX score

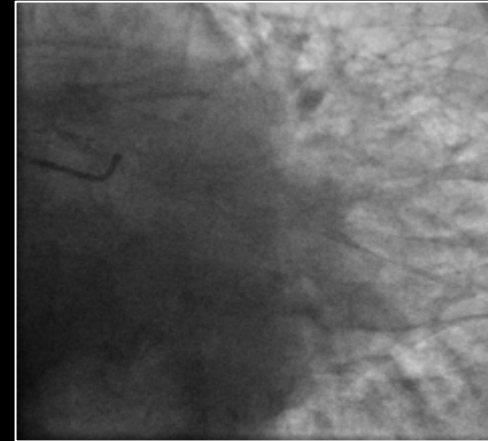
RCA



LAD



LCx



Lesion number	Detail of the lesion	SYNTAX score
RCA proximal (Seg 1)		2 Points
LAD mid (Seg 7)	Bifurcation (0,1,0) long lesion	7 Points
LCX / OM (Seg 11/12a/13)	Bifurcation (1,1,1) tortuosity	11 Points

Total SYNTAX score 20 points

SYNTAX score II and Treatment Recommendation

Variables	Input
Angio SYNTAX Score I	20
Age	74
CrCl ml/min	38
LVEF(%)	50
Left Main	No
Gender	Male
COPD	No
PVD	No

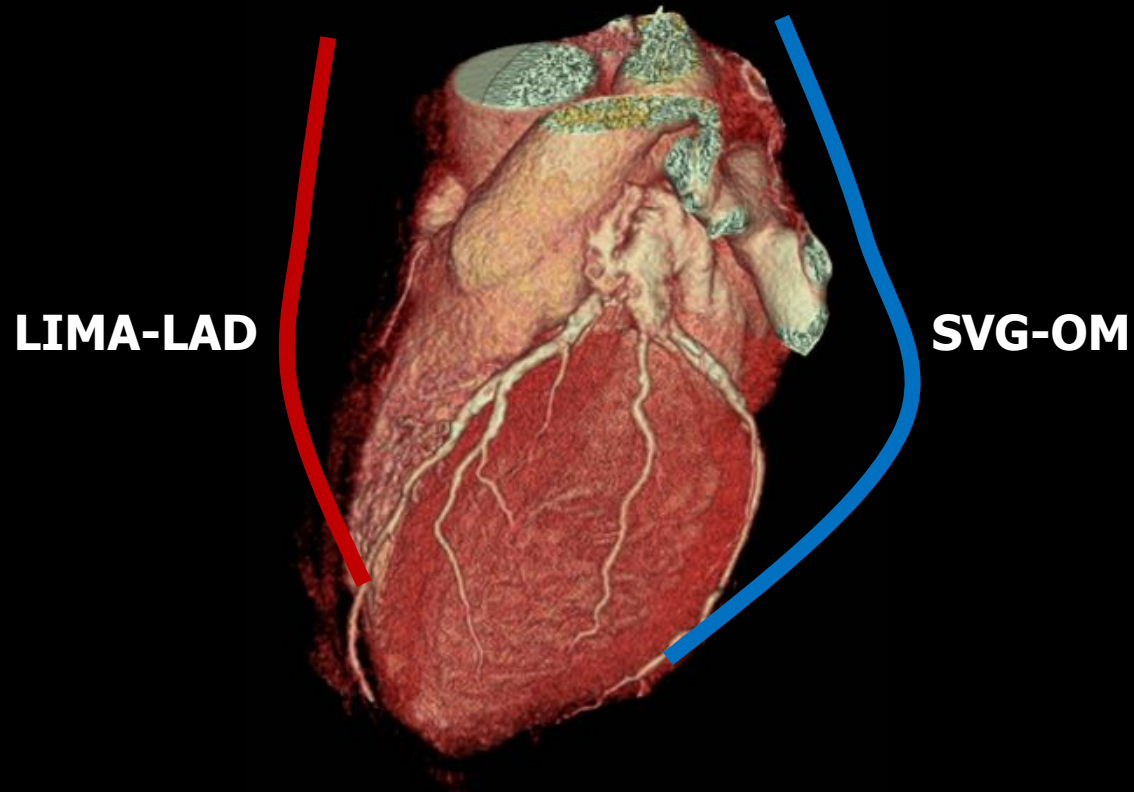
PCI	
SYNTAX Score II	38.9
PCI 4 Year Mortality	13.9%
CABG	
SYNTAX Score II	36.6
CABG 4 Year Mortality	11.6%

Recommendation
CABG or PCI

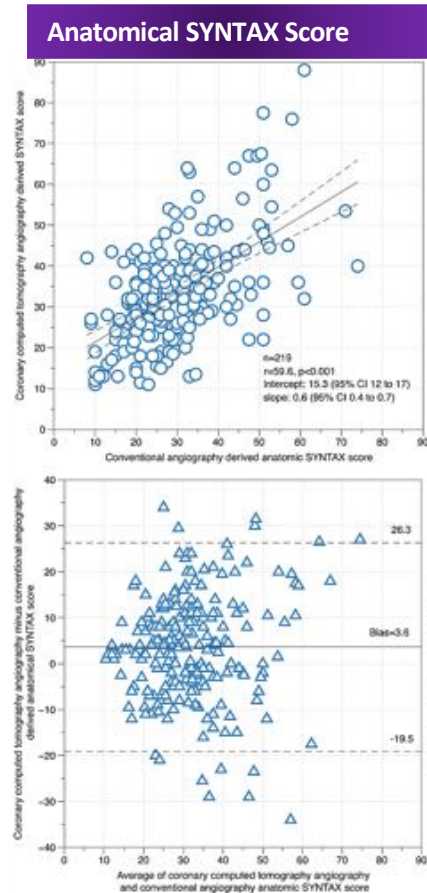
www.syntaxscore.com

Decision Brussels

CABG



Anatomical SYNTAX score and SYNTAX score II



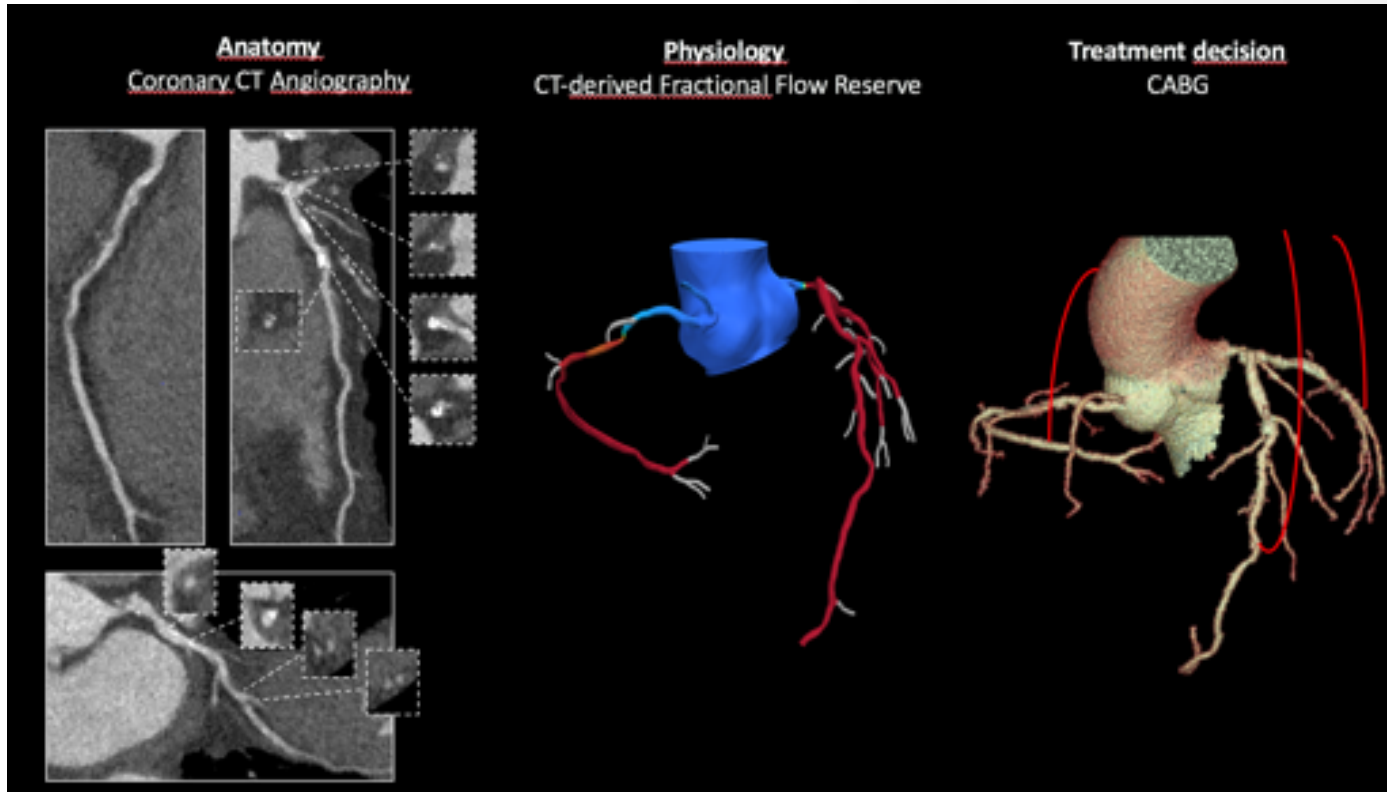
SYNTAX III Revolution

Primary End-Point

	Heart team treatment recommendation based on coronary computed tomography angiography		
Heart team treatment recommendation based on conventional angiography	CABG	PCI/Equipoise CABG and PCI	
CABG	23.4% (52/222)	2.7% (6/222)	26.1% (58/222)
PCI/Equipoise CABG and PCI	4.5% (10/222)	69.4% (154/222)	73.9% (164/222)
	27.9% (62/222)	72.1 (160/222)	92.8%(206/222)
Cohen's kappa 0.82 (95% CI 0.73 to 0.91)			

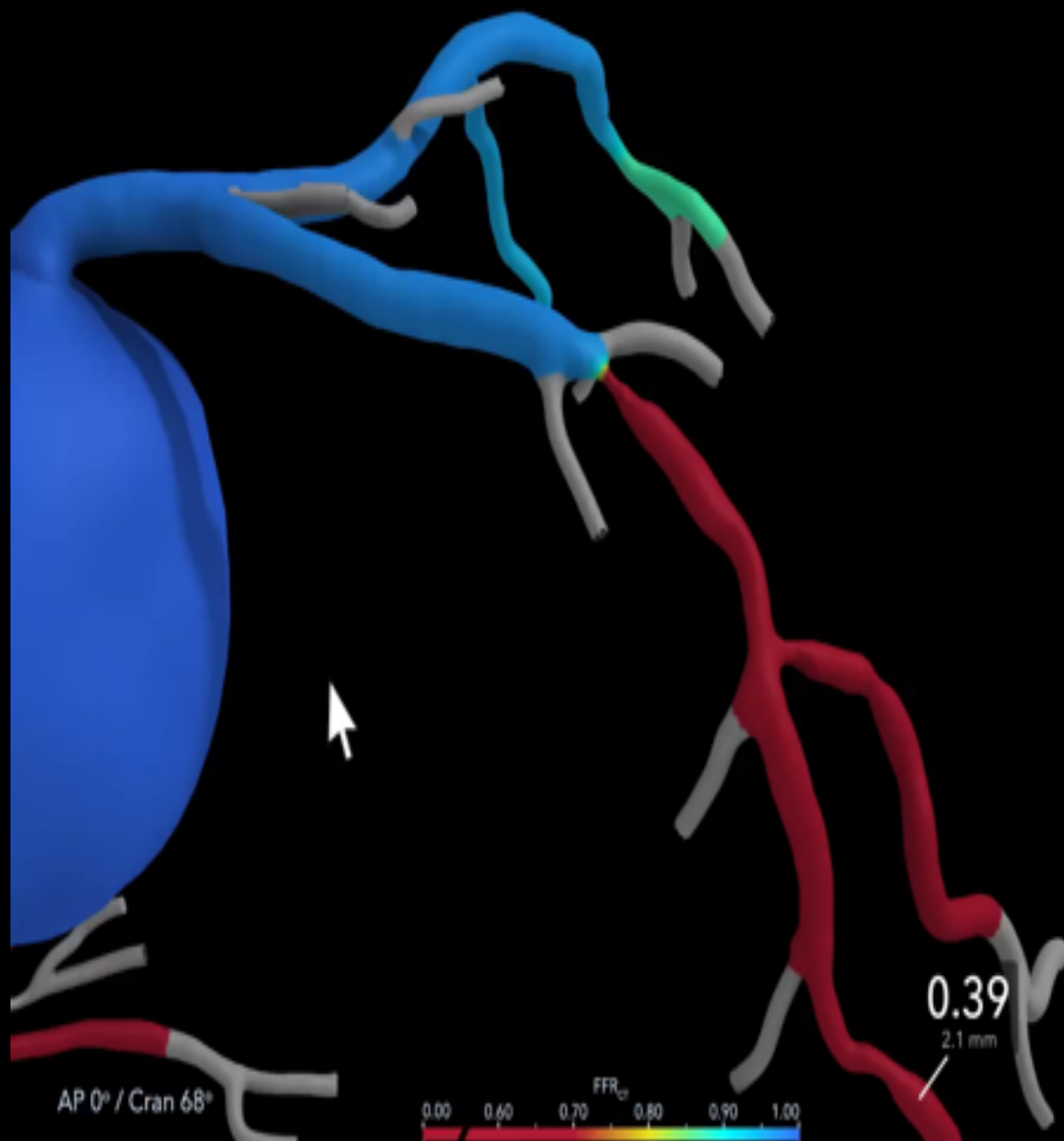
Ongoing trial: CABG Revolution

CABG without ICA



In patients with left main or three-vessel coronary artery disease, a heart team treatment decision-making based on coronary CTA showed an almost perfect agreement with the decision derived from conventional coronary angiography suggesting the potential feasibility of a treatment decision-making and planning based solely on this non-invasive imaging modality.

Non-invasive coronary physiology in PCI planning





Clinical Characteristics

Age 53 yrs, male, BMI 23.5 kg/m²

Medical history: Hypertension, post smoker

Echo EF 63%. Creatinine 1,04 mg/dl

CT acquisition

HR 47 /min

Nitrates: Nitroglycerin spray 0.8 mg (0.4mg x2)

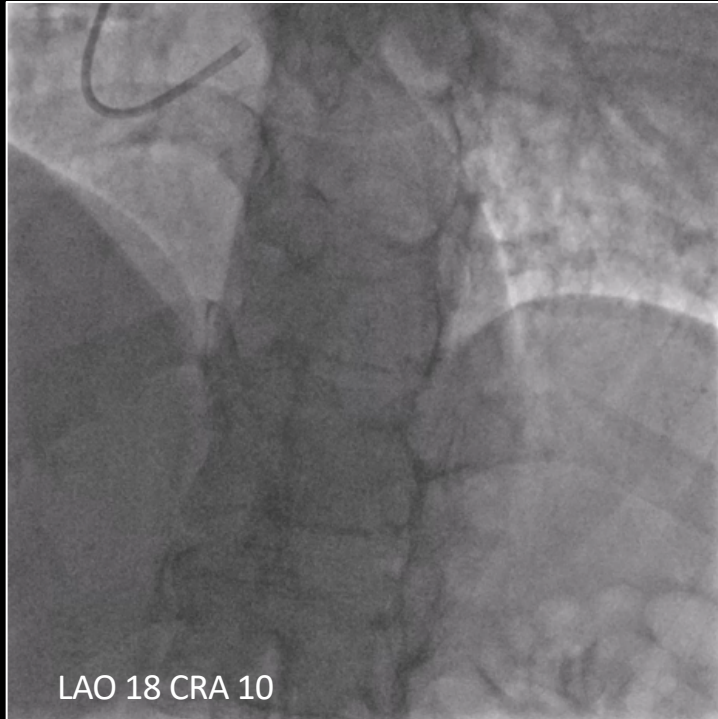
Radiation dose: Total DLP 160mGycm

Contrast: 100ml (Lomeron®350)

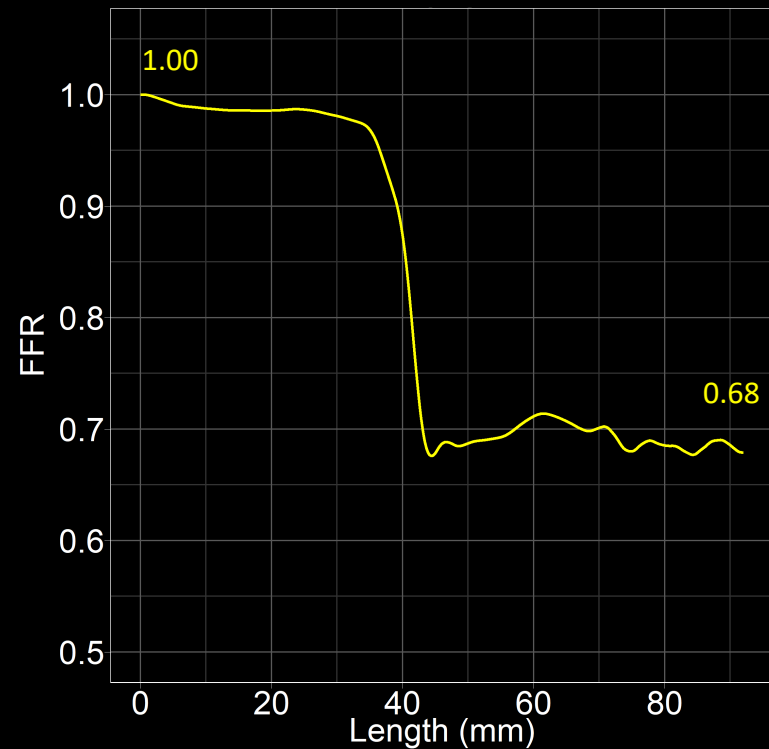
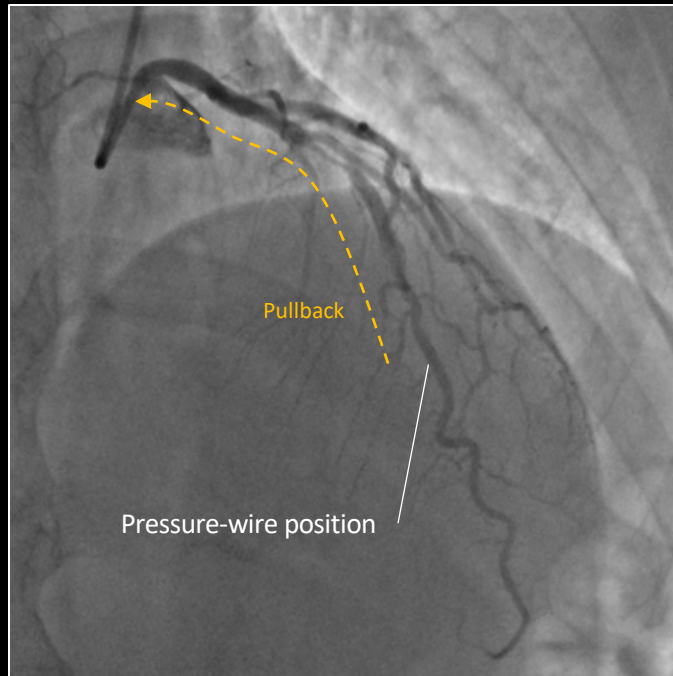
Conventional angiography



Conventional angiography



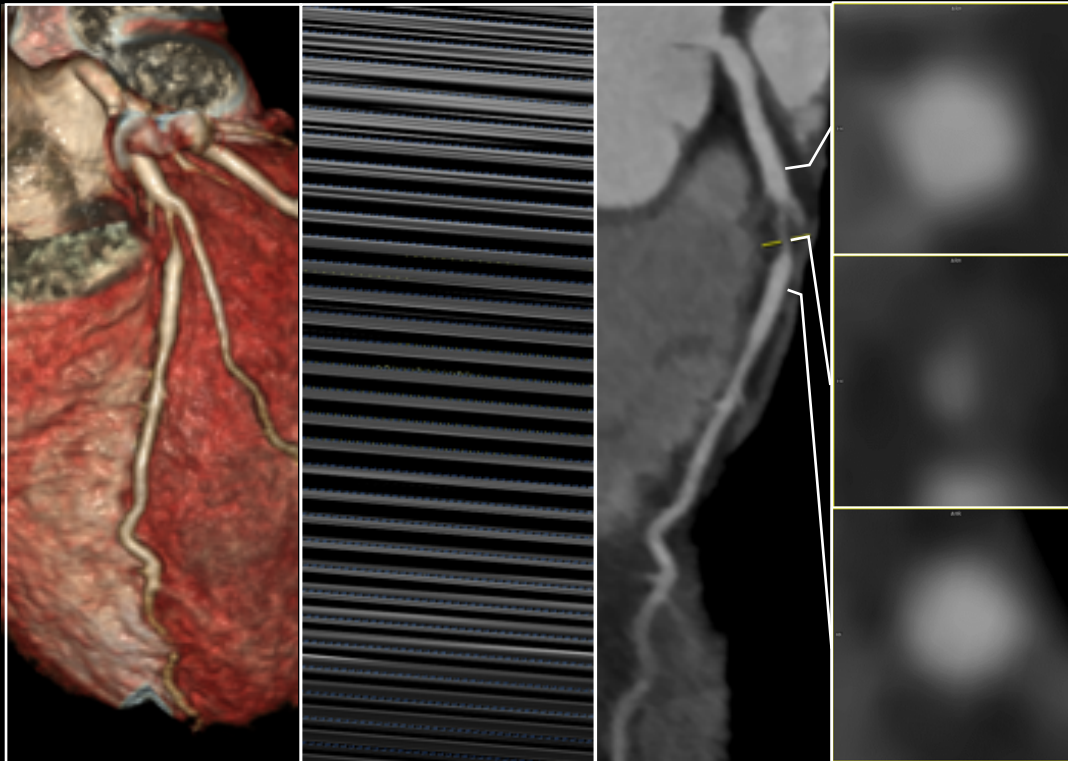
FFR pullback pre PCI



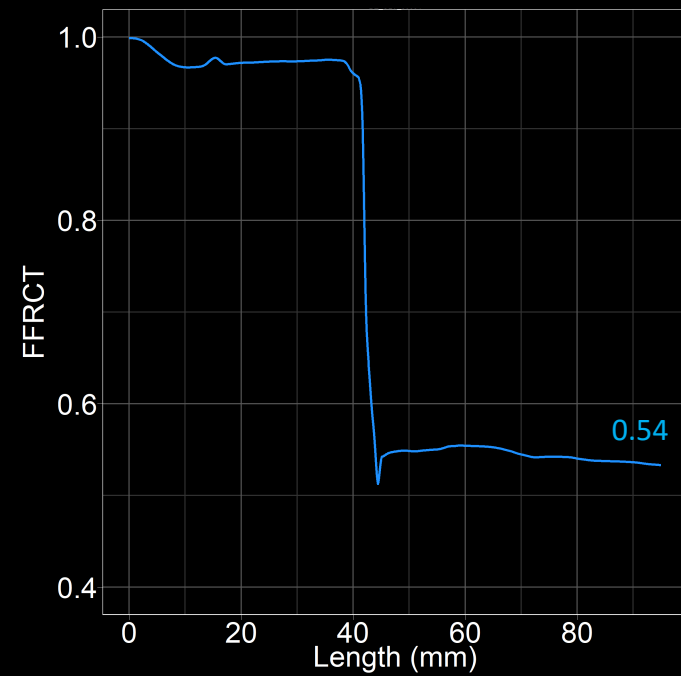
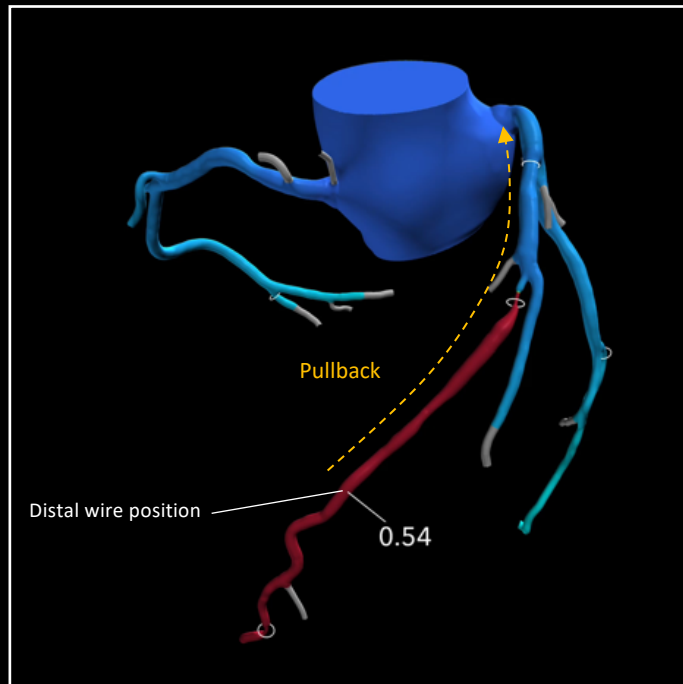
* Drift correction algorithm applied

Sonck et al. FFR pullback accuracy and reproducibility. Subm CCI

Coronary CTA

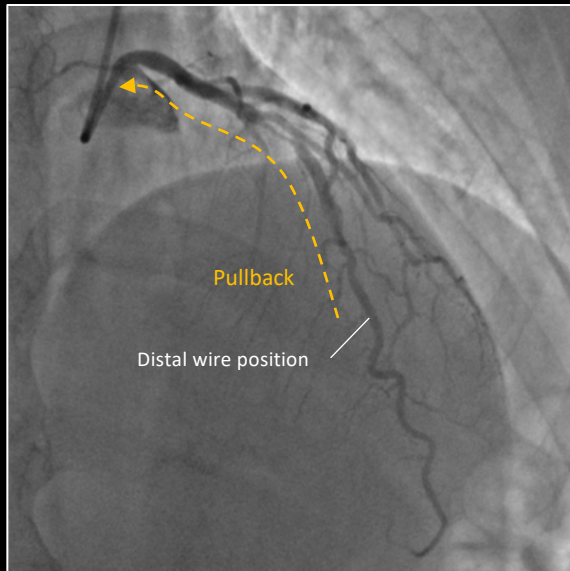


FFR_{CT} pullback pre PCI



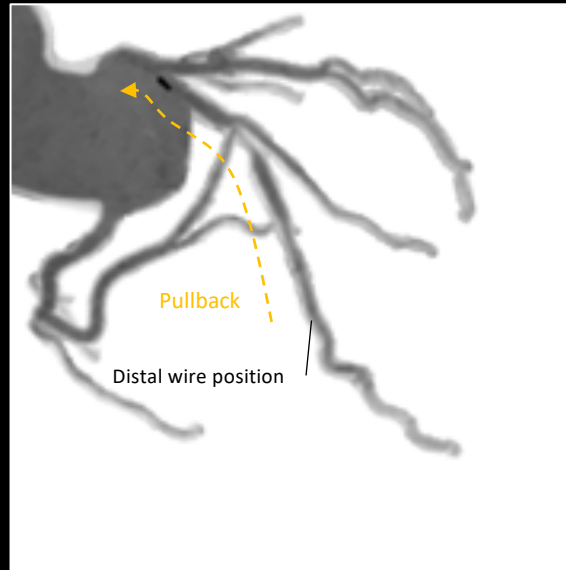
Co-localization using pressure-sensor position

Angiography



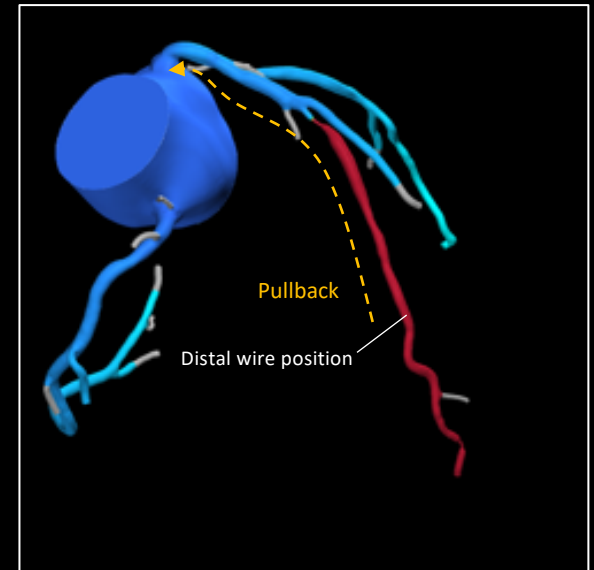
Pullback length in cath-lab: 92mm
Pullback length in core-lab: 92 mm

Coronary CTA



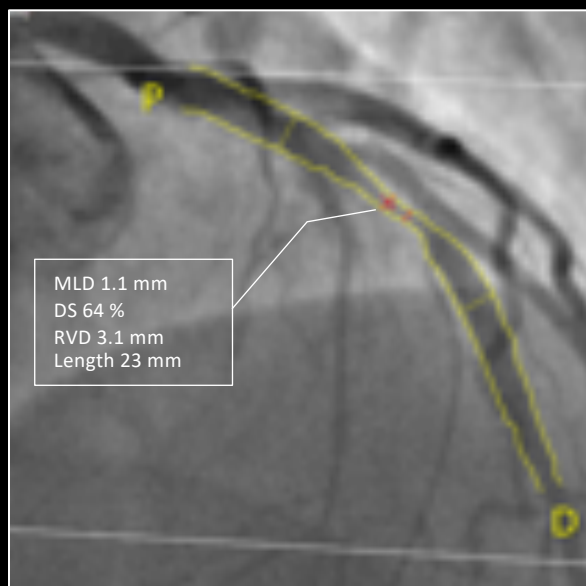
Pullback length in CTA: 87mm

FFR_{CT}

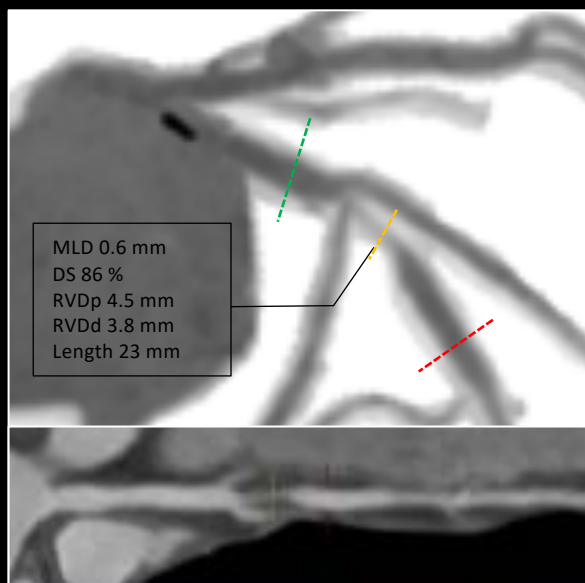


Pre PCI assessment

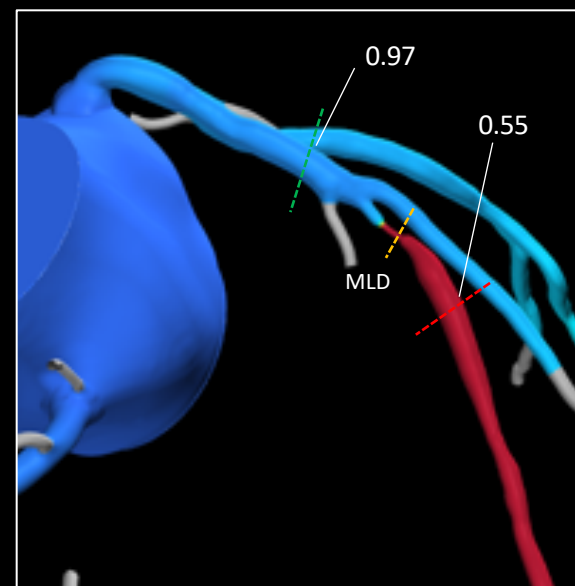
Angiography



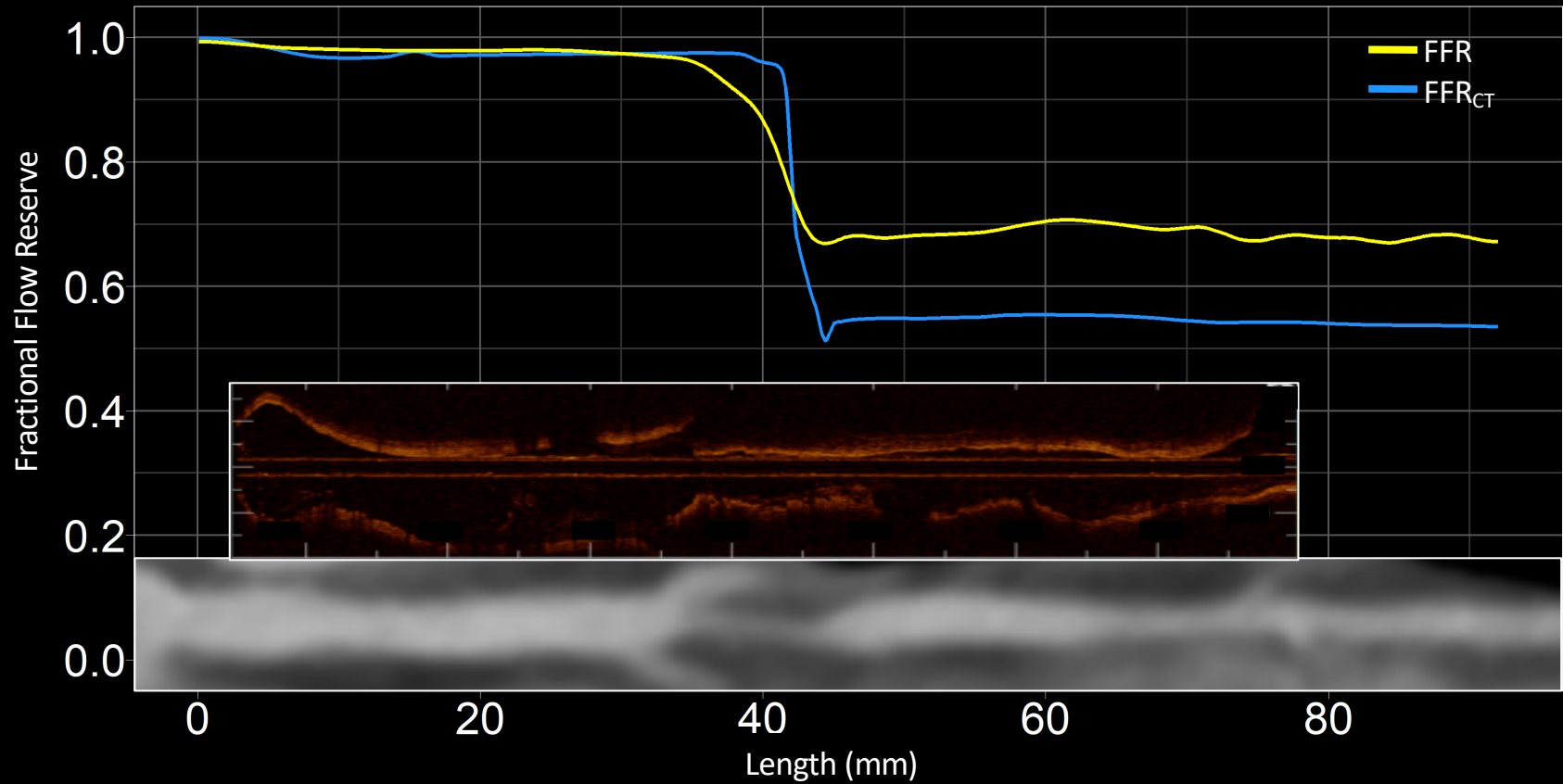
Coronary CTA



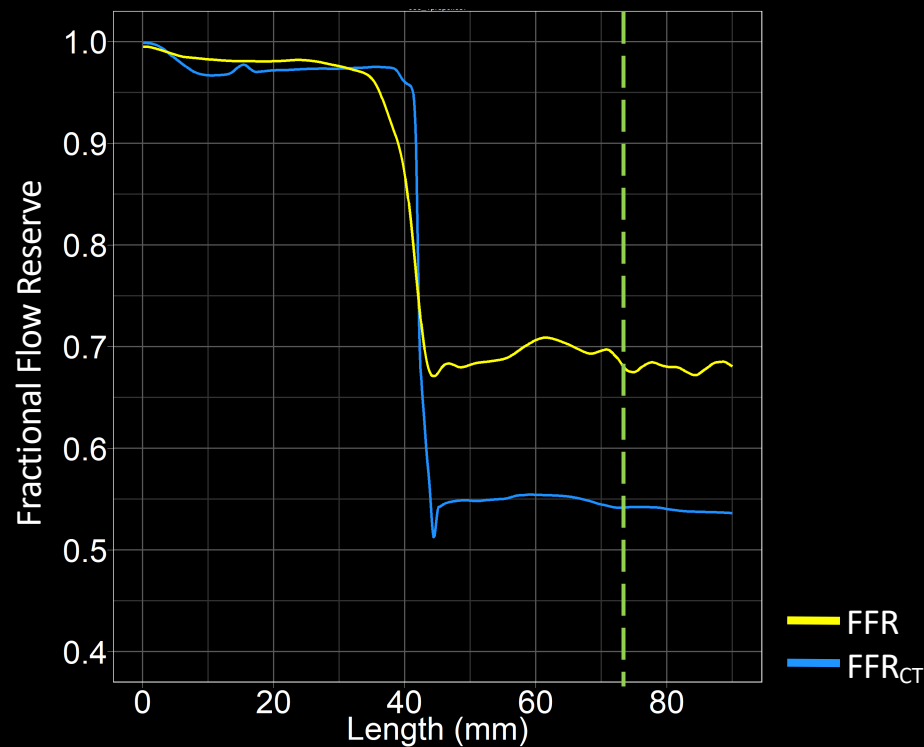
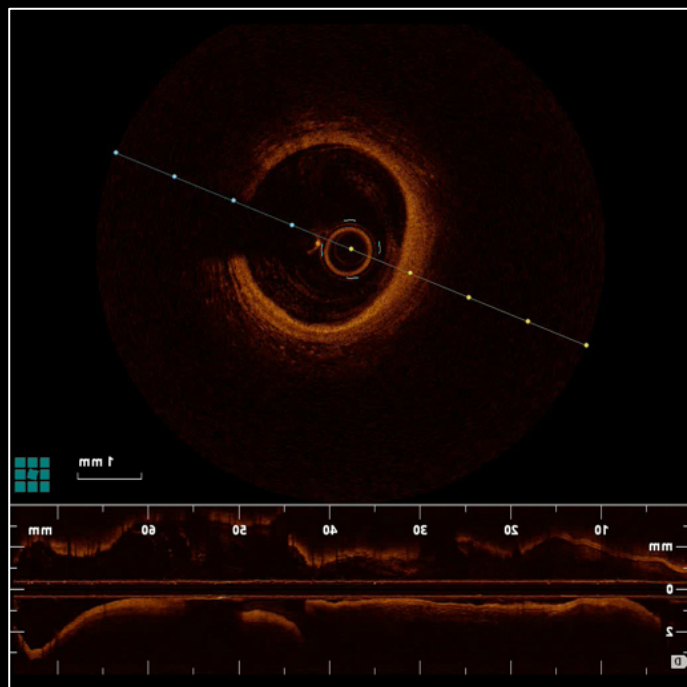
FFR_{CT}



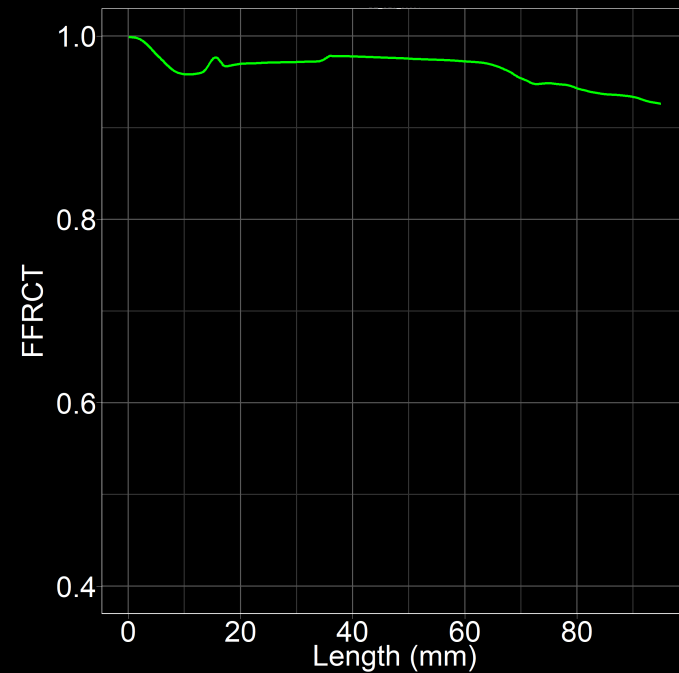
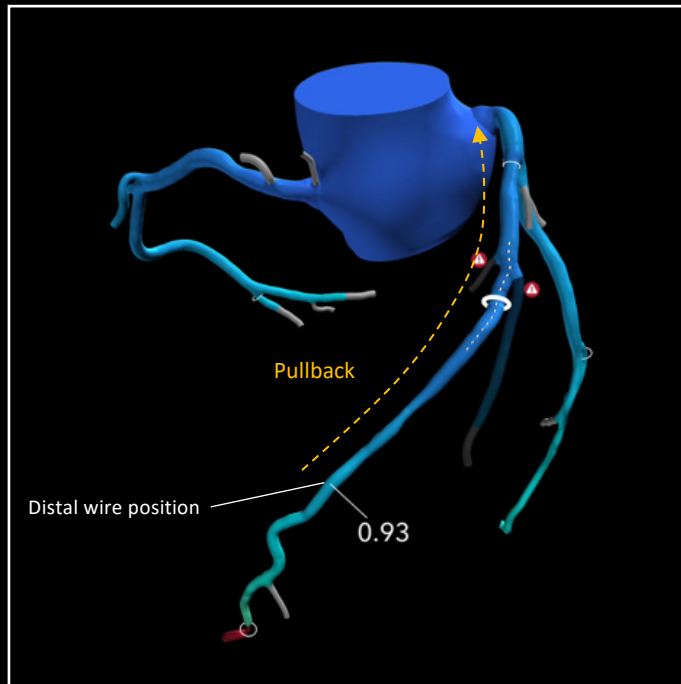
Pre PCI FFR_{CT} and FFR pullback



Comparison between FFR_{CT} and FFR pullbacks and OCT pre PCI



FFR_{CT} Planner



PCI



Stent Position

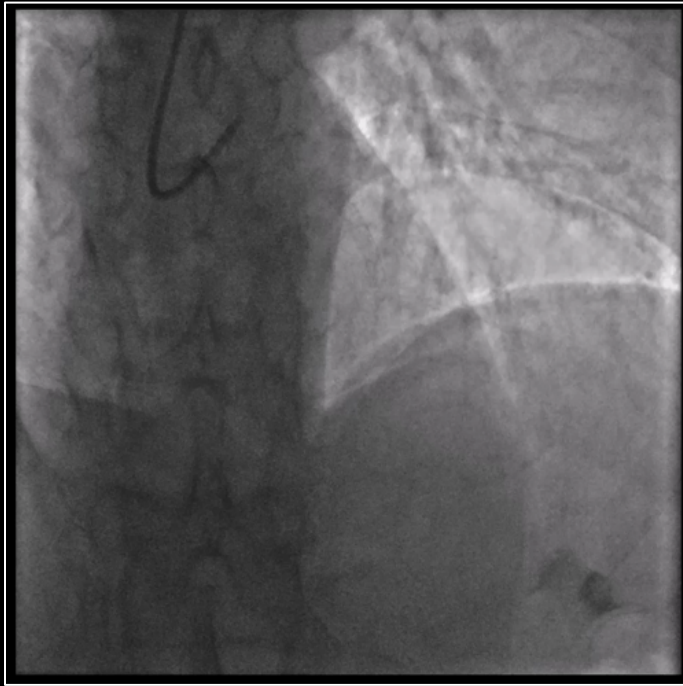


DES 3.5 x 23mm

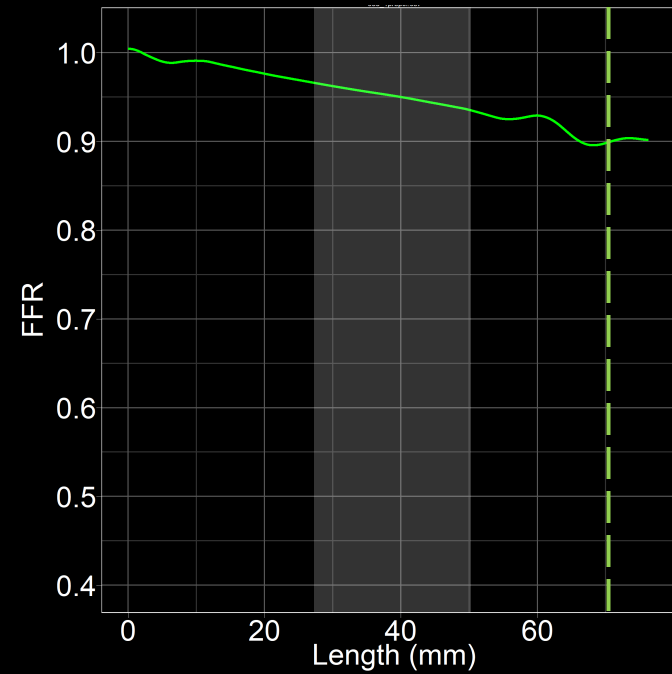
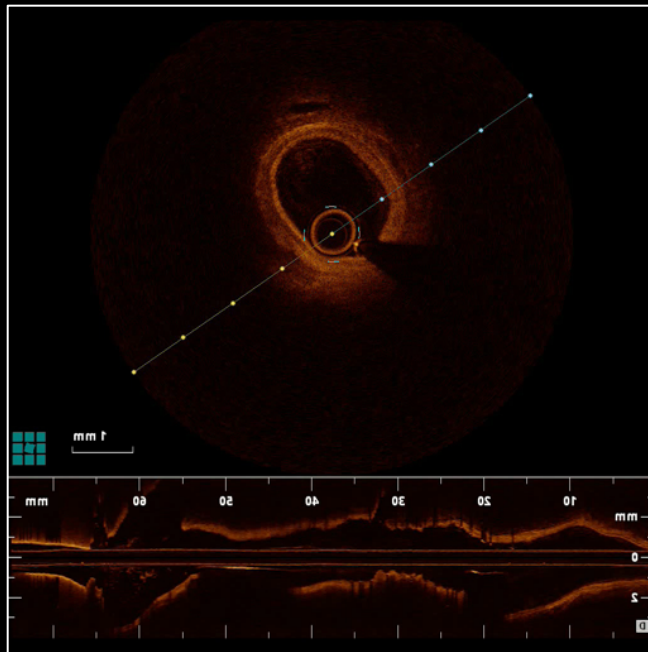


Angio result

Post PCI angiography

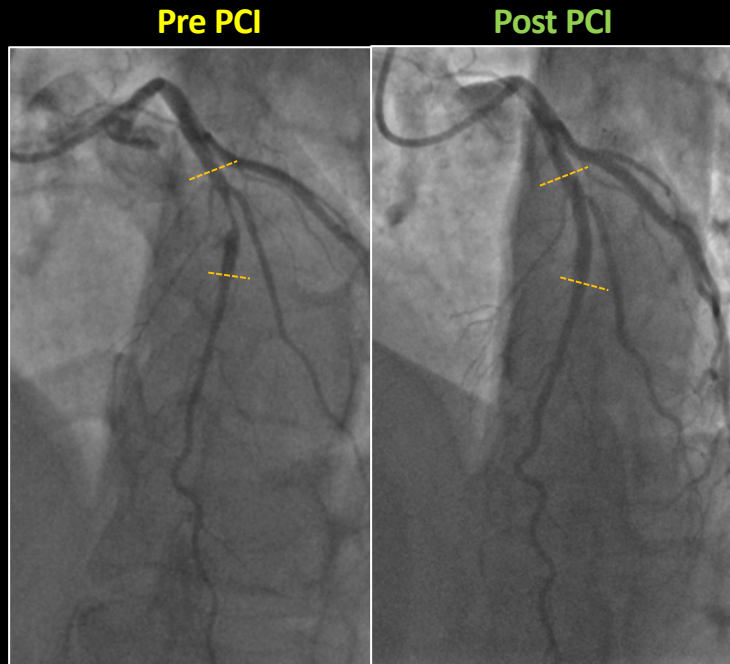


Comparison between FFR pullback and OCT post PCI

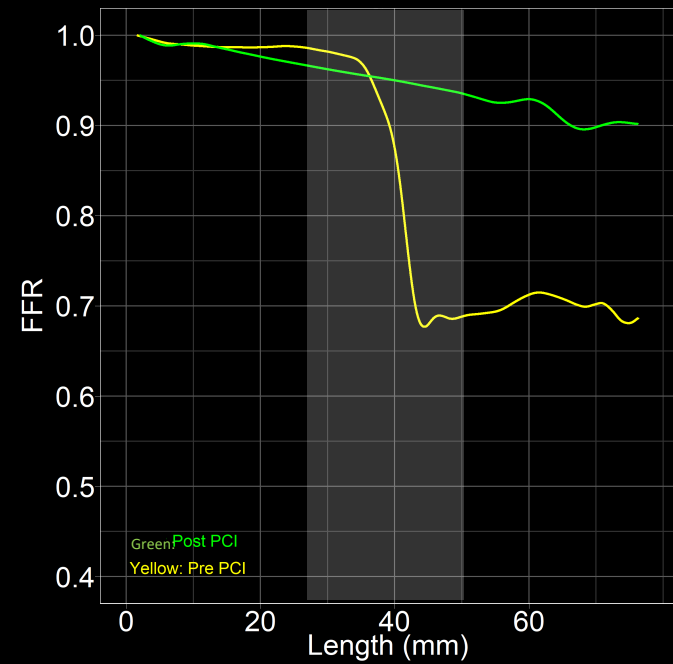


Shaded area: stent position

Comparison between invasive FFR pullback pre and post PCI



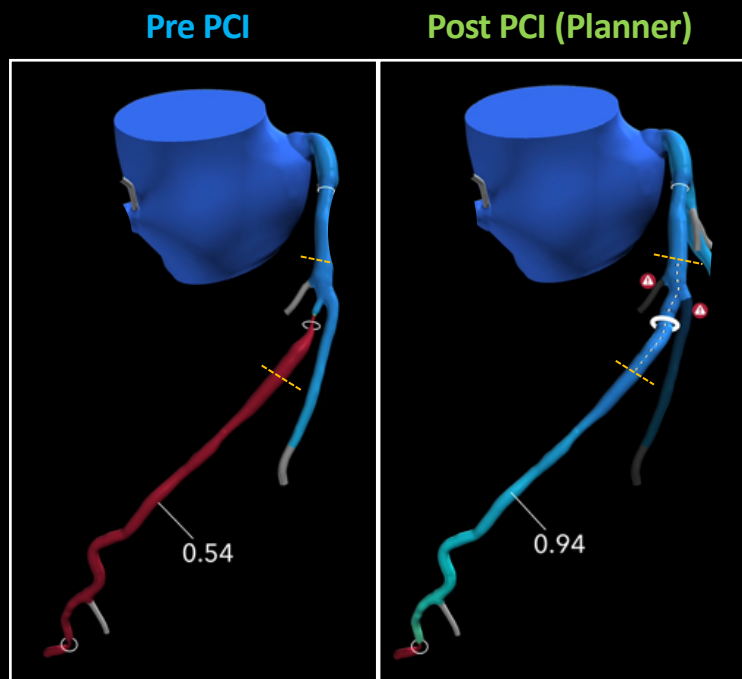
Dash line: edge of stent



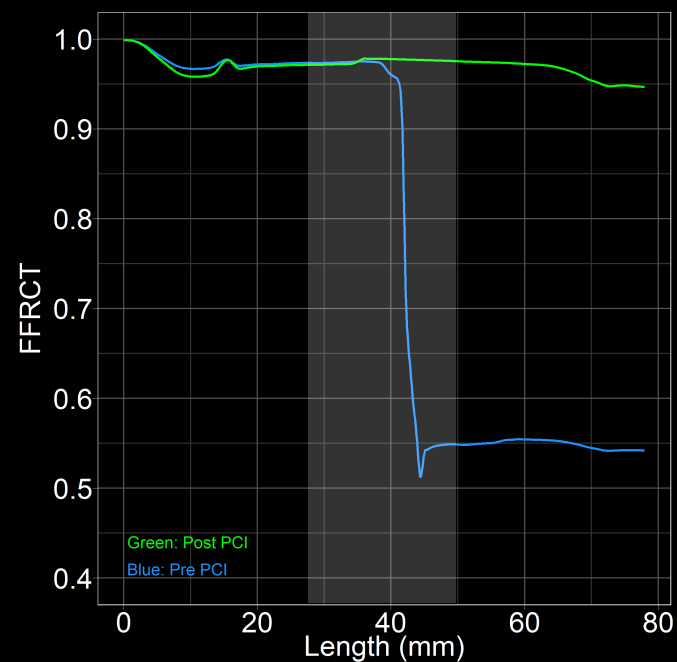
Shaded area: stent position

Comparison between FFR_{CT} pullback pre and post PCI

HeartFlow Planner

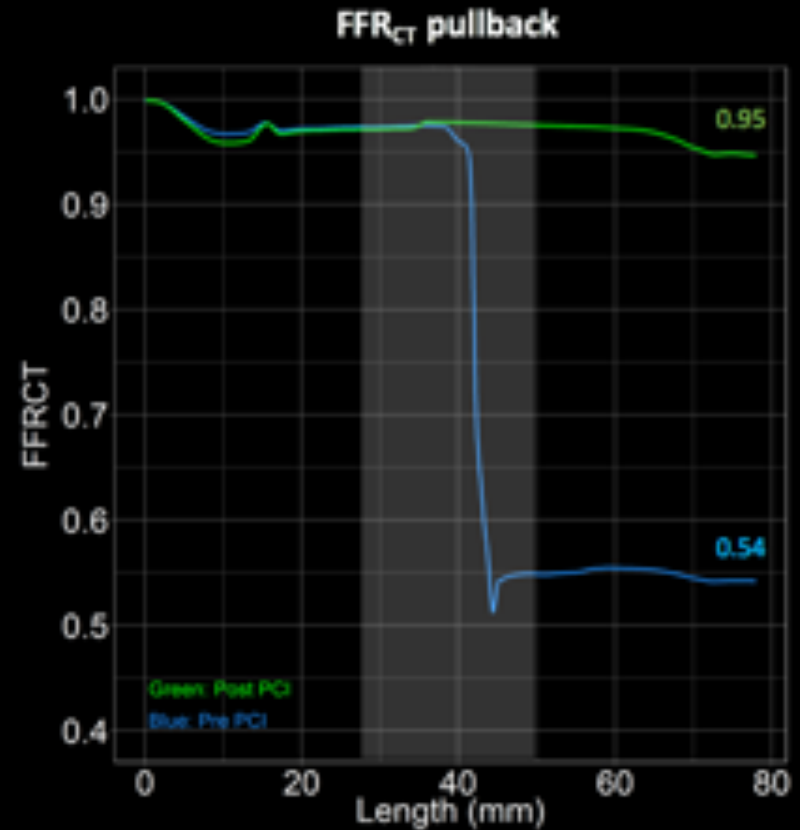
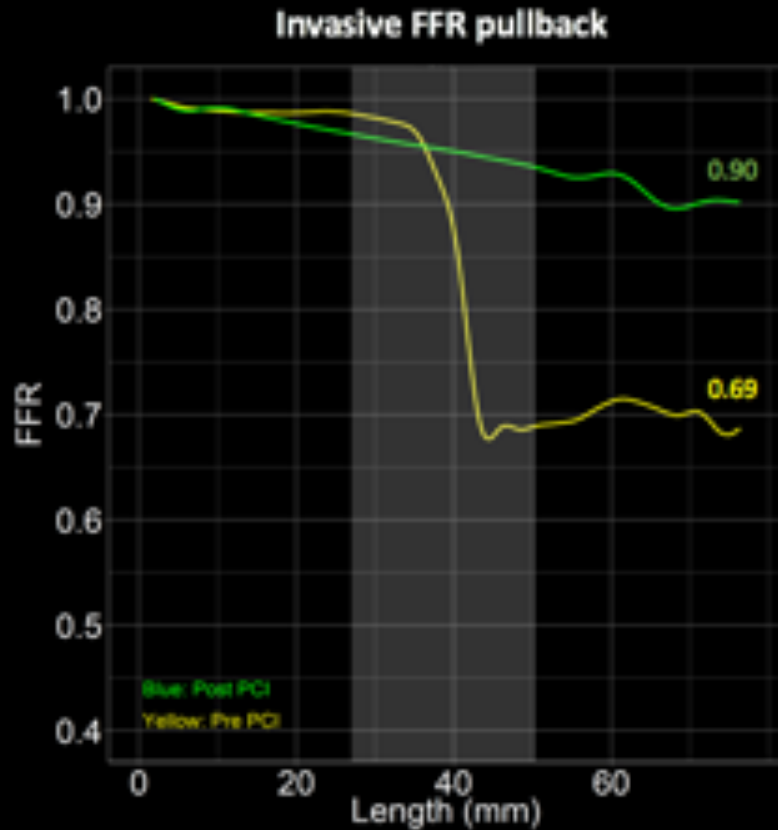


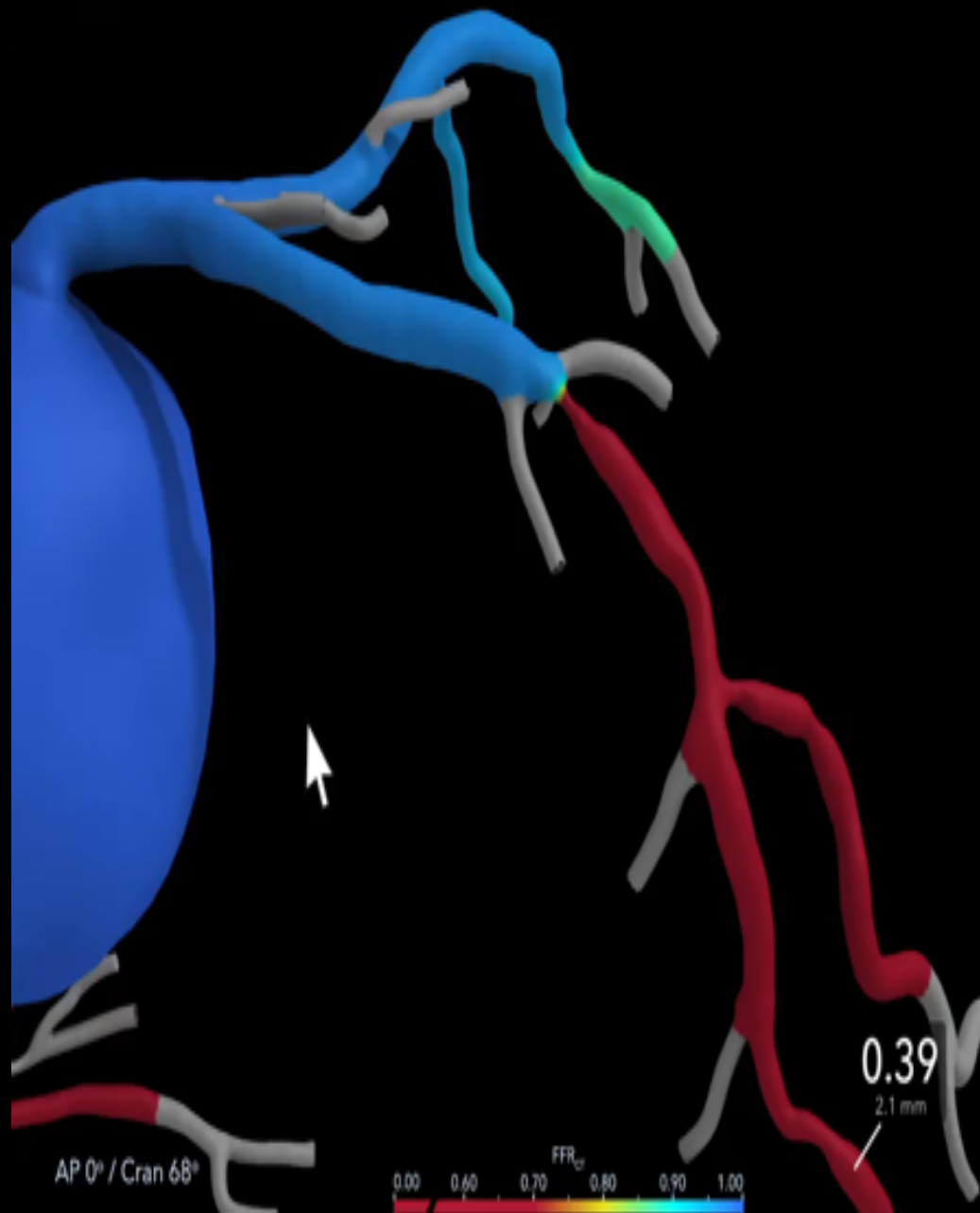
Dash line: edge of stent



Shaded area: stent position

Invasive FFR and HeartFlow Planner pre- and post-PCI





The future of FFR_{CT}:

- Mobile, On-Demand, Integrated & Interactive.
- Refine risk stratification with coronary physiology parameters on top of anatomy and known adverse plaque characteristics.
- May allow for decision-making between CABG and PCI and treatment planning in the non-invasive setting.
- Guide which lesions require an invasive assessment in the lab and select the optimal revascularization strategy.
- Improve cathlab efficiency.

