Diagnostic Accuracy of Fractional Flow Reserve from Anatomic Computed TOmographic Angiography: The DeFACTO Study

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Disclosures

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Background

- Coronary CT angiography is a non-invasive test that demonstrates high accuracy to invasive angiography but cannot determine the hemodynamic significance of a coronary lesion[1]
- Fractional flow reserve (FFR) is the gold standard for diagnosis of lesion-specific ischemia[2], and its use to guide coronary revascularization improves event-free survival and lowers healthcare costs[3,4]
- Computational fluid dynamics is a novel technology that enables calculation of FFR from CT (FFR_{CT}), and may represent a non-invasive method for determination of lesion-specific ischemia[5]

- To date, the diagnostic performance of FFR_{CT} has not been tested in a large-scale prospective multicenter study

[1]Min et al. J Am Coll Cardiol 2010; 55: 957-65; [2]Piljs et al. Cath Cardiovasc Interv 2000; 49: 1-16; [3]Tonino et al. N Engl J Med 2009; 360: 213-24; [4]Berger et al. J Am Coll Cardiol 2005; 46: 438-42; [5]Kim et al. Ann Biomed Eng 2010; 38: 3195-209; [6]Erglis et al. ESC 2010 Scientific Sessions; Abstract 951

Objective

- The **OVERALL OBJECTIVE** of the DeFACTO study was to determine the diagnostic performance of FFR_{CT} for the detection and exclusion of hemodynamically significant CAD in a prospective multicenter international study.

Study Endpoints

- **Primary**: Per-patient diagnostic accuracy of FFR_{CT} plus CT to determine the presence or absence of at least one hemodynamically significant coronary stenosis, as compared to an invasive FFR reference standard*
  - Study hypotheses tested at one-sided 0.05 Type I error rate, with null hypothesis to be rejected if lower bound of 95% CI > 0.70
    - 0.70 threshold chosen b/c this represented the mid-point of test accuracy for stress imaging testing[1], 3-fold higher accuracy than recent large-scale reports of "real world" testing[2], and higher than the point of concordance of stress imaging testing with invasive FFR
  - Assuming 0.35 rate of CAD, 238 patients (assuming 11% rate of nonevaluable CTs[3]) needed to achieve 95% statistical power
- **Secondary**:
  - Additional diagnostic performance characteristics (e.g., sensitivity / specificity)
  - Diagnostic performance for lesions of intermediate stenosis severity
  - Per-vessel correlation of FFR_{CT} value to FFR measured value

[1]Mowatt et al. Health Technol Assess 2004; 30: 1-207; [2]Madder RD et al. J Cardiovasc Comput Tomogr 2011; 5: 165-71; [3]Budoff MJ et al. J Am Coll Cardiol 2008; 52: 1724-32; [3]Melikian N et al. JACC Cardiovasc Interv 2010; 3: 307-14

Inclusion / Exclusion Criteria

Inclusion Criteria:

- Age ≥ 18 years
- Providing written informed consent
- Scheduled to undergo clinically-indicated non-emergent ICA
- ≥64-row CT within 60 days prior to ICA
- No cardiac interventional therapy between CT and ICA

Exclusion Criteria (Cardiac-specific):

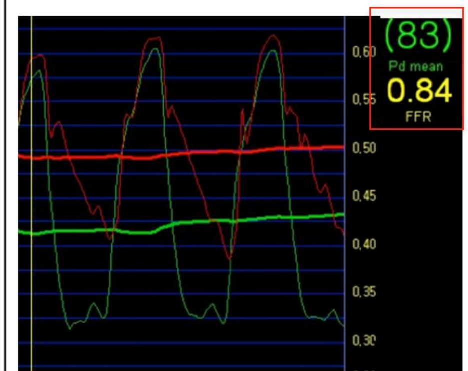
- Prior coronary artery bypass surgery
- Prior PCI with suspected in-stent restenosis
- Suspicion of acute coronary syndrome
- Prior myocardial infarction within 40 days of ICA

Study Procedures

All studies (CT, QCA, FFR, FFR_{CT}) interpreted in blinded fashion by 4 independent core labs.

CT Stenosis Severity: 0-24%, 25-49%, 50-69%, $\geq$70%, $\geq$90%, 100%

QCA %DS = 50.68



FFR 0.84 → no ischemia

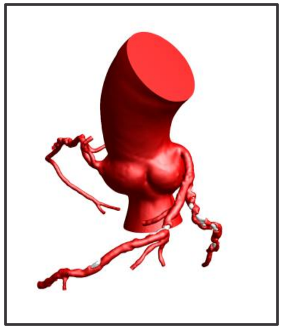
- **CT:** Image acquisition / interpretation in accordance with societal guidelines on $\geq$64-row CT
- **QCA:** % diameter stenosis determined in standard fashion using commercially available software
- **FFR:** Standard fashion by commercially available equipment after administration of nitroglycerin and intravenous adenosine at rate of 140 mcg/kg/min through a central vein
  - FFR = (mean distal coronary pressure) / (mean aortic pressure) during hyperemia
- **Definitions:** Anatomic obstructive CAD defined as $\geq$50% diameter stenosis for CT and QCA; Lesion-specific ischemia defined as $\leq$0.80 for both FFR and FFR_{CT}[1]
  - FFR: Per protocol, subtotal (99%) or total (100%) occlusions assigned value of 0.50
  - FFR_{CT}: Per protocol, subtotal / total occlusions assigned value of 0.50, and vessels with <30% maximal stenosis assigned value of 0.90

[1]Tonino PA et al. N Engl J Med 2009; 360: 213-24

Computation of FFR_{CT}

FFR_{CT} performed by HeartFlow scientists in blinded fashion.

(1)



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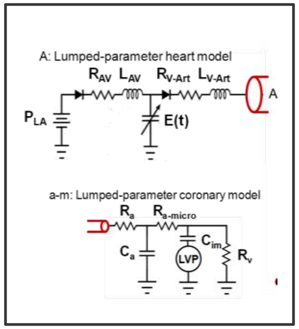

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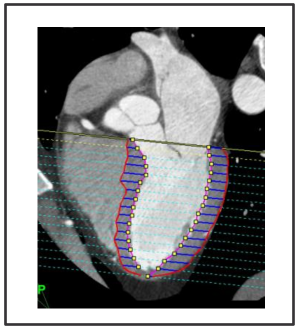

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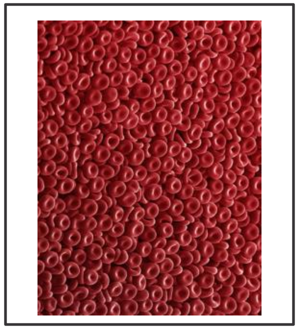


(6)

1. **Image-based Modeling** – Comprehensive segmentation of coronary arteries and aorta to determine patient-specific coronary geometry
2. **Heart-Vessel Interactions** – At aortic and coronary outlets, enforced relationships b/w pressure and flow (e.g., aortic impedence)
3. **Segmentation of Left Ventricular Myocardial Mass** – Relate time-varying coronary resistance (i.e., pulsatile) to intramyocardial pressure
4. **Calculation of microcirculatory resistance** – Use of allometric scaling laws to relate patient-specific "form –function relationships (e.g. mass / size of object related to physiology)
5. **Patient-specific Physiologic Conditions** - Fluid viscocity (hematocrit), blood pressure
6. **Modeling of Hyperemia** – Standard prediction model to "virtually" force complete smooth muscle cell relaxation (arteriolar vasodilatation)
7. **Calculation of Fluid Dynamic Phenomena** – Application of universality of fluid dynamics, based upon Conservation of mass and momentum balance (e.g., airflow over jet; water flow in a river, etc.)

Computation of FFR_{CT}

Patient-Specific Hyperemic Flow and Pressure:

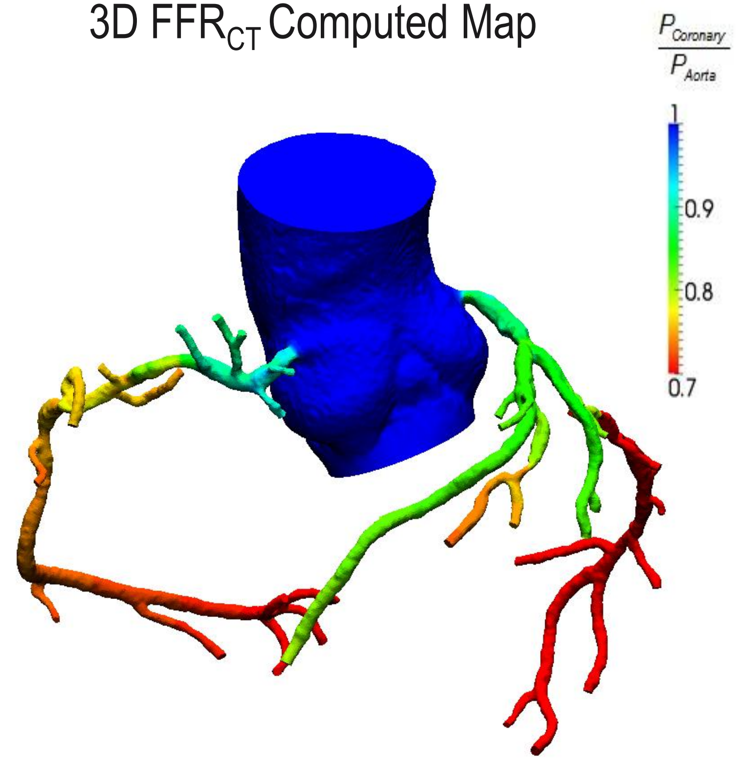
1. Numerical method using governing equations
2. Obtain solution for velocity and pressure throughout coronary vascular bed
3. Simultaneous solution of millions of non-linear partial differential equations
4. Repeat process thousands of time intervals within cardiac cycle

FFR_{CT} does not require:

1. Modification to imaging protocols (i.e., prospective /retrospective ECG gating; fast pitch helical; FBP or IR)
2. Administration of adenosine
3. Additional image acquisition (i.e., no additional radiation)
4. Single-point assessment (i.e., FFR_{CT} selectable on any point in coronary vascular bed)

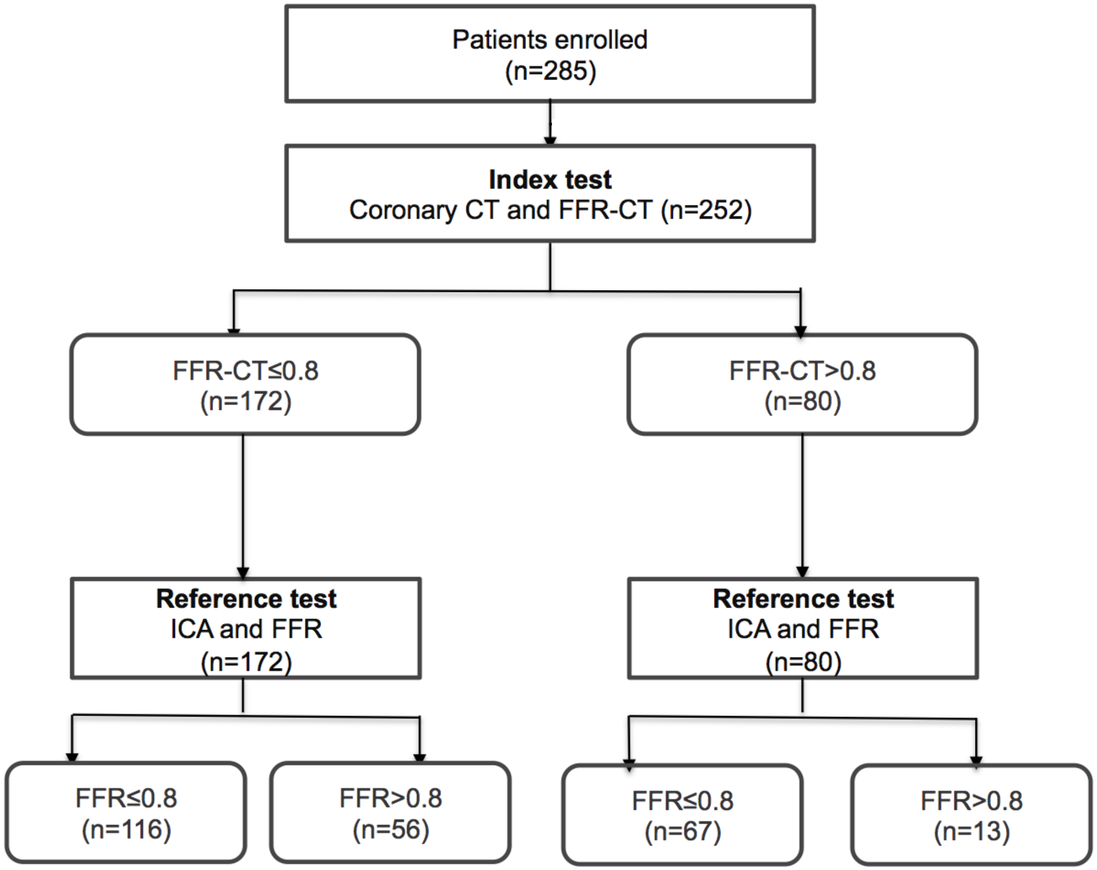
FFR_{CT} derived from a typically acquired CT

3D FFR_{CT} Computed Map



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

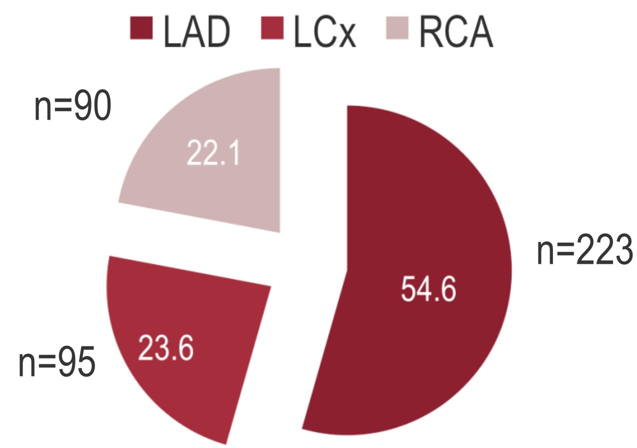
Patient Enrollment



- Enrollment occurred between October 2010 – October 2011 at 17 centers in 5 countries [Belgium (1), Canada (1), Latvia (1), South Korea (2), United States (12)]
- 33 patients excluded due to non-evaluable CTs as determined by the CT Core Laboratory (n=31), and inability to integrate CT / FFR wire placement as determined by the Integration Core Laboratory (n=20

Study Characteristics

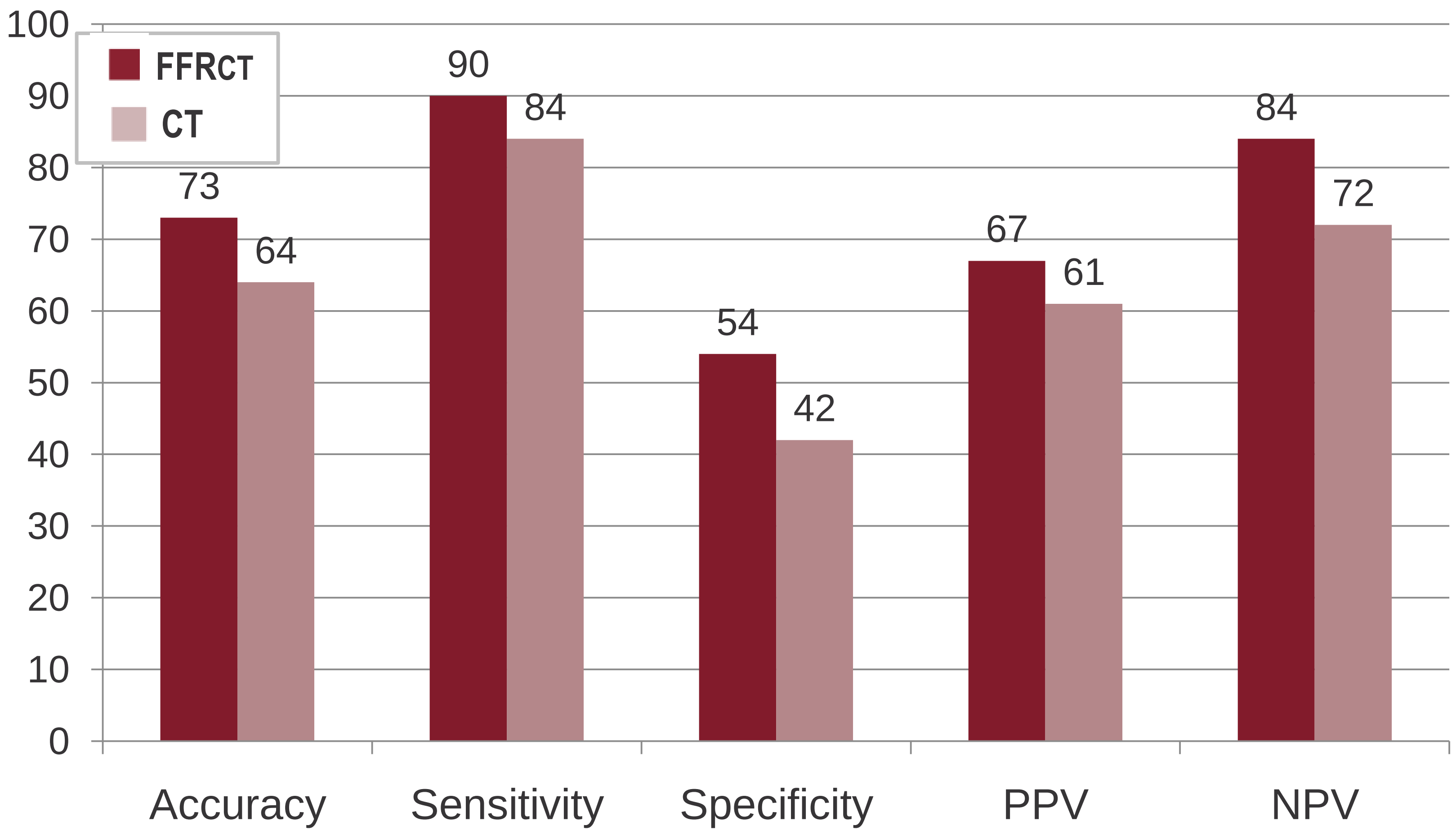
Variable	Mean $\pm$ SD or N (%)
Age (years)	62.9 $\pm$ 8.7
Prior MI	15 (6.0)
Prior PCI	16 (6.3)
Symptoms	
Stable	201 (79.7)
Worsening	43 (17.2)
Other (e.g., silent ischemia)	8 (3.1)
Male gender	178 (70.6)
Race / Ethnicity	
White	169 (67.1)
Asian	78 (31.0)
Other	5 (2.0)
Diabetes mellitus	53 (21.2)
Hypertension	179 (71.2)
Hyperlipidemia	201 (79.8)
FH of CAD	50 (19.9)
Current smoker	44 (17.5)



Variable	Mean $\pm$ SD or N (%)
Invasive Test Characteristics*	
Stenosis $\geq$50%	190 (46.5)
Average stenosis (%)	46.8 $\pm$ 15.7
FFR $\leq$0.80	151 (37.1)
Non-invasive Test^	
Stenosis $\geq$50%	216 (53.2)
>90% Stenosis	79 (19.5)
Coronary Calcium (Agatston units)	381.5 $\pm$ 401.0

*N=408 vessels from 252 patients; ^N=406 vessels from 252 patients

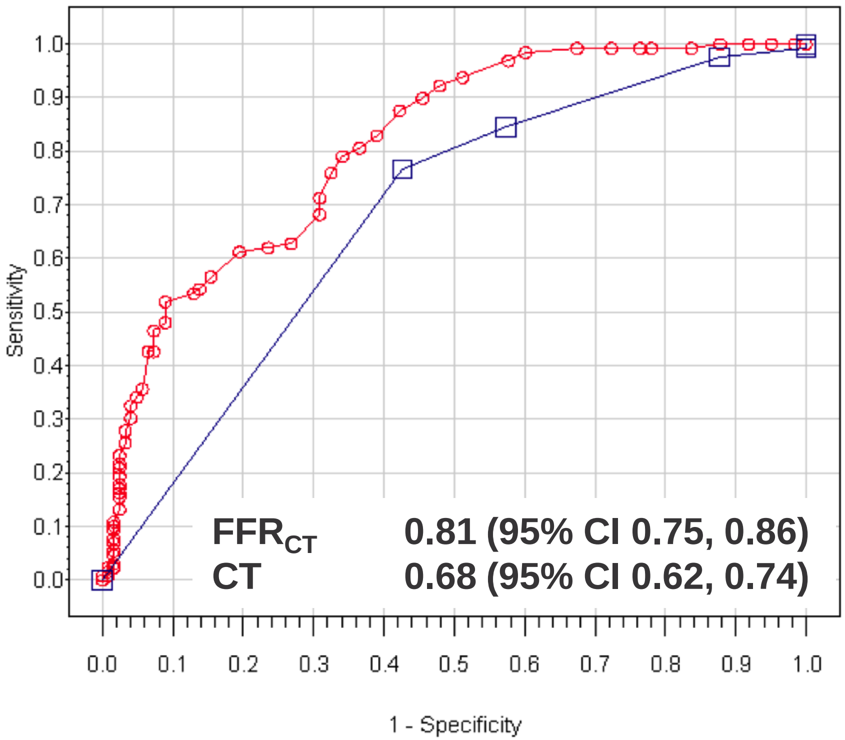
Per-Patient Diagnostic Performance



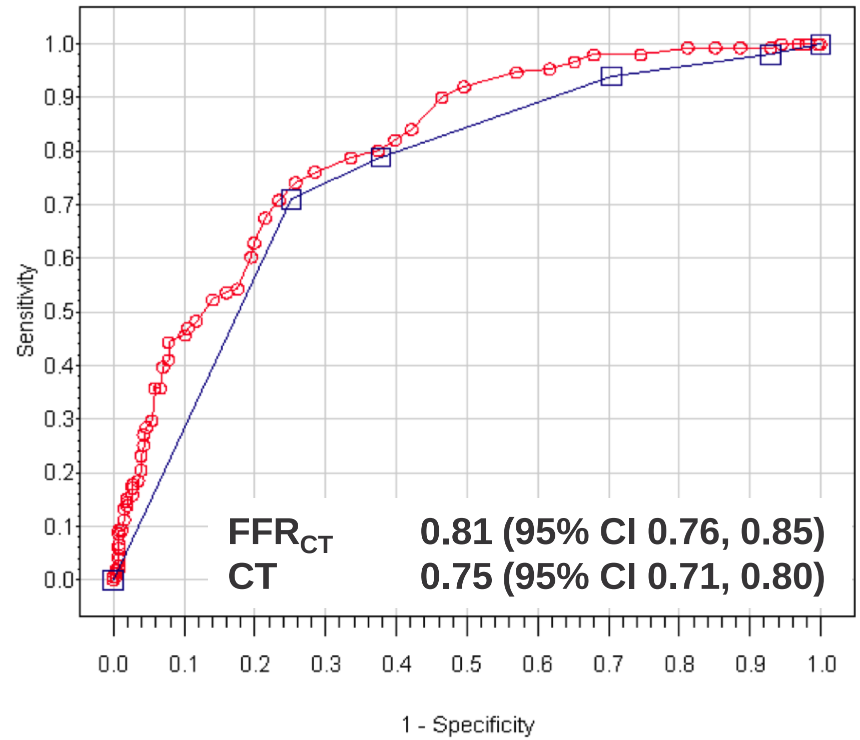
	Accuracy	Sensitivity	Specificity	PPV	NPV
	95% CI	95% CI	95% CI	95% CI	95% CI
FFRct	67-78	84-95	46-83	60-74	74-90
CT	58-70	77-90	34-51	53-67	61-81

Discrimination

Per-Patient

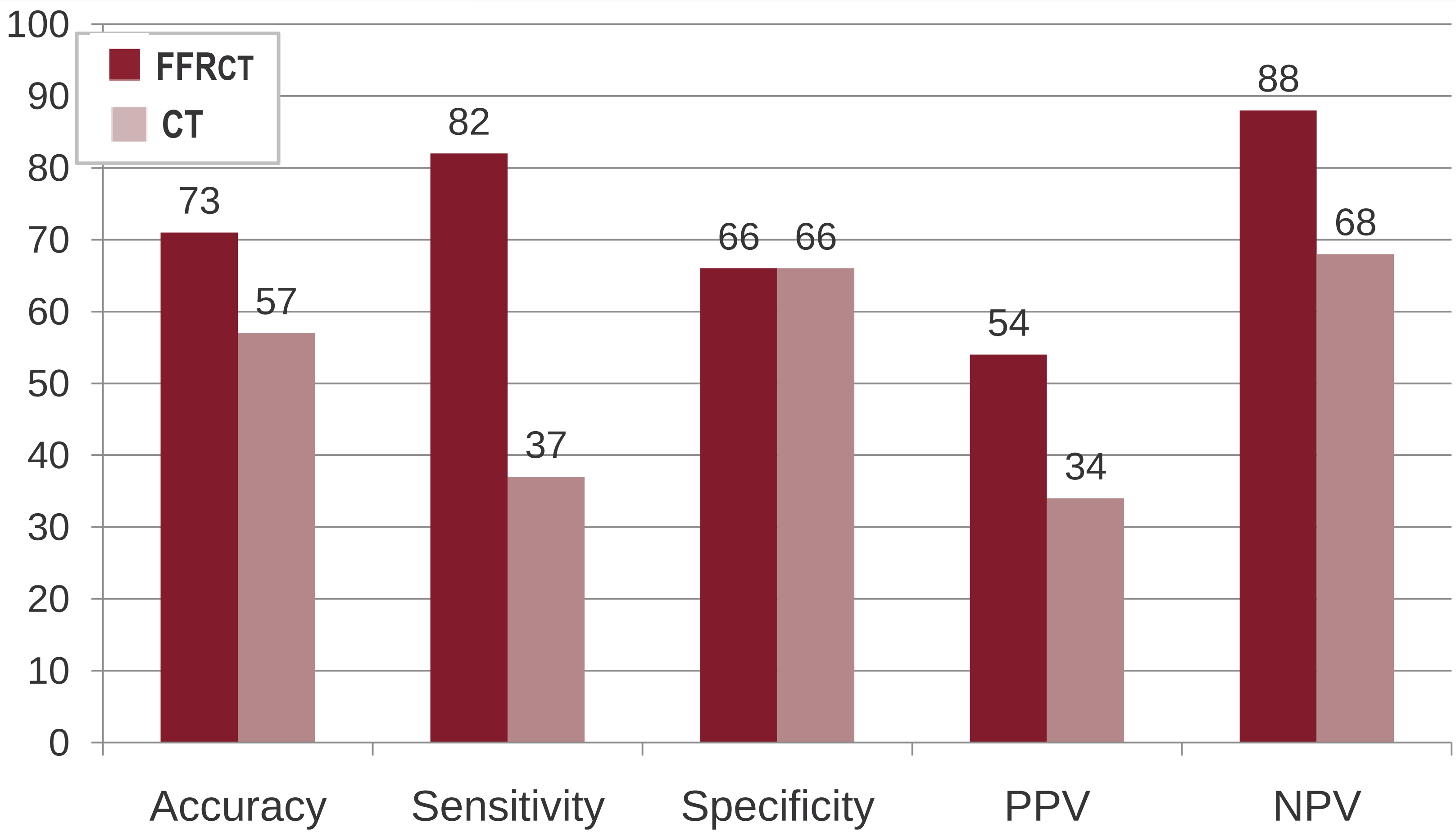


Per-Vessel



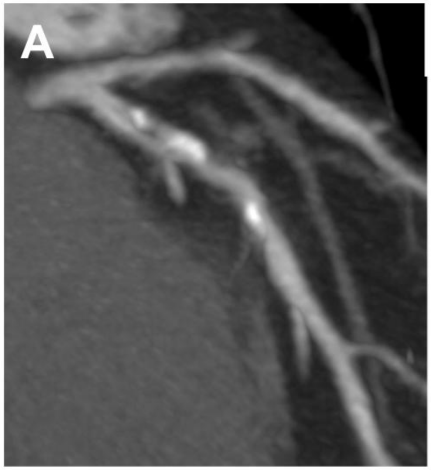
- Greater discriminatory power for FFR$_{CT}$ compared to CT stenosis on per-patient ($\Delta = 0.13$) and per-vessel basis ($\Delta = 0.06$)

Per-Patient Diagnostic Performance for Intermediate Stenoses by CT (30-70%)

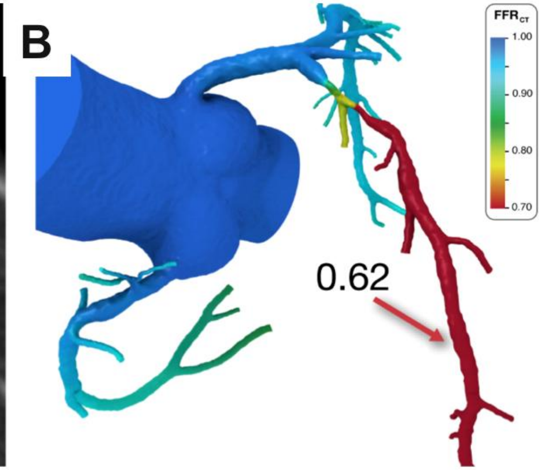


	Accuracy	Sensitivity	Specificity	PPV	NPV
	95% CI	95% CI	95% CI	95% CI	95% CI
FFRCT	61-80	63-92	53-77	39-68	75-95
CT	63-92	53-77	53-77	20-53	55-79

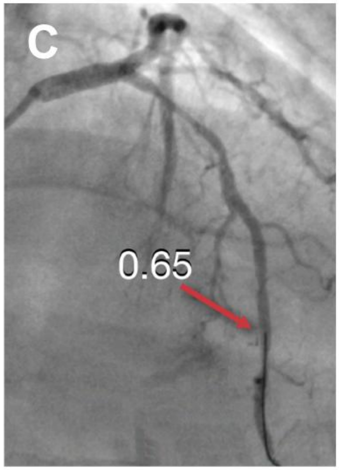
Case Examples



CT stenosis of the proximal LAD

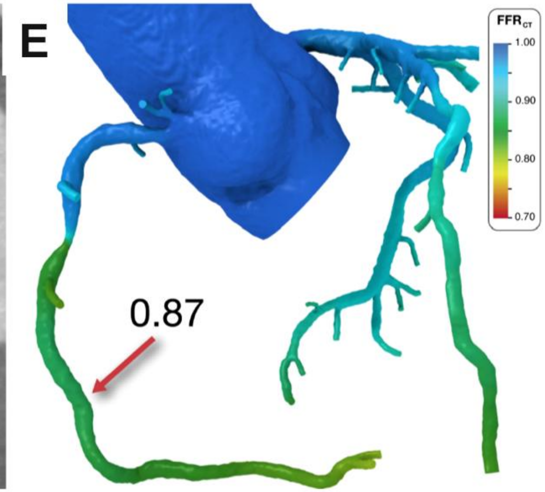


FFR_{CT} of 0.62, indicating vessel ischemia

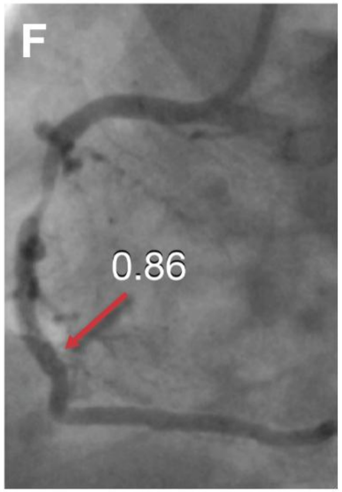


ICA stenosis of LAD, and FFR of 0.65, indicating vessel ischemia

CT stenosis of the mid RCA



FFR_{CT} of 0.87, indicating no vessel ischemia



ICA stenosis of mid RCA, and FFR of 0.88, indicating no vessel ischemia

Limitations

- Enrollment criteria disqualified individuals with prior CABG or suspected in-stent restenosis after PCI

- Not every vessel was interrogated in study participants
  - Only vessels deemed clinically-indicated for evaluation

- Unknown whether revascularization of ischemic lesions by FFR_{CT} reduces ischemia
  - FFR_{CT} algorithms enable calculation after “virtual” revascularization[1]

- Study did not exclusively enroll patients considered anatomically indeterminate by CT (30-70%)[2,3]
  - FFR_{CT} compared favorably to CT stenosis in subset

[1]Koo BK et al. 2012 EuroPCR Scientific Sessions, [2]Fearon et al. Am J Cardiol 2000: 86: 1013-4; [2]Melikian N et al. JACC Cardiovasc Interv 2010; 3: 307-14

Conclusions

- In stable patients with suspected CAD, **FFR_{CT} demonstrated improved diagnostic accuracy** over CT stenosis for diagnosis of both patients and vessels who manifest ischemia
  - Did not satisfy its pre-specified primary endpoint of Dx accuracy >70% of lower bound of the one-sided 95% CI
  - High sensitivity and NPV implies low rate of FN
  - Considerable increase in discriminatory power

- In patients with **stenoses of intermediate severity** by CT—which are the most clinically ambiguous for ischemia determination—FFR_{CT} demonstrated higher diagnostic performance compared to CT alone

- Proof of feasibility of $FFR_{CT,}$ and represent **first large-scale prospective demonstration of use of computational models** to accurately calculate FFR from typically acquired CT images

Thank you.