Noninvasive Fractional Flow Reserve from Coronary CT Angiography

Bon-Kwon Koo, MD, PhD

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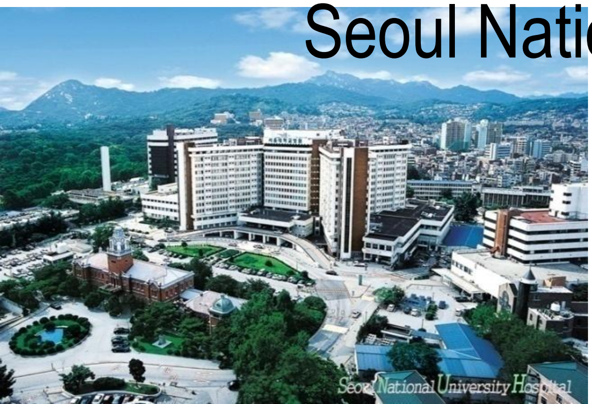
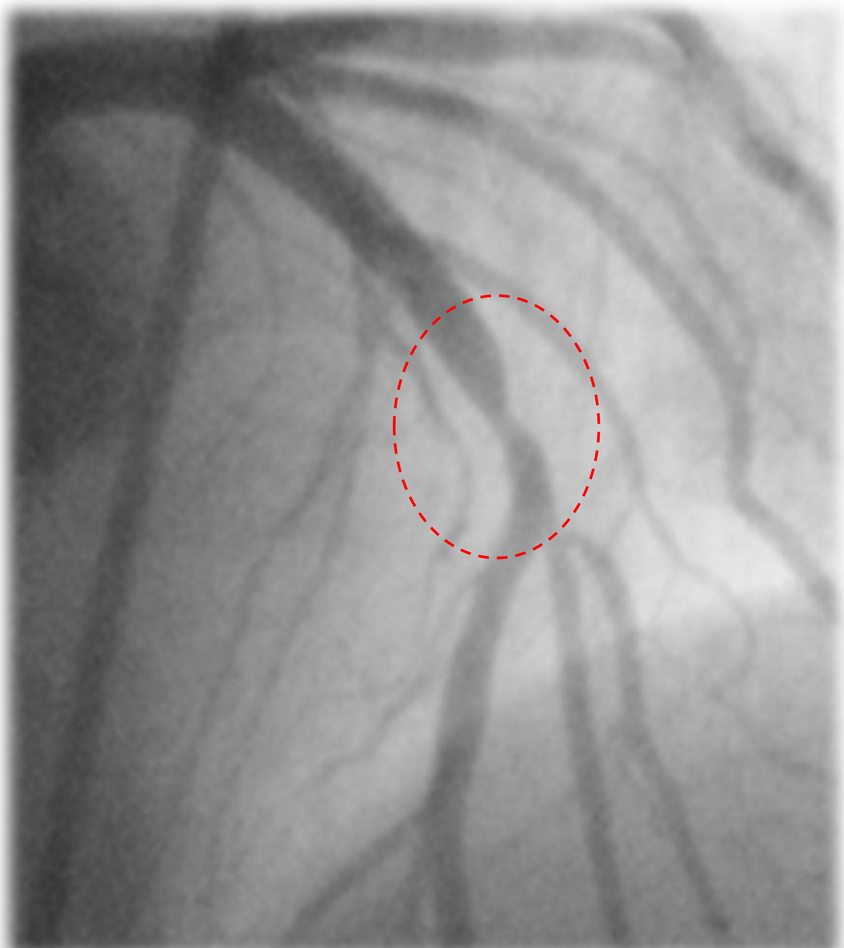
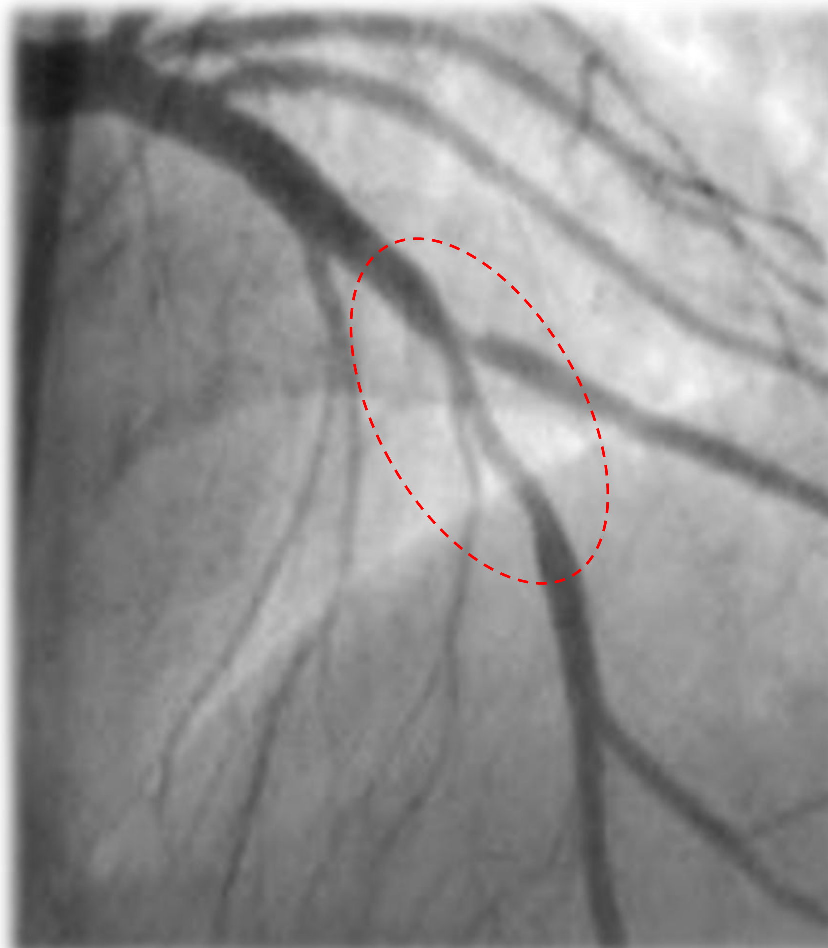


Why the hemodynamics for coronary artery disease?

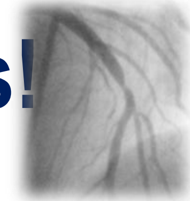
Q: Which is a significant stenosis? Please choose one.

Coronary angiogram: left anterior descending coronary artery





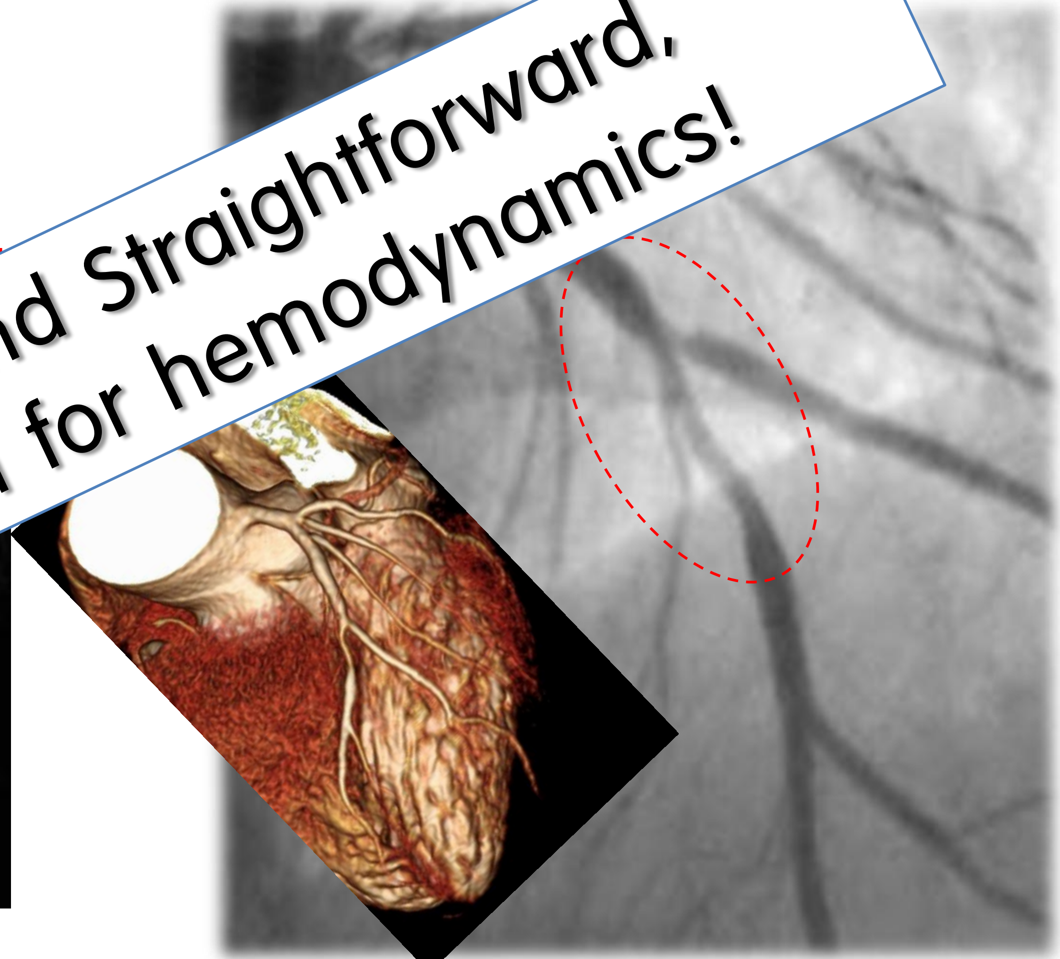
This one should be a significant stenosis!



Angiography: significant

CT angiography: significant

Intravascular ultrasound: signi

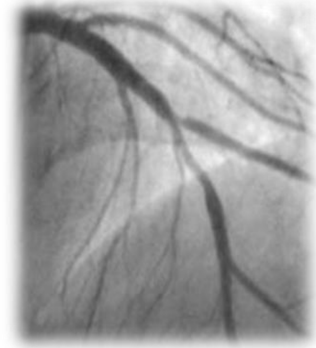


Simple and Straightforward,
No room for hemodynamics!

Significant stenosis → Ischemia/Chest pain → Stent or surgery → Better prognosis

Which is a significant stenosis?

: Anatomy ***vs. Ischemia***



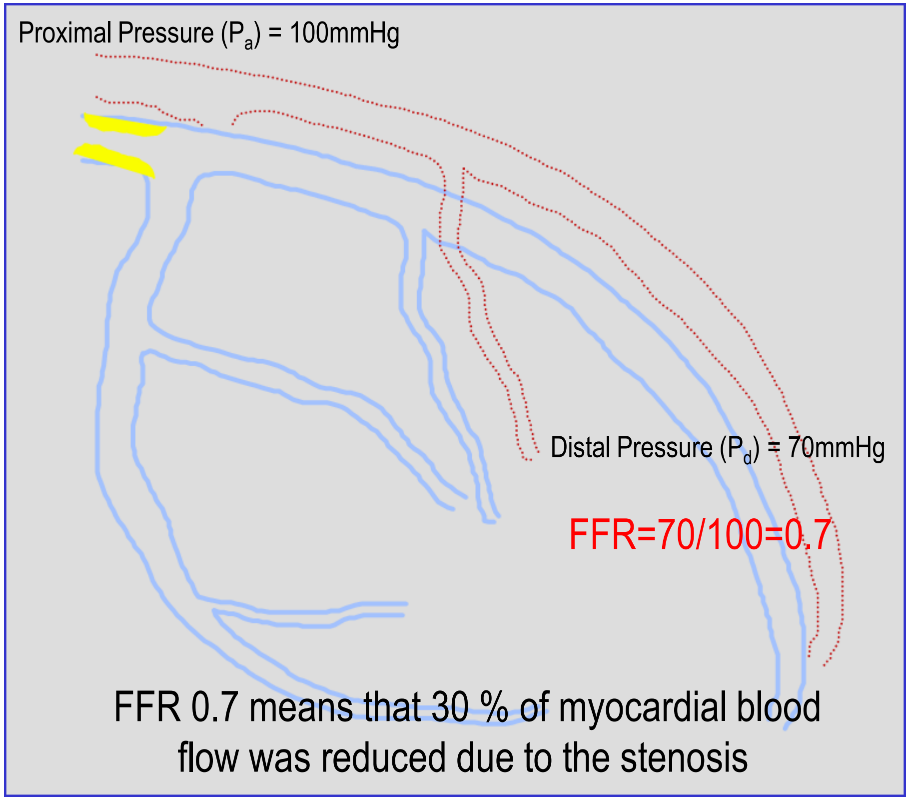
- Stenosis severity by CT, angiography, intravascular US, ...
- Extent of the perfusion territory
- Presence of myocardial infarction
- Myocardial blood flow including collaterals
- Microvascular function

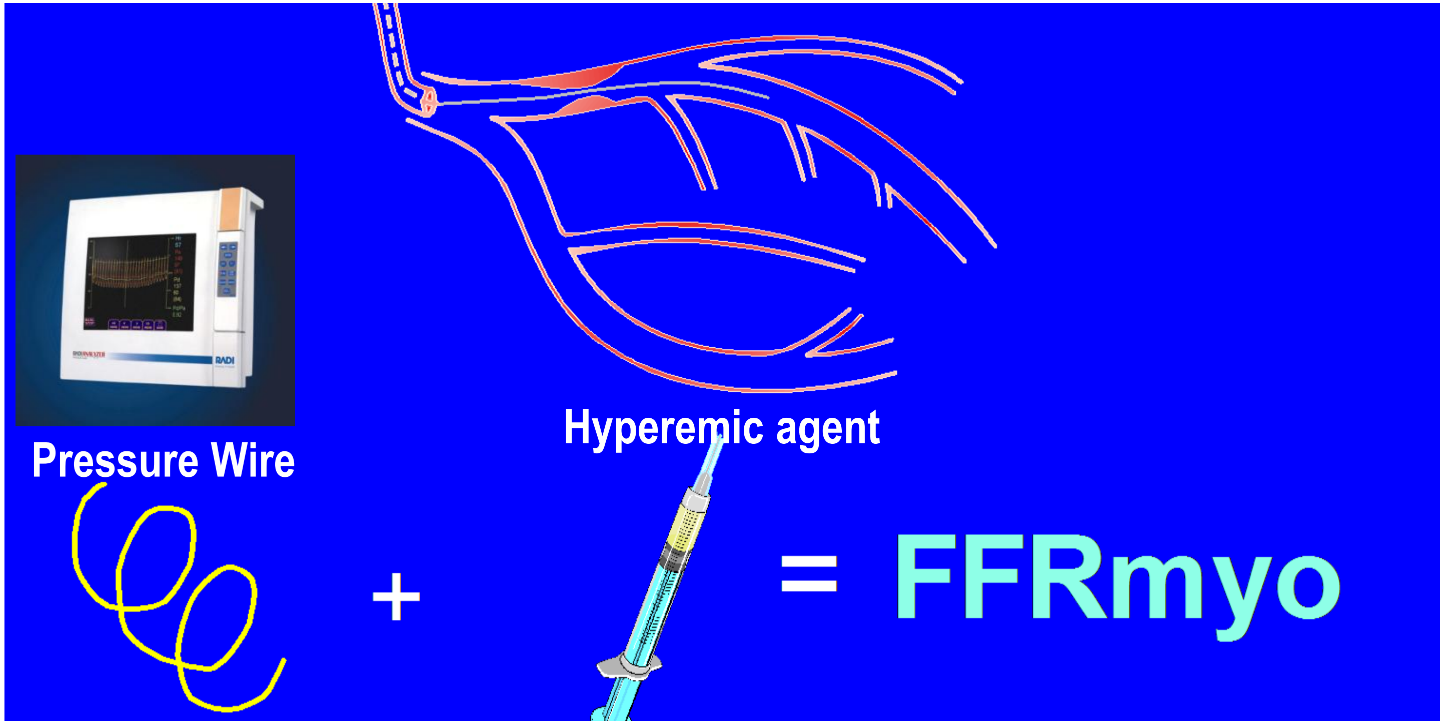
→ ***Physiologic or functional evaluation***

"Fractional Flow Reserve (FFR)"

- Invasive physiologic test in a cath lab with very high spatial resolution

$$FFR = \frac{\text{Maximum flow in presence of stenosis}}{\text{Normal maximum flow}} = \frac{Q^S_{max}}{Q^N_{max}} = \frac{(Pd-Pv)/R}{(Pa-Pv)/R} = \frac{\text{Distal Pr } (P_d)}{\text{Proximal Pr } (P_a)}$$

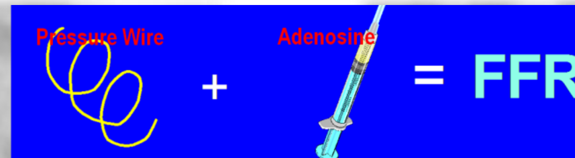


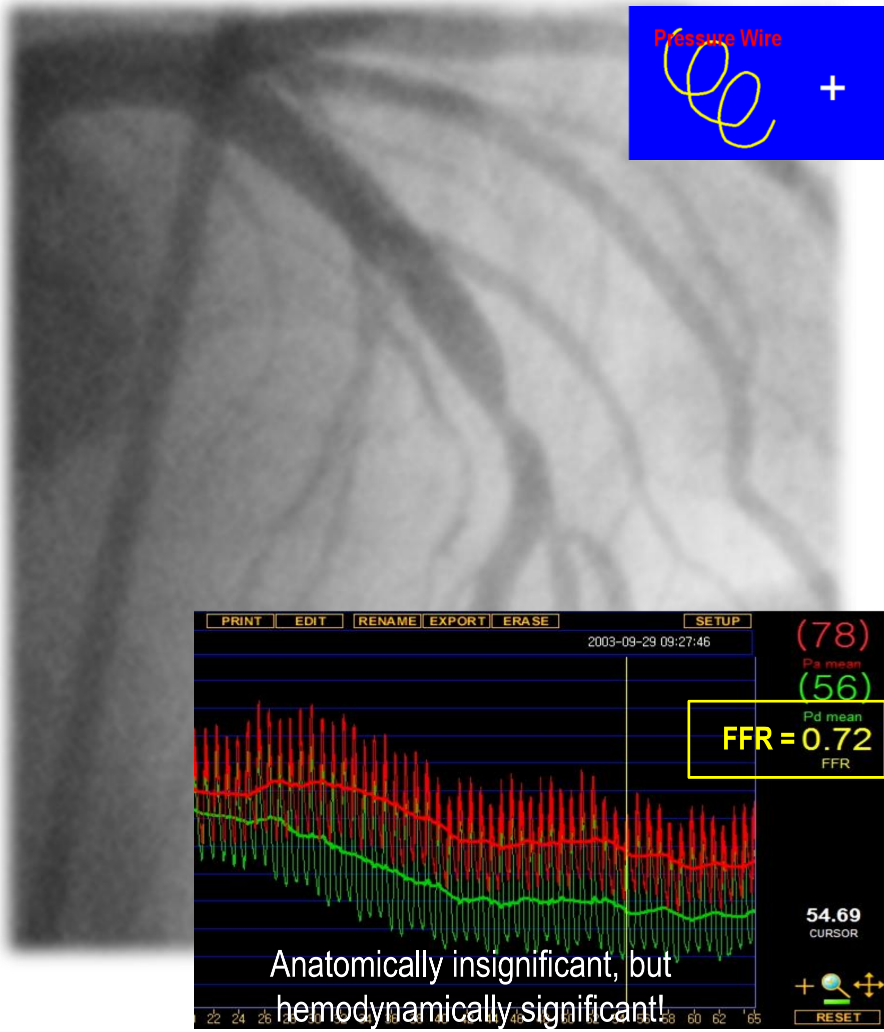


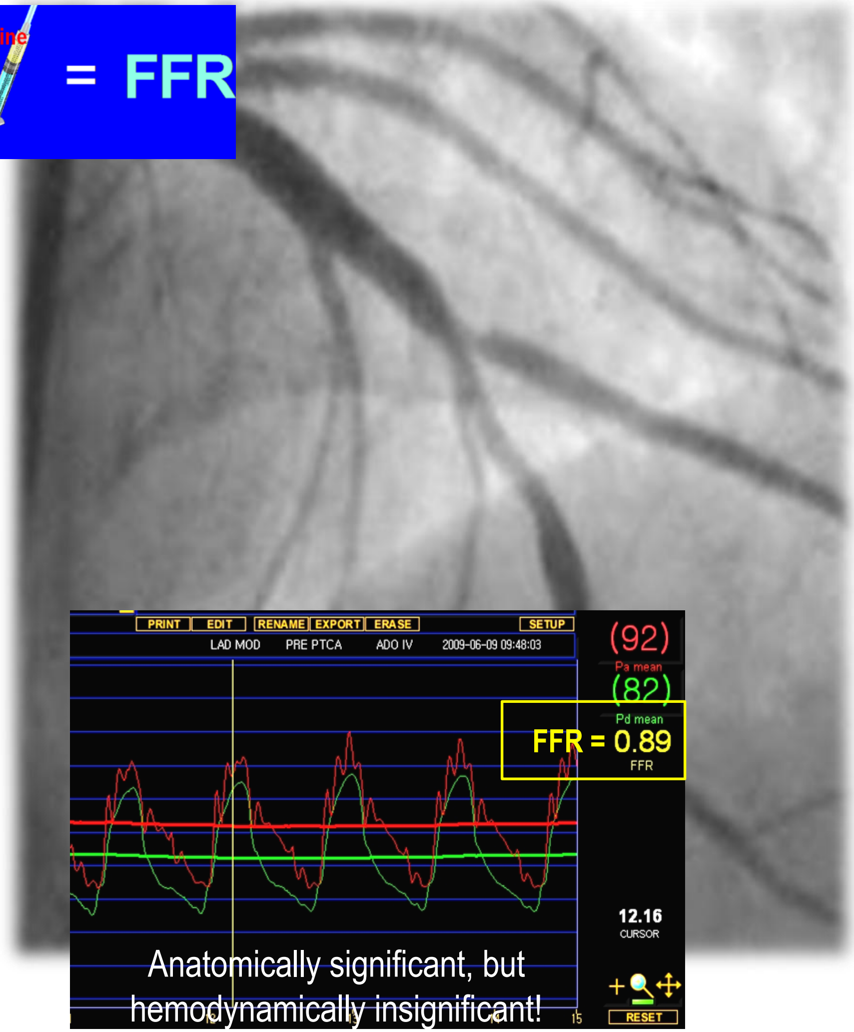
FFR vs. Myocardial ischemia

Q: Which is a significant stenosis? Please choose one.

Coronary angiogram: left anterior descending coronary artery







PCI: percutaneous coronary intervention

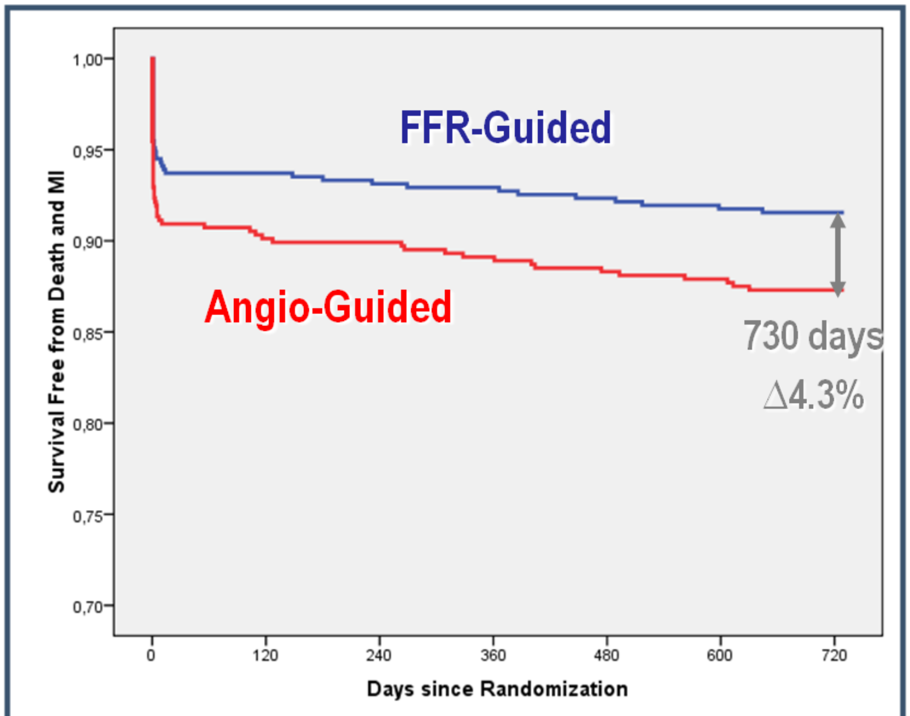
FAME study

Patient with ≥ 2 vessel disease
(N=1005)

Angiography-guided PCI
(N=496)

FFR-guided PCI
(N=509)

2 Year Death/Myocardial infarction-free survival



FFR (hemodynamics)-guided vs. Anatomy-guided

- Less stent
- Less cost
- Same procedural time
- Better clinical outcomes

Tonino, et al. NEJM 2009; Pijls, et al. JACC 2010

FFR is good for the patients and (relatively) simple………

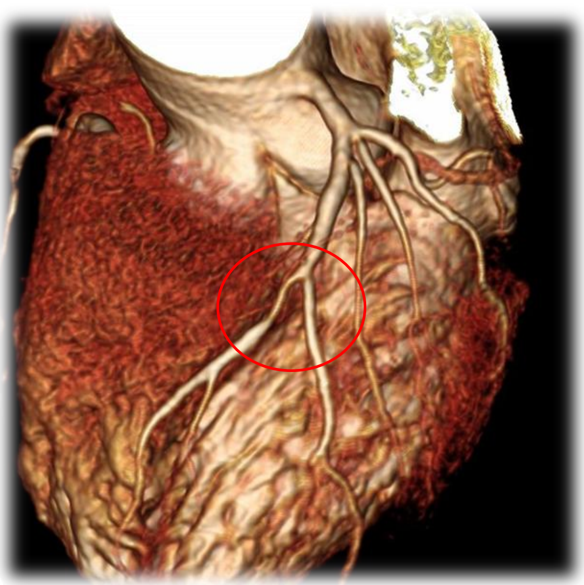
European Heart Journal (2010) 31, 2501–2555
doi:10.1093/eurheartj/ehq277
ESC/EACTS GUIDELINES

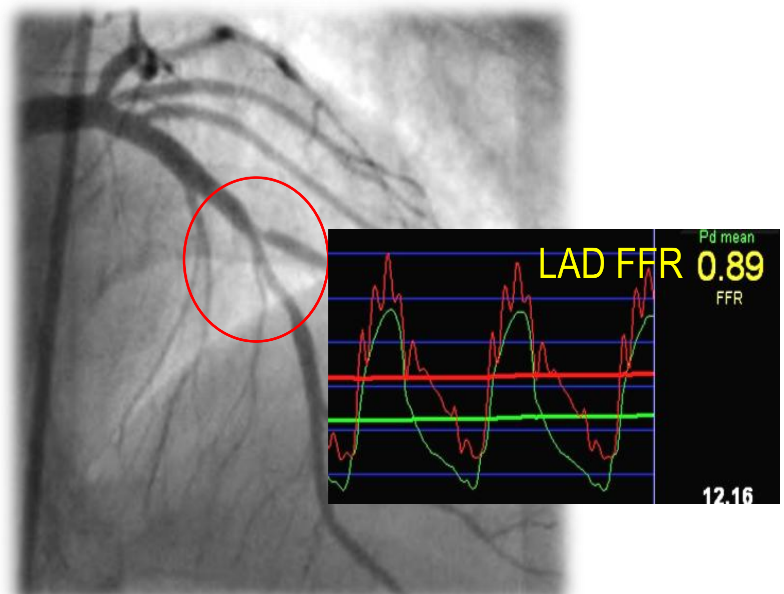
Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

	Class[a]	Level[b]
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A
DES[d] are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT	I	A

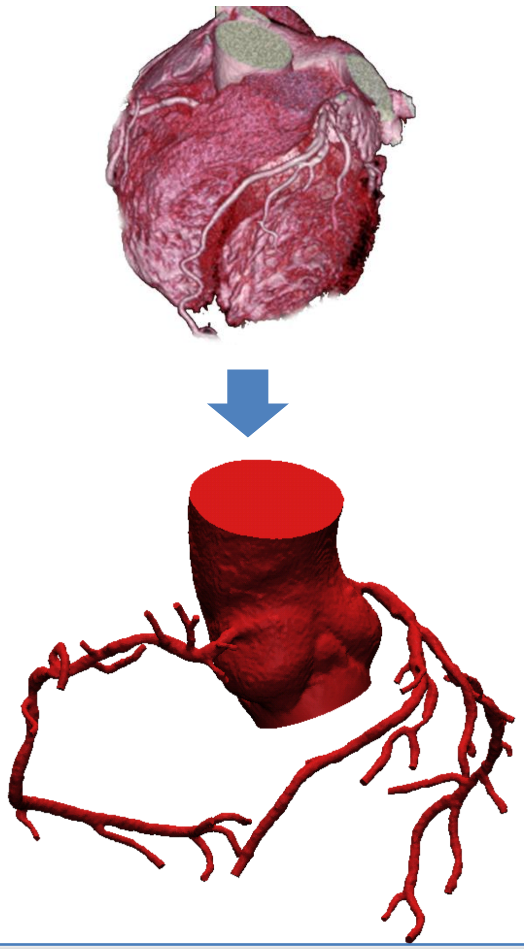
But, requires invasive procedure and expensive (>1,000 USD)…… cannot provide 3D anatomical information….





How to assess hemodynamics from static images?

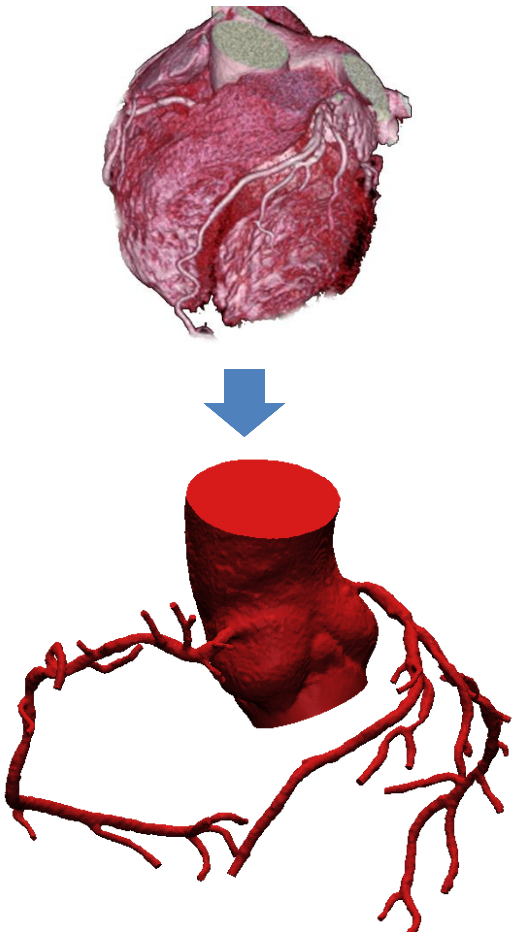
3-D Model based on CCTA



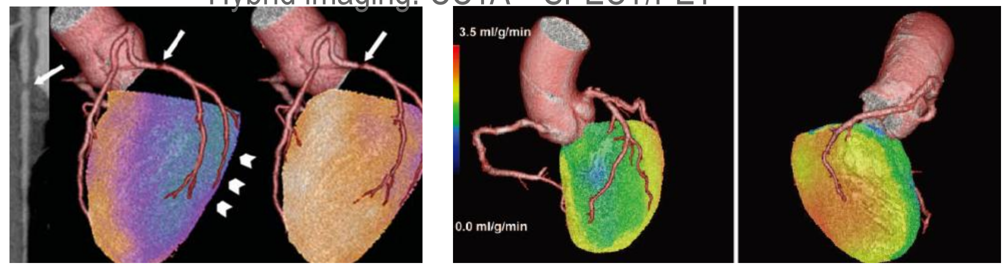
?

Integration of non-invasive coronary imaging and hemodynamic lesion assessment

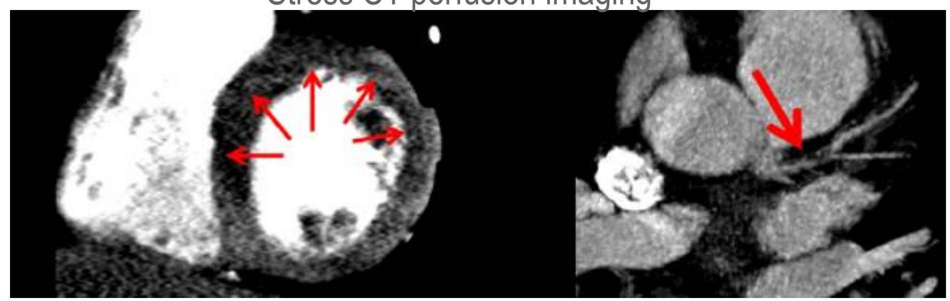
3-D Model based on CCTA



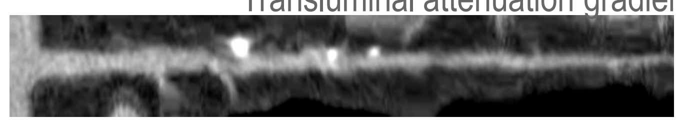
Hybrid imaging: CCTA + SPECT/PET

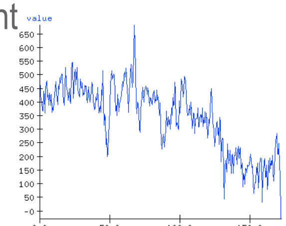


Stress CT perfusion imaging



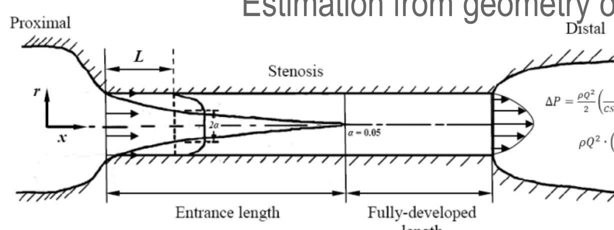
Transluminal attenuation gradient





TAG = -15.42 (HU/10mm)

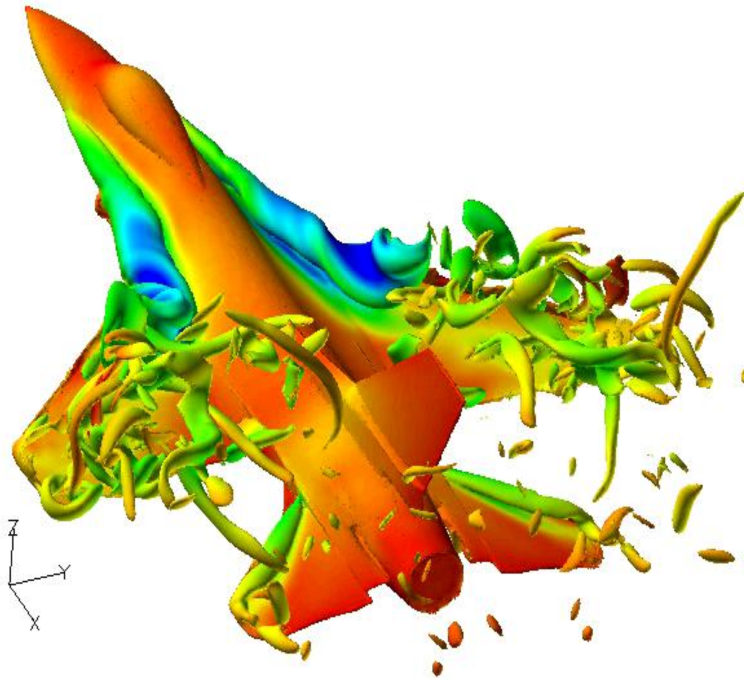
Estimation from geometry of stenosis



$$\Delta P = \frac{\rho Q^2}{2}\left(\frac{1}{CSA_{outlet}^2} - \frac{1}{CSA_{inlet}^2}\right) + \frac{\rho Q^2}{2\cdot CSA_{stenosis}^2}\frac{96}{5}\int_{0.05}^{1}\frac{(1+4\alpha+9\alpha^2+4\alpha^3)}{\alpha(3+2\alpha)(3+2\alpha+\alpha^2)^2}d\alpha + \int_0^{L_{vessel}-L_{entrance}}\frac{8\pi\mu}{CSA^2}Q\,dx + \rho Q^2\cdot\left(\frac{1}{CSA_{stenosis}} - \frac{1}{CSA_{distal}}\right)\cdot\left(\frac{1}{CSA_{stenosis}} - \frac{1}{3}\cdot\frac{1}{CSA_{distal}}\right) \quad [A12]$$

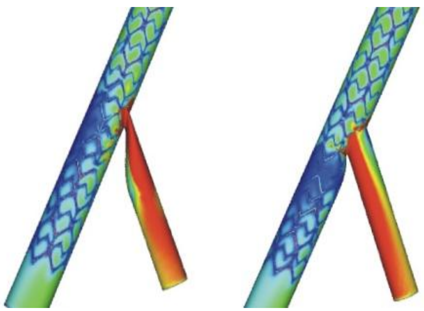
Computational Fluid Dynamics (CFD)

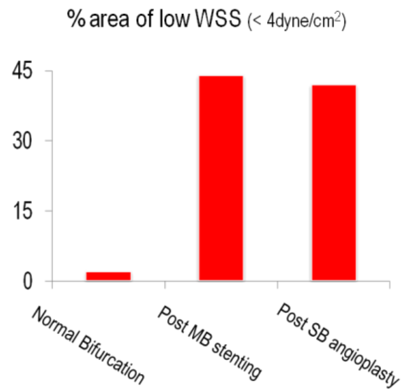
- Computational fluid dynamics (CFD) quantifies fluid pressure and velocity, based on physical laws of mass conservation and momentum balance.
- CFD is widely used in the aerospace and automotive industries for design and testing.

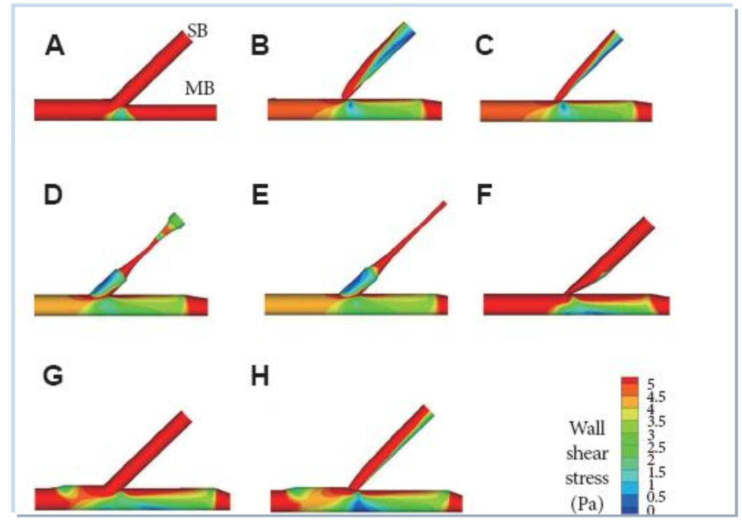


Courtesy of C. Taylor, HeartFlow

CFD in simple and idealized coronary models

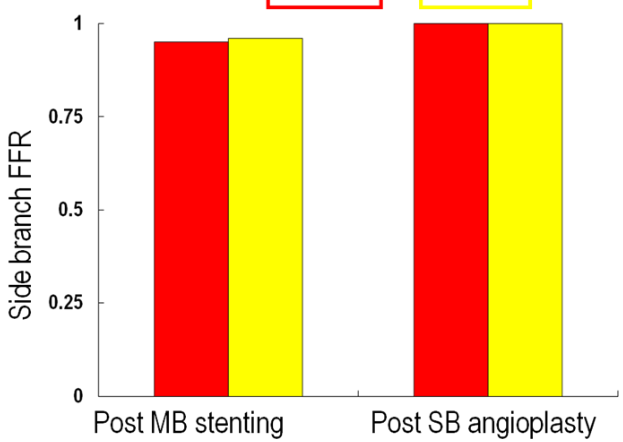


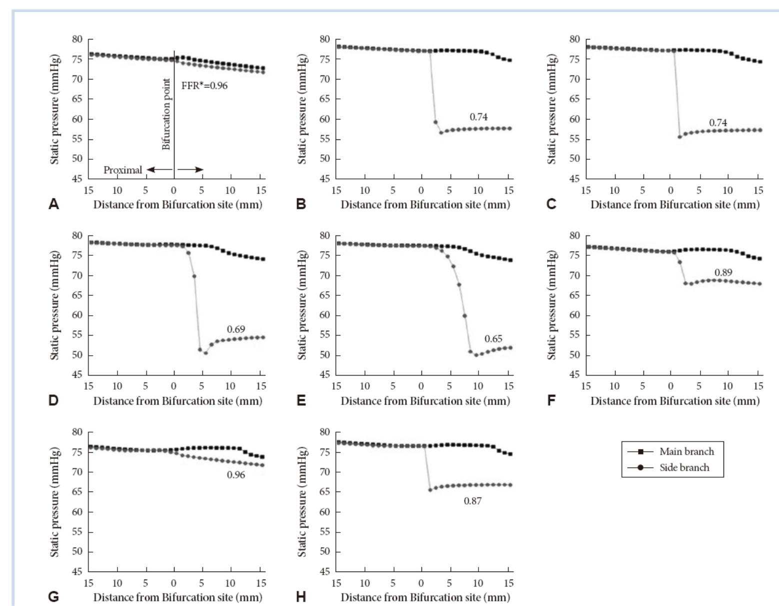




FLOW PRESSURE

$$FFR = \frac{Q^{S}_{max}}{Q^{N}_{max}} = \frac{P_d}{P_a}$$

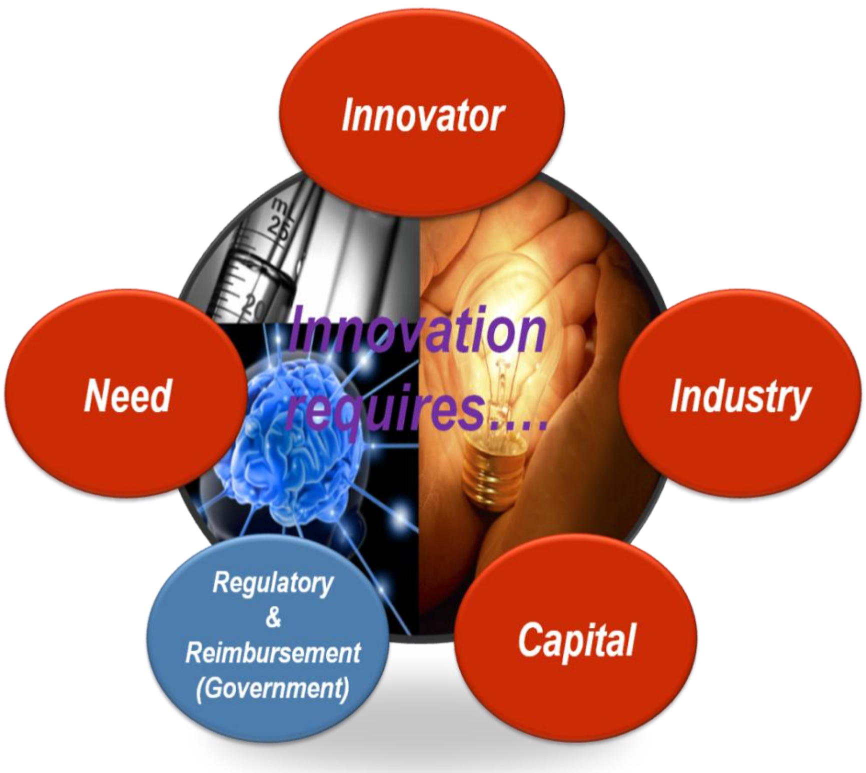




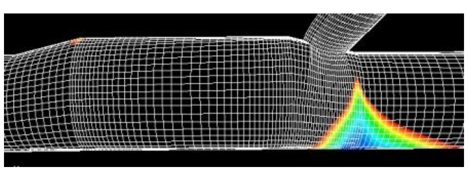
Williams & Koo, et al. J Appl Physiol 2010

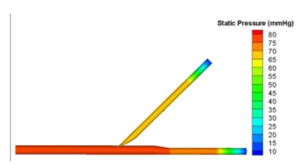
Na SH, Koo BK, et al. Korean Circ J 2011

cCTA + CFD = Pt-specific non-invasive FFR

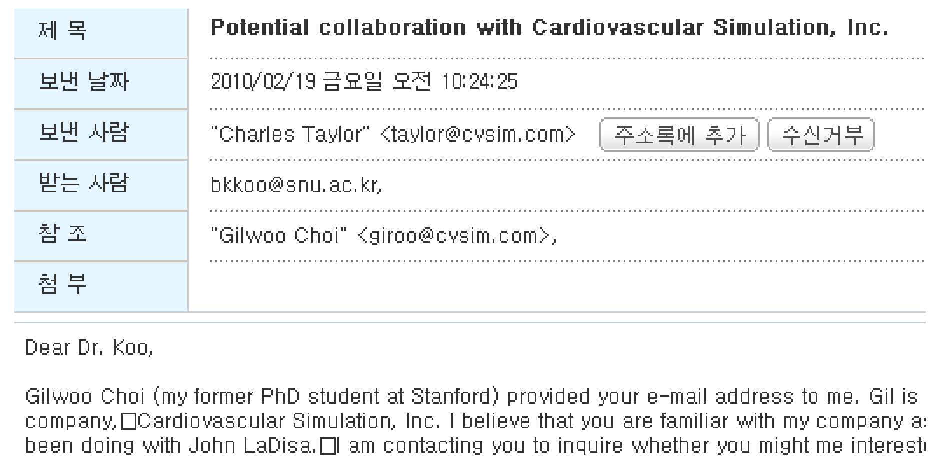


- *2009: Project started*





- *Feb 2010: Collaboration with CV SIM*



제 목	**Potential collaboration with Cardiovascular Simulation, Inc.**
보낸 날짜	2010/02/19 금요일 오전 10:24:25
보낸 사람	"Charles Taylor" <taylor@cvsim.com> 주소록에 추가 수신거부
받는 사람	bkkoo@snu.ac.kr,
참 조	"Gilwoo Choi" <giroo@cvsim.com>,
첨 부	

Dear Dr. Koo,

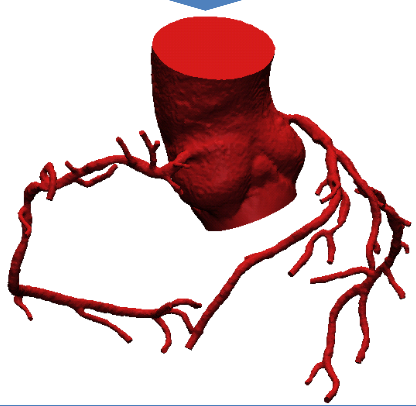
Gilwoo Choi (my former PhD student at Stanford) provided your e-mail address to me. Gil is company, Cardiovascular Simulation, Inc. I believe that you are familiar with my company a been doing with John LaDisa. I am contacting you to inquire whether you might me interest

Patient-specific non-invasive FFR using CT & CFD

Computational Model based on CCTA

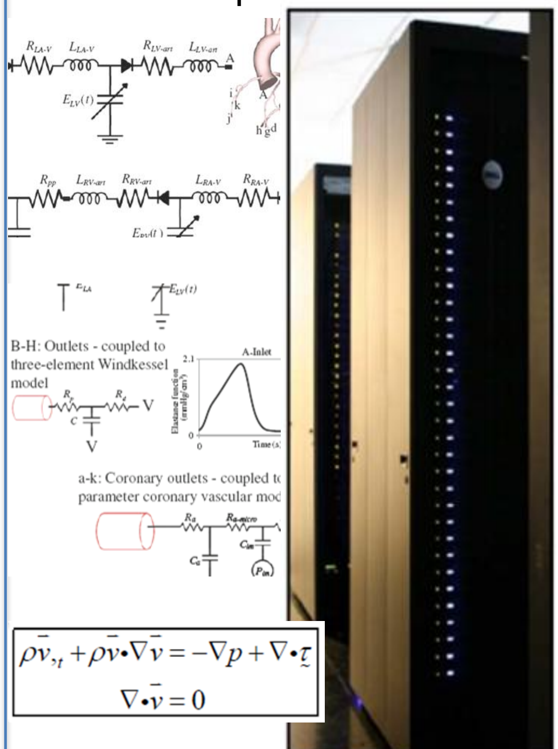
3-D anatomic model from CCTA

No additional imaging
No additional medications



Blood Flow Solution

Blood flow equations solved on supercomputer



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

Physiologic models

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

Koo BK, EBC 2011, EuroPCR 2012

Patient-specific non-invasive FFR using CT & CFD

Computational Model based on CCTA

3-D anatomic model from CCTA

No additional imaging
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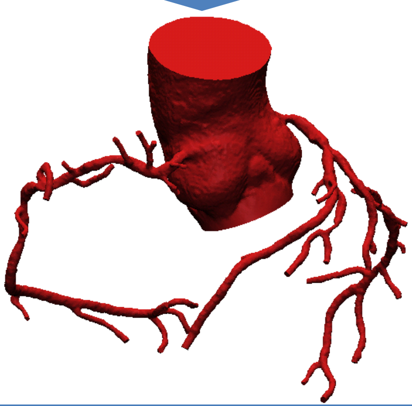

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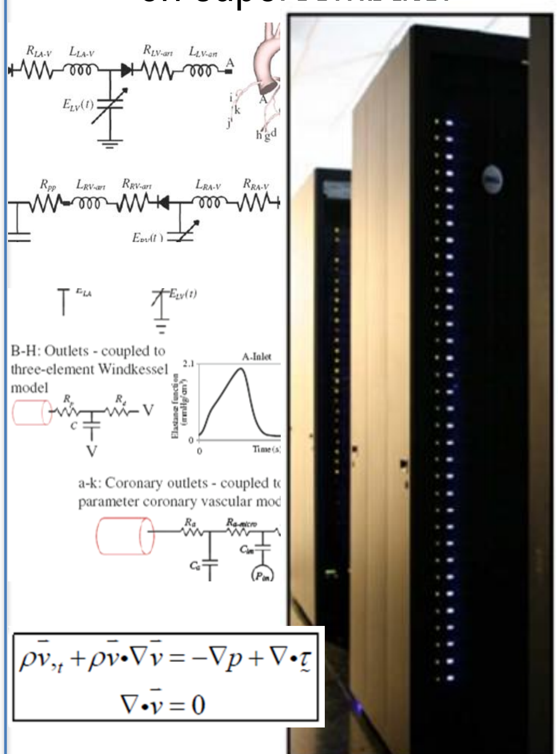

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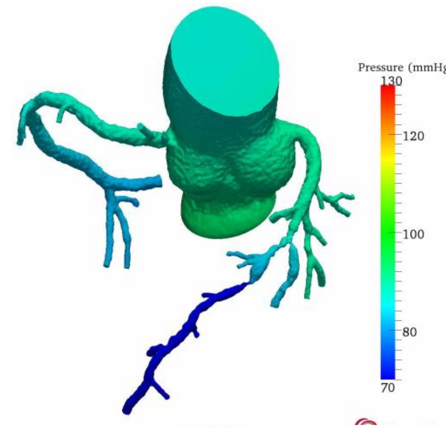
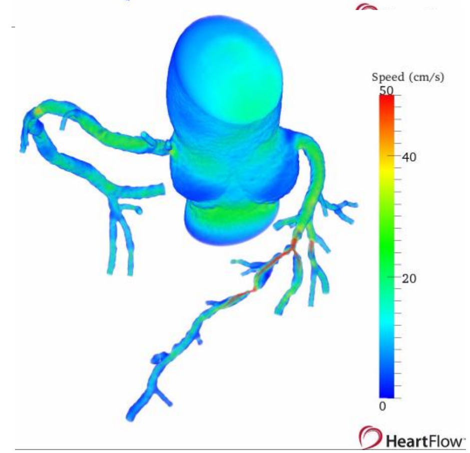
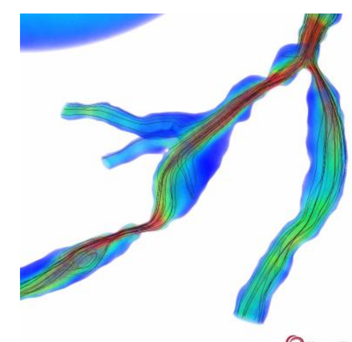






Koo BK, EBC 2011, EuroPCR 2012

Current pathway

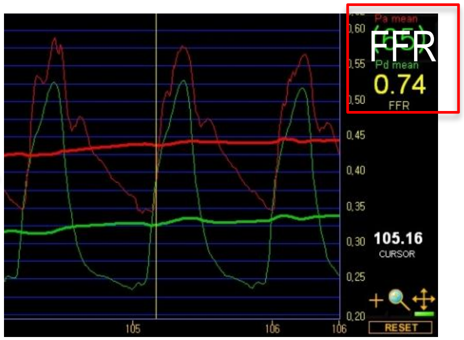
CCTA

>50% diameter stenosis

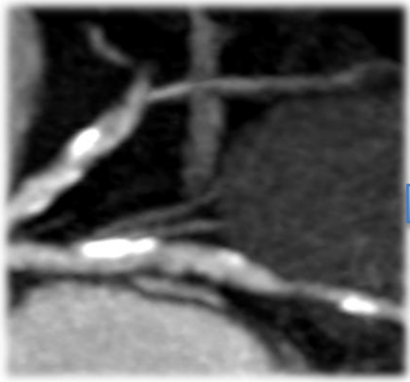
Invasive angiography

>50% diameter stenosis

FFR

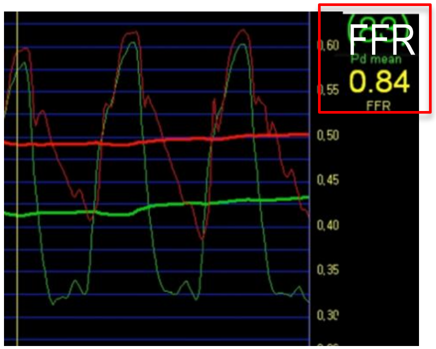


FFR 0.74 → PCI



>50% diameter stenosis

>50% diameter stenosis



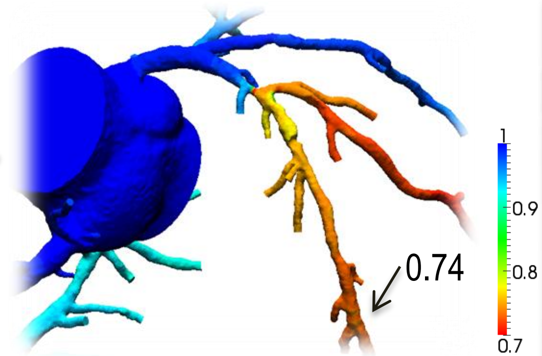
FFR 0.84
→ Medical treatment

How this novel technology can change our daily practice?

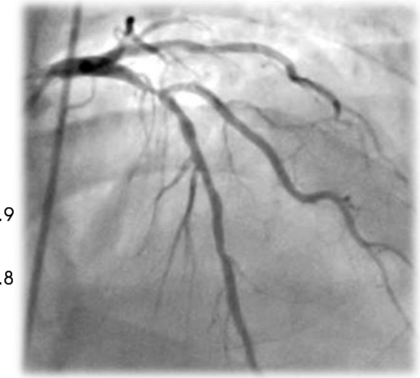
Novel (risk-free, non-invasive, cost-saving) **pathway**

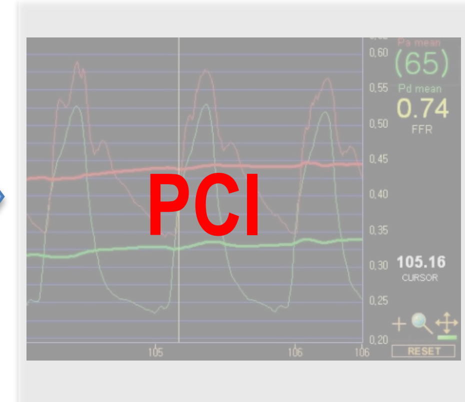
CCTA

FFR$_{CT}$



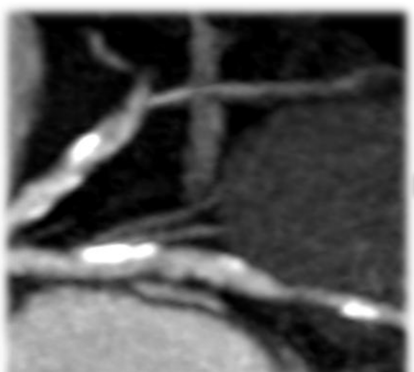
Invasive angiography and PCI

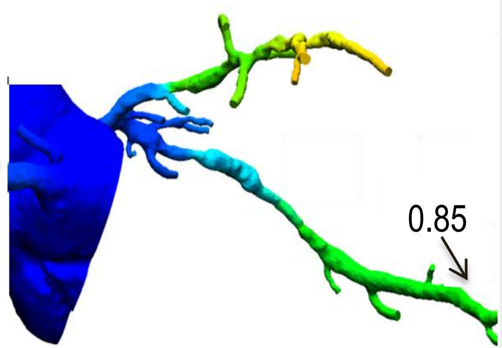


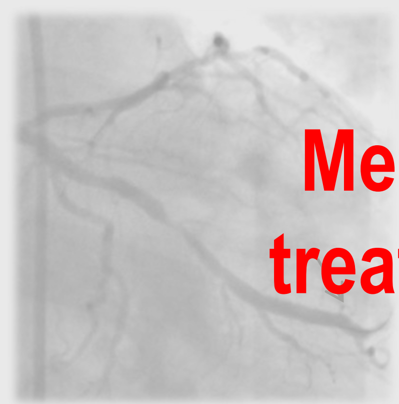


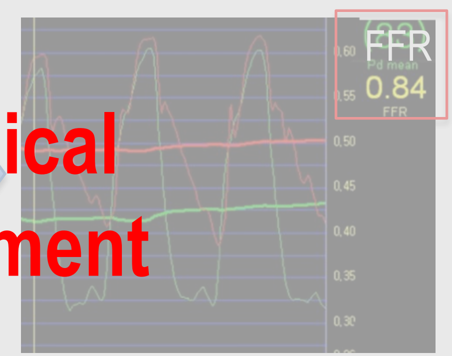
>50% diameter stenosis

FFR$_{CT}$ 0.74 → Invasive procedures









Medical treatment

>50% diameter stenosis

>50% diameter stenosis

FFR 0.84 → no ischemia

DISCOVER-FLOW study

First-in-Human study

- To evaluate the feasibility and diagnostic performance of FFRCT
- Prospective, multicenter study
- 159 vessels in 103 patients
- Oct 2009 – Jan 2011

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

Objectives The aim of this study was to determine the diagnostic performance of a new method for quantifying fractional flow reserve (FFR) with computational fluid dynamics (CFD) applied to coronary computed tomography angiography (CCTA) data in patients with suspected or known coronary artery disease (CAD).

Background Measurement of FFR during invasive coronary angiography is the gold standard for identifying coronary artery lesions that cause ischemia and improves clinical decision-making for revascularization. Computation of FFR from CCTA data (FFR_{CT}) provides a noninvasive method for identifying ischemia-causing stenosis; however, the diagnostic performance of this new method is unknown.

Methods Computation of FFR from CCTA data was performed on 159 vessels in 103 patients undergoing CCTA, invasive coronary angiography, and FFR. Independent core laboratories determined FFR_{CT} and CAD stenosis severity by CCTA. Ischemia was defined by an FFR_{CT} and FFR ≤0.80, and anatomically obstructive CAD was defined as a CCTA with stenosis ≥50%. Diagnostic performance of FFR_{CT} and CCTA stenosis was assessed with invasive FFR as the reference standard.

Results Fifty-six percent of patients had ≥1 vessel with FFR ≤0.80. On a per-vessel basis, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFR_{CT} and were 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for CCTA stenosis. The area under the receiver-operator characteristics curve was 0.90 for FFR_{CT} and 0.75 for CCTA ($p = 0.001$). The FFR_{CT} and FFR were well correlated ($r = 0.717$, $p < 0.001$) with a slight underestimation by FFR_{CT} (0.022 ± 0.116, $p = 0.016$).

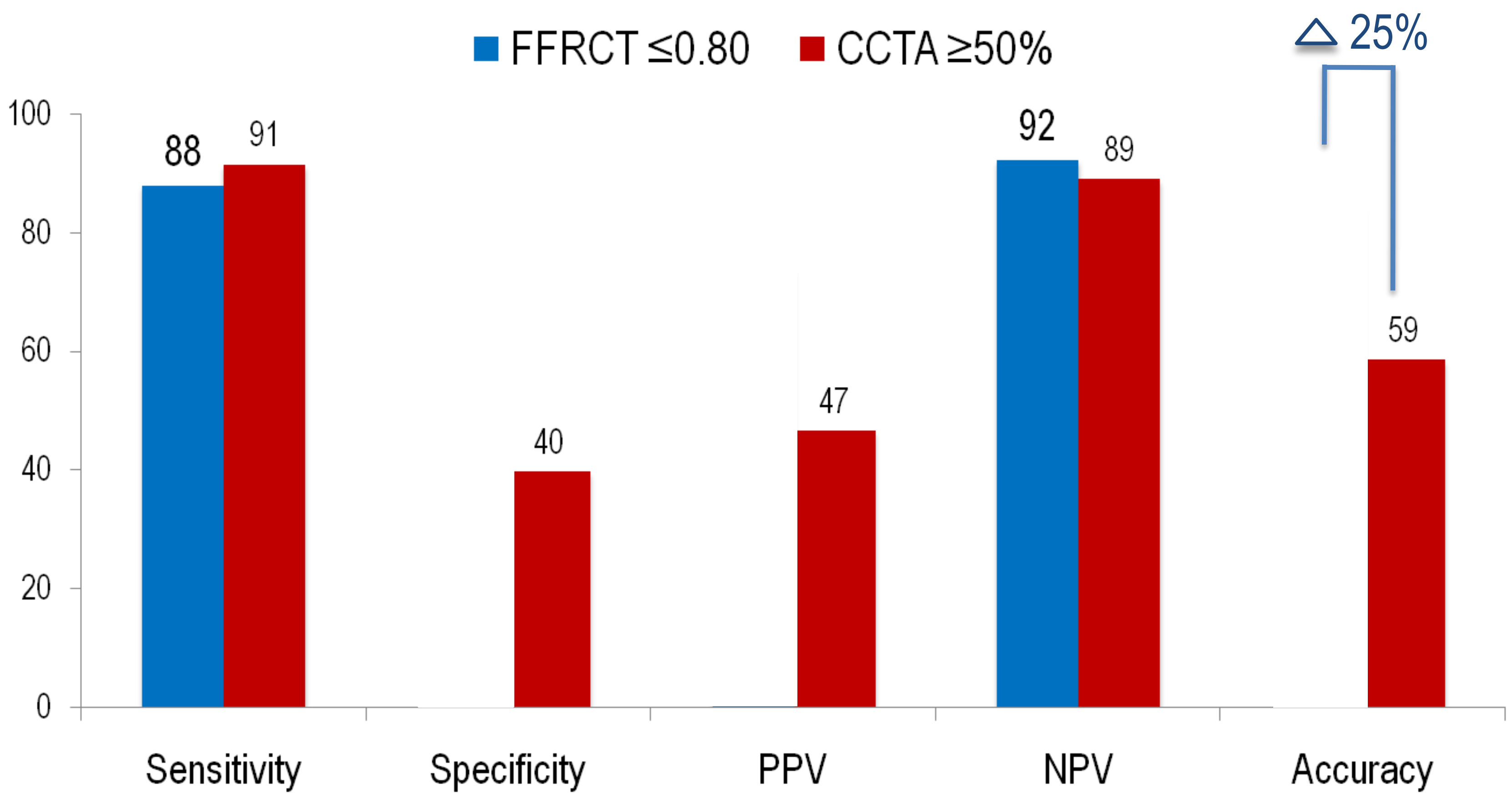
Conclusions Noninvasive FFR derived from CCTA is a novel method with high diagnostic performance for the detection and exclusion of coronary lesions that cause ischemia. (The Diagnosis of ISChemia-Causing Stenoses Obtained Via NoninvasivE FRactional FLOW Reserve; NCT01189331) (J Am Coll Cardiol 2011;58:1989–97) © 2011 by the American College of Cardiology Foundation

Koo BK, et al, J Am Coll Cardiol, 2011

DISCOVER-FLOW study

Diagnostic performance of FFR_{CT} and CCTA

Per-vessel analysis (n=159)



PPV: positive predictive value, NPV: negative predictive value

DISCOVER-FLOW: Koo BK, et al, J Am Coll Cardiol, 2011

Clinical Evidences on Diagnostic Performance

- **DISCOVER-FLOW**
  - 5 center FIH clinical trial
  - Completed 2011
  - N=103 patients
  - Published in JACC
- **DeFACTO**
  - 17 center clinical trial
  - Completed 2012
  - N=252 patients
  - Published in JAMA
- **NXT**
  - 10 center clinical trial
  - Completed August, 2013
  - N=251 patients
  - Published in JACC

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Vol. 58, No. 19, 2011
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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

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ORIGINAL CONTRIBUTION

ONLINE FIRST

Diagnostic Accuracy of Fractional Flow Reserve From Anatomic CT Angiography

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Context Coronary computed tomographic (CT) angiography is a noninvasive anatomic test for diagnosis of coronary stenosis that does not determine whether a stenosis causes ischemia. In contrast, fractional flow reserve (FFR) is a physiologic measure of coronary stenosis expressing the amount of coronary flow still attainable despite the presence of a stenosis, but it requires an invasive procedure. Noninvasive FFR computed from CT (FFR_{CT}) is a novel method for determining the physiologic significance of coronary artery disease (CAD), but its ability to identify ischemia has not been adequately examined to date.

Objective To assess the diagnostic performance of FFR_{CT} plus CT for diagnosis of hemodynamically significant coronary stenosis.

Design, Setting, and Patients Multicenter diagnostic performance study involving 252 stable patients with suspected or known CAD from 17 centers in 5 countries who underwent CT, invasive coronary angiography (ICA), FFR, and FFR_{CT} between October 2010 and October 2011. Computed tomography, ICA, FFR, and FFR_{CT} were interpreted in blinded fashion by independent core laboratories. Accuracy of FFR_{CT} plus CT for diagnosis of ischemia was compared with an invasive FFR reference standard. Ischemia was defined by an FFR or FFR_{CT} of 0.80 or less, while anatomically obstructive CAD was defined by a stenosis of 50% or larger on CT and ICA.

Main Outcome Measures The primary study outcome assessed whether FFR_{CT} plus CT could improve the per-patient diagnostic accuracy such that the lower boundary of the 1-sided 95% confidence interval of this estimate exceeded 70%.

Results Among study participants, 137 (54.4%) had an abnormal FFR determined by ICA. On a per-patient basis, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of FFR_{CT} plus CT were 73% (95% CI, 67%-78%), 90% (95% CI, 84%-95%), 54% (95% CI, 46%-83%), 67% (95% CI, 60%-74%), and 84% (95% CI, 74%-90%), respectively. Compared with obstructive CAD

Diagnostic performance of FFR_{CT}

	Patient No	Sensitivity	Specificity	PPV	NPV	Accuracy
DISCOVER-FLOW	103	93%	82%	85%	91%	87%
DeFACTO	252	90%	54%	67%	84%	73%
NXT	251	86%	79%	65%	92%	81%
	Total: 606	**90%**	**72%**	**72%**	**89%**	**80%**

Non-invasive tests/FFR$_{CT}$/Angiography vs. FFR

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FDA News Release

FDA allows marketing of non-invasive device to help evaluate heart blood flow

For Immediate Release — November 26, 2014

Release — The U.S. Food and Drug Administration today allowed marketing of the HeartFlow FFR-CT software, which permits health care professionals to non-invasively evaluate blood flow in the coronary arteries of patients showing signs and symptoms of coronary artery disease.

Inquiries

Media

Leslie Quander Wooldridge
240-402-4504

Consumers

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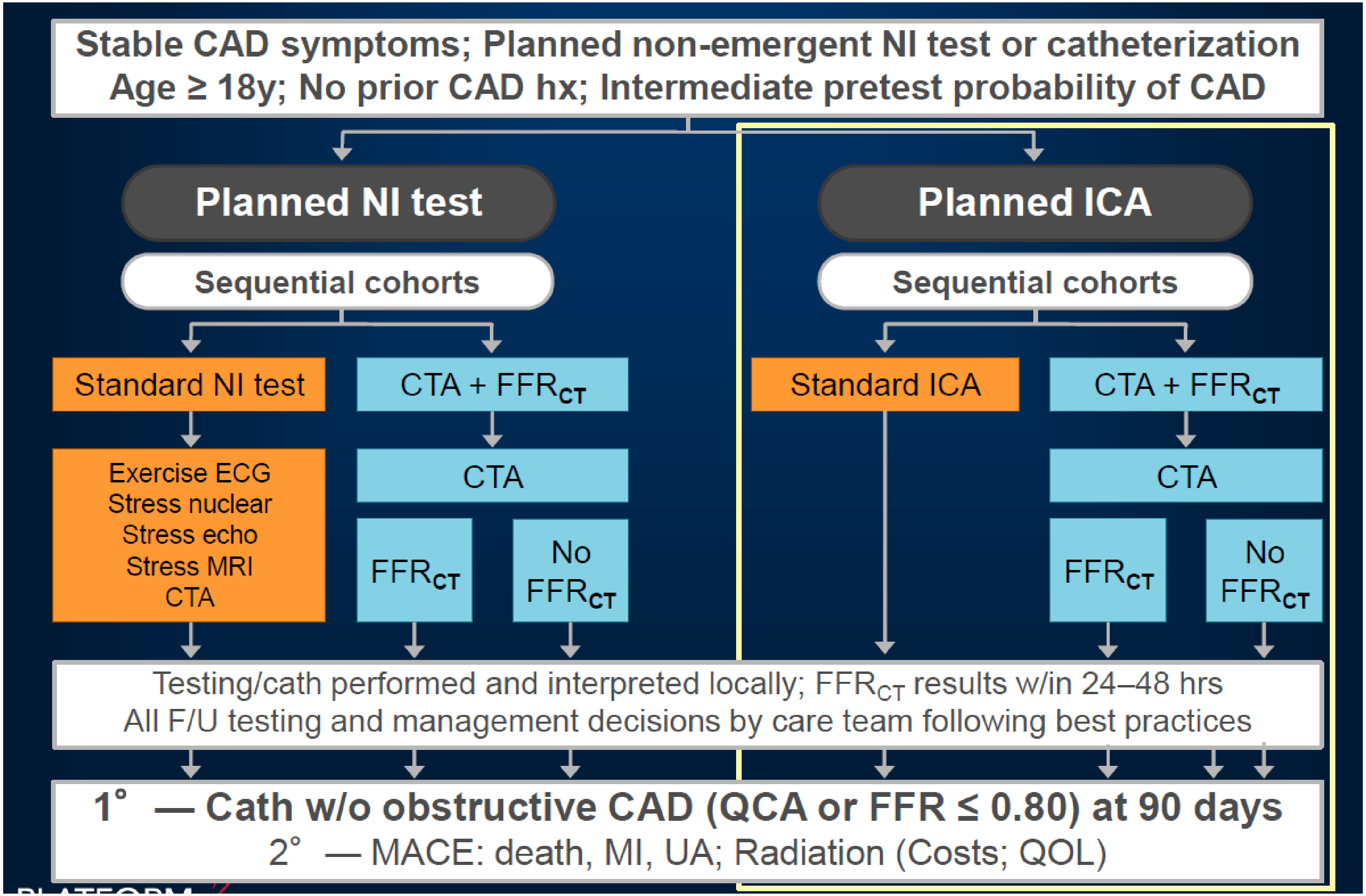
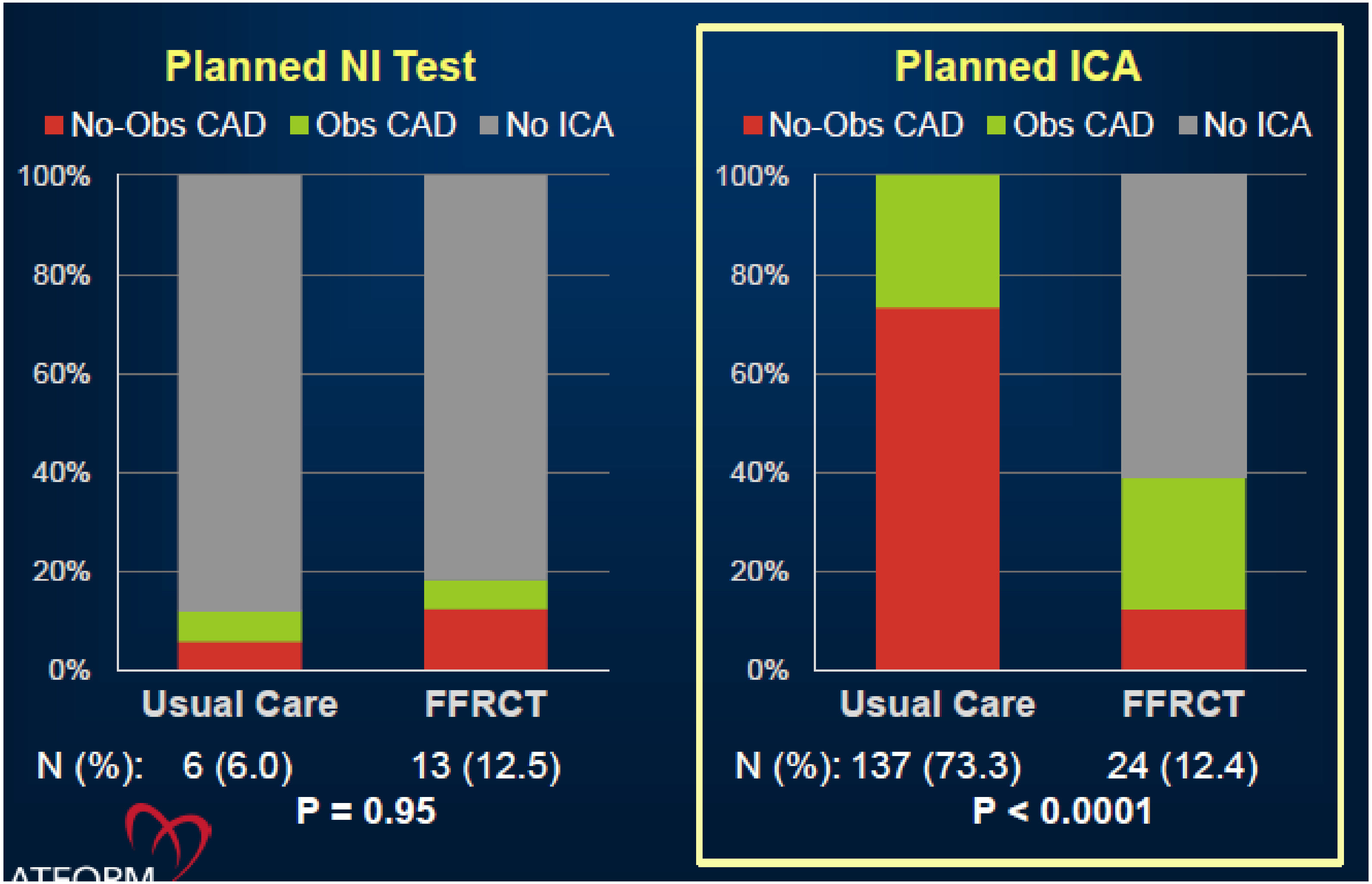
t al. JACC 2012
4. Min et al. JAMA 2012;308:1237-1245
8. Norgaard et a. JACC 2014

Clinical outcomes of FFRCT-guided decision



Douglas PS, et al. EHJ 2015

Clinical outcomes of FFR$_{CT}$-guided decision

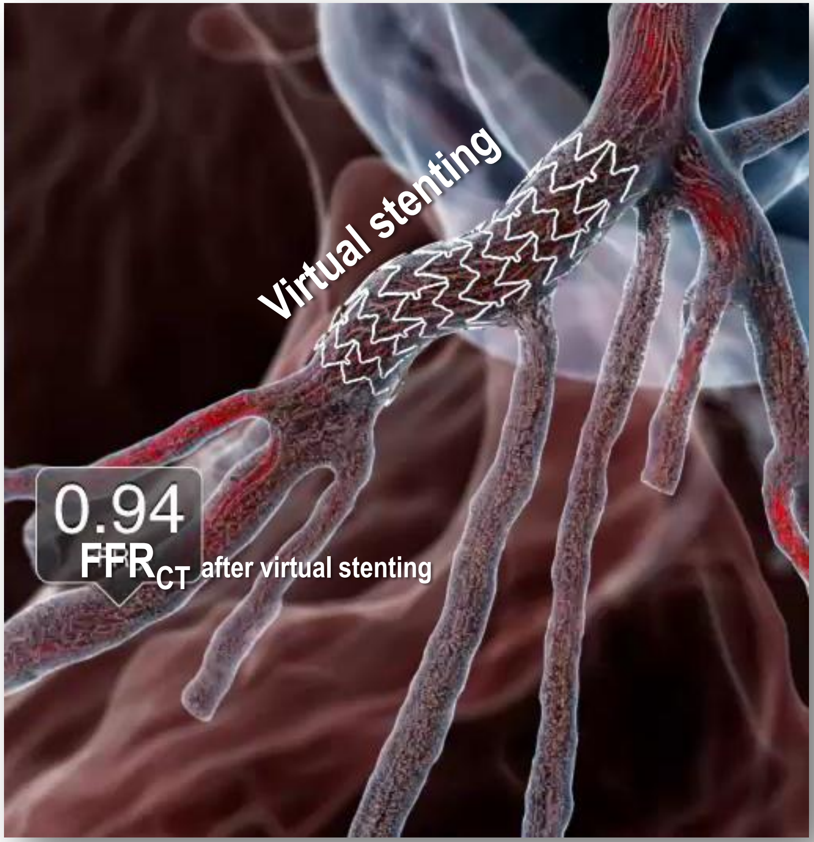


Douglas PS, et al. EHJ 2015

From CTA to CT-FFR and its beyond…

Planning the treatment strategy using

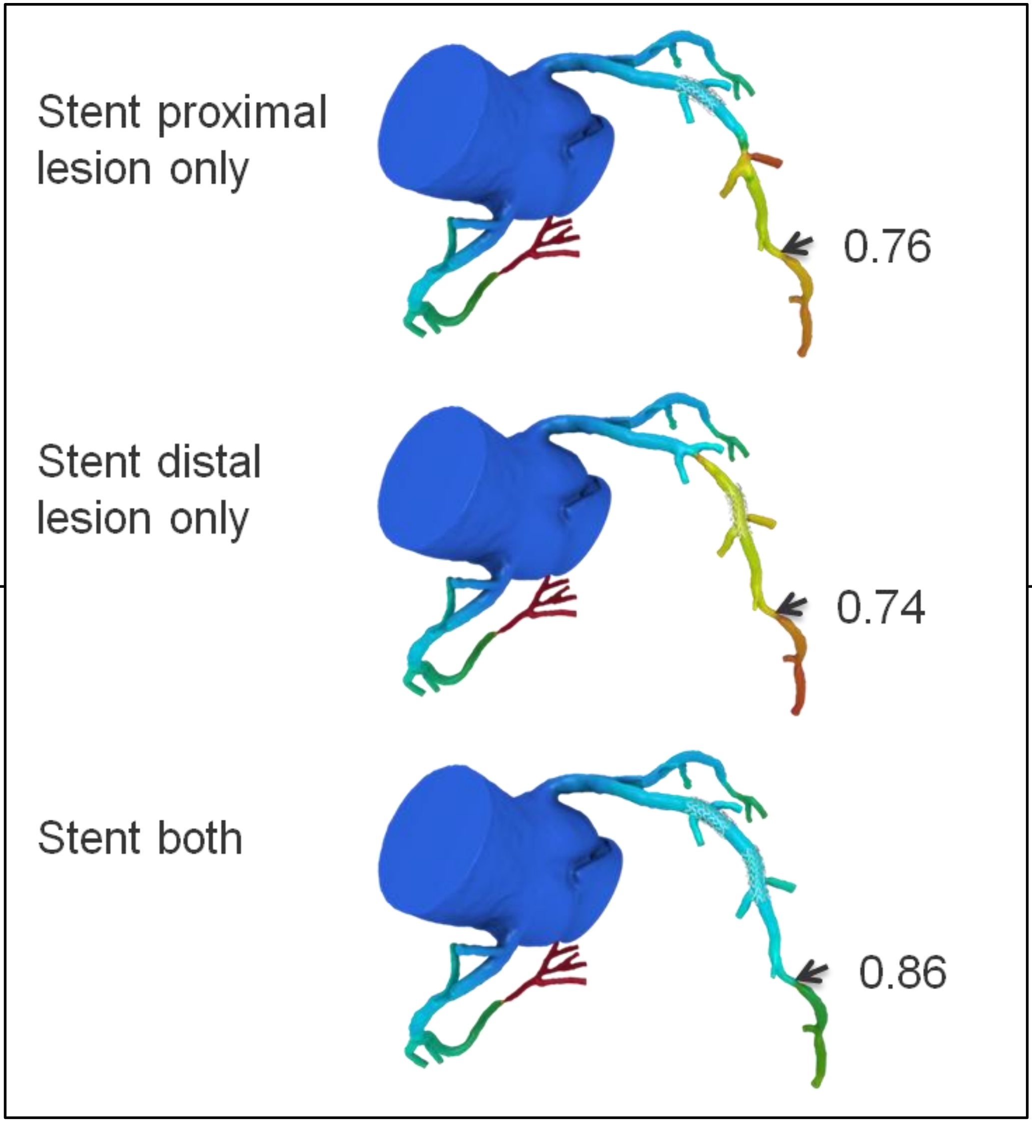
Virtual revascularization & CT-derived computed FFR



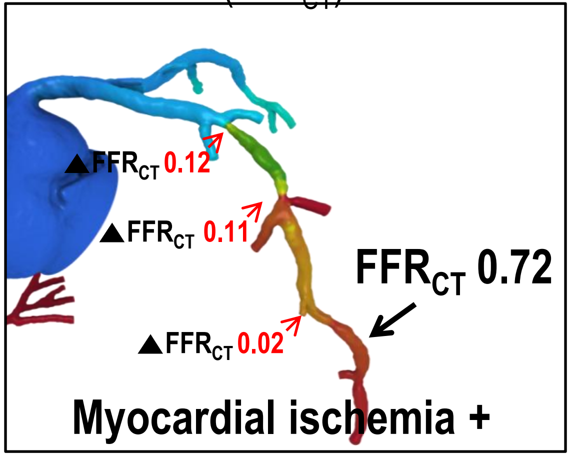
Planning the treatment strategy using
Virtual revascularization & CT-derived computed FFR

Before Stenting

After Stenting

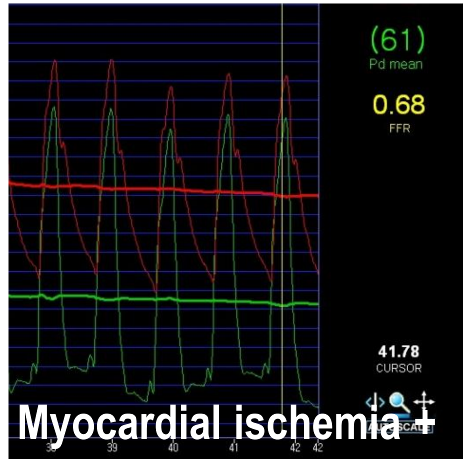
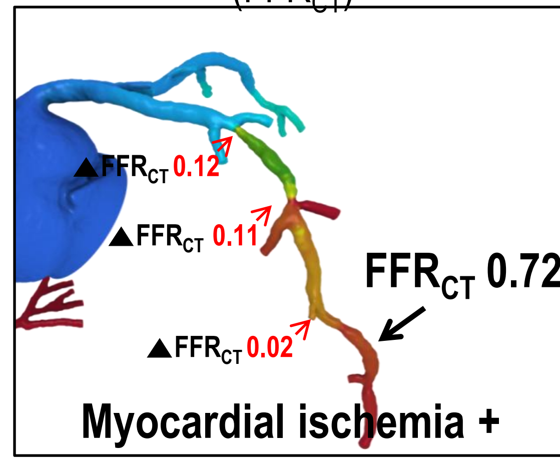
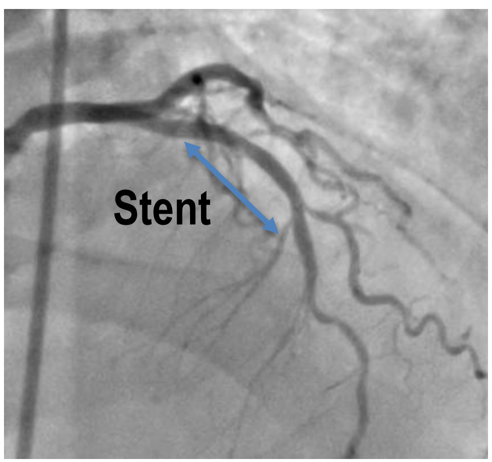
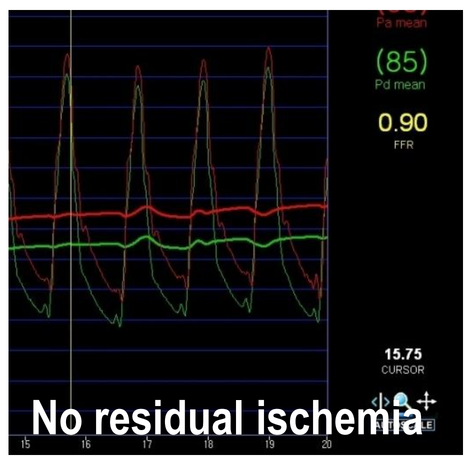
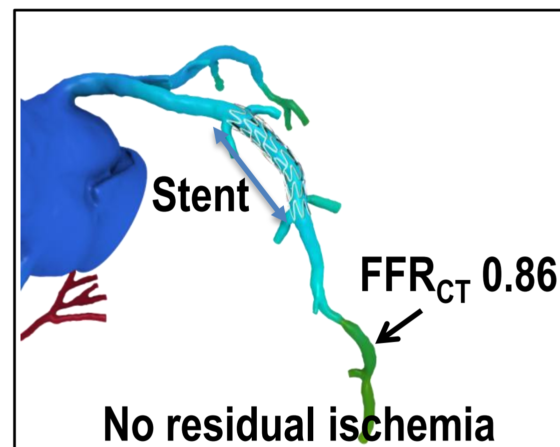


CT-derived computed FFR (FFR_{CT})



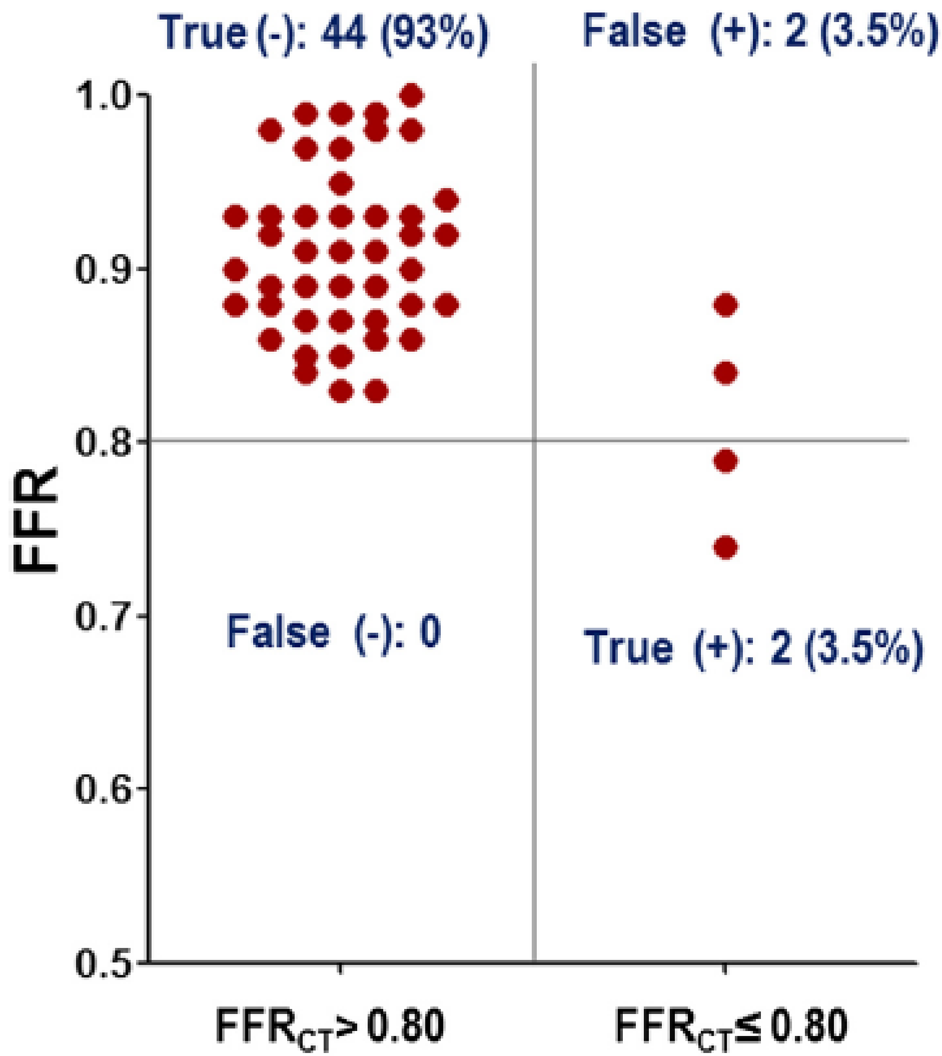
Kim KH, Koo BK, et al. JACC interv 2014

Planning the treatment strategy using
Virtual revascularization & CT-derived computed FFR

	Angiography	Invasive FFR	CT-derived computed FFR (FFR_{CT})
Before Stenting			
After Stenting			

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

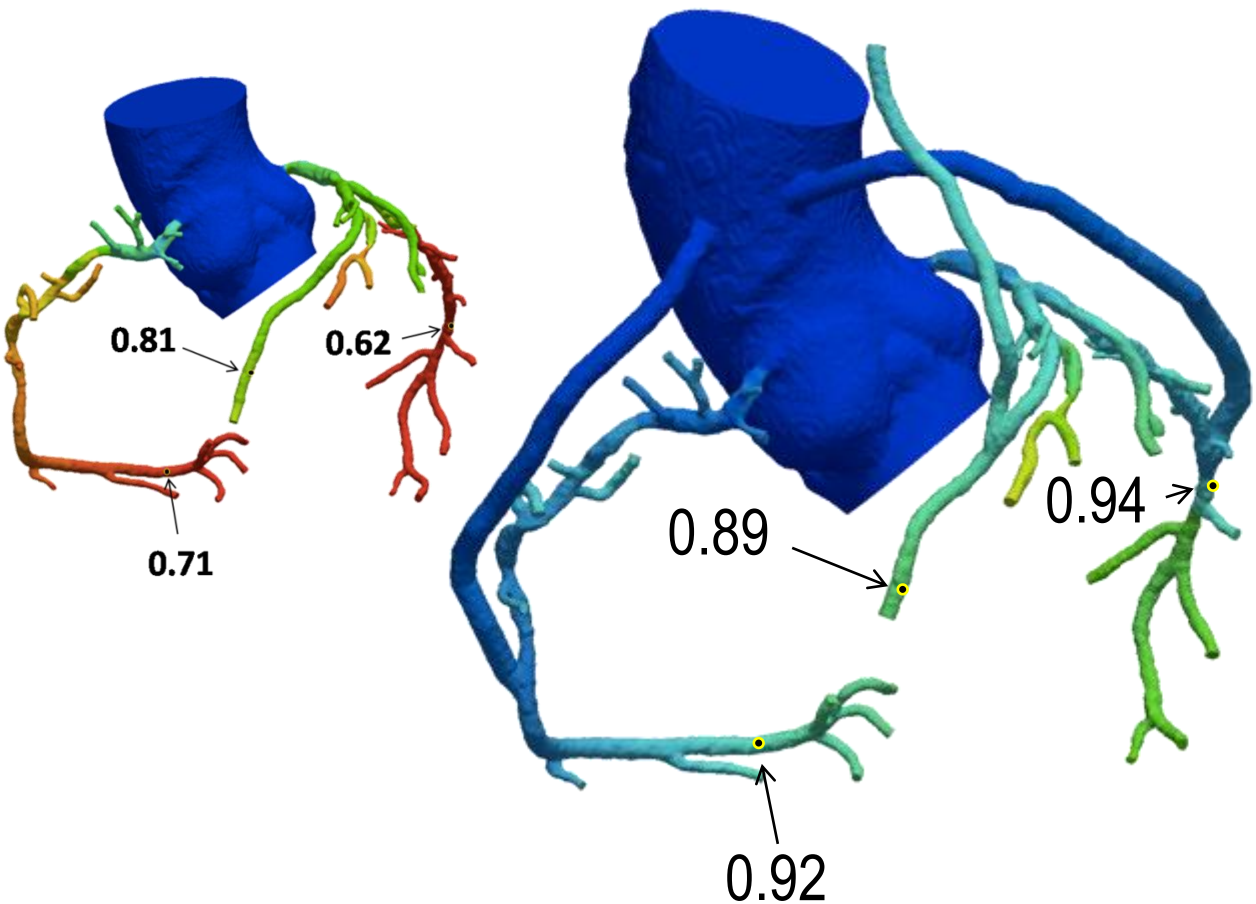
Diagnostic performance of FFR_{CT} after virtual stenting to predict the residual ischemia



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

Virtual surgery before the surgery, with your computer

FFR_{CT} after one arterial graft and 2 saphenous vein grafts



Koo BK, EuroPCR

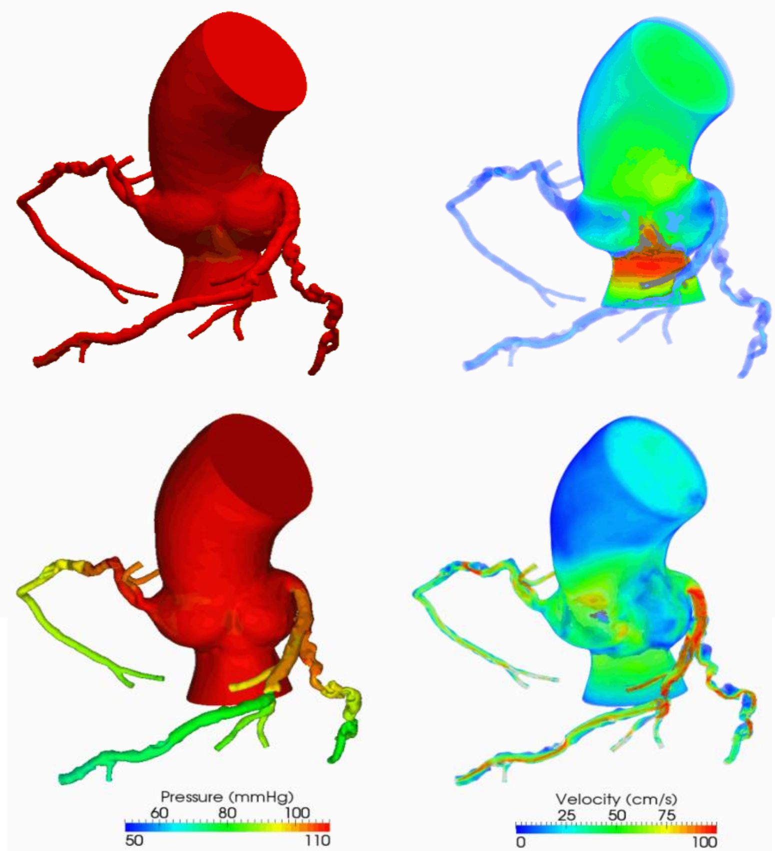
Non-invasive hemodynamic measurement
: Can we do more?

Coronary CT angiography + Computational fluid dynamics

Pressure **Velocity**

Rest

Hyperemia



Non-invasive hemodynamic force measurement : Is this feasible?

Coronary CT angiography + Computational fluid dynamics

Simulation

Velocity
Pressure

Cauchy Stress Tensor

$$\boldsymbol{T} = -p\boldsymbol{I} + \mu((\nabla \boldsymbol{v}) + (\nabla \boldsymbol{v})^T)$$

Traction vector

$$\boldsymbol{t} = \boldsymbol{T}\boldsymbol{n} = -p\boldsymbol{n} + \mu((\nabla \boldsymbol{v}) + (\nabla \boldsymbol{v})^T)\,\boldsymbol{n}$$

Wall Shear Stress (WSS)

$$\tau_{mean} = \left| \frac{1}{T} \int_0^T t_s dt \right|$$

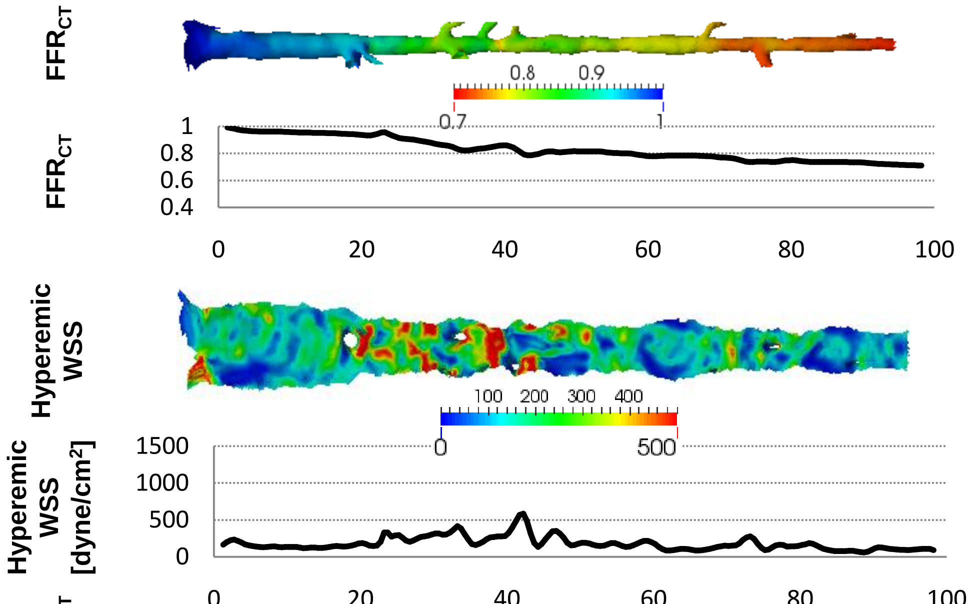
$$t_s = t - (t \cdot n)n$$

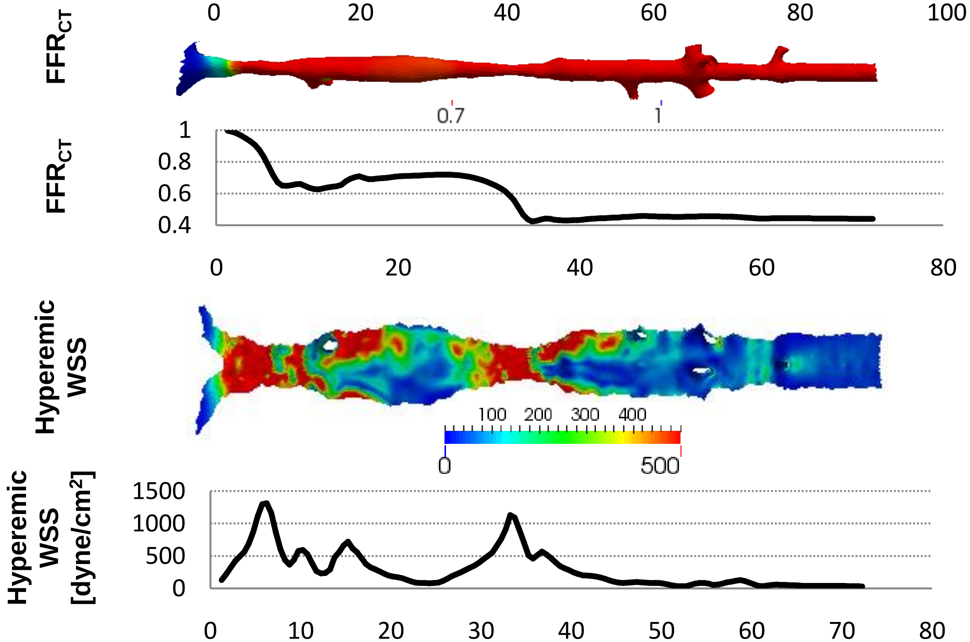
Oscillatory Shear Index (OSI)

$$OSI = \frac{1}{2}\left(1 - \frac{\left| \frac{1}{T} \int_0^T t_s dt \right|}{\frac{1}{T} \int_0^T |t_s| dt} \right)$$

Particle Residence Time,
Turbulent Kinetic Energy,
…

Non-invasive WSS assessment using cCTA and CFD

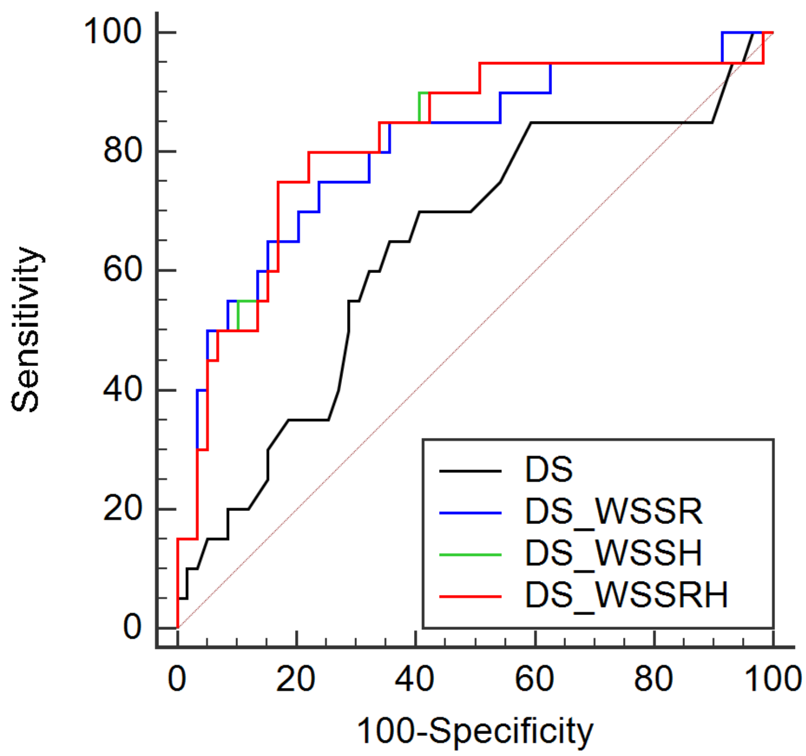




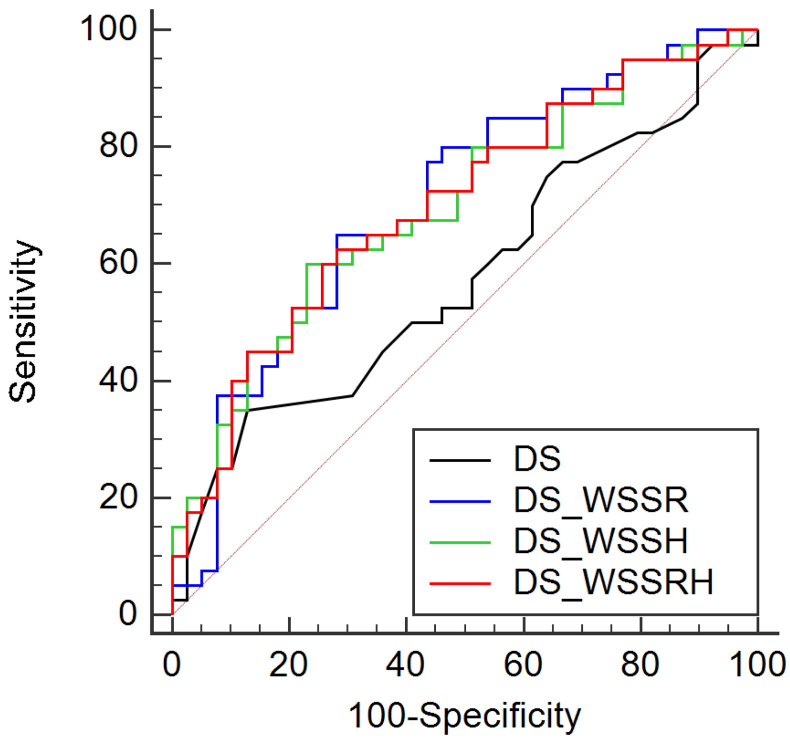
Koo BK. International Symposium on Biomechanics 2014

Association with Adverse plaque characteristics
: WSS vs. % diameter stenosis

Napkin ring sign



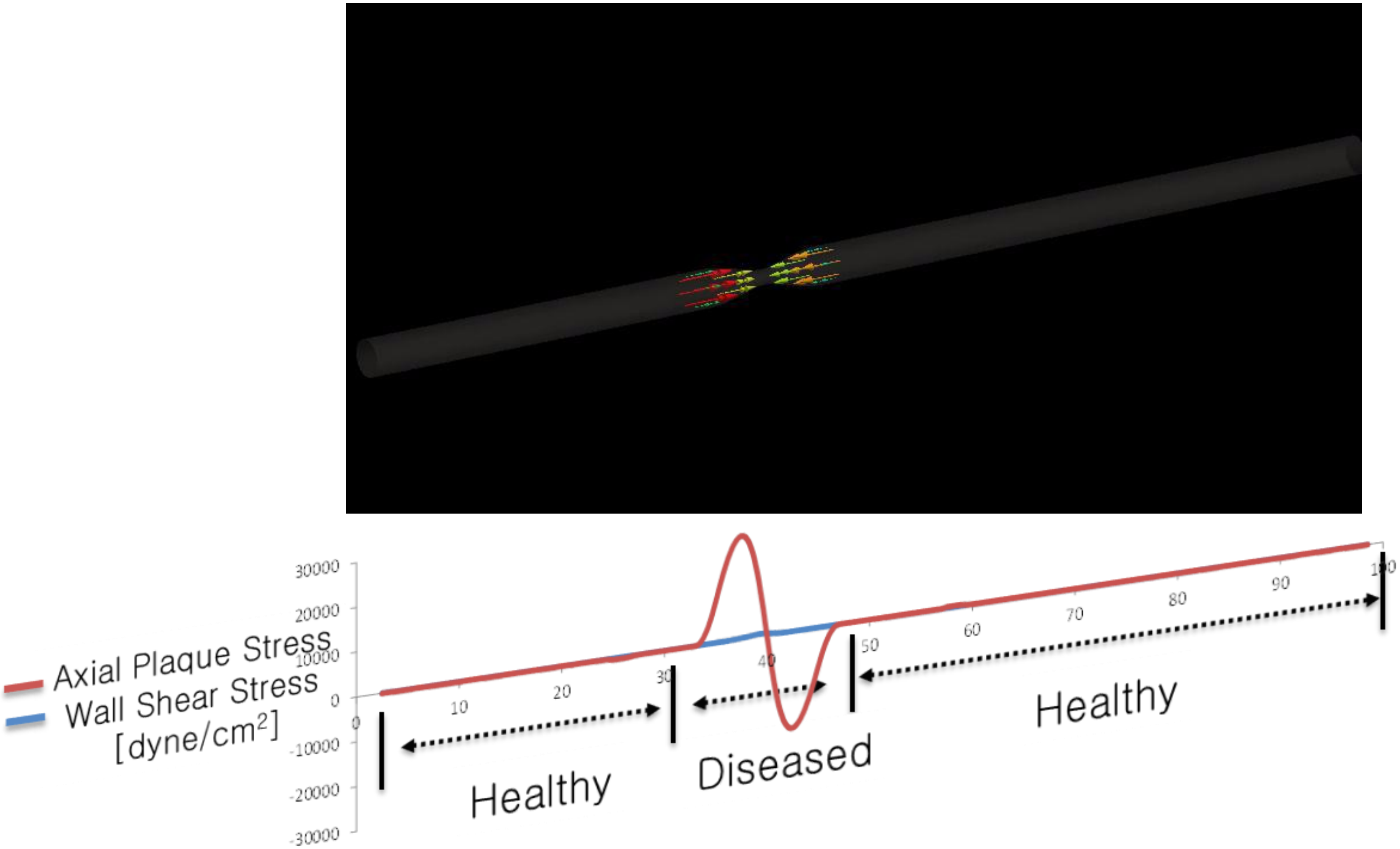
Positive remodeling



DS: % diameter stenosis, **WSSR:** resting wall shear stress, **WSSH:** hyperemic wall shear stress

Park JB, Koo BK, Taylor C, et al. Submitted

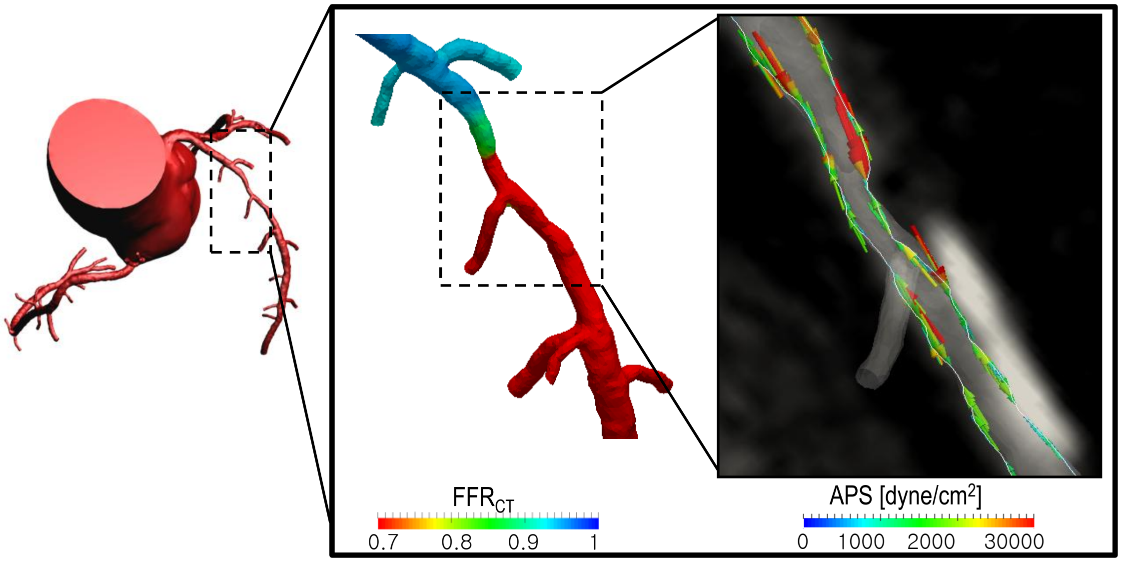
Novel hemodynamic index: Axial Plaque Stress

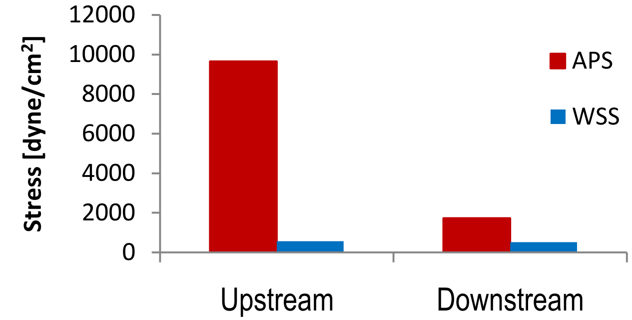


Axial plaque stress uniquely characterizes the diseased segment of both upstream and downstream.

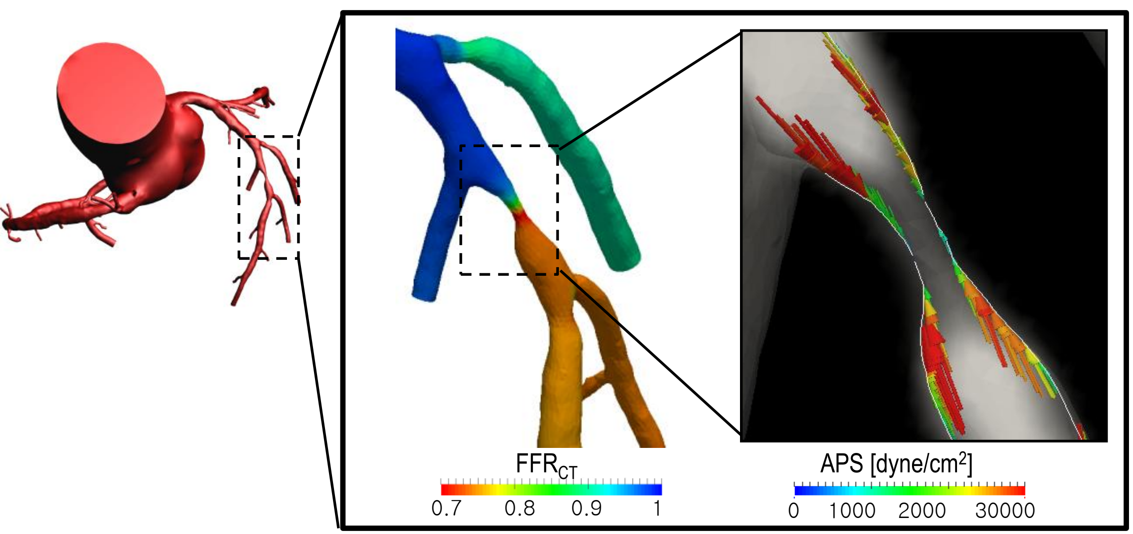
Choi GW…Koo BK. JACC imaging 2015

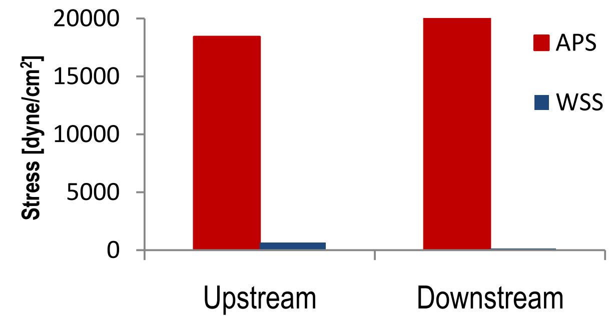
Distribution of Axial Plaque Stress in patients





	Upstream	Downstream
|Radius Gradient|	0.14	0.049
|APS| (dyne/cm^2)	9660	1740





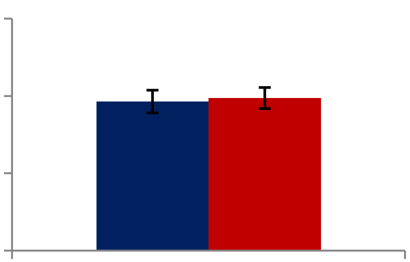
	Upstream	Downstream
|Radius Gradient|	0.14	0.22
|APS| (dyne/cm^2)	18428	21383

Choi GW…Koo BK. JACC imaging 2015

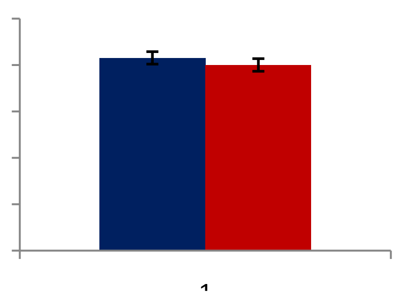
Influence of "Lesion Shape" on Hemodynamic Parameters
(n=114)

Upstream-dominant lesion (n=56) Downstream-dominant lesion (n=58)

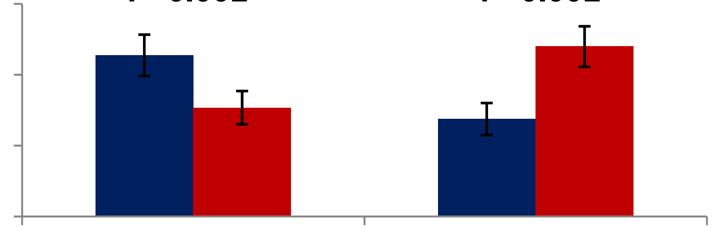
% Diameter Stenosis



FFR_{CT}

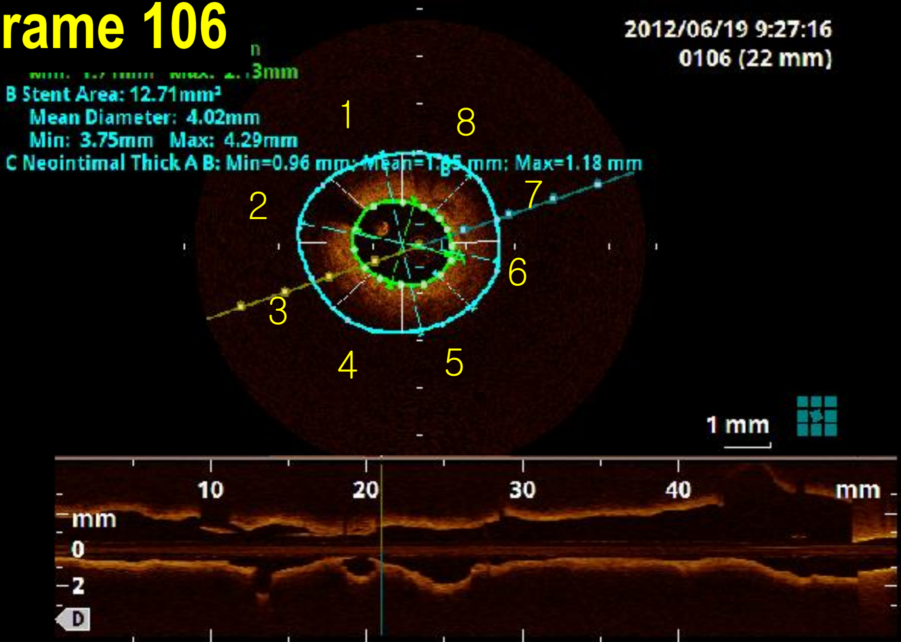


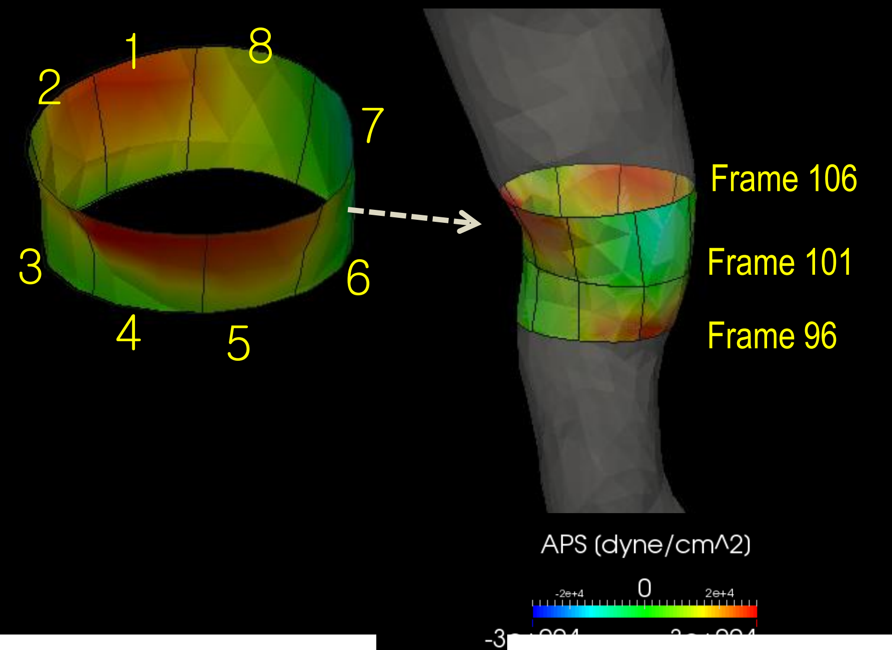
| Axial Plaque Stress | (dyne/cm²)



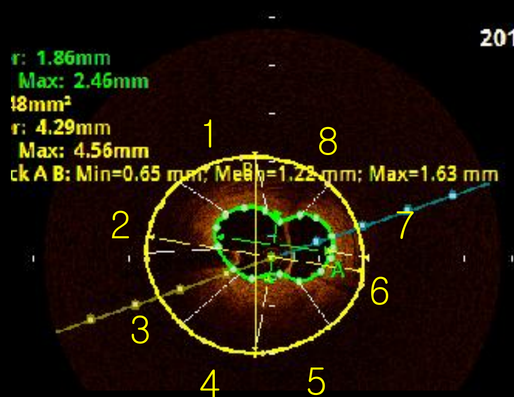
Choi GW…Koo BK. JACC imaging 2015

Frame 106



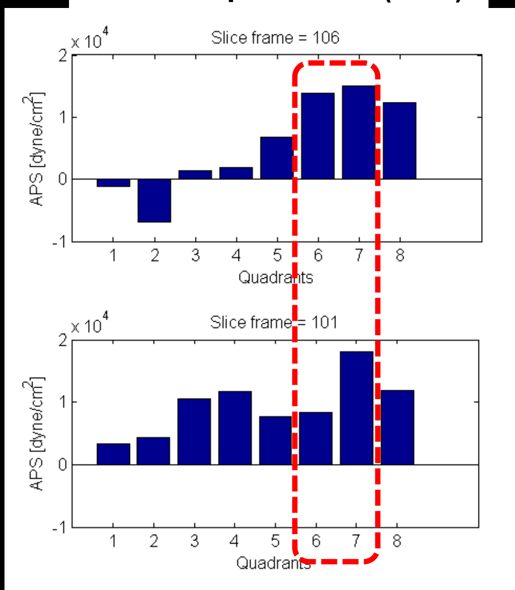


Frame 96

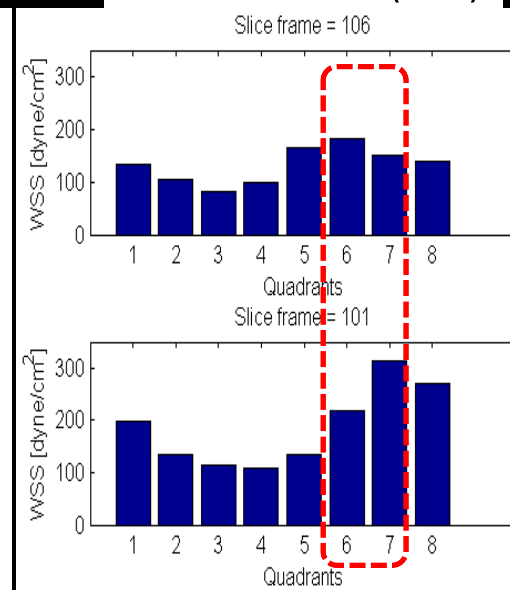


Plaque rupture
at segments 6 and 7

Axial Plaque Stress (APS)



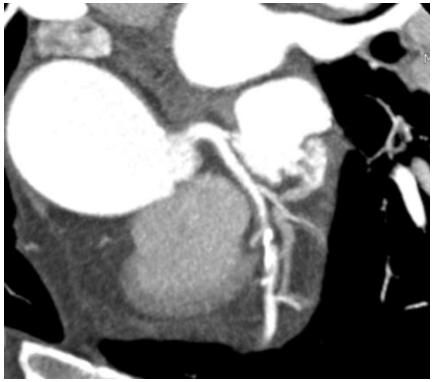
Wall Shear Stress (WSS)



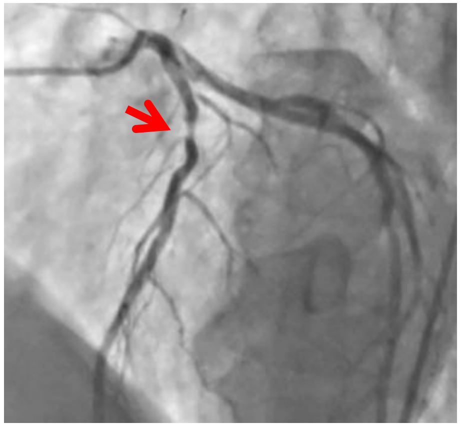
Choi GW, TPF workshop 2014, Incheon

APS and Future Event: CASE

2011-04 CT, Asymptomatic



2012-06 Acute MI



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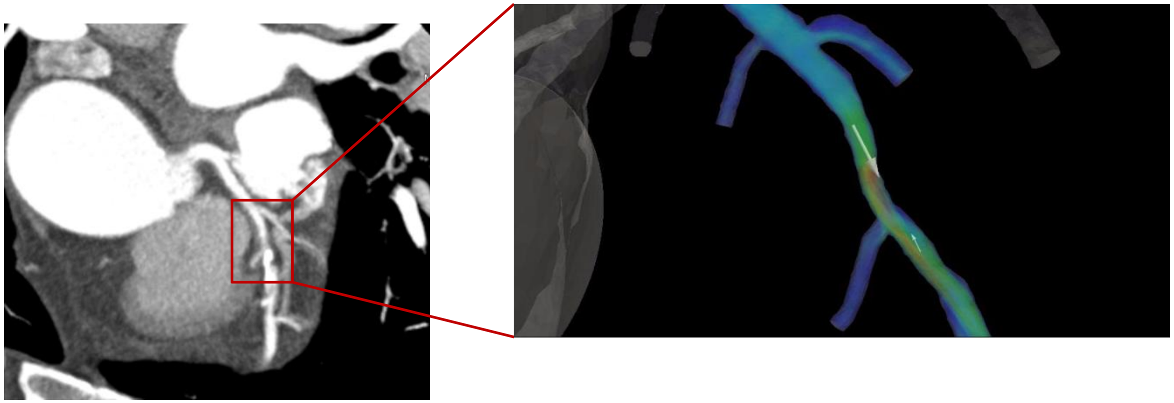
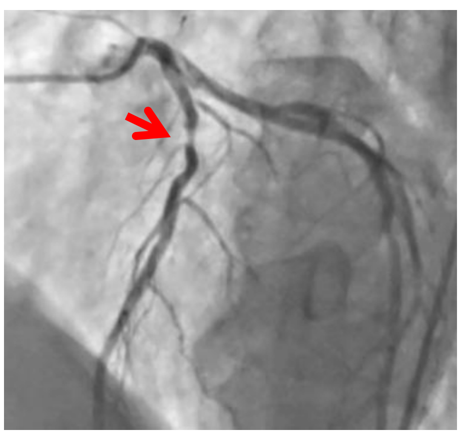
APS and Future Event: CASE

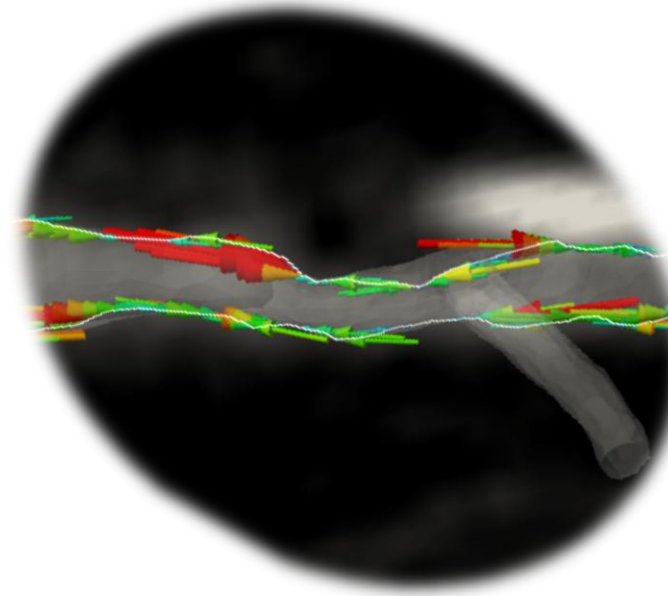
2011-04 CT, Asymptomatic

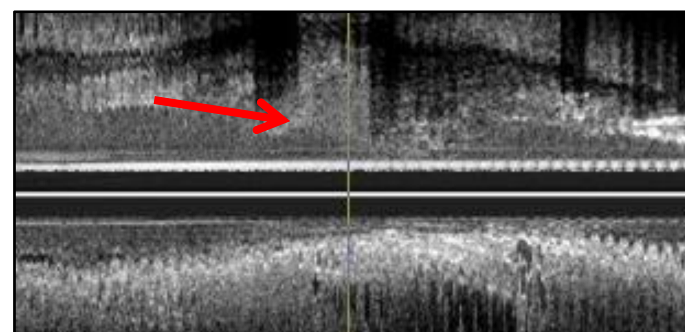


2012-06 Acute MI



	APS
Upstream	**9960 dyne/cm^2**
Downstream	1740 dyne/cm^2



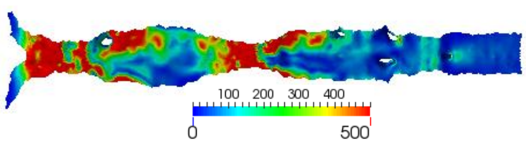


Choi GW…Koo BK. JACC imaging 2015

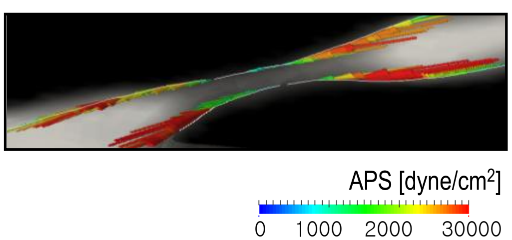
Comprehensive non-invasive assessment for CAD using cCTA and CFD

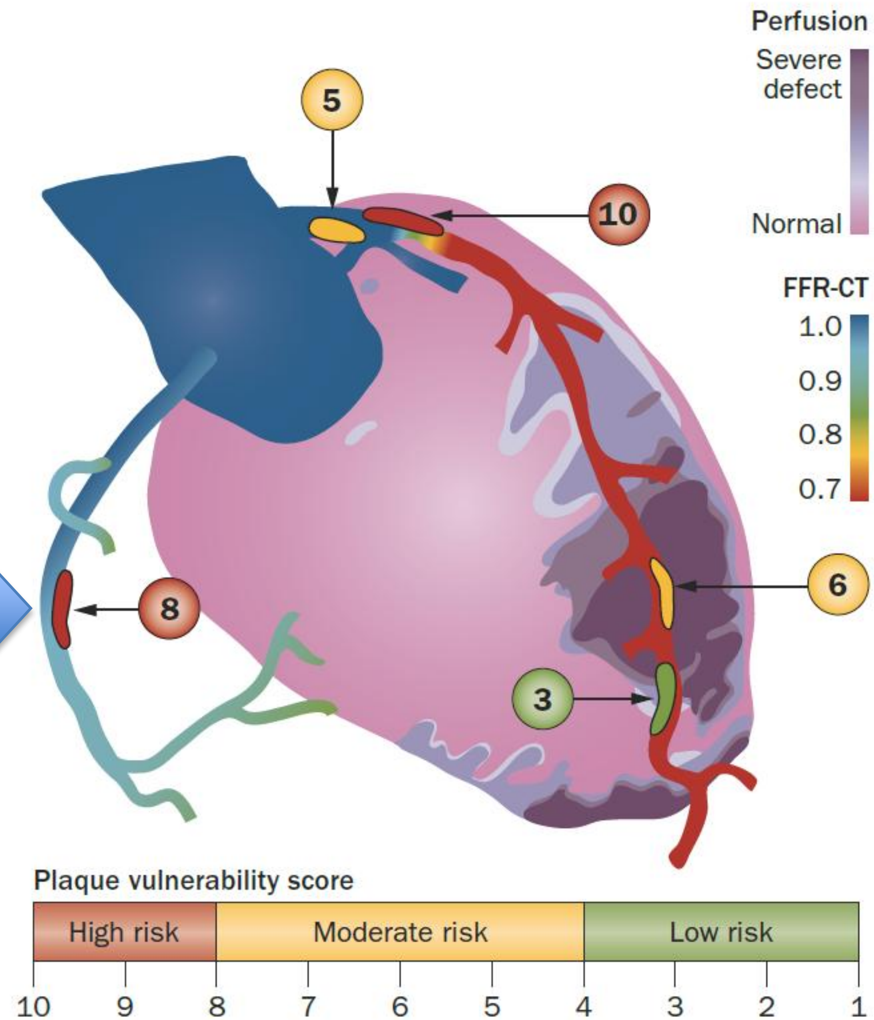
▪ **Non-invasive hemodynamic assessment**

- Wall shear stress



- Axial plaque stress





Mauroich_Horvat P,…, Hoffman U. Nat Rev Cardiol 2014

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Inje university, Korea: Joon-Hyung Doh, MD, PhD

Keimyung university, Korea**:** Chang-Wook Nam, MD, PhD

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Kobe university, Japan: Hiromasa Otake, MD, PhD