

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.



ORIGINAL ARTICLE

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[®]







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 which patients may benefit from revascularization using percutaneous based therapies.





lesions with FFR>0.8

posite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. (ClinicalTrials.gov number, NCT06267774.)

Tonino et al. NEJM 2009, 360: 213

TO NEW ENGLAND POTENAL OF MEDICINE



ORIGINAL ARTICLE

Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

Perform PCI for lesions with FFR≤0.8

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 swascularization 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; IAME 2 ClinicalTrials.gov number, NCI01132405.)

Xaplanteris et al. NEJM 2018



1001



180

Days since Randomization

3 68

366

1240



MACE



Myocardial infarction



Xaplanteris P et al. NEJM 2018



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 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 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

0.92

0.94

89.0

0.98

0.92

post-PCI FFR

0.94

0.96

P < .0001

1.00

P = .0013

1.00

0.98

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





From 3D Patient Specific Geometry to FFR_{CT}





FFR_{CT}: The white box



(c) Acquisition or coronary compute comparison comparison comparison (c) (c) (c) coronary artery segmentation to become and time-order vesses; and (c) application or subwool resolution techniques. In this example, a cross-section of a coronary artery segmentation by take (left) and (left) and (lata (left) dilustrates 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 testhadedal vertices are reconstructed in 3 dimensions and are continuous even at the branch points to accurately calculate coronary computed tomography angiographyderived fractional flow reserve (FFR_C) at these areas commonly affected by plaque. Reduced order methods that do not us 3-dimensional angies are less accurate at these points. (C) Relationship of the location and size of coronary resistance index at a adenosine dose of 140 µg/lsg/lmin (Wilson et al. (25)), (IO 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_C).





The FFR_{CT} Analysis Process



FFR_{CT} 3D patient specific model





FFR_{CT} studies

		Sites	Regions	Study Design	Population	PE Published	FFRct 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 FFRcr 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 FFRcT 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 FFRcr 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 ± FFRcr instead of usual care on ICA showing no obstructive disease
RIPCORD FFRct	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 + FFRcτ
PROMISE FFRct 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 FFRcr 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 FFRct
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 + FFRct, 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 + FFRcr or conventional angiography
PACIFIC FFRct 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 FFRcr using invasive FFR as the gold standard, and compare to cCTA, SPECT, and [¹⁵ O]H2O PET.



Non-invasive coronary physiology on top of plaque evaluation



Plaque Assessment





High Risk Plaques and Clinical Outcomes

Low attenuation plaque. Positive remodeling. Spotty calcification

Cite: Anarican College of Cardinings In the American College of Cardinings Provide

Computed Tomographic Angiography Characteristics of Atherosclerotic Plagues Subsequently Resulting in Acute Coronary S)

Salako Monwama, MD, PrD,9 Masaroshi Sarai, MD, PrD,9 Hinno ofani Anno, MD, PriD, F Kaori Inova, MD," Tomonori Han, MD, Jurichi Ishii, MD, PriD,* Himshi Hishida, MD, PriD,* Nathan D. Wu Takeshi Kondo, MD, PrD. [Takio Onaki, MD, PrD,* Japat Naralu, N Tsynah and Tahashi, Japan Insins, Galifernia; and Galifersharg, Maryla

Operation	It is computed torongogiths (CC engineering to state, we described in that were prescripted with subsequent investigation of acute process
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In 1,050 patients who protowers (1) anglegicades, attorneous rest ne. Fil and U.W. The nerved-tring index, and plaque and U.W. an a characteristics of instance resulting in IGS starting the follow-a

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properties relation to AUX has not inser produced, theories.

The automa demonstration and who remaining and we append at ent a higher that of ACS booking over time when compared with a schematics. () fore Carl Careful 2008/06/08 (7) () 2008 by the day

requiption (CTD) anging mphy is a samilal tool. Comparing to only concern and provide a second problem of the seco calcined plaques (NC) CT anging up to an annual (27/28) - units scherotic plaques (2) dag (PR) (34). The odpek heires characteristically

tarietics on CT angin Control of the successor of accharacteristics in the p installer (17.30) 8 graphic findings in schemelic plaques in on the presence of 21

2009

Napkin-Ring Sign on Coronary CT Angiography for the Prediction of Acute Coronary Syndrome

Kenichiro Osuka, MD,⁴ Shota Fukuda, MD,4 Atsubi Tataka, MD,8 Hanouki Tagushi, MD,9 Junishi Yoshikawa, MD,9 Kenzi Shimada, N Minora Toshiyama, MDP Oaks. Tanah, and Nubinemits, Jahan

OBJECTIVES. The aim of this study was to determine the predictive valon coronary computed tomography angiography ICTXL for future acute corons in patients with coronary artery disease.

BACKGROUND. Room statles have reported a close association between coronary CTA and thin-cap fibroatheroma.

METHODS The subjects of this prospective study were BHS connecal went coronary CTR examination and were followed for >1 year. The prime event loandiac death, nonfatal mysolandial infanction, or unstable angina per analysis included the presence of obstructive plaque, positive remodels plaque (LAP), and the napkin-ring sign. The napkin-ring sign was defined 1) the presence of a ring of high attenuation around cartain coronary attenuation of the ring presenting higher than those of the adjacent Hoursfield units.

RESULTS Of the 12,727 segments, 1,174 plaques were observed, inclu 138 segments (1.0%), LAP in 107 segments (0.8%), and napkin-ring sign Thirty-six of the 45 plaques with sapkin-ring signs (80%) overlapped with or LAP. During the follow-up period (2.3 ± 0.8 years), 24 patients (2.8%) and plaques developed in 67% with a naphin-ting sign. Segment-based (models analysis showed that PH (p < 0.001), LAP (p = 0.007), and the naple were independent predictive factors for future ACS events. Kaplan Weier at plaques with napkin-sing signs showed a higher risk of ACS events companapkin-ring sign.

CONCLUSIONS The present study demonstrated for the first time t demonstrated on conseary CTA was strongly associated with Subare ACL ever high-risk conseary CTA features. Detection of the napkin-ring sign could hel disease patients at high risk of future ACS events. () Am Coll Cardiol Img 201 American Callege of Candiology Foundation



DESIGNAL INVESTIGATIONS

Plague Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up

Table Mercury, MJ, N.J.-Y Haine In, MJ, N.J.-Messenit Levi, MJ, Role Talenk Keels, MJ, Role Balle Rawa, MD, Feller Tanamitt Nagelanis, MD, "Biole Tangapa, MD, Feller's Blanc Raw, MD, Indiana Rawa, ND, Feller, Howert Tabalanda, Str. J. Biowedd Rawaw, ND, Feller's Schler Tanish India, ND, Feller Wenny Therby, MD, Lander J. Sawa, PALAY Falls (Statistical, ND, Feller), Sagar Katala, ND, Feller Kong, Tanish, MD, Lander J. Sawa, PALAY Falls (Statistical, ND, Feller), Sagar Katala, ND, Feller Kong, Nather, ND, Feller, Sawa, PALAY Falls (Statistical, ND, Feller), Sawa, S

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LAD #6





2015

Low Attenuation Plaques

Voxel with HU< 30



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





Identification of High Risk Plaques



Adverse Hemodynamic characteristics (AHC) defined as lesions that have low FFR_{CT} (<0.80), high Δ FFR_{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



Number & location of lesions

Dominance

Left Main

Calcification

SYNTAX Score

Thrombus

Total Occlusion

3 Vessel

Bifurcation

Tortuosity

 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

Serruys P et al. NEJM 2009;360:961.



SYNTAX Score and Clinical Outcomes



Mohr et al. Lancet. 2013 Feb 23;381(9867):629-38.

PCI



Study name

CTA vs. Angiography: SYNTAX Score Calculation

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

	Difference in means	Lower limit	Upper limit	p-Value	Relative weight	
Papdopoulou e	et al2.5	-7.2	2.2	0.302	9.4%	
Suh et al.	0.0	-1.1	1.1	1.000	17%	
Shalev et al.	0.7	-0.6	2.0	0.291	16.8%	
Pozo et al.	3.0	-1.2	7.2	0.171	10.3%	
Kerner et al.	-1.9	-4.2	0.4	0.118	14.6%	
Yüceler et al.	-0.4	-2.8	2.0	0.751	14.4%	
Wolny et al.	4.5	3.5	5.4	0.000	17.3%	
Summary	0.6	-1.4	2.7	0.553		

Statistics for each study

Random effect-model Heterogeneity Cochran Q= 56.9, I² 57%, p 0.0001

Difference in means and 95% CI



Coronary CTA – Angiography SYNTAX Score

Collet et al. Cardiovasc Diagn Ther. 2017 Apr;7(2):151-158.





Non-Invasive FFR_{CT}



















MSCT Assessment 3D - Maximum Intensity Projection (MIP)

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



CT-derived SYNTAX score

RCA



LAD





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







Segment $1 = 2 \rightarrow 0$ points

Segment 1 ostial = $3 \rightarrow 0$ points



Segment 7, >20 mm = 5 points



Segment 7 = 6 pts

Segment 11, 12a 1.1.1 <70° = 8 points



Functional SYNTAX Score

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

Total functional SYNTAX score 19 points

SYNTAX score II and Treatment Recommendation

Variables	Input	PCI		
Functional CT SYNTAX	19	SYNTAX Score II 38.7		
Score I	19	PCI 4 Year Mortality 13.6%		
Age	74	CABG		
CrCl ml/min	38	SYNTAX Score II 36.7		
LVEF(%)	50	CABG 4 Year 11.6%		
Left Main	No	Horeancy		
Gender	Male	Recommendation		
COPD	No	CABG or PCI		
PVD	No	www.syntaxscore.com		



Decision Monzino



Angiogram Assessment

Angio-derived SYNTAX score



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	PCI		
Angio Syntay	20	SYNTAX Score II	38.9	
Score I	20	PCI 4 Year Mortality	13.9%	
Age	74	CABG		
CrCl ml/min	38	SYNTAX Score II	36.6	
LVEF(%)	50	CABG 4 Year Mortality	11.6%	
Left Main	No	Mortancy		
Gender	Male	Recommendation		
COPD	No	CABG or PCI		
PVD	No	www.syntaxscore.com		



Decision Brussels







Anatomical SYNTAX score and SYNTAX score II







SYNTAX III Revolution Primary End-Point

	Heart team treatme based on coro tomography				
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







Pre PCI assessment

AngiographyCoronary CTAFFRctImage: Distance of the second seco





Pre PCI FFR_{CT} and FFR pullback







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







FFR_{CT} Planner













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



1.0 0.9 0.8 0.7 0.6 0.5 0.4 CreenPost PCI 0.4 0 20 40 mm

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

Invasive FFR pullback 1.0 0.90 0.9 0.8 0.69 ¥ 0.7 0.6 0.5 Blue: Post PCI Yellow: Pre PCI 0.4 40 Length (mm) 0 20 60



FFR_{ct} pullback













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.



