Non-invasive Hemodynamic Assessment for ACS Risk

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Invasive physiologic assessment is strongly recommended…..

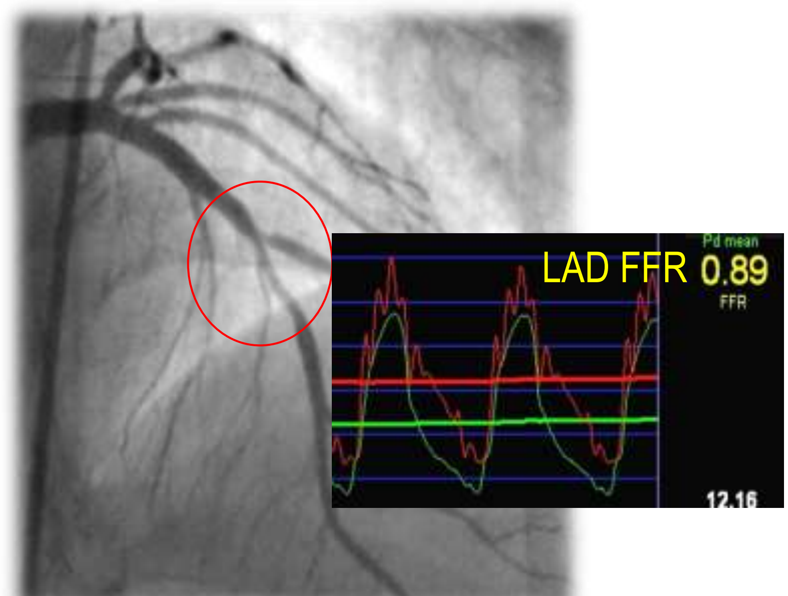
ESC/EACTS GUIDELINES

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)

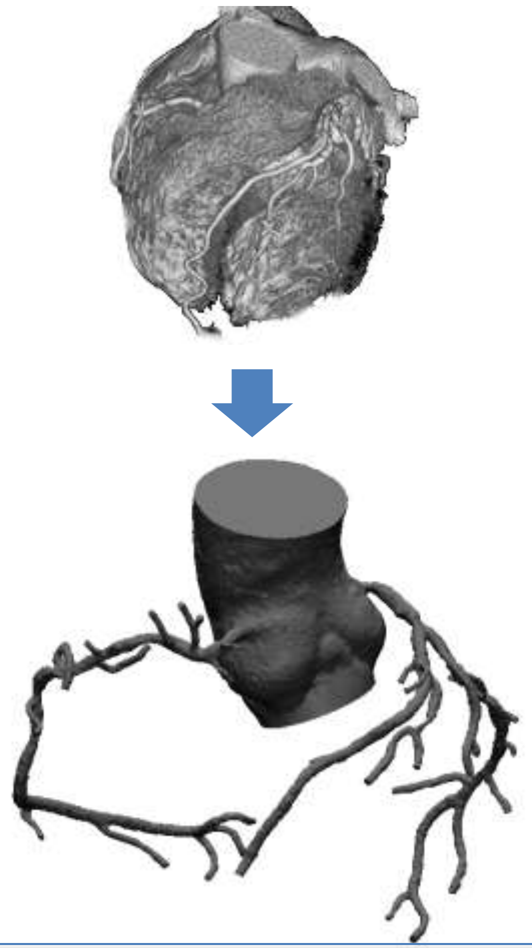
	Class[a]	Level[b]
FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available.	I	A
DES[d] are recommended for reduction of restenosis/re-occlusion, if no contraindication to extended DAPT	I	A

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



?

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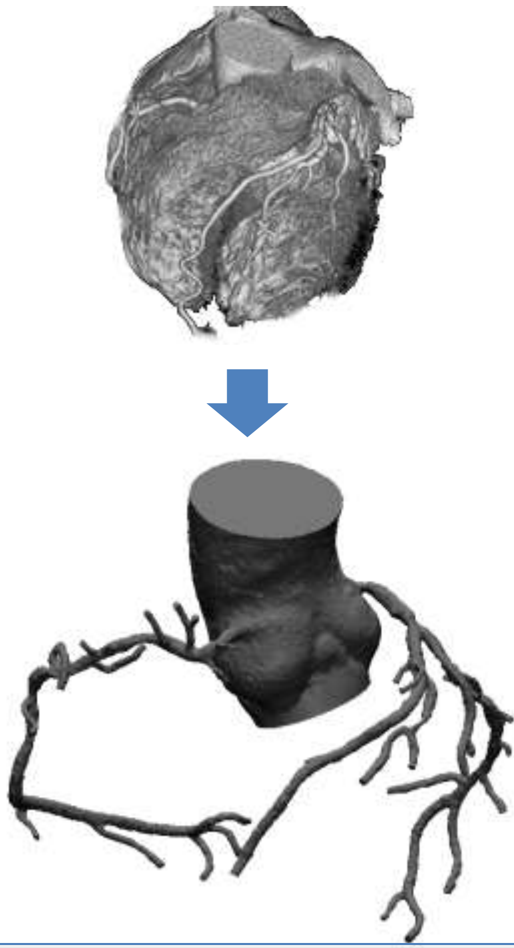
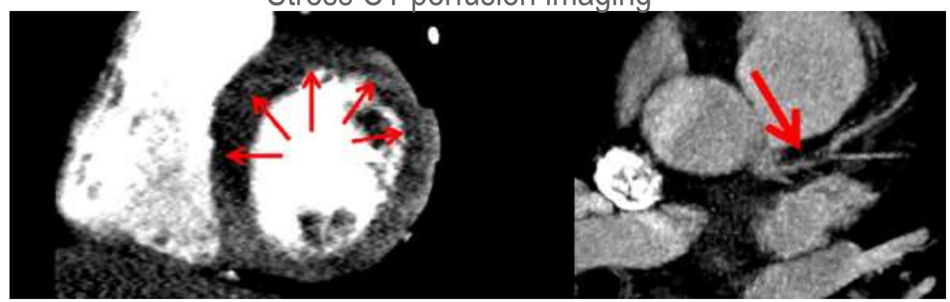
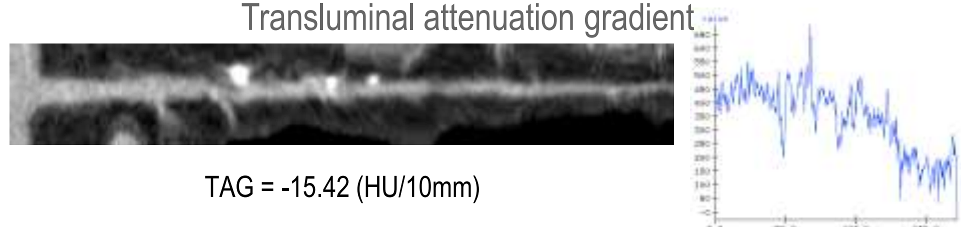


Hybrid imaging: CCTA + SPECT/PET

Stress CT perfusion imaging

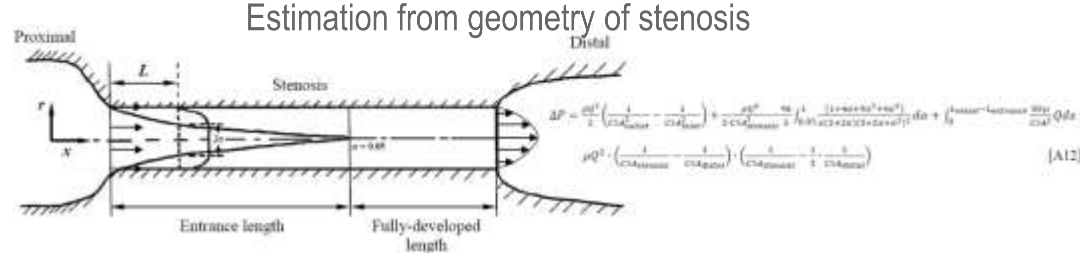


Transluminal attenuation gradient



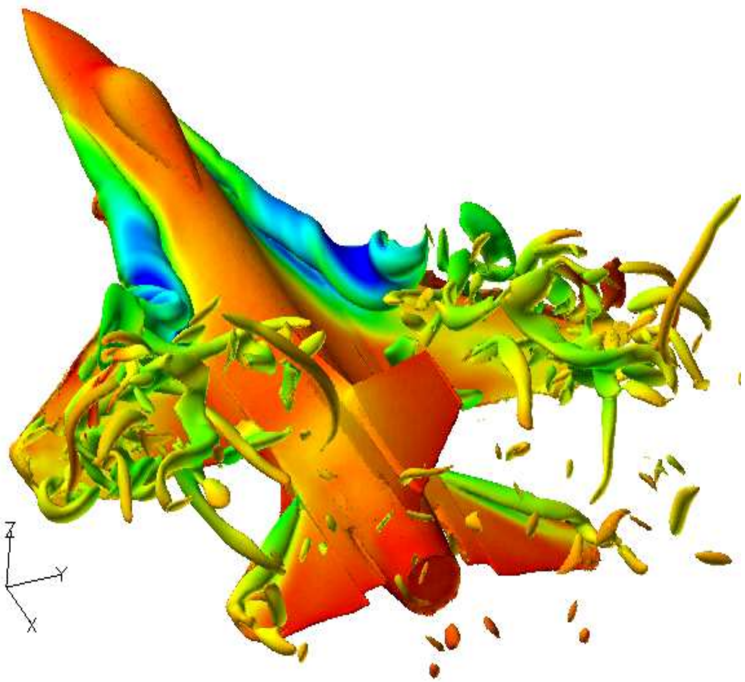
TAG = -15.42 (HU/10mm)

Estimation from geometry of stenosis



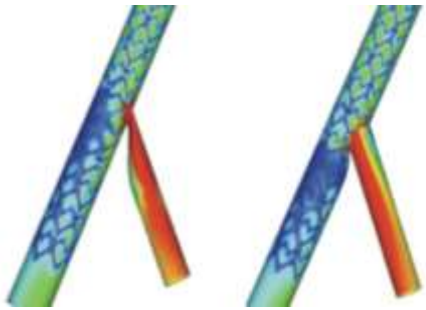
Computational Fluid Dynamics (CFD)

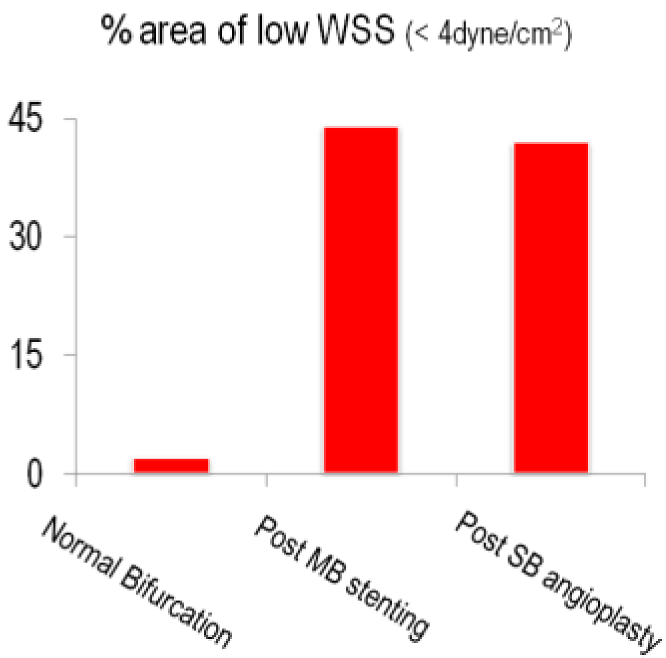
- Computational fluid dynamics (CFD) quantifies fluid pressure and velocity, based on physical laws of mass conservation and momentum balance.
- CFD is widely used in the aerospace and automotive industries for design and testing.



Courtesy of C. Taylor, HeartFlow

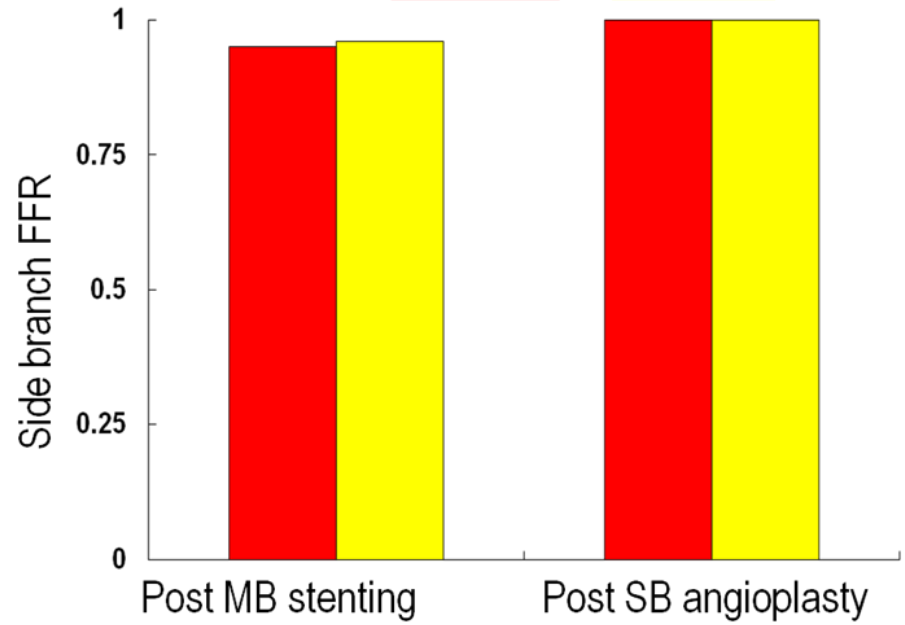
CFD in simple and idealized coronary models





FLOW PRESSURE

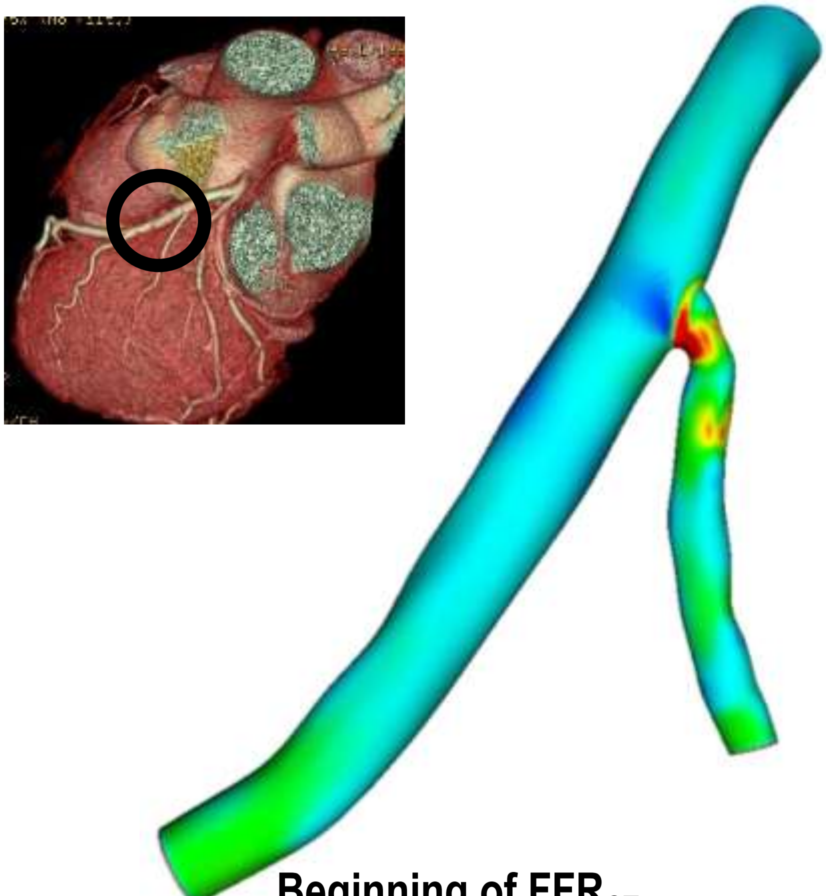
$$FFR = \frac{Q^{S}_{max}}{Q^{N}_{max}} = \frac{P_d}{P_a}$$



Williams & Koo, et al. J Appl Physiol 2010

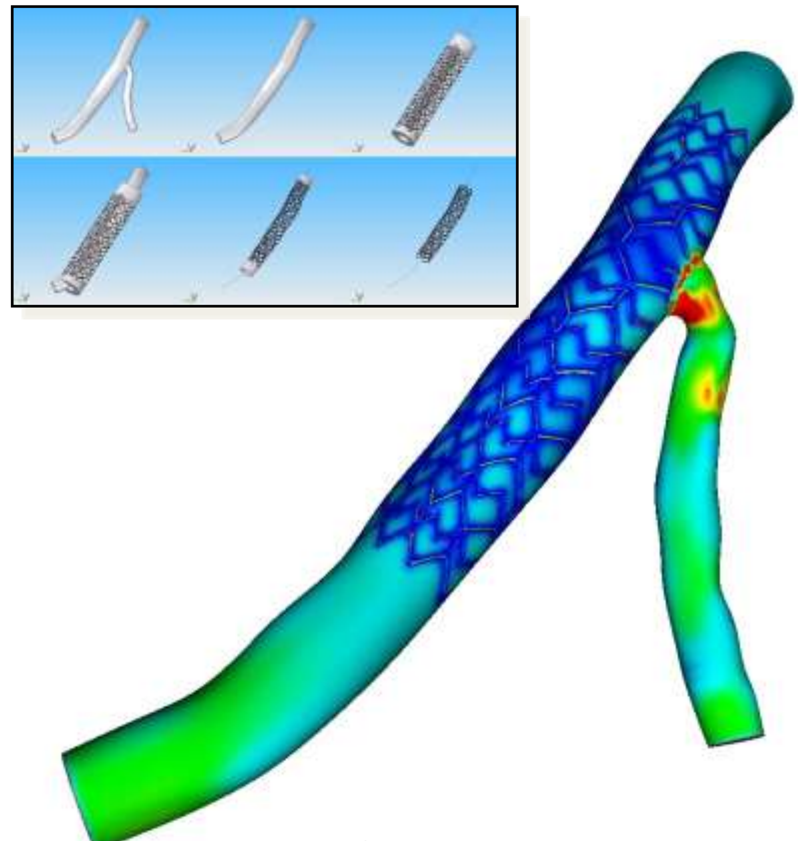
Patient Specific CFD models

Pre-Stent



Beginning of FFR_{CT}

Post-Stent



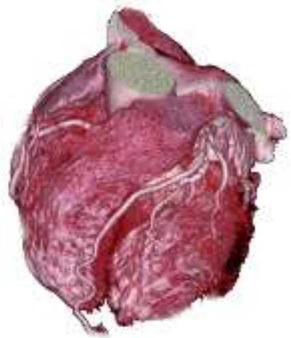
Beginning of Treatment Planner

Williams, Koo, LaDisa 2008

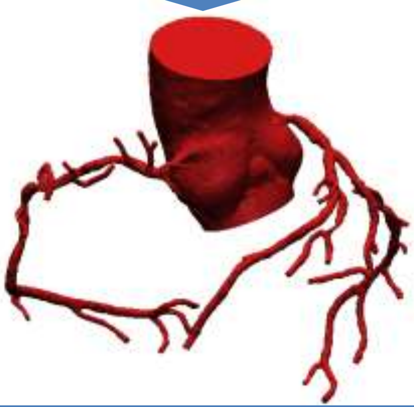
Patient-specific non-invasive FFR using CT & CFD

Computational Model based on CCTA

3-D anatomic model from CCTA

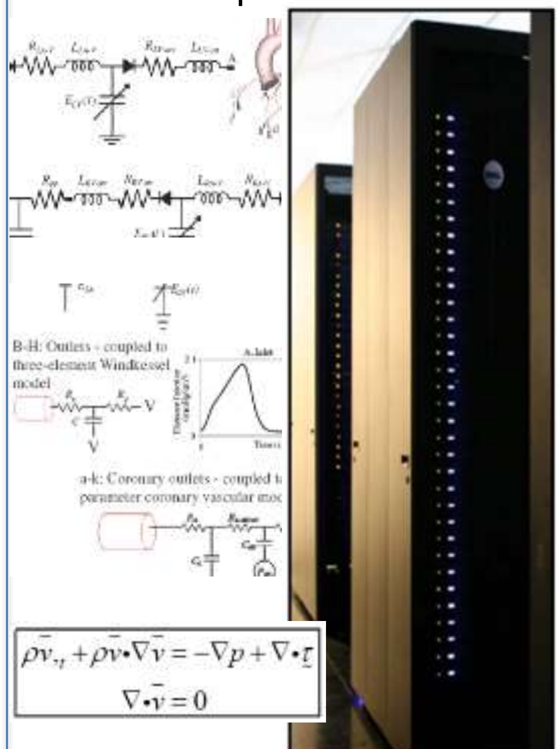


No additional imaging
No additional medications



Blood Flow Solution

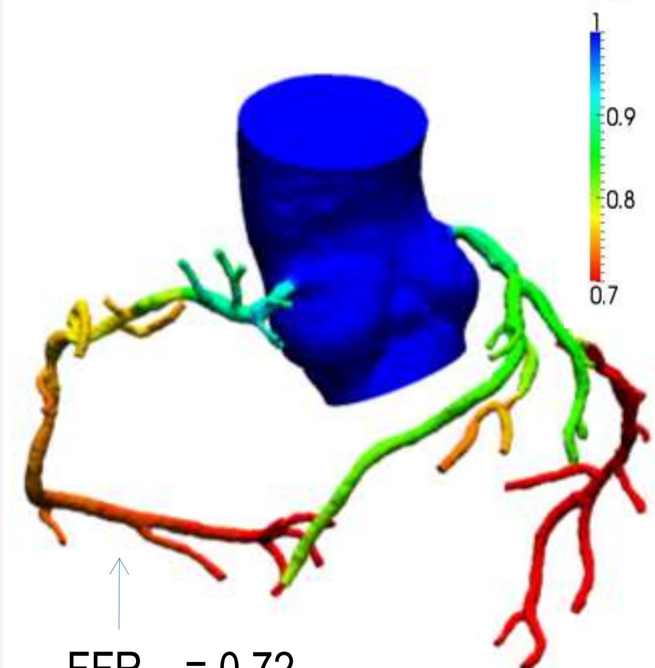
Blood flow equations solved on supercomputer



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

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

Establishing the clinical relevance.....

- **DISCOVER-FLOW**

  5 center FIH clinical trial

  N=103 patients

  Published in JACC

- **DeFACTO**

  17 center clinical trial

  N=252 patients

  Published in JAMA

- **NXT**

  10 center clinical trial

  N=251 patients

  Published in JACC

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doi:10.1016/j.jacc.2011.06.066

Cardiac Imaging

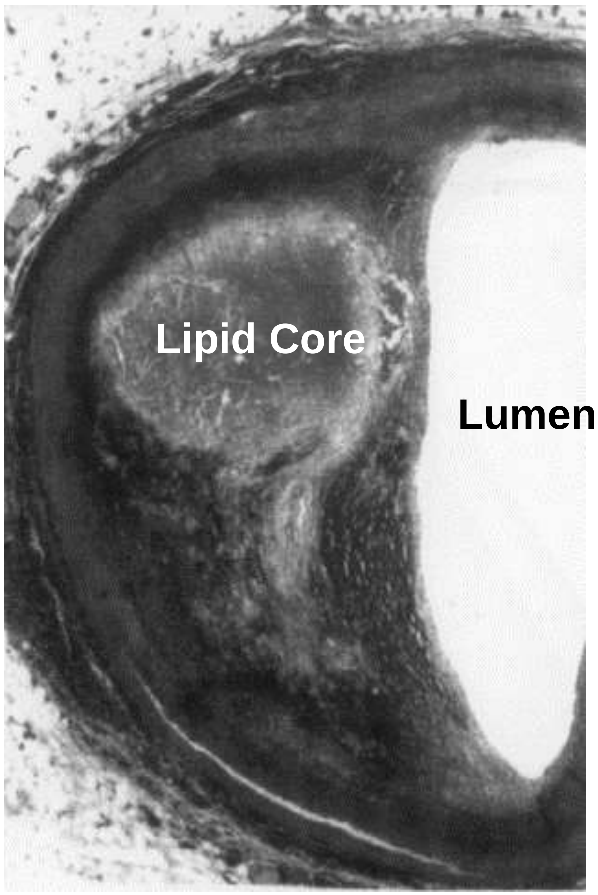
Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms

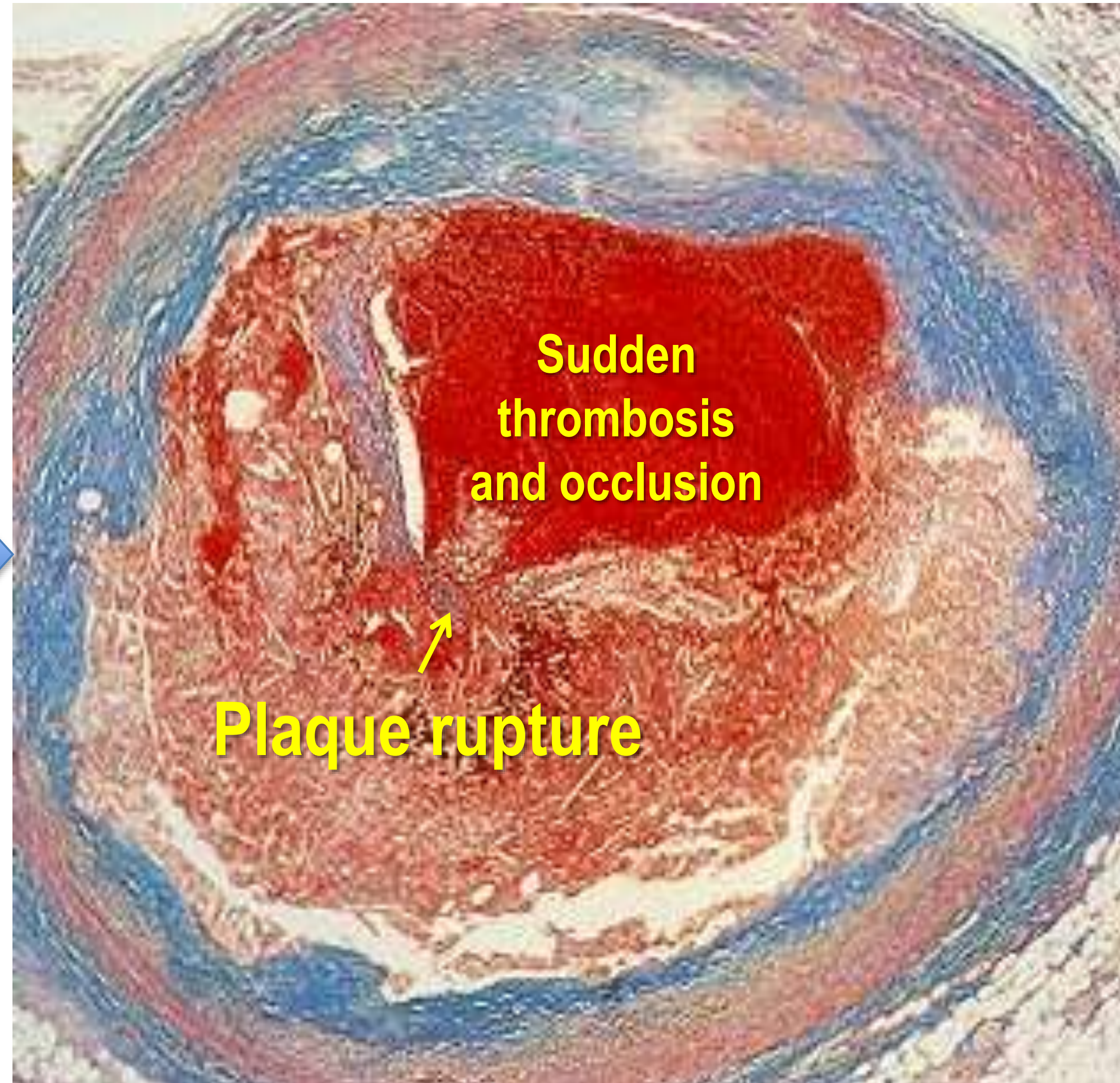
Results From the Prospective Multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) Study

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%**

Ischemia is bad, but plaque rupture is fatal!

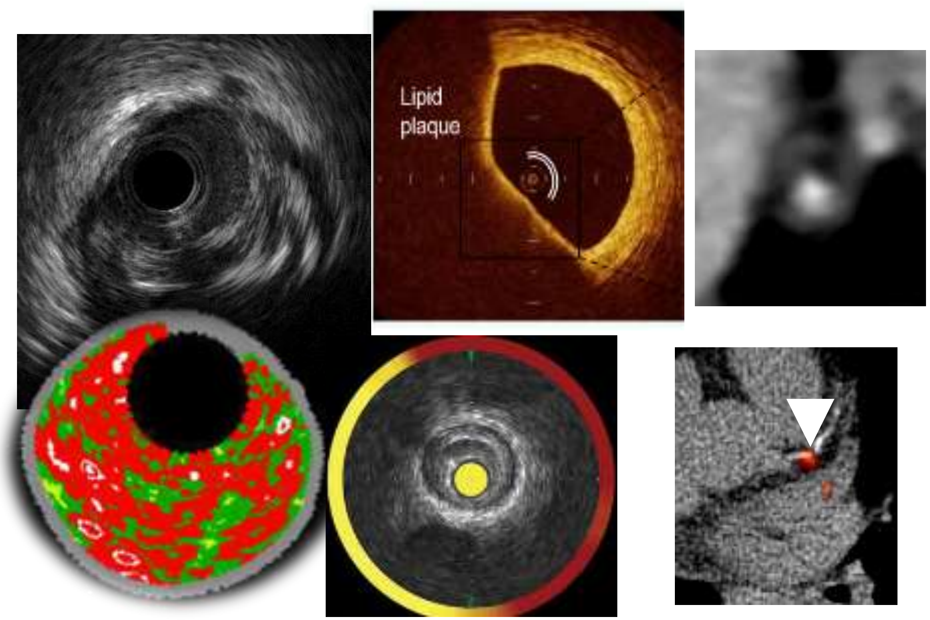




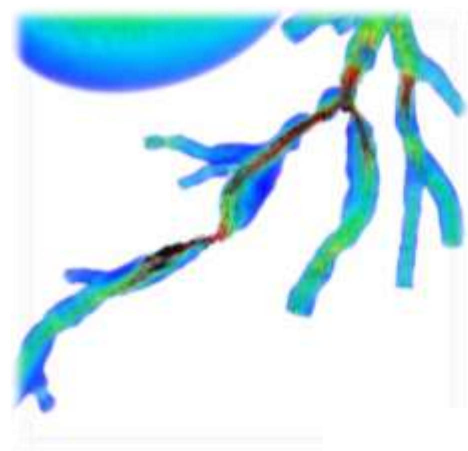
Vulnerability?

Plaque characteristics

Positive remodeling, posterior attenuation, lipid, cap thickness, TcFA, calcium, napkin ring, low density,…….



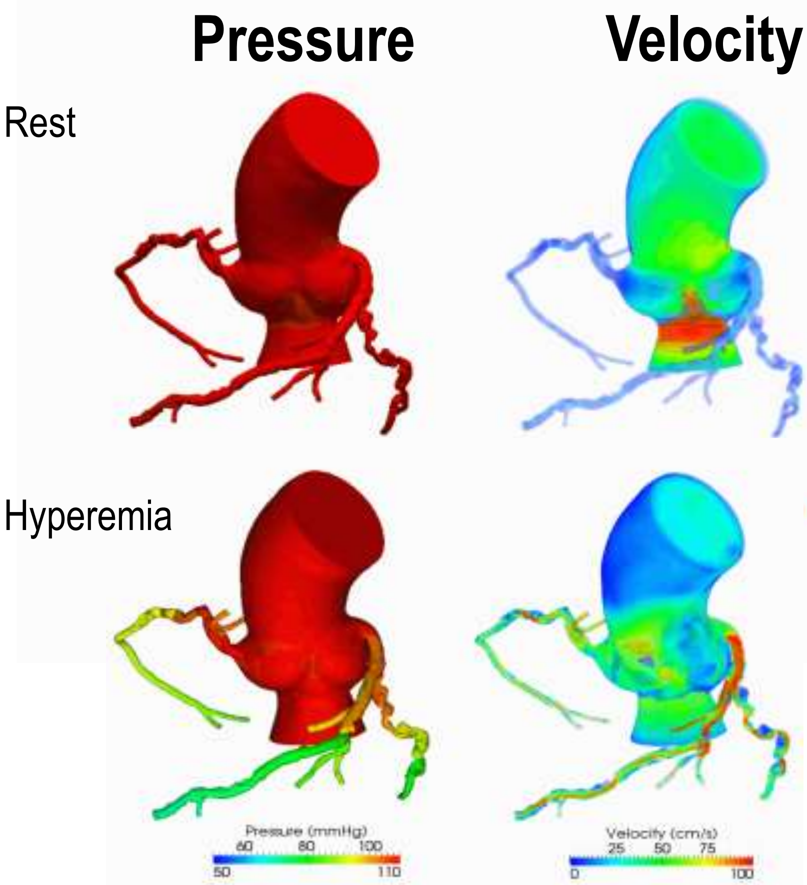
Hemodynamics



- Pressure
  - Pressure difference
  - Pressure gradient
  - Pressure recovery
  - FFR
- Flow velocity
- Flow rate
- Shear rate
- Wall shear stress
- Traction
- Oscillatory shear index
- Particle residence time
- Turbulent kinetic energy, ...

Non-invasive measurement of hemodynamics

Coronary CT angiography + Computational fluid dynamics



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)

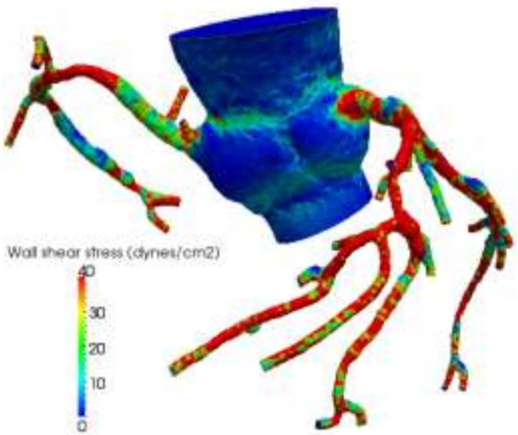
$$OSI = \frac{1}{2}\left(1 - \frac{\left|\frac{1}{T}\int_0^T t_s dt\right|}{\frac{1}{T}\int_0^T |t_s| dt}\right)$$

Particle Residence Time,
Turbulent Kinetic Energy,
...

Koo BK & HeartFlow, inc
Total plaque force project since 2013

Total Plaque Force Project

- To investigate the clinical relevance of hemodynamic force acting on the plaque
- **Project launching: Mar 12, 2013**



1st WSS model
: Mar 10, 2013

- **Projects**

  # 1: Validation of concept/methodology, role of WSS: *Heart 2016*

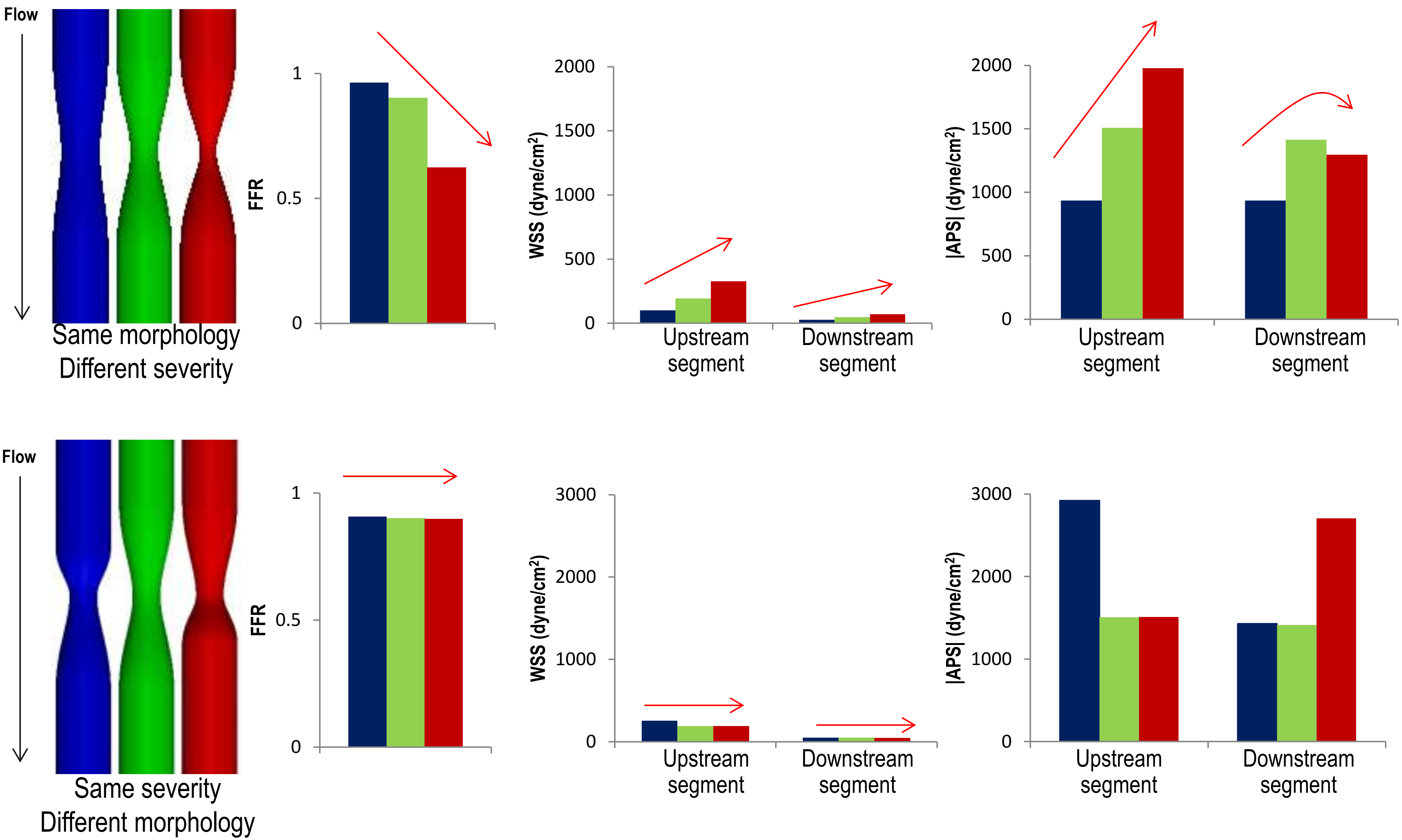
  # 2: Establishment of novel indices: APS and RG: *JACC imaging 2015*

  # 3: Validation of APS and RG using IVUS data: *JACC imaging 2017*

  # 4: Clinical validation of total plaque stress analysis: *JACC imaging 2018*

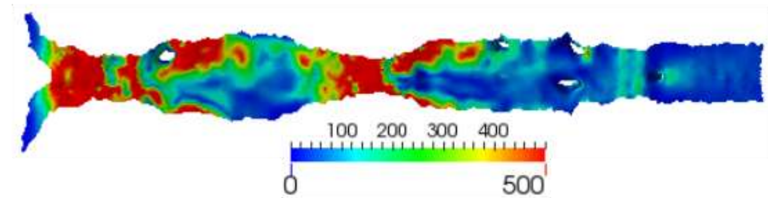
  # 5, 6, 7………………………..

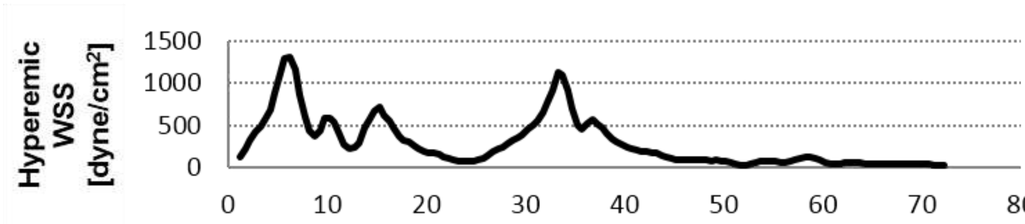
From Simple Idealized Models

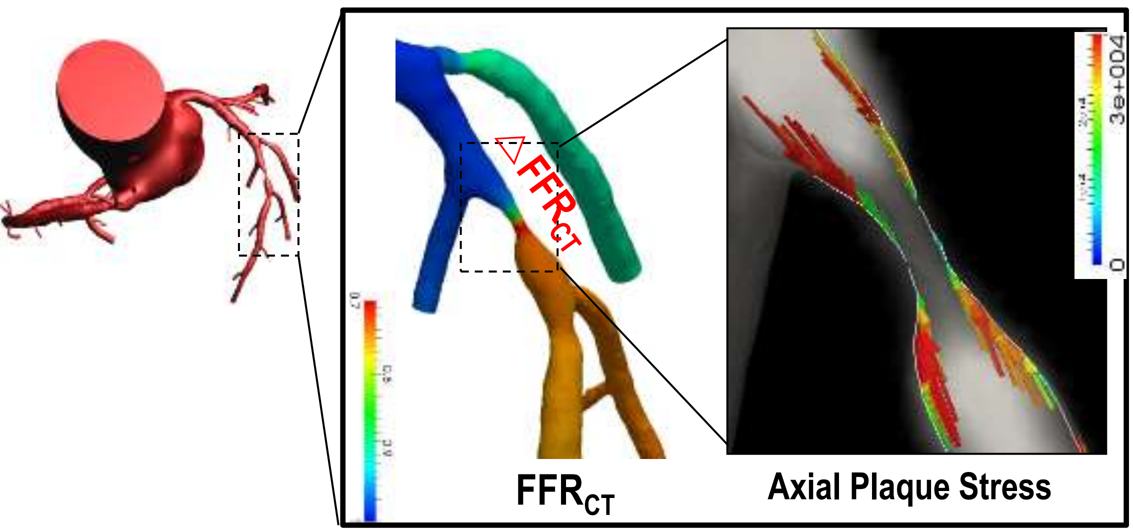


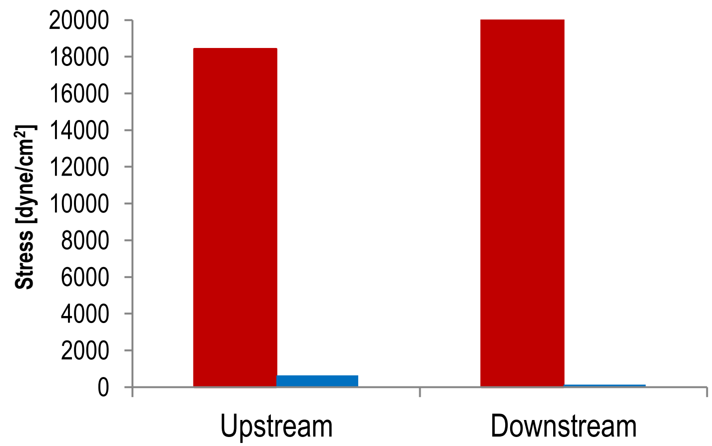
Choi G & Lee JM, Koo BK, et al. JACC imaging 2015

To Patient-specific Models









Choi G & Lee JM, Koo BK, et al. JACC imaging 2015
Park JB, Koo BK, et al. Heart 2016
Lee JM, Koo BK, et al. JACC imaging 2016

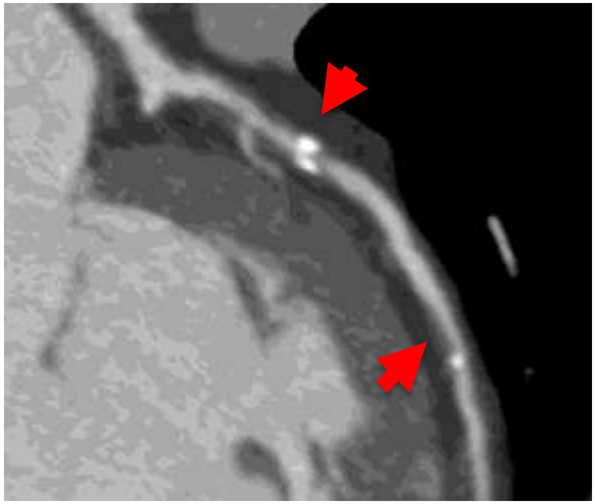
Non-invasive hemodynamic metrics

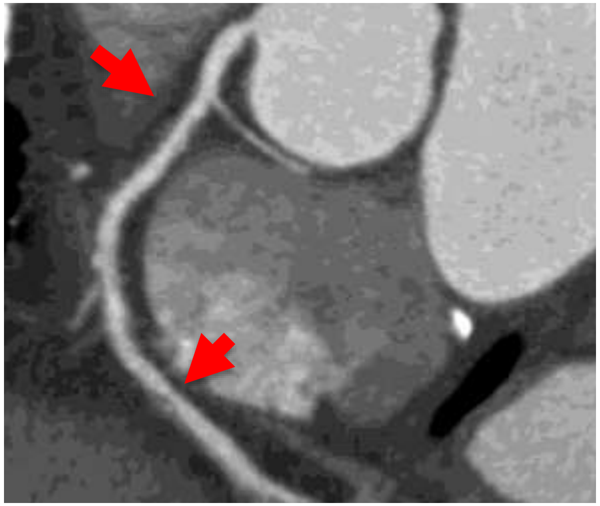
: FFR_{CT}, $\triangle FFR_{CT}$, WSS, APS…..

: Just another toy or Clinically relevant index?

How can we identify the culprit (vulnerable) lesion for future ACS?

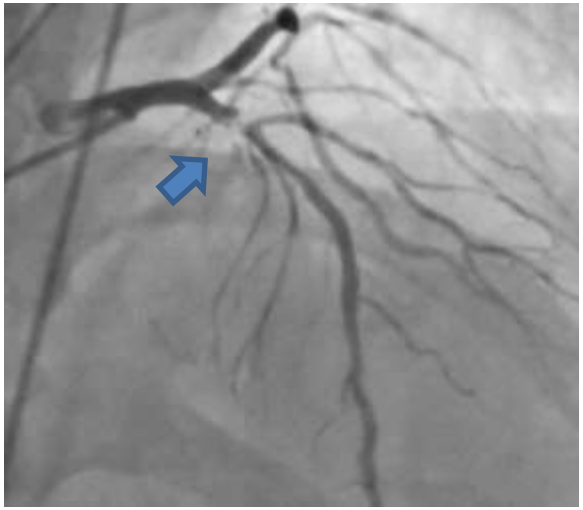
M/69, Asymptomatic

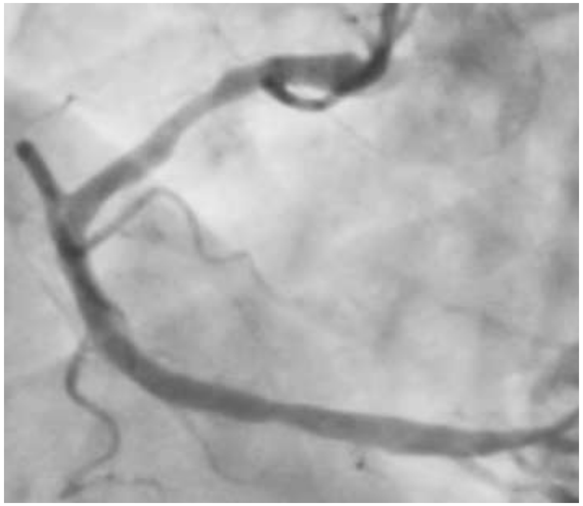




116 days later, the patient visited ER.

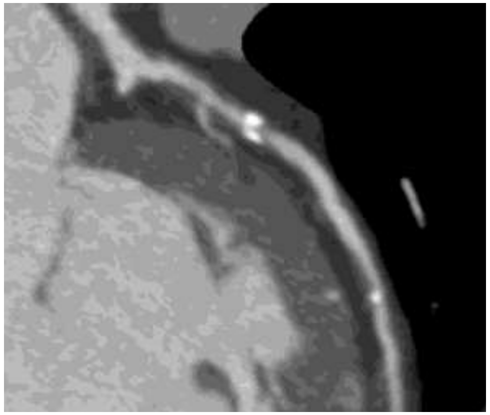
M/70, Non-ST elevation MI



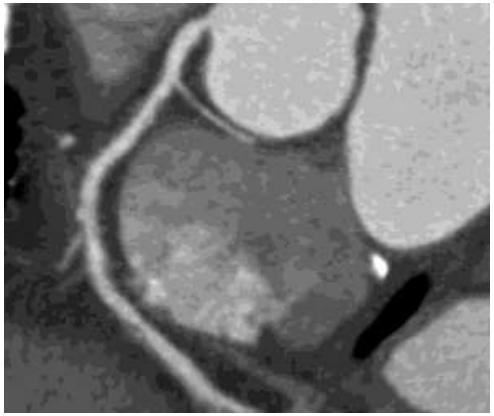


How can we identify the culprit lesion for future ACS?

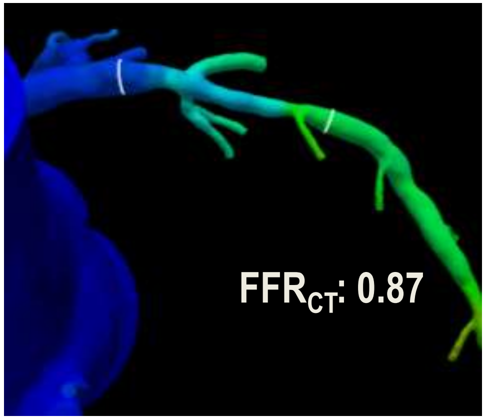
Current Paradigm

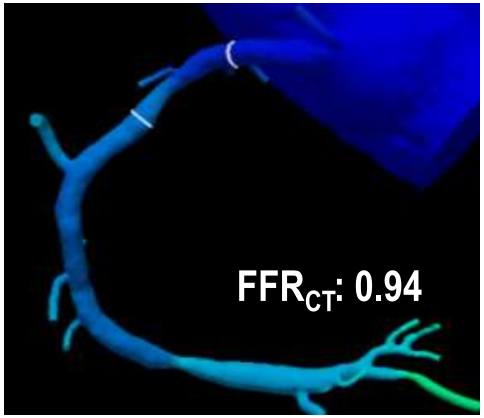


Stenosis severity
Adverse plaque characteristics



Non-invasive hemodynamic assessment





$$\triangle FFR_{CT} = \text{proximal } FFR_{CT} - \text{distal } FFR_{CT} = \frac{P_X}{P_{Aorta}} - \frac{P_Y}{P_{Aorta}} = \frac{\Delta P}{P_{Aorta}}$$

where X and Y represent the lesion start and ending points, respectively, and P represents pressure.

$$WSS_{lesion} = \frac{1}{A}\int_X^Y \left\|\overrightarrow{WSS}\right\| dA$$

where A represents the surface area of defined lesion from X and Y

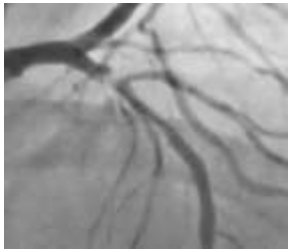
$$|\text{Axial Plaque Stress}_{lesion}| = \left|\frac{1}{A}\int_X^Y (\vec{t}\cdot\vec{c})\, dA\right|$$

where $\vec{t}\cdot\vec{c}$ represents the dot product of the traction vector ($\vec{t}$) and tangential vector of vessel centerline ($\vec{c}$).

De Bruyne B, et al. N Engl J Med 2014:371:1208-17
Samady H, et al. Circulation 2011;124:779
Park JB, et al. Heart 2016;102:1655-61
Choi G & Lee JM, et al. JACC Cardiovasc Imaging 2015;8:1156-66
Lee JM, et al. JACC Cardiovasc Imaging 2016

EMERALD study

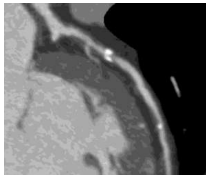
Exploring the **ME**chanism of the Plaque **R**upture in **A**cute Coronary Syndrome using Coronary CT Angiography and ComputationaL Fluid **D**ynamics

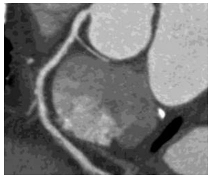


Patients with Acute Coronary Syndrome
From 11 International Cardiovascular Centers
(Korea, Japan, Belgium, Denmark, the Netherlands)

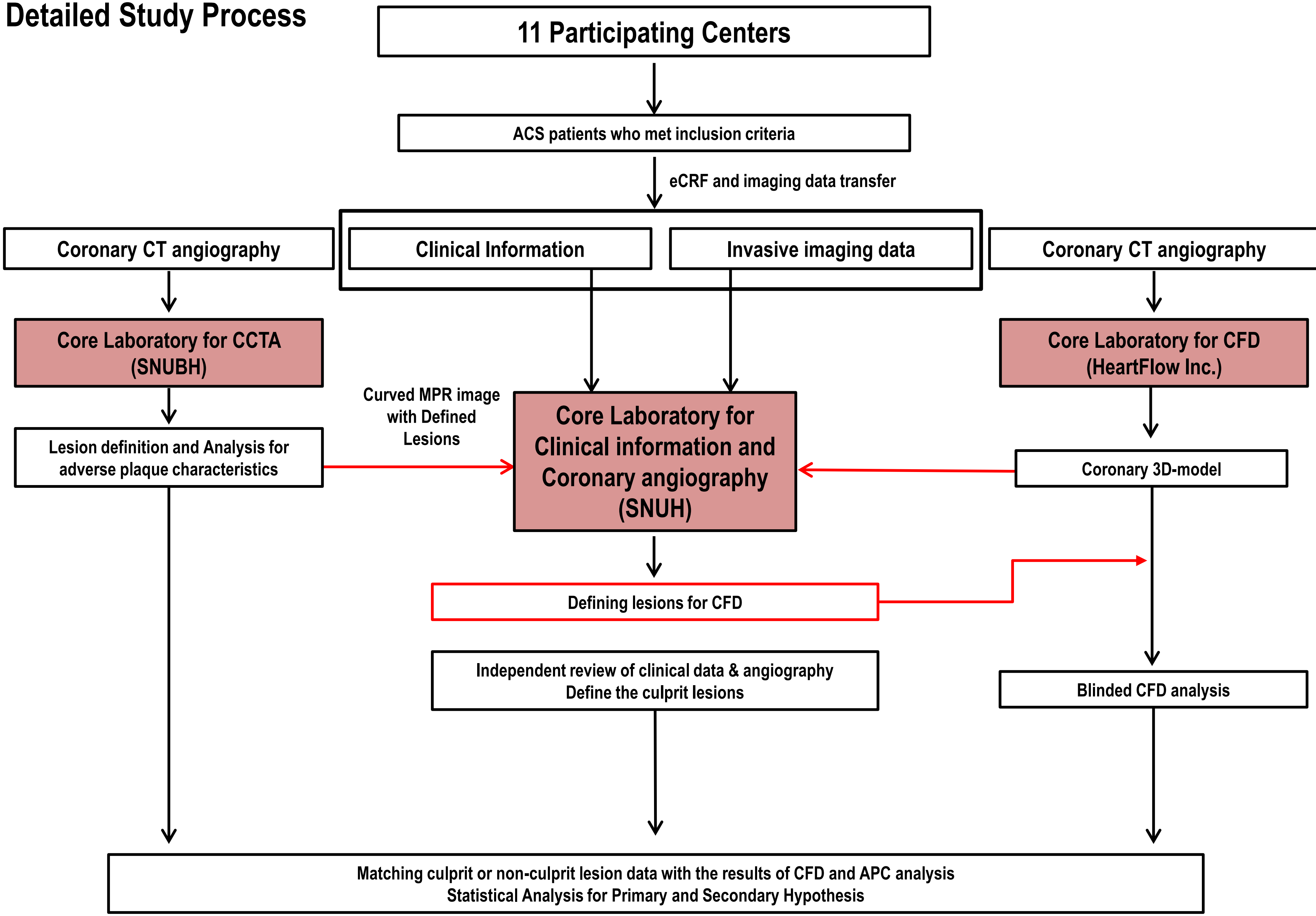
↓

Patients who underwent Coronary CT angiography
before ACS event (1 month – 2 year before the event)
(N=120)





Detailed Study Process



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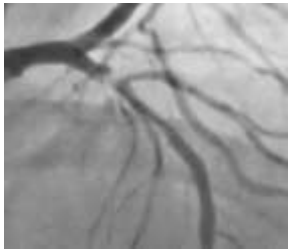

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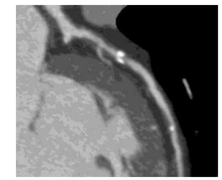
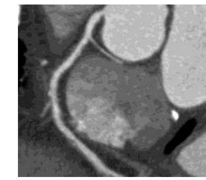




Patients who underwent Coronary CT angiography
before ACS event (1 month – 2 year before the event)
(N=120)

↓

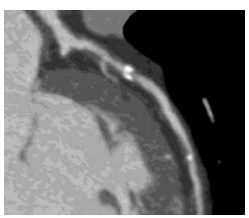
Validation with clinical data, cCTA and coronary angiography (3 independent core labs)

→ **Exclusion (N=41)**
- No adequate CT image: 27
- Unclear diagnosis or No definite culprit lesion on Angiography: 10
- No definite lesion on cCTA: 4

Exclusion by core laboratory due to CT image quality (N=7)

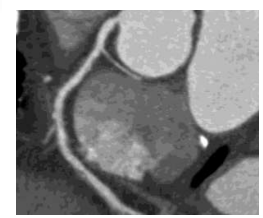
↓

Final Enrollment for cCTA and CFD analysis
(72 patients, 216 lesions)



CASE
Culprit for subsequent ACS (N=66)

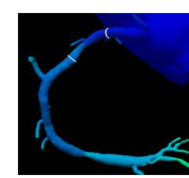
CONTROL
Non- Culprit Lesion (N=150)



cCTA analysis
adverse plaque characteristics
(Core Lab – SNU Bundang Hospital)

\+

CFD analysis
Non-invasive hemodynamics
(Core Lab - HeartFlow Inc.)



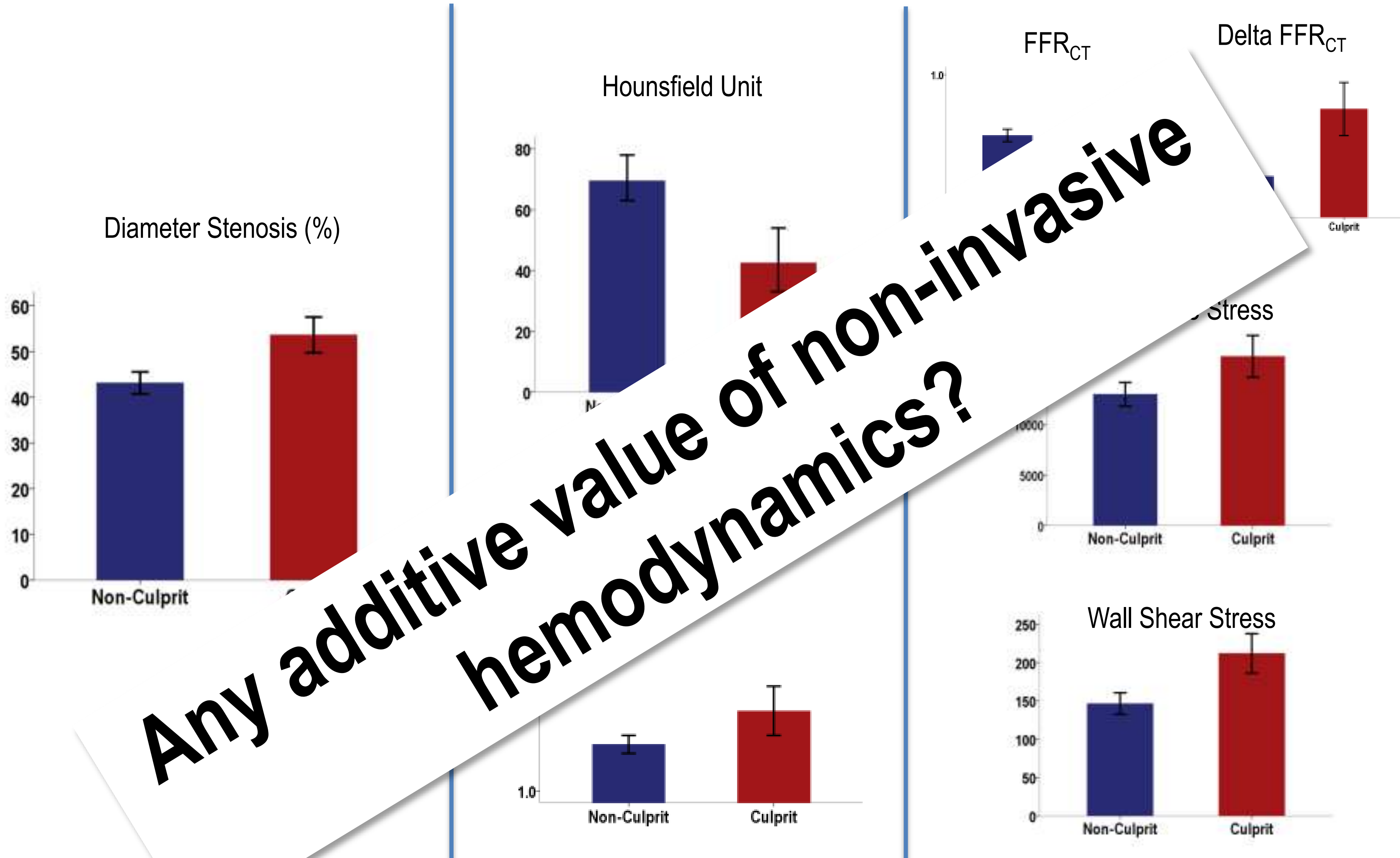
Characteristics of the Patients and Lesions

Patients (n = 72)	
Age, years	69·9 ± 12·7
Male	54 (75·0%)
Median interval between cCTA and ACS, days	**338·0 (161·5-535·0)**
Cardiovascular Risk Factors	
Hypertension	46 (63·9%)
Diabetes mellitus	37 (51·4%)
Hypercholesterolemia	35 (48·6%)
Clinical Presentation	
Myocardial infarction	**67 (93·0%)**
NSTEMI	41 (56·9%)
STEMI	26 (36·1%)
Unstable angina	5 (6·9%)

Lesion characteristics (n = 216)	
Lesion location	
Left main to LAD	**87 (40·3%)**
LCX / RCA	48 (22·2%) / 81 (37·5%)
Culprit vessel (n=66)	
Left main to LAD	39 (59·1%)
LCX / RCA	9 (13·6%) / 18 (27·3%)
Lesion profile	
Minimal lumen area, mm^2	2·75 ± 1·59
Diameter stenosis, %	**46·9 ± 16·1**
Distance from ostium to MLA, mm	47·1 ± 22·6
Lesion length, mm	17·6 ± 7·4
FFR_{CT}	0·77 ± 0·15

Lee JM & Choi GW, Koo BK….. JACC imaging 2018

EMERALD study: Culprit vs. Non-culprit



SNUH
Seoul National University Hospital
Cardiovascular Center

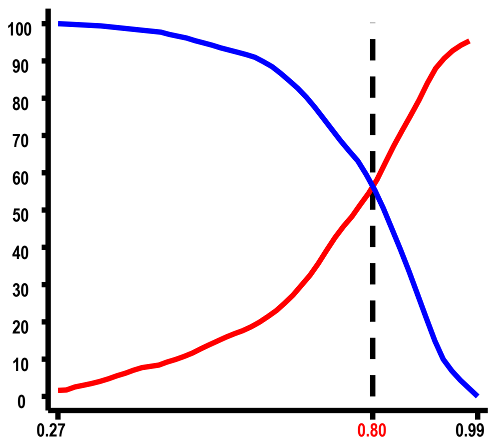
All P values: significant

Lee JM & Choi GW, Koo BK….. JACC imaging 2018

Cut-off Value for Adverse Hemodynamic Characteristics (AHC)

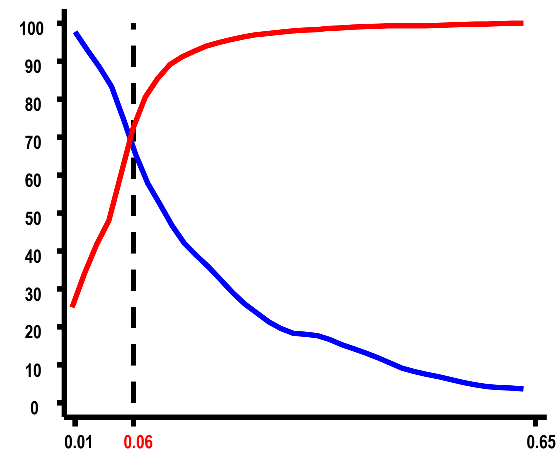
Sensitivity
Specificity

FFR_{CT}: 0.80



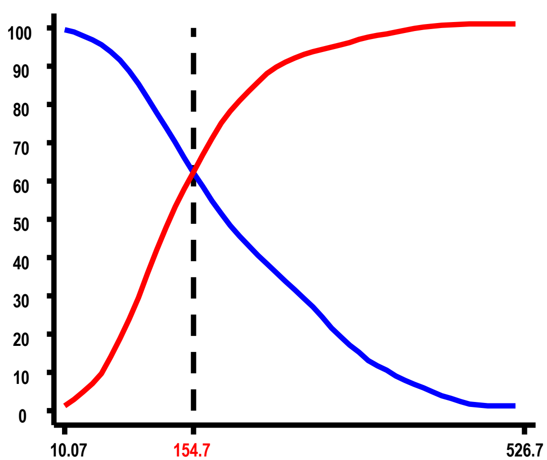
FFR_{CT}	
BCV	0.80
Sensitivity	54.6%
Specificity	58.0%
PPV	40.0%
NPV	71.3%
Accuracy	56.8%

△FFR_{CT}: 0.06



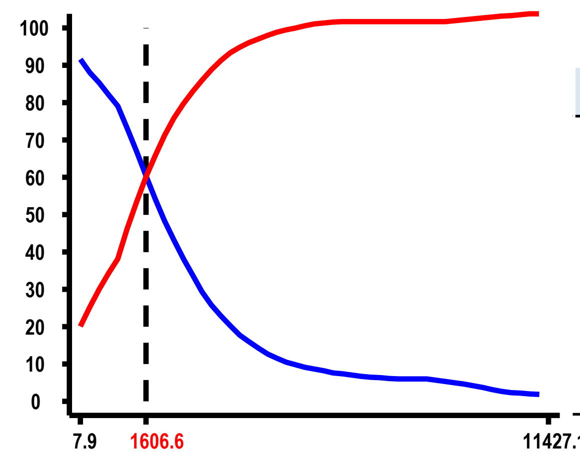
Delta FFR_{CT}	
BCV	0.06
Sensitivity	62.3%
Specificity	71.3%
PPV	52.8%
NPV	78.7%
Accuracy	68.2%

Wall Shear Stress (dyn/cm^2): 154.7



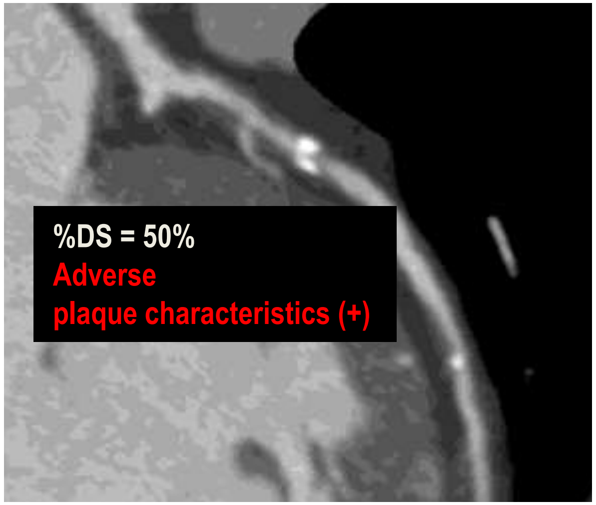
Wall Shear Stress	
BCV	154.7
Sensitivity	64.9%
Specificity	61.3%
PPV	46.3%
NPV	77.3%
Accuracy	62.6%

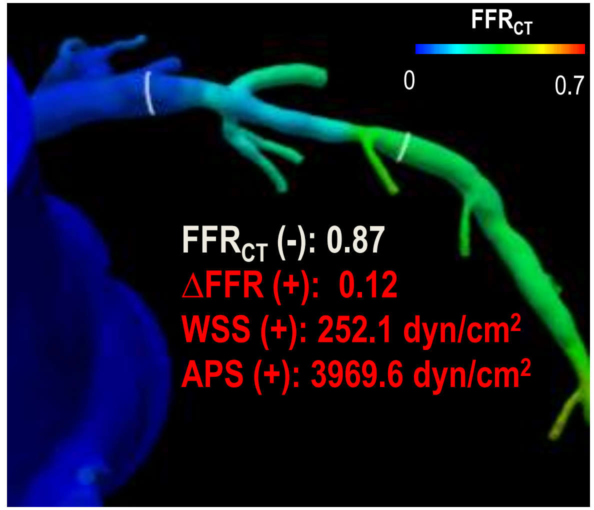
Axial Plaque Stress (dyn/cm^2): 1606.6

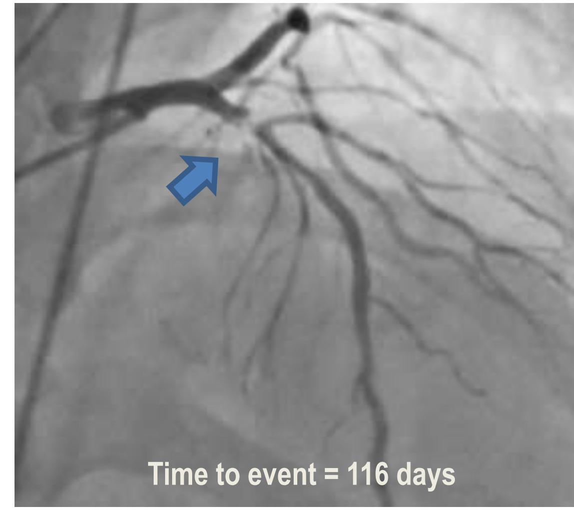


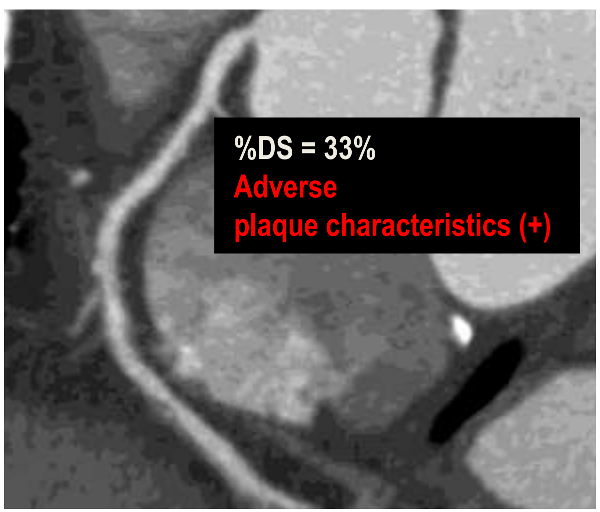
∣Raw APS∣	
BCV	1606.6
Sensitivity	59.7%
Specificity	62.0%
PPV	41.2%
NPV	77.5%
Accuracy	61.3%

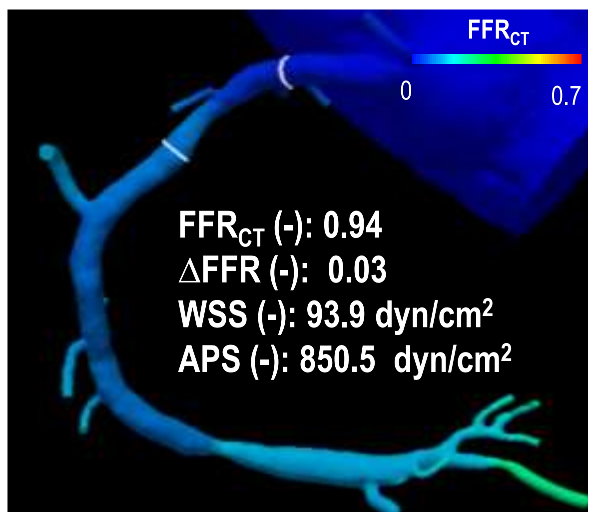
How can we identify the culprit lesion for future ACS?

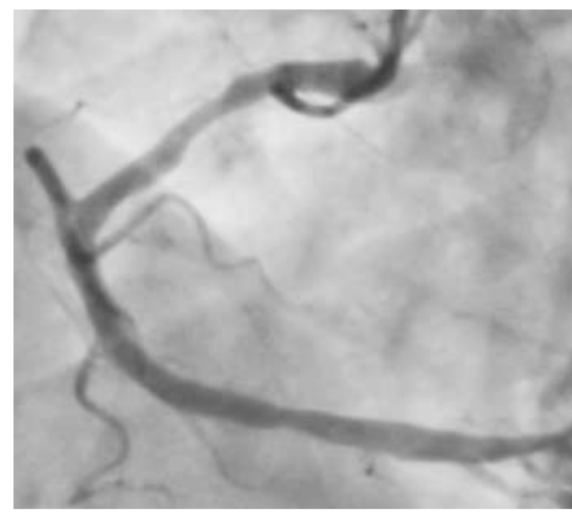












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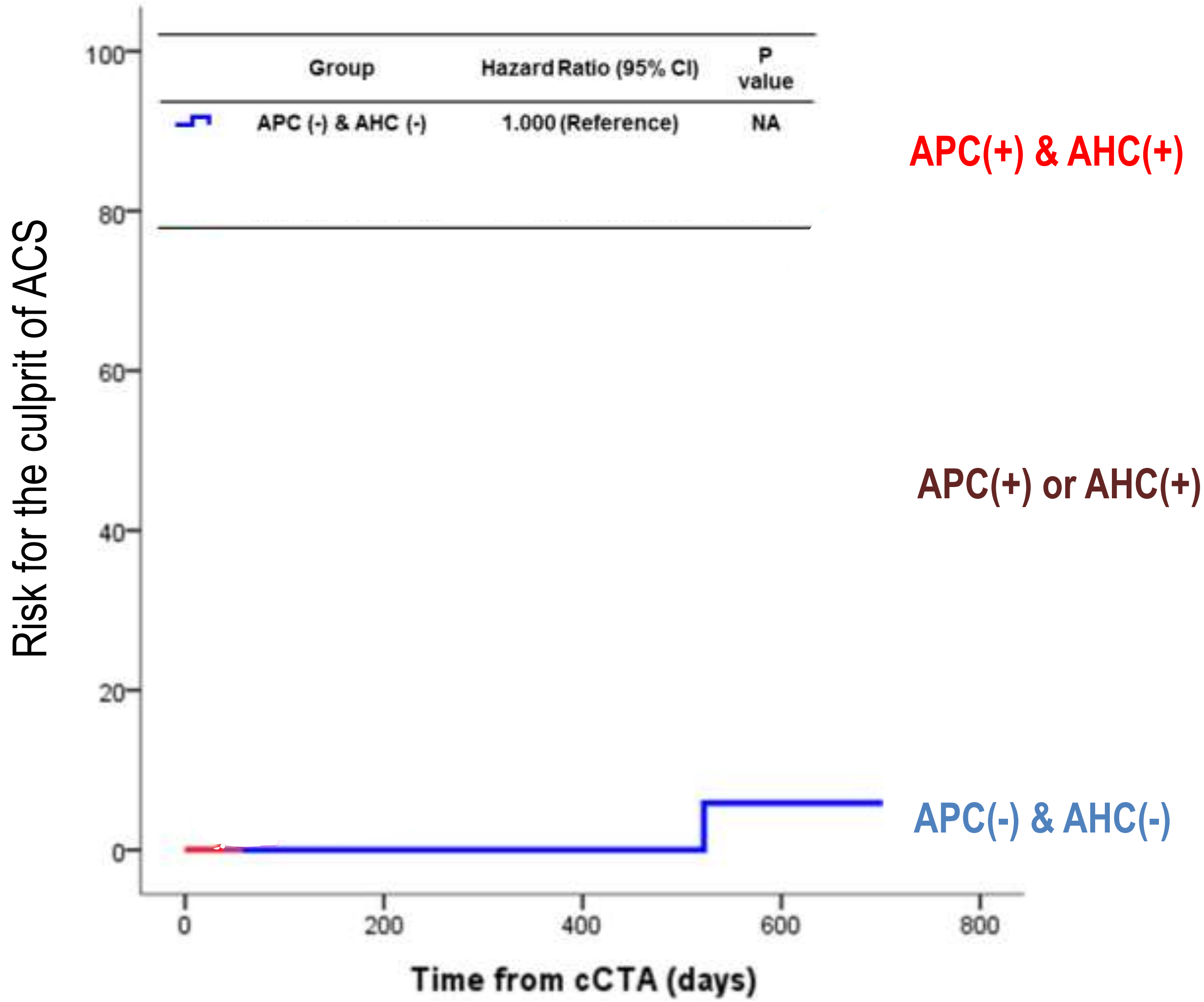
Plaque characteristics (APC), Hemodynamic characteristics (AHC) and Risk for the culprit of future ACS



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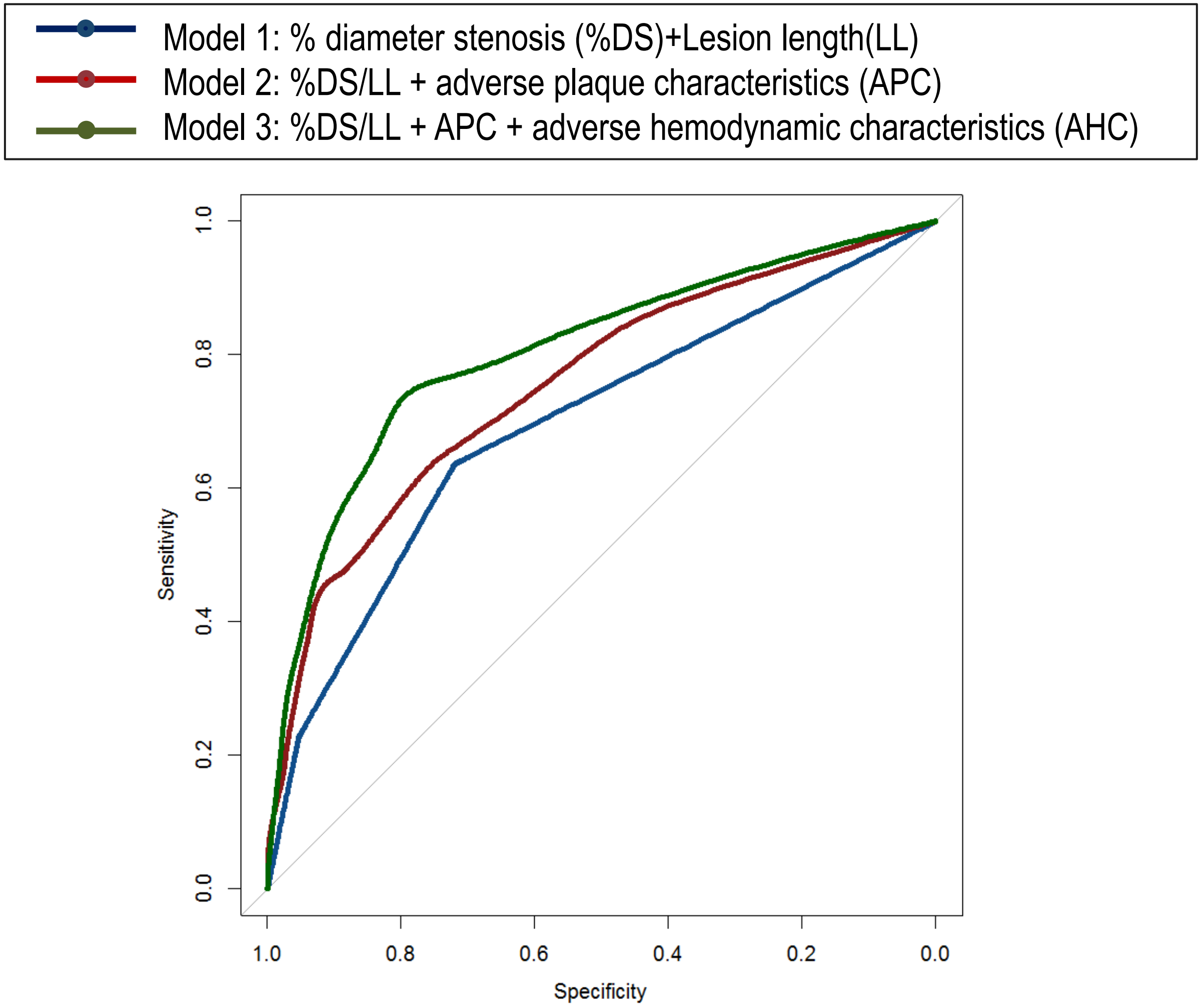
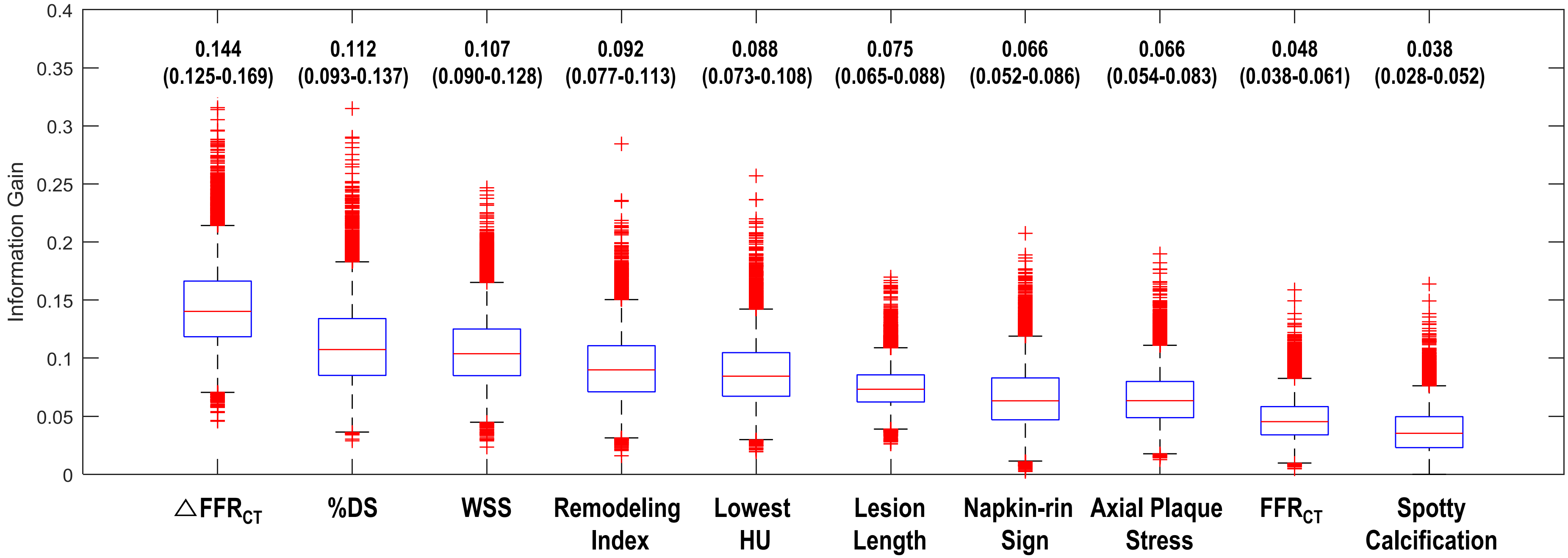
Prediction of ACS risk

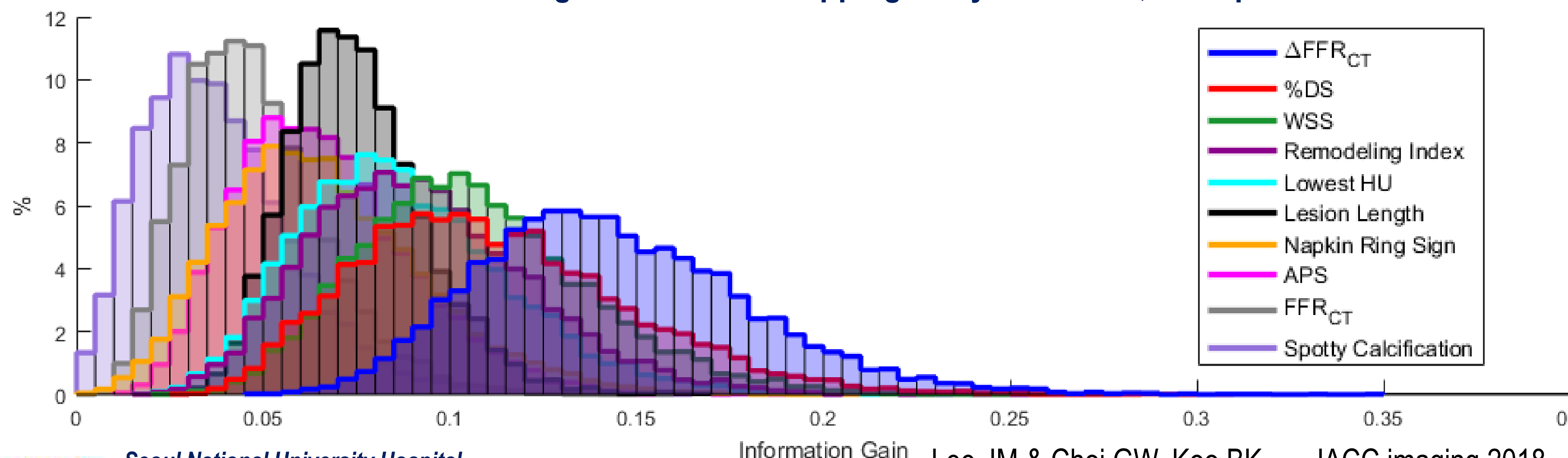


Prediction Model	C-index	Difference with Prev. Model	P value	NRI	P value	IDI	P value
Model 1	0.709						
Model 2	0.747	0.038	0.006	0.355	0.001	0.671	<0.001
Model 3	0.789	0.025	0.014	0.287	0.047	0.368	<0.001

Information gain of each parameter



Distribution of information gain from bootstrapping analysis with 10,000 replicates



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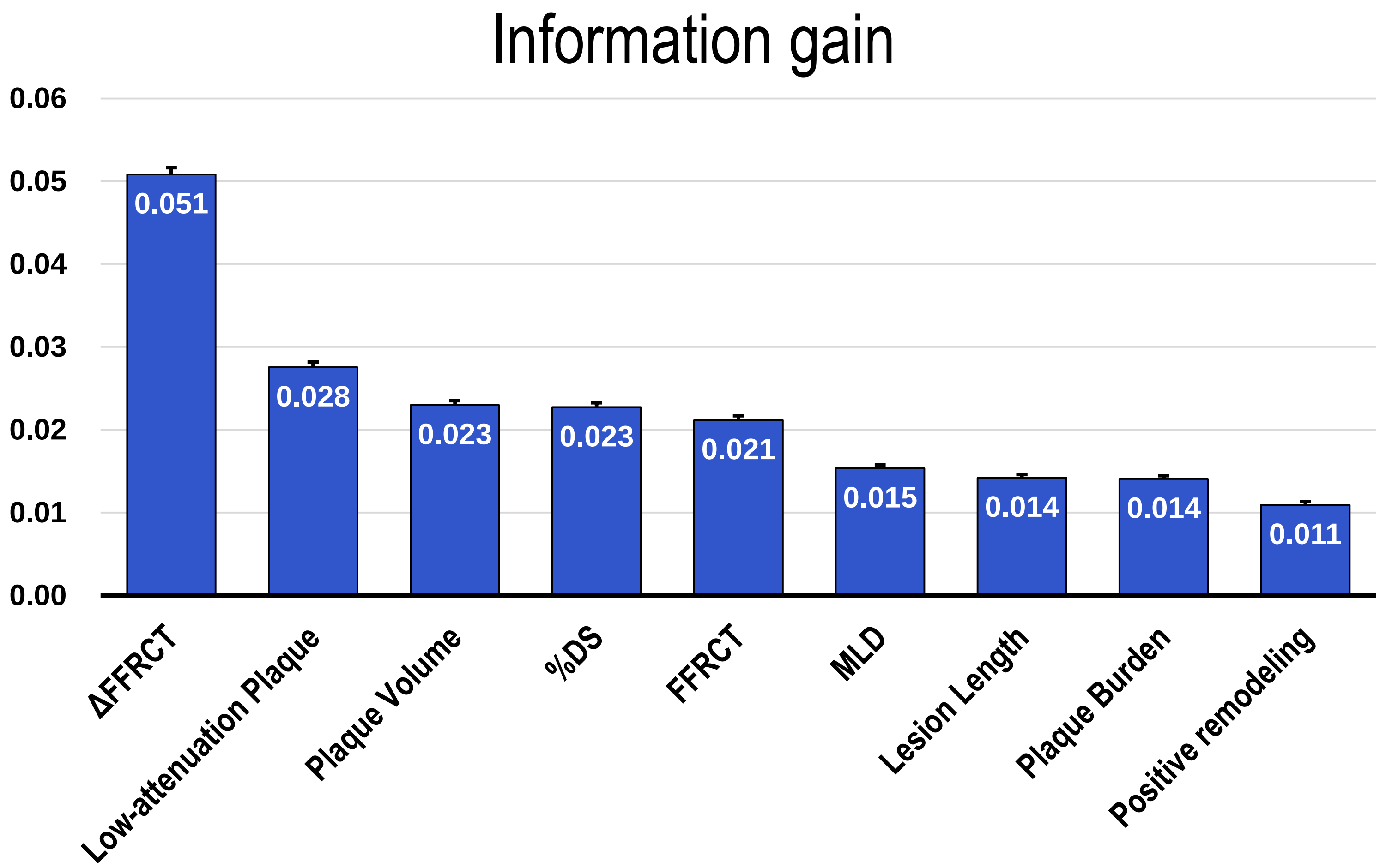
Contribution in Non-Obstructive lesions



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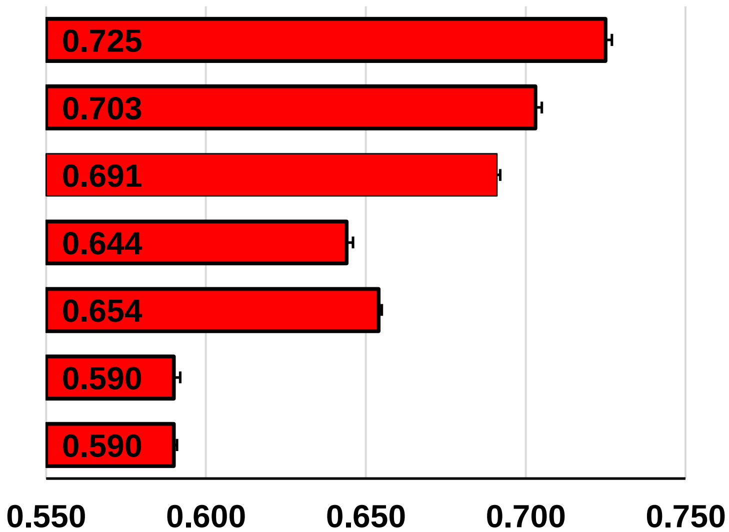
Contribution of different index in Non-Obstructive lesions



Model 7 : Plaque Volume + Low-attenuation plaque + ΔFFR_{CT}

Model 6 : Low-attenuation plaque + ΔFFR_{CT}

Model 5 : Plaque Volume + ΔFFR_{CT}

Model 4 : Plaque Volume + Low-attenuation plaque

Model 3 : ΔFFR_{CT}

Model 2 : Low-attenuation plaque

Model 1 : Plaque Volume

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
AUC	**0.59**	**0.59**	**0.65**	**0.64**	**0.69**	**0.70**	**0.73**

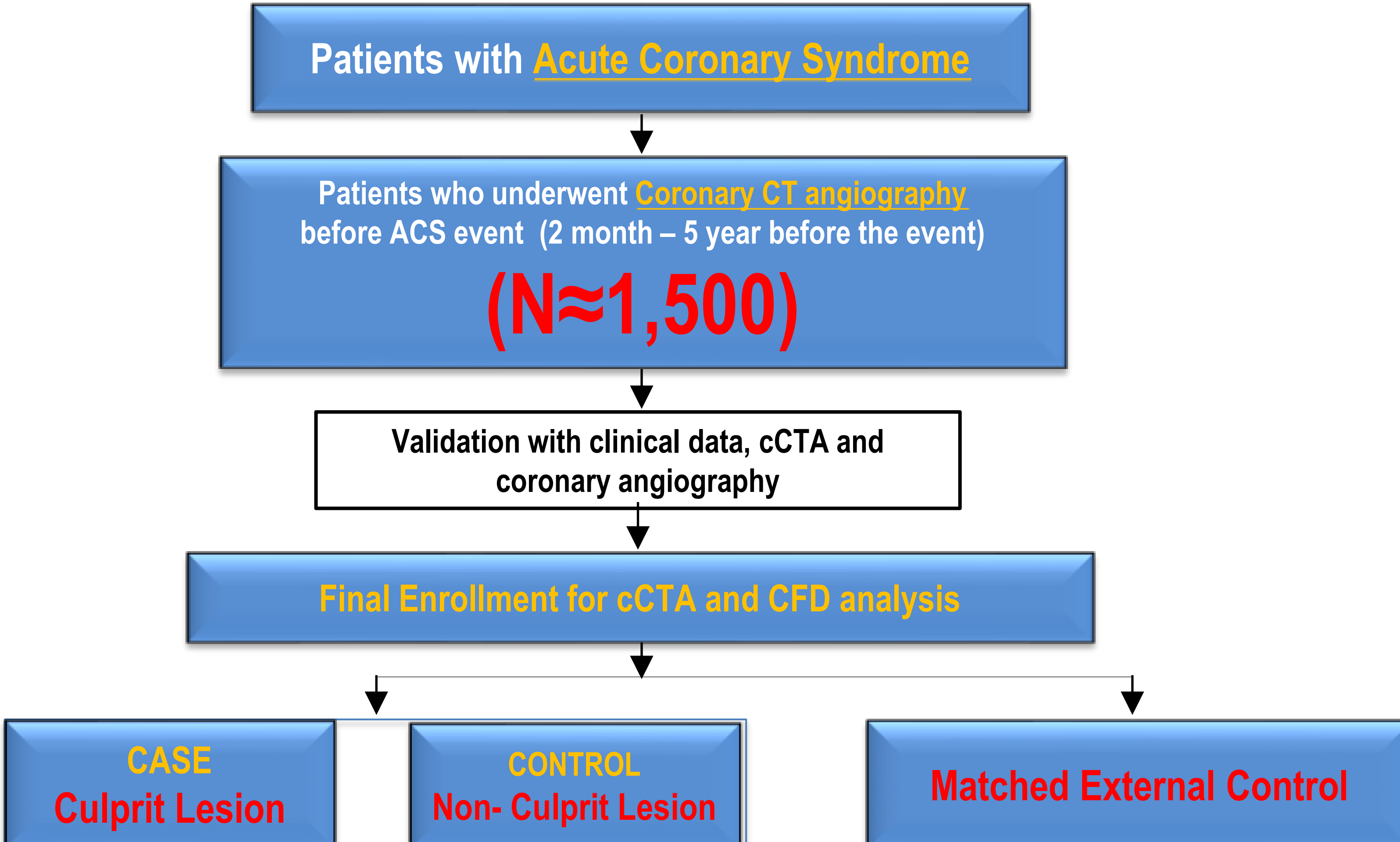
P for difference	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Model 1	.	0.92	<0.001	<0.001	<0.001	<0.001	<0.001
Model 2		.	<0.001	<0.001	<0.001	<0.001	<0.001
Model 3			.	<0.001	<0.001	<0.001	<0.001
Model 4				.	<0.001	<0.001	<0.001
Model 5						<0.001	<0.001
Model 6						.	<0.001

Park JS, Lee JM, Koo BK (Unpublished data)

EMERALD II study

Exploring the **ME**chanism of Plaque **R**upture in **A**cute Coronary Syndrome using Coronary CT Angiography and Computationa**L** Fluid **D**ynamics II

- **PI: Bon-Kwon Koo, MD, PhD**



Conclusion

- Non-invasive hemodynamic assessment enhanced the identification of vulnerable plaques that subsequently caused ACS.
- Application of this novel technology in daily practice can improve the prediction of ACS risk and may help guide optimal treatment for high risk patients.
- The EMERALD II study will confirm the value of non-invasive hemodynamics in ACS risk assessment.