Non-Invasive Fractional Flow Reserve

W. Wijns, Aalst (B)

Non-Invasive CT - FFR

Attempts at FFR computation from anatomy are not new, but were based on invasive measurements

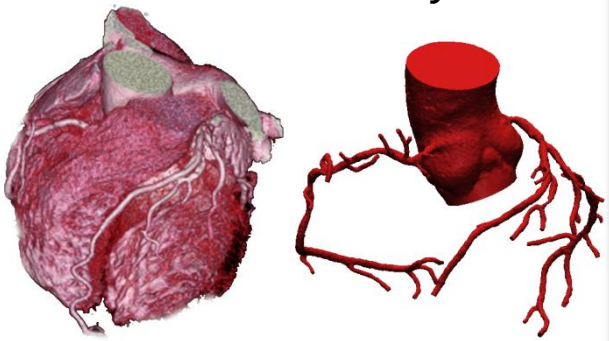
- **2D-angiography**
- **IVUS**
- **3D-angiography**
- **FD-OCT (VRR = 1-FFR)**

FFR computation from Coronary CTA was granted the Innovation of the Year Award at EuroPCR 2011

HeartFlow Process for Obtaining FFR_{CT}

Computational Model based on CCTA

3-D quantitative, anatomic model from coronary CTA



Physiologic models:

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

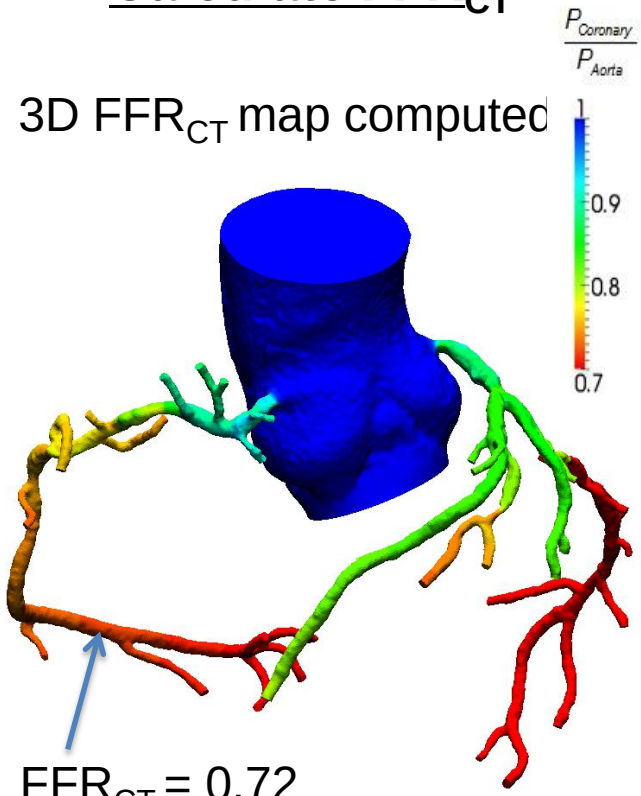
Blood Flow Solution

Blood flow equations solved on supercomputer

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

Calculate FFR_{CT}

3D FFR_{CT} map computed



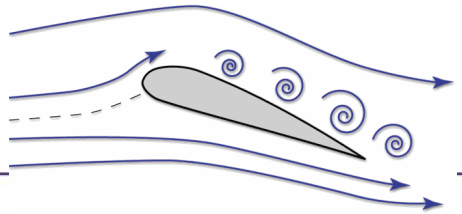
FFR_{CT} = 0.72
(can select any point on model)

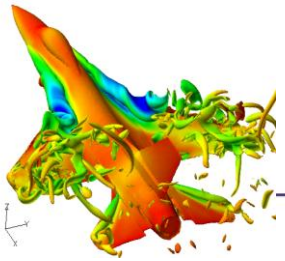
C Taylor, HeartFlow 2011

How does FFR_{CT} work?
An Analogy

Flow around an Airplane

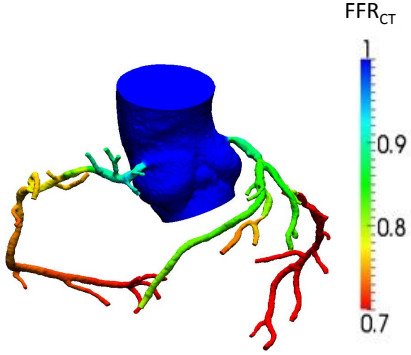
- Input data:
  - **Geometry**– from design specs
  - **Boundary conditions**
    - Velocity of incoming air relative to wing
    - Atmospheric pressure, $P=P_{atm}$
  - **Fluid Properties** – viscosity and density of air
- Calculated data:
  - Velocity and pressure of air in front of, around, behind wing
  - Lift and drag





Flow through an Artery

- Input data:
  - **Geometry** – high quality 64 slice CT
  - **Boundary conditions**
    - Blood pressure
    - Resting coronary flow calculated from myocardial mass
    - Baseline microcirculatory resistance determined from size of feeding vessel
    - Hyperemic microcirculatory resistance derived from model of effect of adenosine
  - **Fluid properties** – viscosity and density of blood
- Calculated data:
  - Velocity and pressure of blood in coronary arteries
  - FFR_{CT} , CFR, etc.

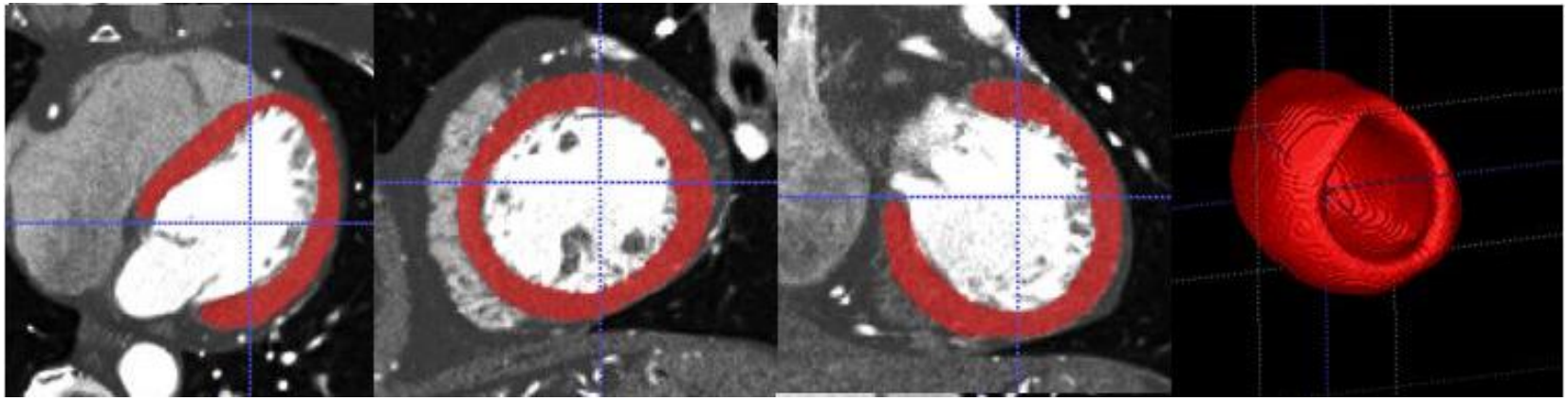


Scientific Principle # 1

Resting coronary blood flow proportional to myocardial mass

Allometric scaling laws can be applied to estimate physiologic parameters, e.g. coronary flow, under baseline conditions given organ mass

$$Q_c^{rest} \propto M_{myo}^{\beta}$$



Left Ventricle Myocardial Volume can be extracted from CT data and used to compute average total coronary blood flow at rest

C Taylor, HeartFlow 2011

Scientific Principle # 2

Resistance of microcirculatory vascular bed at rest is inversely proportional to size of feeding vessel

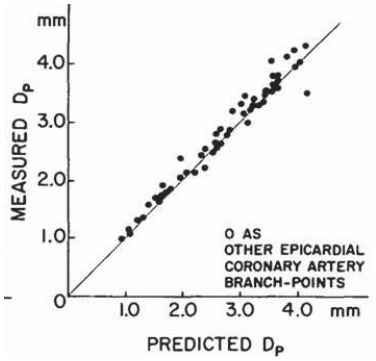
1. Healthy and diseased blood vessels adapt to amount of flow they carry
2. Power law relationships of form $Q \propto d^k$ apply to different vascular beds – including coronary arteries
3. Since mean pressure (P) is essentially constant down the length of the coronary arteries at rest

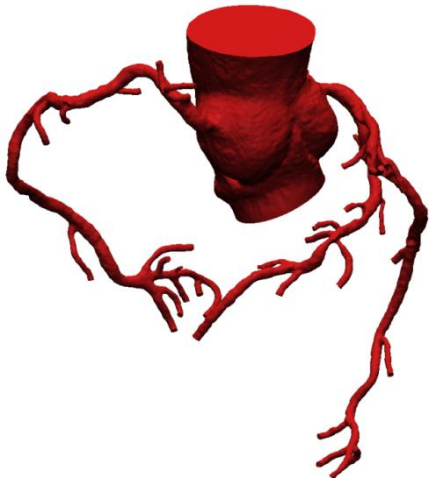
AND **$P=QR$**

AND **$Q \propto d^k$**

THUS **$R \propto d^{-k}$**

Small coronary artery branches have a higher resistance to flow than larger branches





Relative size of coronary arteries offers clue to relative flow

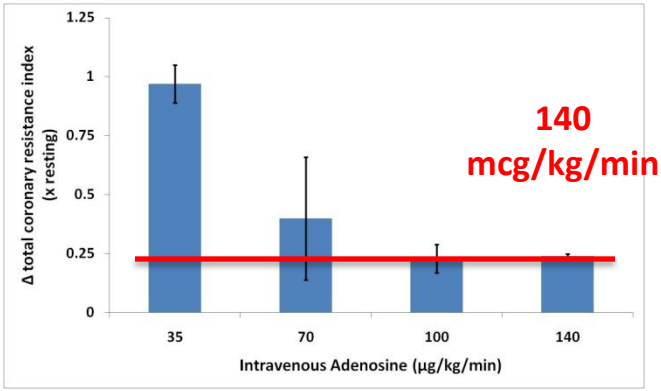
C Taylor, HeartFlow 2011

Scientific Principle # 3

Microcirculation has a predictable response to adenosine

1. When the heart lacks O_2, breakdown of ATP results in release of Adenosine → vasodilation
2. Exogenous administration of Adenosine elicits the maximum hyperemic response by forcing complete smooth muscle cell relaxation
3. Led to standard of care for induction of hyperemia in non-invasive tests and the cath lab

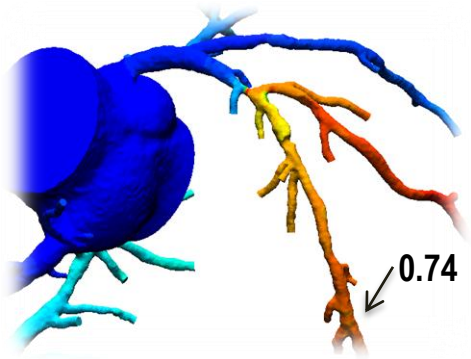
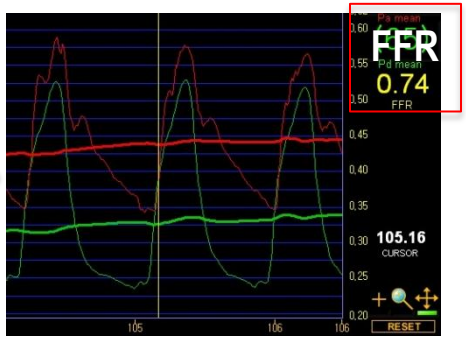
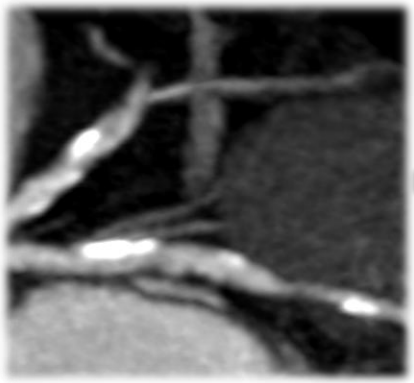
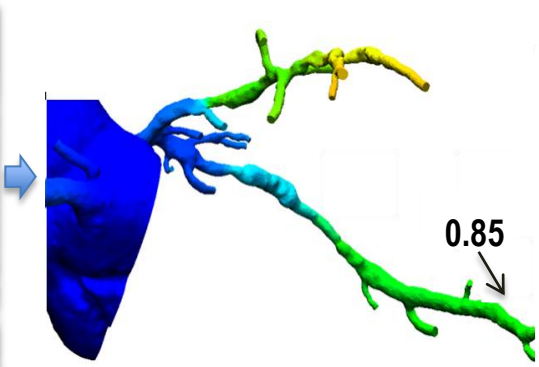
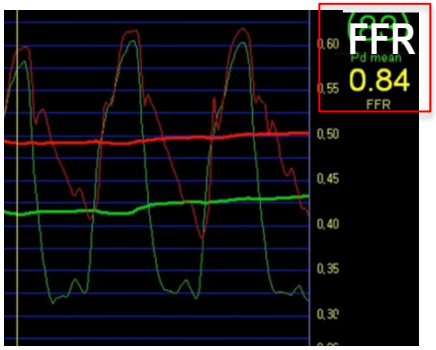
Adenosine relaxes smooth muscle cells lining arterioles resulting in vasodilation



Intravenous administration of adenosine elicits remarkably consistent vasodilatory response at sufficient doses

C Taylor, HeartFlow 2011

Case examples from DISCOVER-FLOW

Coronary CTA	FFR_{CT}	Invasive angiography	FFR
			
>50% diameter stenosis	FFR_{CT} 0.74 → ischemia	>50% diameter stenosis	FFR 0.74 → ischemia
			
>50% diameter stenosis	FFR_{CT} 0.85 → no ischemia	>50% diameter stenosis	FFR 0.84 → no ischemia

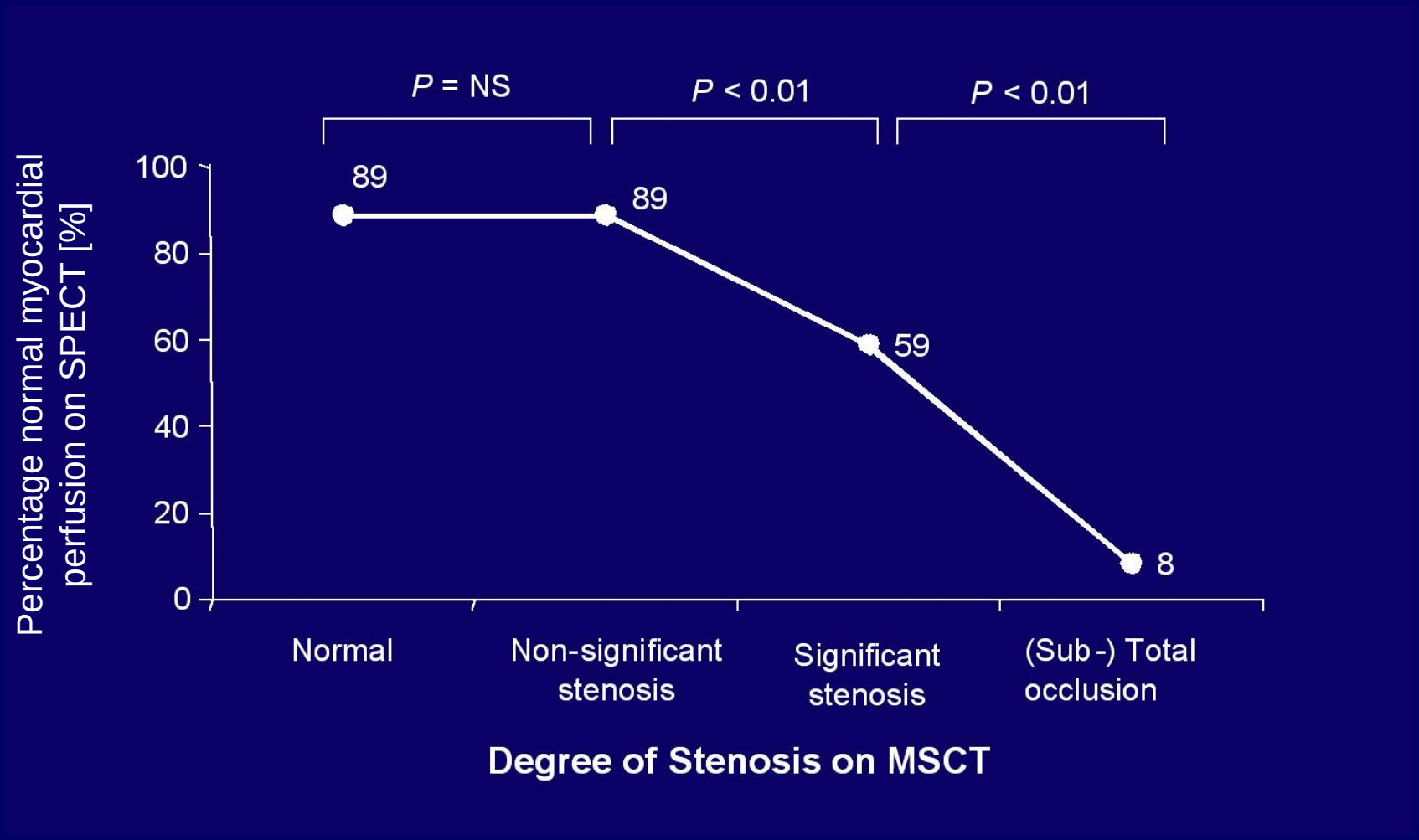
Koo et al. J Am Coll Cardiol 2011;58:1989-97

Non-Invasive CT - FFR

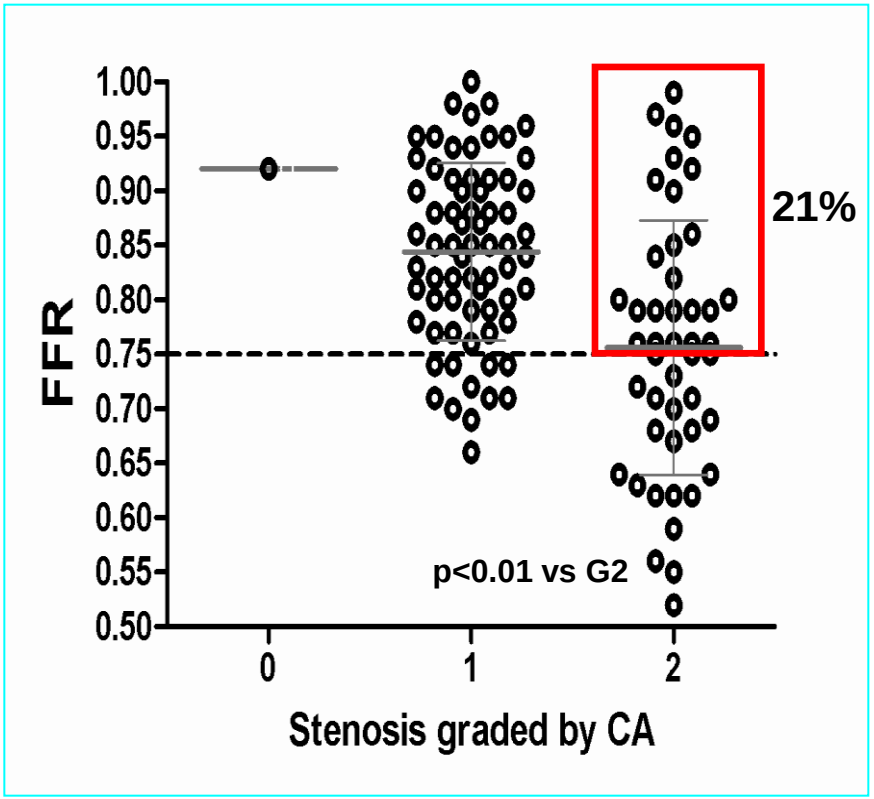
No question: there is a need . . .

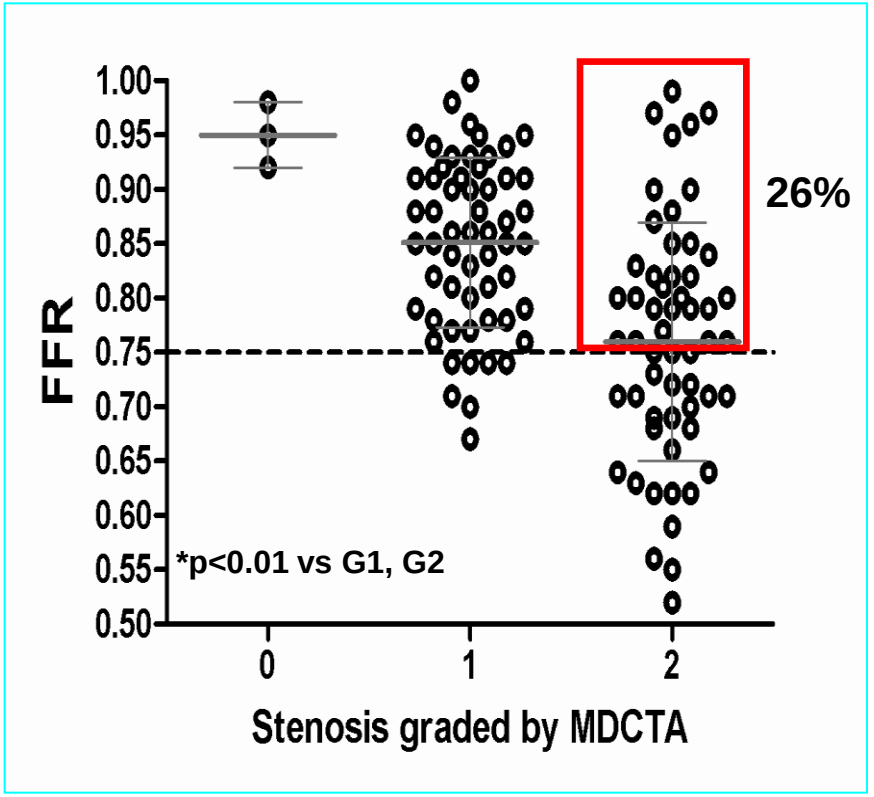
- **Well known limitations of non-invasive functional imaging**
- **Combined anatomic and functional imaging is feasible but complex, expensive and associated with high radiation burden (Spect/PET – CT)**
- **Well known limitations of non-invasive anatomical imaging (Coronary CTA)**

Relation between Stenosis Severity on MSCT and **Myocardial Perfusion on SPECT**



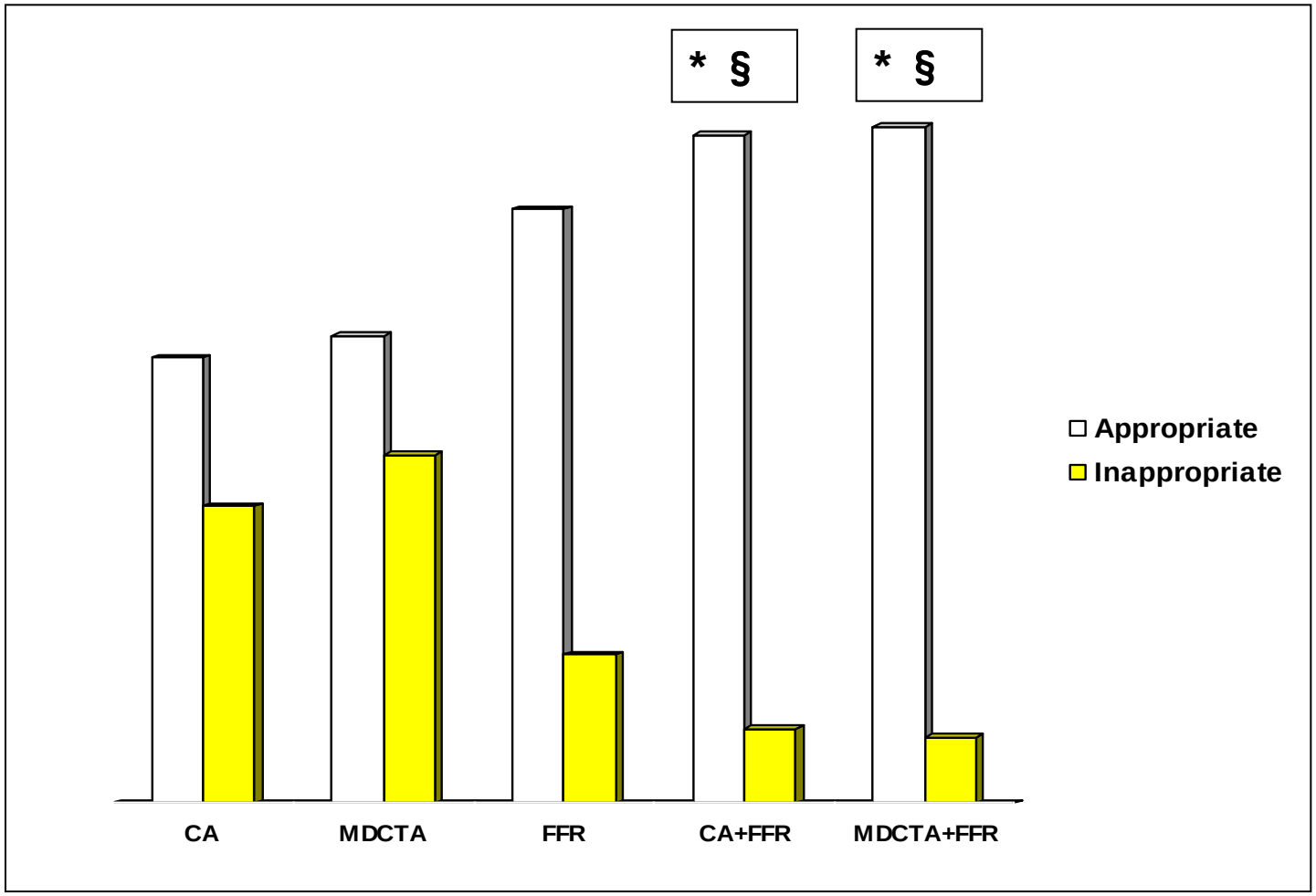
Stenosis severity (by FFR) versus invasive angiography (left) & non-invasive MDCT Angiography (right)





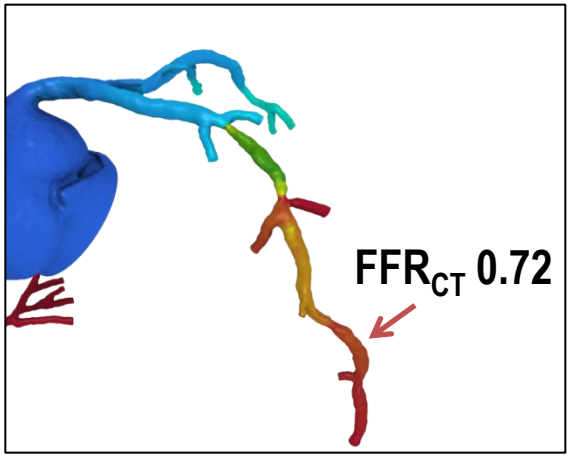
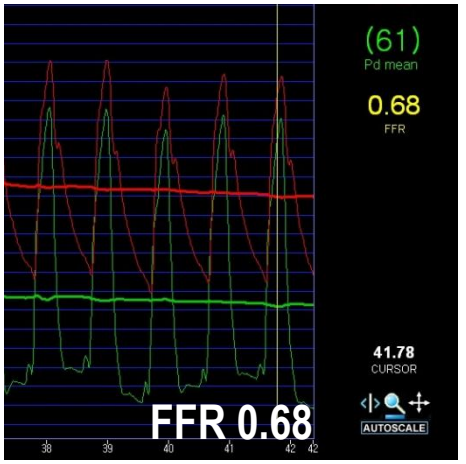
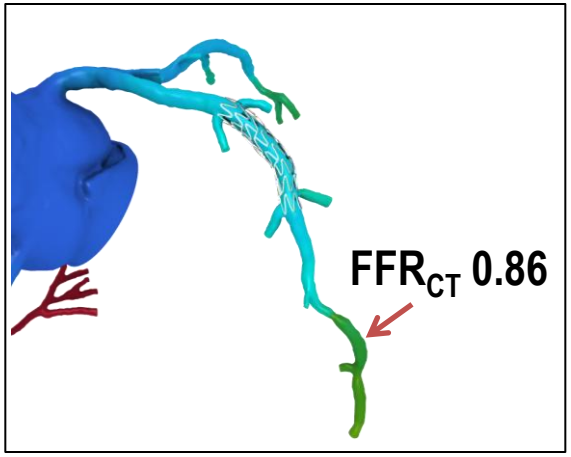
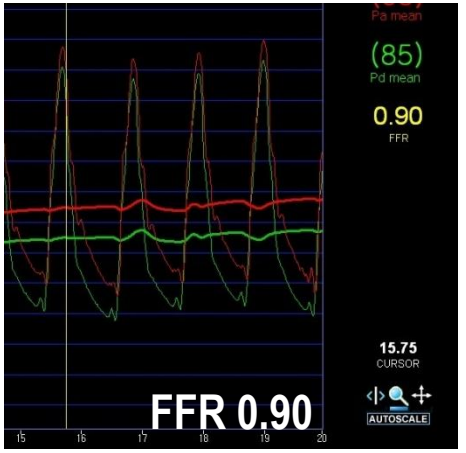
Sarno et al. JACC 2009;2:550-7

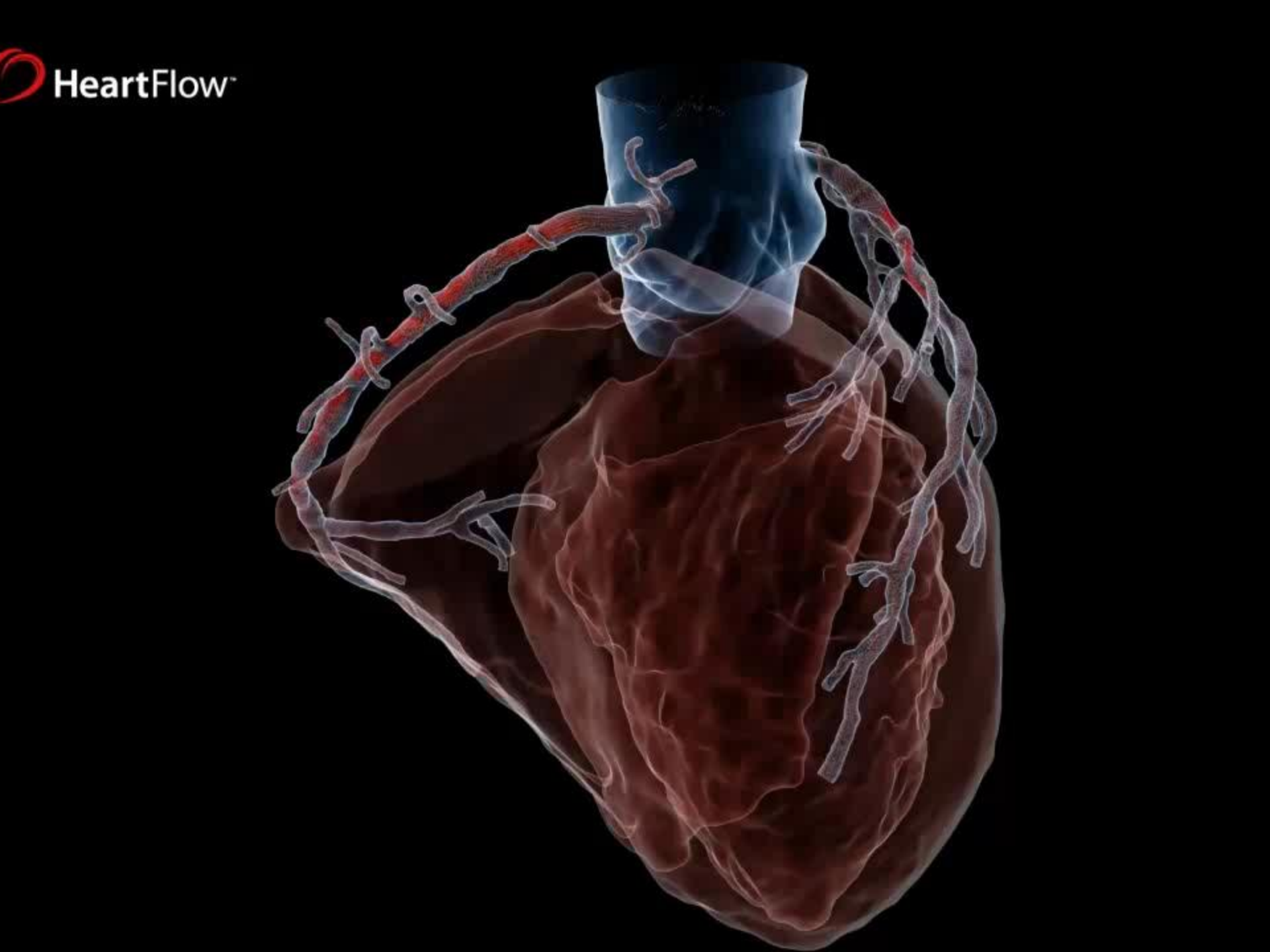
Percent appropriate and inappropriate treatment decisions based on the results of individual or combined diagnostic techniques



* = p<0.001 vs CA and § = p<0.001 vs MDCTA

PCI Planner Case Study

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


HeartFlow

Non-Invasive CT - FFR

When appropriately validated, such non-invasive "one-stop shop" evaluation of function and anatomy by FFR – CT may be disruptive of non-invasive diagnostic work-up strategies in patients with suspected CAD

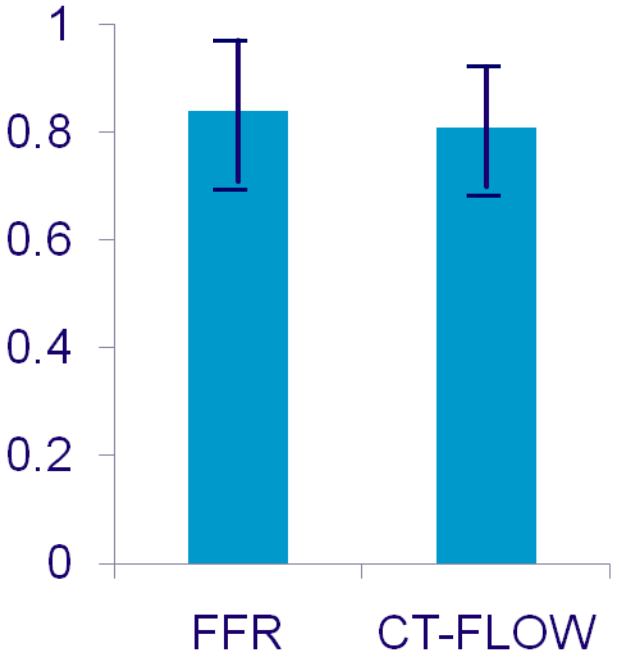
Treatment planning may impact on indications and practice of revascularisation procedures, both PCI and CABG

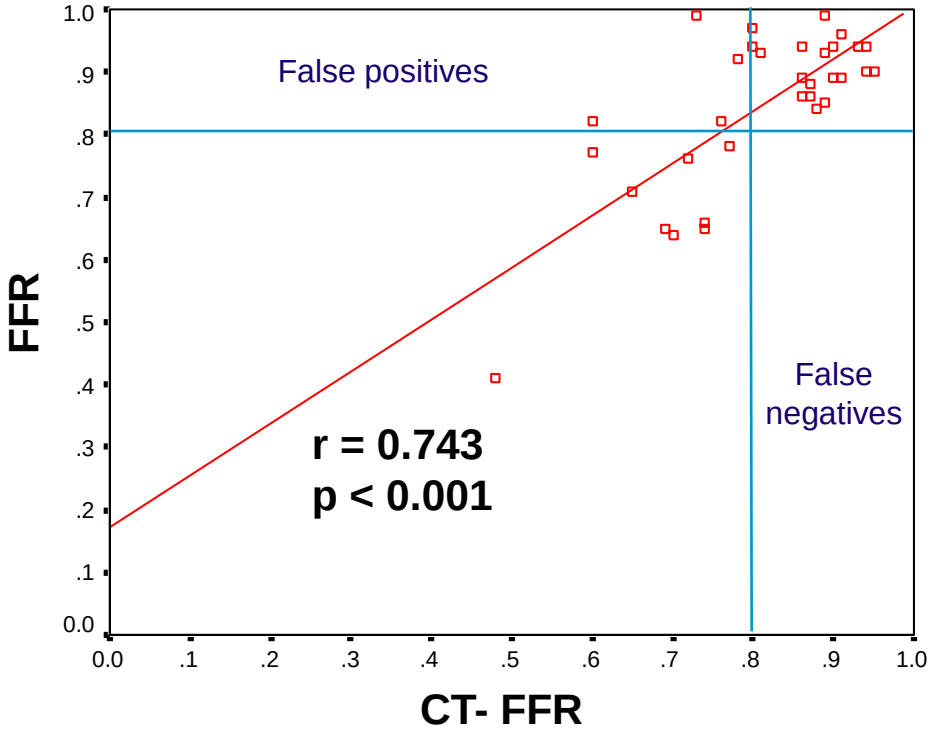
As a result of a potential widespread use of this technology, the clinician, the interventional cardiologist and the cardiac surgeon may eventually end-up speaking the same langague (common metric)

First Diagnostic Correlation

CT- FLOW vs. Invasive FFR

per lesion analysis (n=33)



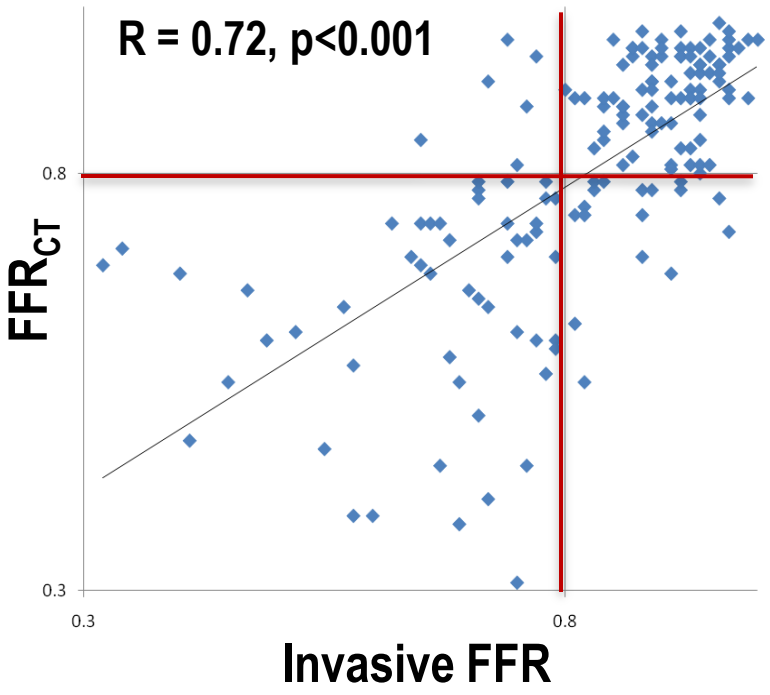


FFR	**0.84 ± 0.13**
CT- FFR	**0.81 ± 0.11**

Erglis et al. ESC 2010

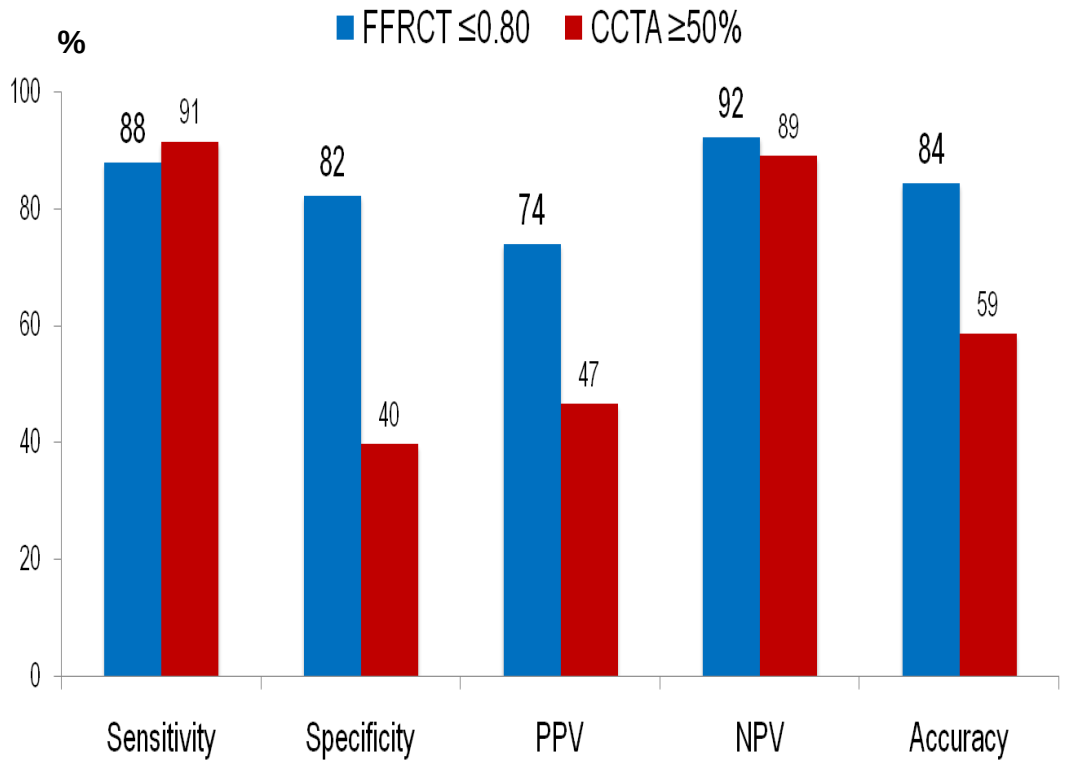
Diagnostic performance of FFR_{CT} and CCTA

Correlation With FFR



FFR_{CT}	0.80 ± 0.14
FFR	0.82 ± 0.13

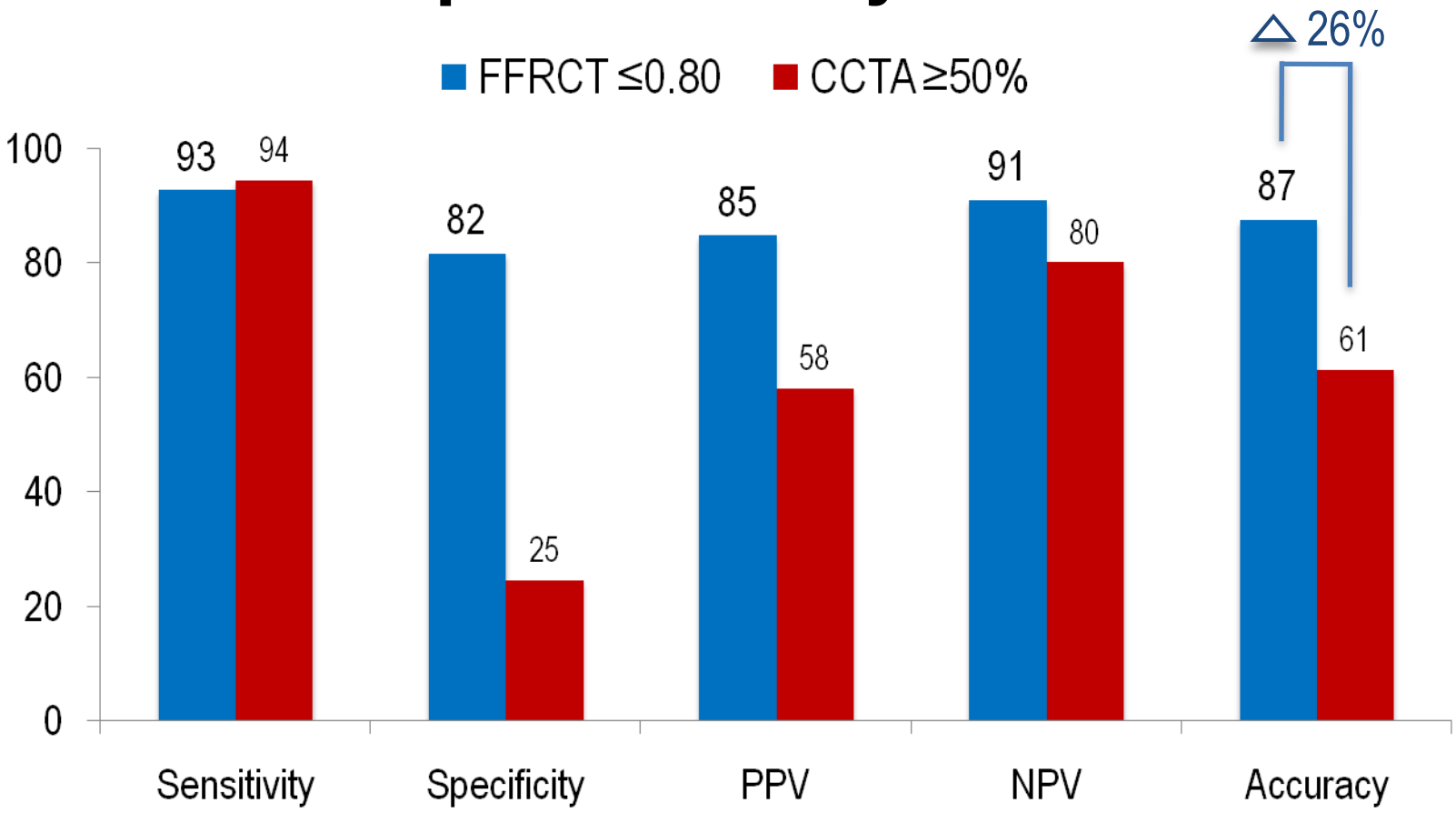
Diagnostic Performance



Per-Vessel Analysis

Diagnostic performance of FFR_{CT} and CCTA

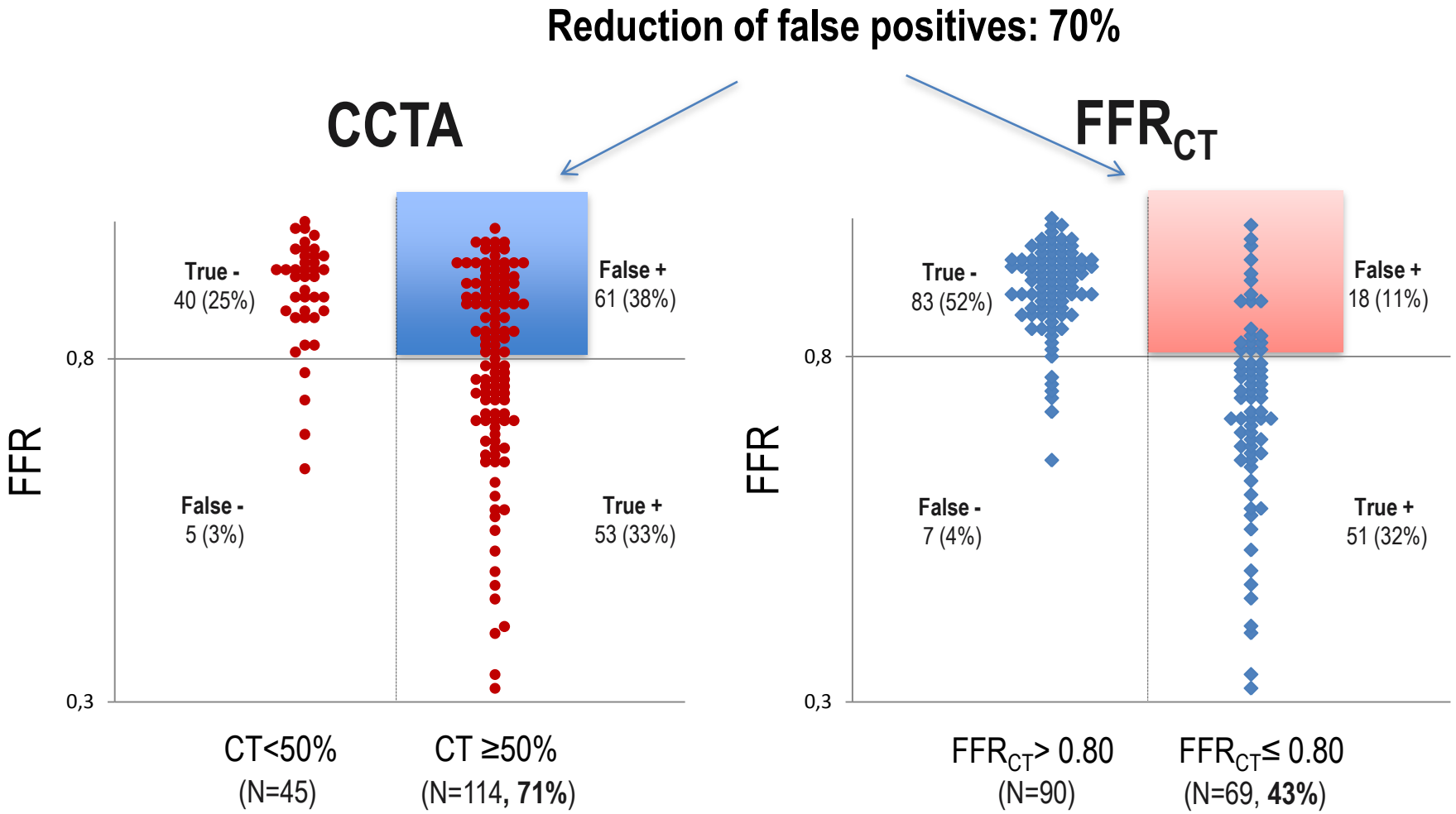
Per-patient analysis (n=103)



PPV: positive predictive value, NPV: negative predictive value

Koo et al. J Am Coll Cardiol 2011;58:1989-97

Reclassification of CCTA data



DISCOVER-FLOW

Koo et al. J Am Coll Cardiol 2011;58:1989-97

DeFACTO: pivotal multicentre study

The diagnostic accuracy of FFR – CT was evaluated in a 238 patients large multicenter trial and failed to meet its pre-defined endpoint (lower CI > 70%)

Per patient diagnostic accuracy was 73%, 95%CI 67-78

Specificity (54%, 95%CI = 46-83%) and positive predictive value (67%, 95%CI = 60-74%) were non-diagnostic

The per-vessel false positive rate can be calculated at 23.6%, meaning that 96 out of 407 vessels had FFR_{CT} ≤0.80 while invasive reference FFR was above 0.80

Min et al. JAMA 2012;308:1237-45

Non-Invasive CT - FFR

- Routine coronary CTA enriched with functional information (CT - FFR) could be tested as a first choice approach in patients with chest pain, with the potential of improved risk stratification and more appropriate use of invasive resources

- **However, current diagnostic performance of CT - FFR precludes its clinical use**

Disclosures for William Wijns
Cardiovascular Center Aalst, Belgium

Consulting Fees: on my behalf go to the Cardiovascular Research Center Aalst

Contracted Research between the Cardiovascular Research Center Aalst and several pharmaceutical and device companies, incl. St Jude and Volcano

Ownership Interest: Cardio³BioSciences, biotechnology start-up on regenerative medicine

Chairman of PCR, Co-Director of EuroPCR and Africa PCR

Frequently Asked Questions

1. How could FFR_{CT} provide better results than coronary CTA alone since it uses the same anatomic data?

   FFR_{CT} technology incorporates a more complete anatomic model and also leverages physical laws of blood flow and established principles of coronary physiology

2. Are the coronary CTA scans performed with Adenosine?

   No, standard coronary CTA scans are used to build Heartflow models. Hyperemia is simulated using known vasodilatory response of Adenosine

3. Does microcirculatory disease or scar tissue affect FFR_{CT}?

   It may, but this is factored into the model since the feeding epicardial coronary arteries remodel in response to elevated microcirculatory resistance and reduced flow

Frequently Asked Questions

4. Can low dose coronary CTA scans be used for FFR_{CT} analysis?

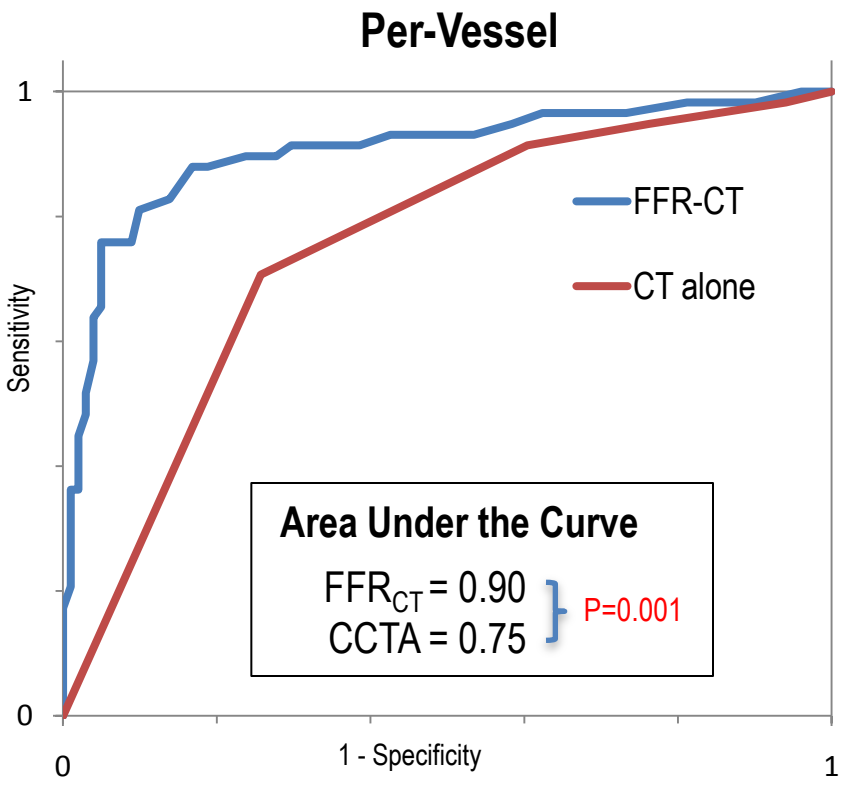
   Yes, any coronary CTA protocol that results in good quality coronary artery images is fine

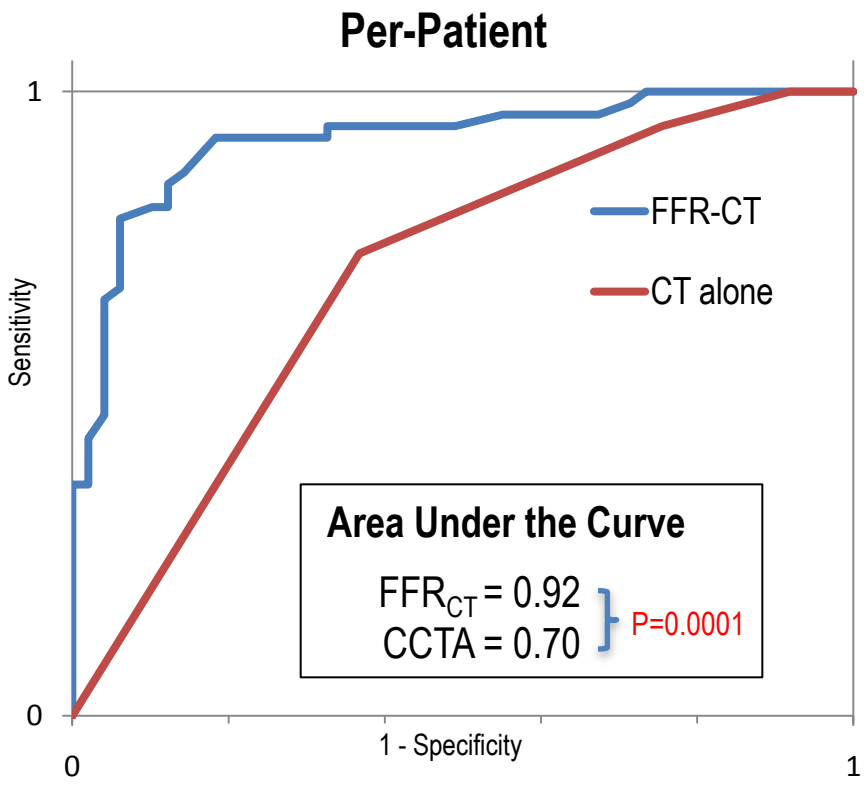
5. Can FFR_{CT} analysis be performed in patients with calcified arteries?

   Yes, provided that the coronary lumen boundary is quantifiable from coronary CTA data

Diagnostic performance of CCTA and FFR_{CT}

ROC curve analysis





Modeling Blood Requires Solving the Governing Partial Differential Equations of Fluid Flow

Mass Conservation (1 equation):

$$\frac{\partial v_x}{\partial x}+\frac{\partial v_y}{\partial y}+\frac{\partial v_z}{\partial z}=0$$

This law states that blood is an incompressible fluid

Momentum Balance (3 equations):

$$\rho\frac{\partial v_x}{\partial t}+\rho\left(v_x\frac{\partial v_x}{\partial x}+v_y\frac{\partial v_x}{\partial y}+v_z\frac{\partial v_x}{\partial z}\right)=-\frac{\partial p}{\partial x}+\mu\left(\frac{\partial^2 v_x}{\partial x^2}+\frac{\partial^2 v_y}{\partial y^2}+\frac{\partial^2 v_z}{\partial z^2}\right)$$

$$\rho\frac{\partial v_y}{\partial t}+\rho\left(v_x\frac{\partial v_y}{\partial x}+v_y\frac{\partial v_y}{\partial y}+v_z\frac{\partial v_y}{\partial z}\right)=-\frac{\partial p}{\partial y}+\mu\left(\frac{\partial^2 v_x}{\partial x^2}+\frac{\partial^2 v_y}{\partial y^2}+\frac{\partial^2 v_z}{\partial z^2}\right)$$

$$\rho\frac{\partial v_z}{\partial t}+\rho\left(v_x\frac{\partial v_z}{\partial x}+v_y\frac{\partial v_z}{\partial y}+v_z\frac{\partial v_z}{\partial z}\right)=-\frac{\partial p}{\partial z}+\mu\left(\frac{\partial^2 v_x}{\partial x^2}+\frac{\partial^2 v_y}{\partial y^2}+\frac{\partial^2 v_z}{\partial z^2}\right)$$

These equations come from the application of Newton's 2nd law, F=ma to a fluid

where ρ is the fluid density, and μ is the fluid viscosity (both assumed known).

We solve these for $v_x(x,y,z,t), v_y(x,y,z,t), v_z(x,y,z,t), p(x,y,z,t)$

for every point in the 3D model and over whatever time interval we are interested in.

These equations were known by 1845, but their solution would have to await the development of the digital computer and numerical methods