# Coronary physiology in AS

## *Is it valid? Which tool?*


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UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

Weatherhead PET Imaging Center

# Disclosure Statement of Financial Interest

Within the past 12+ months, Nils Johnson has had a financial interest/arrangement or affiliation with the organization(s) listed below.

| Affiliation/Financial Relationship | Organizations (alphabetical) |
| --- | --- |
| • Grant/research support (to *institution*) | • St Jude Medical (for CONTRAST study)<br>• Volcano/Philips (for DEFINE-FLOW study)<br>• Abiomed (for DPTI study) |
| • Licensing and associated consulting (to *institution*) | • Boston Scientific (smart-minimum FFR, 510(k) K191008) |
| • Support for educational meetings/training (honoraria/fees donated to *institution*) | • Various, including academic and industry |
| • PET software 510(k) from FDA (application by Lance Gould, to *institution*) | • K113754 (cfrQuant, 2011)<br>• K143664 (HeartSee, 2014)<br>• K171303 (HeartSee update, 2017)<br>• K202679 (HeartSee update, 2020) |
| • Patents filed (USPTO serial numbers 62/597,134 and 62/907,174) | • SAVI and ΔP/Q methods<br>• Correction of fluid-filled catheter signal |

# WARNING

Don’t try this at home…

# Guidelines *against* FFR in AS

ESC (2018/9)

evidence on invasive functional assessment of CAD (with FFR or iwFR) in patients with severe aortic stenosis (AS) is limited to a few small-scale observational studies. These studies support the feasibility of FFR and iwFR in this setting.[302–304] Notwithstanding, the available evidence is insufficient to support the use of invasive functional assessment of coronary lesions in patients with AS, particularly in consideration of the altered haemodynamic condition related to the presence of AS. Therefore, the Task Force is in consensus that indications for myocardial revascularization based on angiographic assessment of CAD should be maintained

SCAI (2018)

**TABLE 7** Summary of recommendations

| *Recommendations* |
| --- |
| **FFR/iFR** |
| **No proven value/should be discouraged:** |
| There are no validation studies in the presence of left ventricular hypertrophy, CHF, pulmonary hypertension, or valvular heart disease. |

Neumann FJ, *EHJ*. 2019 Jan 7;40(2):87-165. (Section 11 text excerpt)
Lofti A, *Catheter Cardiovasc Interv*. 2018 Aug 1;92(2):336-347. (Table 7 portion on physiology in AS)

# ACC/AHA guidelines more supportive

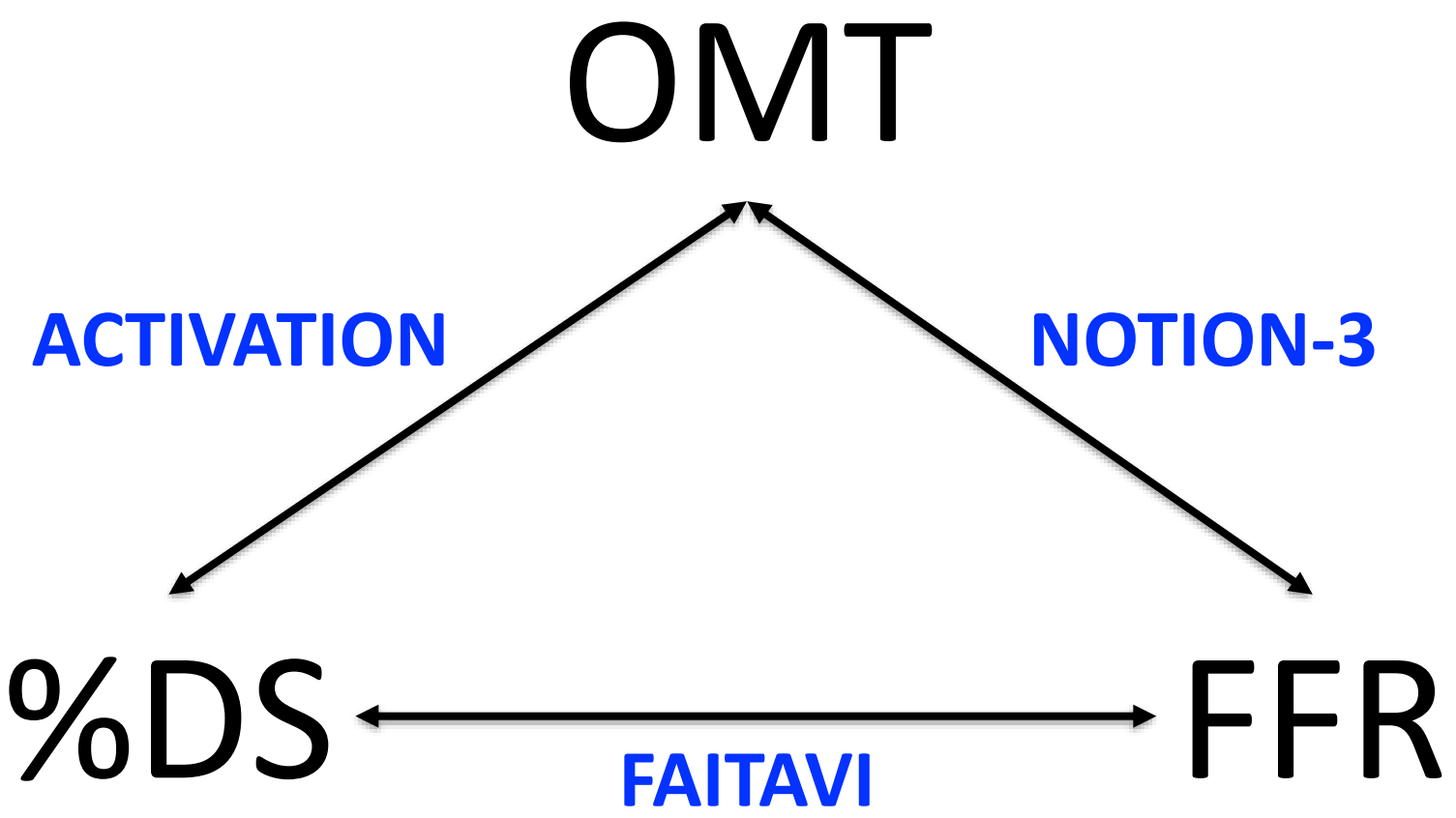
Invasive functional assessment of coronary lesions in TAVI candidates by using fractional flow reserve or instantaneous wave-free ratio is safe and feasible (13-15). Instantaneous wave-free ratio may be particularly attractive because it does not require the administration of a vasodilator and is less influenced by the effect of the stenotic aortic valve, although randomized clinical trials validating the utility of both are ongoing.

2. There are no RCTs to inform clinical practice on the benefits and timing of PCI in patients undergoing TAVI.

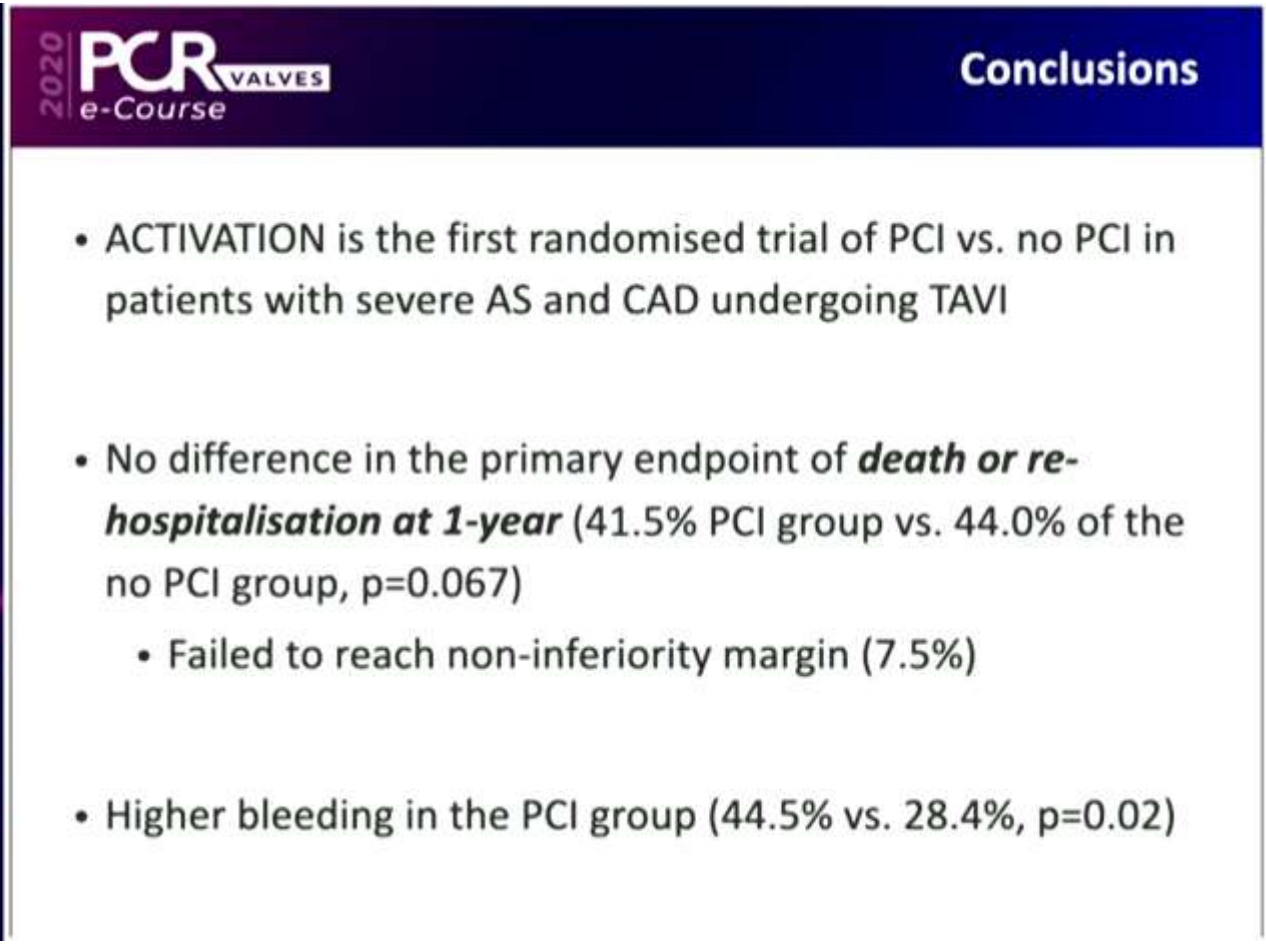
| COR | LOE | RECOMMENDATIONS |
|---|---|---|
| 1 | C-EO | 1. In patients undergoing TAVI, 1) contrast-enhanced coronary CT angiography (in patients with a low pretest probability for CAD) or 2) an invasive coronary angiogram is recommended to assess coronary anatomy and guide revascularization. |
| 2a | C-LD | 2. In patients undergoing TAVI with significant left main or proximal CAD with or without angina, revascularization by PCI before TAVI is reasonable (1,2). |
| 2a | C-LD | 3. In patients with significant AS and significant CAD (luminal reduction >70% diameter, fractional flow reserve <0.8, instantaneous wave-free ratio <0.89) consisting of complex bifurcation left main and/or multivessel CAD with a SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score >33, SAVR and CABG are reasonable and preferred over TAVI and PCI (3,4). |

Otto CM, JACC. 2021 Feb 2;77(4):e25-e197. (Pages e141-e143 with *emphasis*)

# *RCT* completed or in progress



# RCT of *%DS vs OMT*: ACTIVATION


(note: excluded CCS angina class III and IV)

URL https://www.pcronline.com/Cases-resources-images/Resources/Course-videos-slides/2020/PCR-Valves-e-Course-Hotline-I
(accessed February 22, 2021, excerpt taken from video plus exclusion criteria slide)

# RCT of *FFR vs OMT*: NOTION-3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ClinicalTrials.gov

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Save this study

**Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation (NOTION-3)**

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03058627

Recruitment Status : Recruiting
First Posted : February 23, 2017
Last Update Posted : February 27, 2020

See Contacts and Locations

**Sponsor:**
Rigshospitalet, Denmark

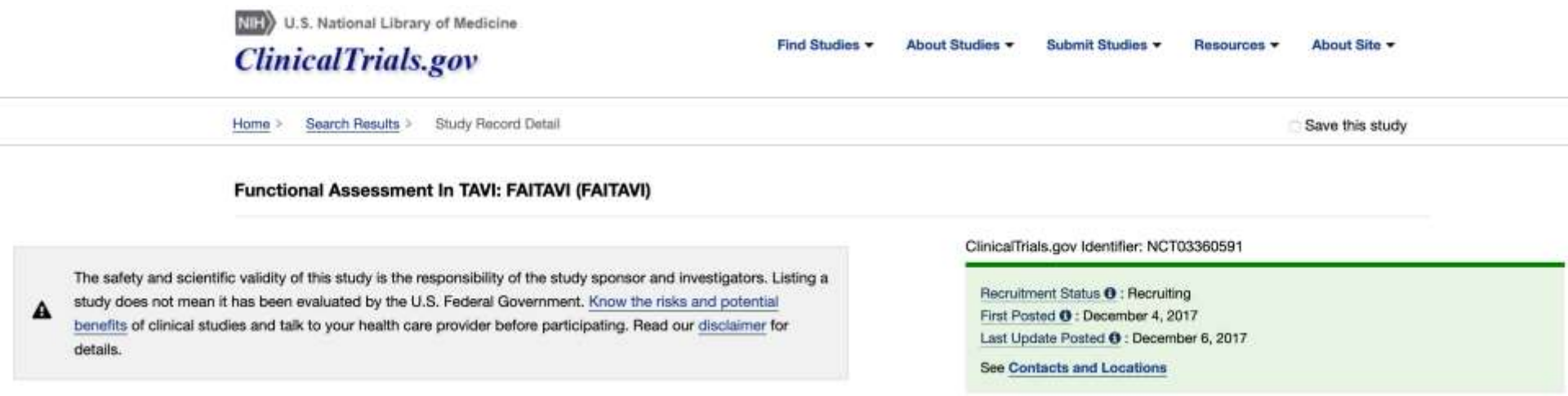
**Collaborators:**
Aarhus University Hospital
Aalborg University Hospital
Odense University Hospital
Lund University Hospital
Karolinska University Hospital
Rikshospitalet University Hospital
Haukeland University Hospital
Helsinki University Central Hospital
Tampere University Hospital
Oulu University Hospital
Turku University Hospital
Kuopio University Hospital
Sahlgrenska University Hospital, Sweden

**Information provided by (Responsible Party):**
Thomas Engstrom, Rigshospitalet, Denmark

- N=452 subjects
- started Sept 2017
- endpoint: 1-year death, MI, urgent PCI
- randomized 1:1
  - ✓TAVI as per current guidelines
  - ✓standard TAVI + PCI if >90%DS or FFR<0.8

URL https://clinicaltrials.gov/ct2/show/NCT03058627, accessed February 22, 2021.

# RCT of *FFR vs %DS*: FAITAVI


U.S. National Library of Medicine
ClinicalTrials.gov

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Home > Search Results > Study Record Detail

Save this study

**Functional Assessment In TAVI: FAITAVI (FAITAVI)**

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03360591

Recruitment Status : Recruiting
First Posted : December 4, 2017
Last Update Posted : December 6, 2017

See Contacts and Locations

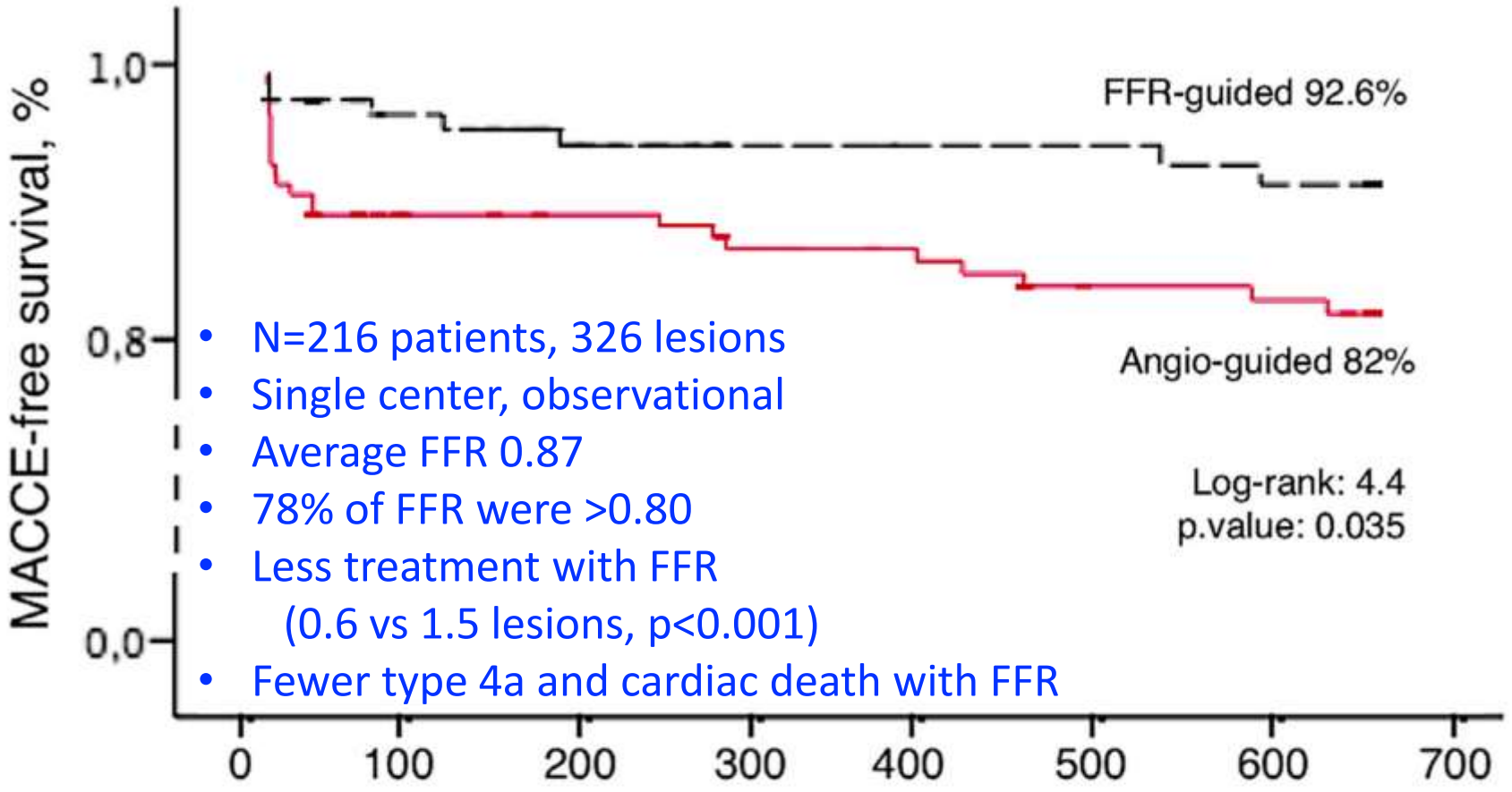
**Sponsor:**
Universita di Verona

**Information provided by (Responsible Party):**
Flavio Ribichini, Universita di Verona

- N=320 subjects
- started Nov 2017
- endpoint: 1-year death, MI, CVA, TVR, bleed
- randomized 1:1 to TAVI plus
  - ✓PCI if ≥50%DS in ≥2.5mm vessel
  - ✓PCI if FFR≤0.80 before *or after* TAVI

URL https://clinicaltrials.gov/ct2/show/NCT03360591, accessed February 22, 2021.

# *Observational*: FFR better than %DS




- N=216 patients, 326 lesions
- Single center, observational
- Average FFR 0.87
- 78% of FFR were >0.80
- Less treatment with FFR
  (0.6 vs 1.5 lesions, p<0.001)
- Fewer type 4a and cardiac death with FFR

| Number at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| FFR-guided | 94 | 85 | 74 | 66 | 62 | 61 | 60 | 59 |
| Angio-guided | 122 | 99 | 97 | 93 | 83 | 80 | 73 | 70 |

Lunardi M, *J Am Heart Assoc*. 2019 Nov 19;8(22):e012618. (Figure 1 plus results)

# Is vasodilation safe in severe AS?

| Author | Citation | N | Drug | Technique | Safety issues |
|---|---|---|---|---|---|
| Roy | Nucl Med Commun 1998;19:789 | 12 | dipy | SPECT | no |
| Carpeggiani | J CV Med 2008;9:893 | 15 | dipy | PET | no |
| Liu | Sci Rep 2019;9:12443 | 15 | dipy | SPECT | no |
| Burwash | Heart 2008;94:1627 | 20 | dipy | PET | no but 16 excluded |
| Rajappan | Circulation 2002;105:470 | 20 | dipy | PET | no |
| Nemes | Herz 2002;27:780 | 21 | dipy | TTE | no |
| Baroni | Heart 1996;75:492 | 25 | dipy | TTE | no |
| Huikuri | AJC 1987;59:336 | 27 | dipy | SPECT | 2 hypotension |
| Demirkol | Cardiology 2002;97:37 | 30 | dipy | SPECT | no |
| Nemes | Clin Physiol Funct Imaging 2009;29,:447 | 49 | dipy | TTE | no |
| Avakian | IJC 2001;81:21 | 110 | dipy | SPECT | no |
| Camugila | JACC 2014;63:1808 | 10 | IC adeno | Doppler wire | no |
| Vendrik | JAHA 2020;9:e015133 | 13 | IC adeno | FFR | no |
| Wiegerinck | Circ CV Int 2015;8:e002443 | 27 | IC adeno | Combo | no |
| Ahmad | JACC CV Int 2018;11:2019 | 28 | IC adeno | FFR | no |
| Scarsini | EuroIntervention 2018;13:1512 | 66 | IC adeno | FFR | no |
| Di Gioia | AJC 2016;117:1511 | 106 | IC adeno | FFR | no |
| Scarsini | J Cardiovasc Transl Res 2019;12:539 | 82 | IC/IV adeno | FFR | no |
| Stähli | Cardiology 2012;123:234 | 4 | IV adeno | FFR | no |
| Stundl | Clin Res Cardiol 2019;Epub | 13 | IV adeno | FFR | no |
| Lumley | JACC 2016;68:688 | 19 | IV adeno | FFR | no |
| Burgstrahler | IJ CV Img 2008;24:195 | 20 | IV adeno | CMR | no |
| Hildick-Smith | JACC 2000;36:1889 | 27 | IV adeno | TTE | 1 "tolerated poorly" |
| Mahmod | JCMR 2014;16:29 | 28 | IV adeno | CMR | no |
| Samuels | JACC 1995;25:99 | 35 | IV adeno | SPECT | 2 hypotension, 2 AV block |
| Gutiérrez-Barrios | Int J Cardiol 2017;236:370 | 36 | IV adeno | FFR | no |
| Stoller | EuroIntervention 2018;14:166 | 40 | IV adeno | FFR | no |
| Takemoto | JASE 2014;27:200 | 41 | IV adeno | TTE/Combo | no |
| Patsilinakos | Angiology 1999;50:309 | 50 | IV adeno | TTE/SPECT | no |
| Stanojevic | J Inv Card 2016;28:357 | 72 | IV adeno | FFR | no |
| Patsilinakos | JNC 2004;11:20 | 75 | IV adeno | SPECT | 9 AV block |
| Yamanaka | JACC CV Int 2018;11:2032 | 95 | IV adeno | FFR/SPECT | 1 AV block, 10% SBP<40mmHg |
| Ahn | JACC 2016;67:1412 | 117 | IV adeno | CMR | no |
| Marko | Echo 2014;31:428 | 127 | IV adeno | TTE | no |
| Singh | EHJ 2017;38:1222 | 174 | IV adeno | CMR | no |
| Nishi | Coron Artery Dis 2018;29:223 | 9 | mixed | FFR | no |
| Arashi | Cardiovasc Interv Ther 2019;34:269 | 13 | mixed | FFR | no |
| Hussain | JNC 2017;24:1200 | 95 | mixed | SPECT | no |
| Banovic | Coron Artery Dis 2019;Epub | 4 | NR | FFR | no |
| Cremer | JNC 2014;21:1001 | 50 | rega | PET | 2 hypotension |

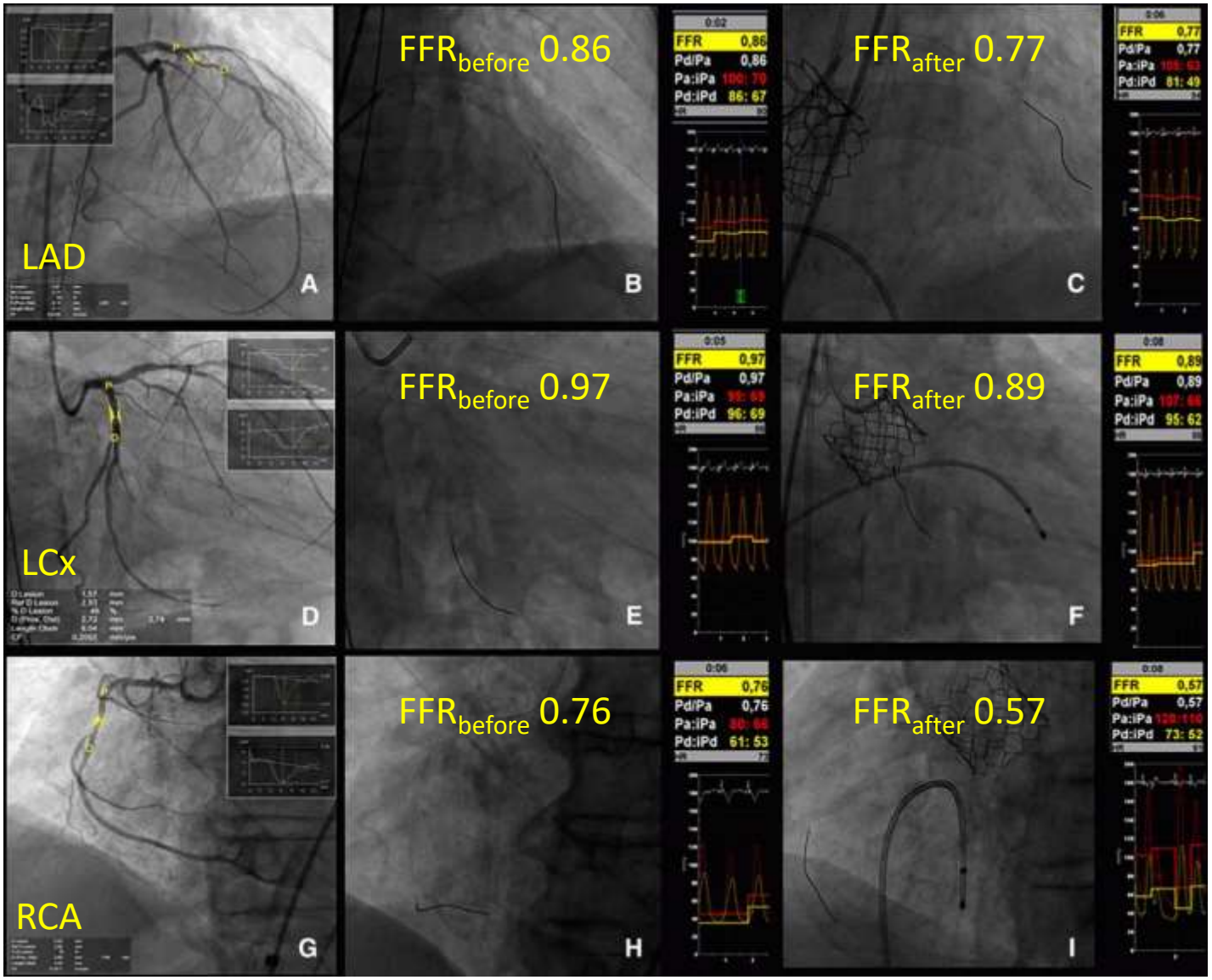
N = 1820 patients
40 papers, 30+ years
no safety issues

Zelis JM, *J Interv Cardiol*. 2020 Jul 22;2020:4603169. (Table 1 with modifications)

# Before vs after

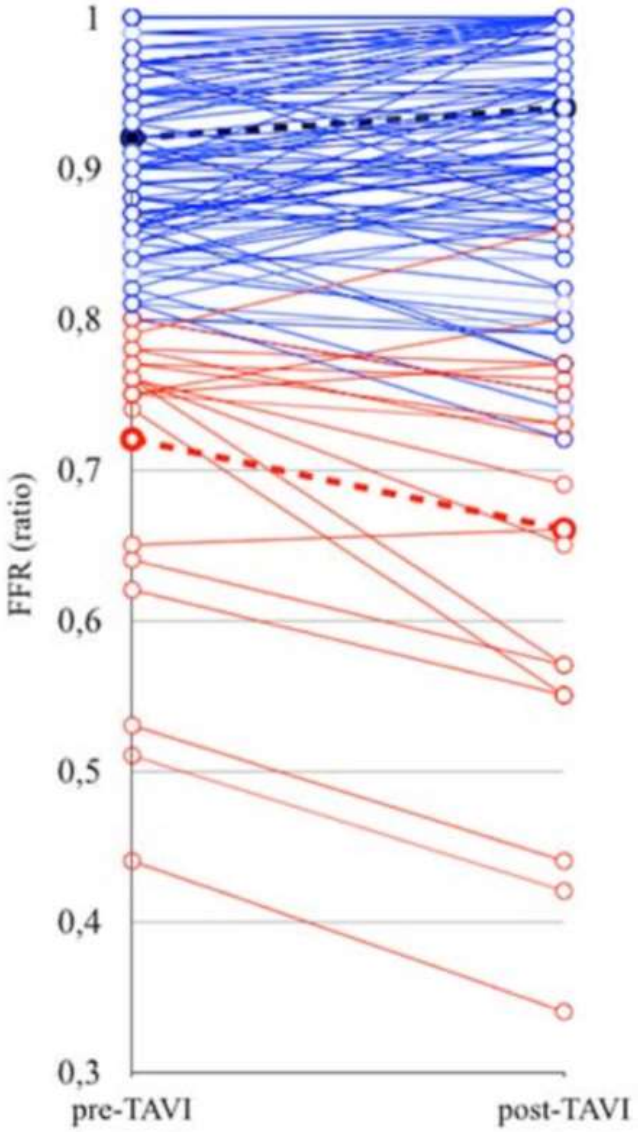
What does AS change?

# Is FFR stable before/after TAVI?




Pesarini G, *Circ Cardiovasc Interv*. 2016;9:e004088. (Figure 1 with annotations)

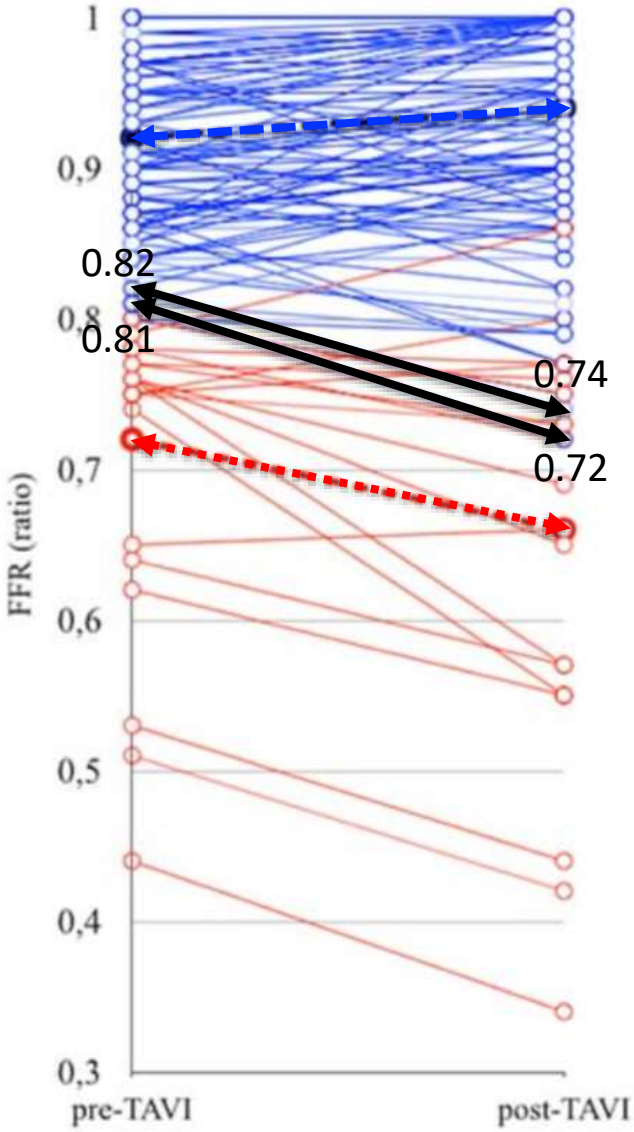
# Is FFR stable before/after TAVI?




- 133 lesions from 54 patients
- FFR
  - ✓ before 0.89 ± 0.10
  - ✓ after 0.89 ± 0.13
  - ✓ p=0.73 for pairs

Pesarini G, *Circ Cardiovasc Interv*. 2016;9:e004088. (Figure 2, overall)

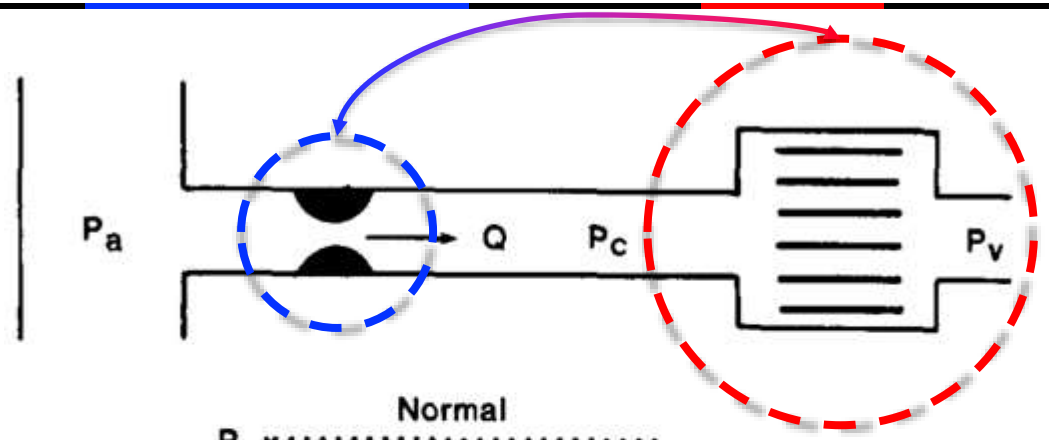
# Is FFR stable before/after TAVI?

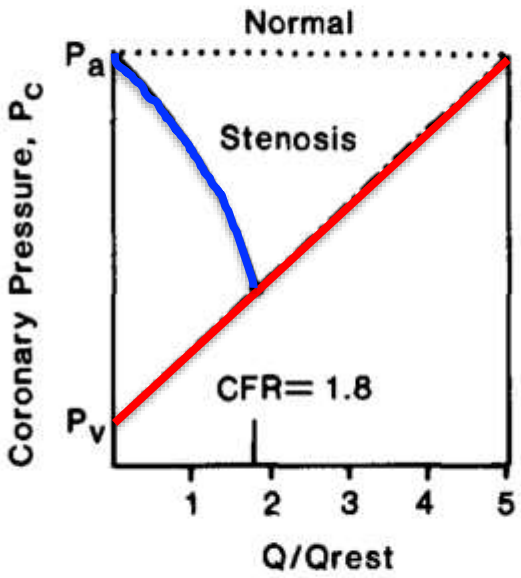



- 133 lesions from 54 patients
- FFR
  - ✓ before 0.89 ± 0.10
  - ✓ after 0.89 ± 0.13
  - ✓ p=0.73 for pairs
- interaction between Δ and FFR=0.8
  - ✓ FFR>0.8 the Δ=+0.01
  - ✓ FFR<0.8 the Δ=-0.05
- 8 lesions crossed FFR=0.80
- 3 lesions switched "grey zone"
  - ✓ 0.83 to 0.75 (LAD)
  - ✓ 0.82 to 0.74 (LAD)
  - ✓ 0.81 to 0.72 (RCA)

Pesarini G, *Circ Cardiovasc Interv*. 2016;9:e004088. (Figure 2, overall, with annotations)

# How do stenosis and bed interact?

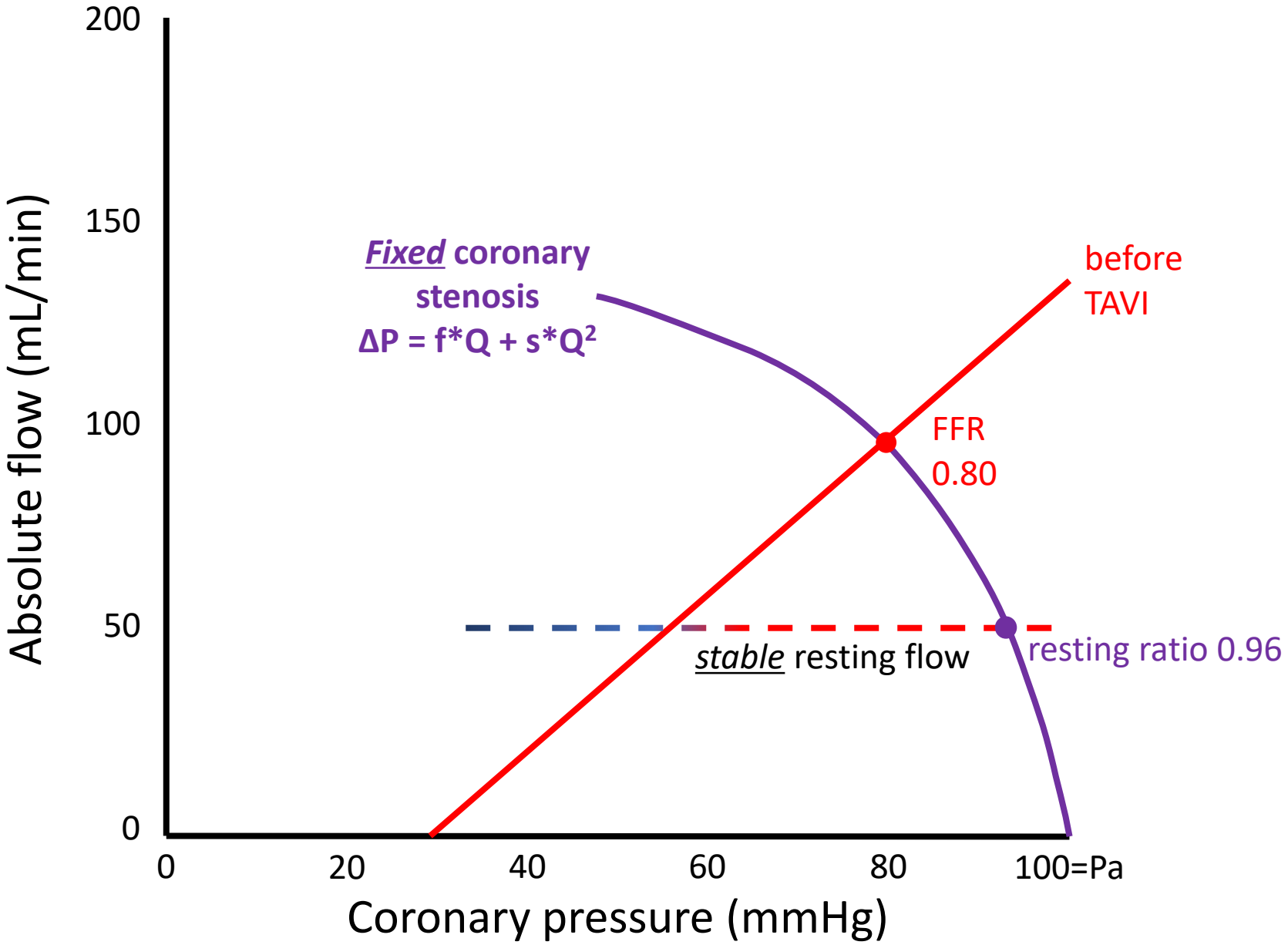


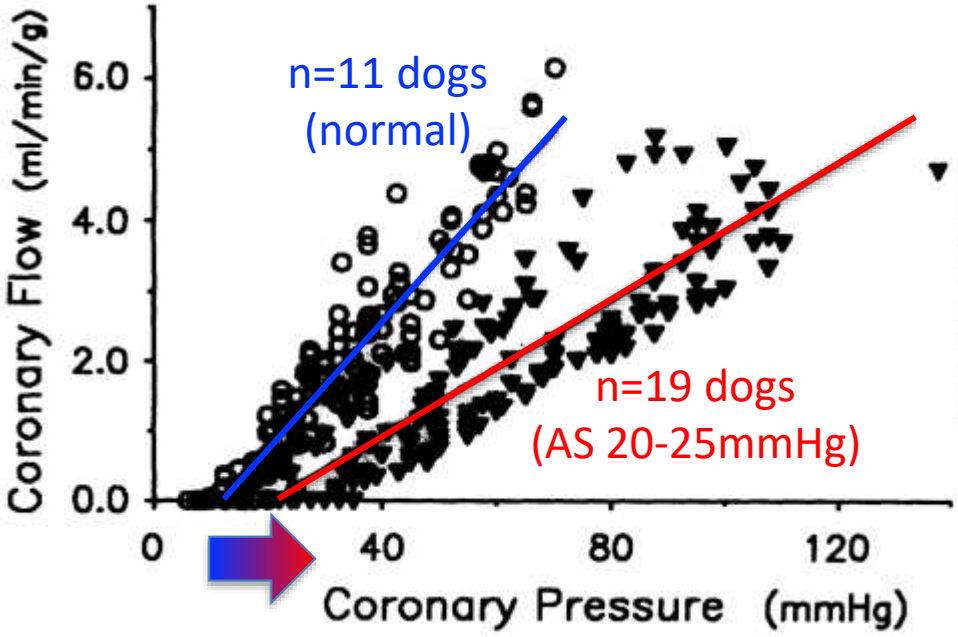

$$Pc = Pa - \underbrace{\left[A(Q/Qrest) + B\,(Q/Qrest)^2\right]}_{\text{Stenosis Pressure Drop}}$$

Kirkeeide RL, *JACC*. 1986 Jan;7(1):103-13. (Figure 2 with annotations)

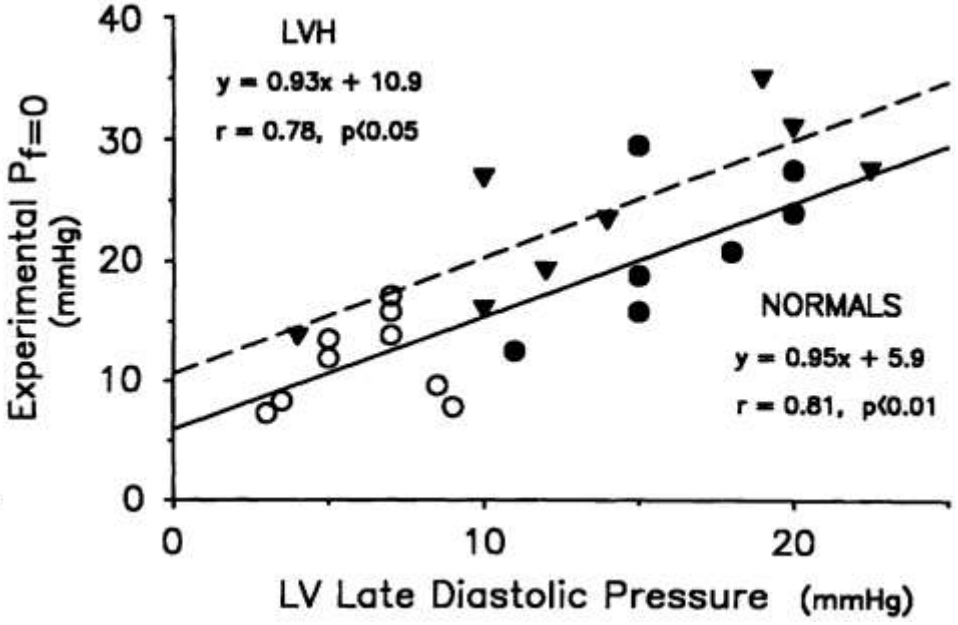
# Coronary/valvular coupling for FFR/AS



# How does bed change with AS?



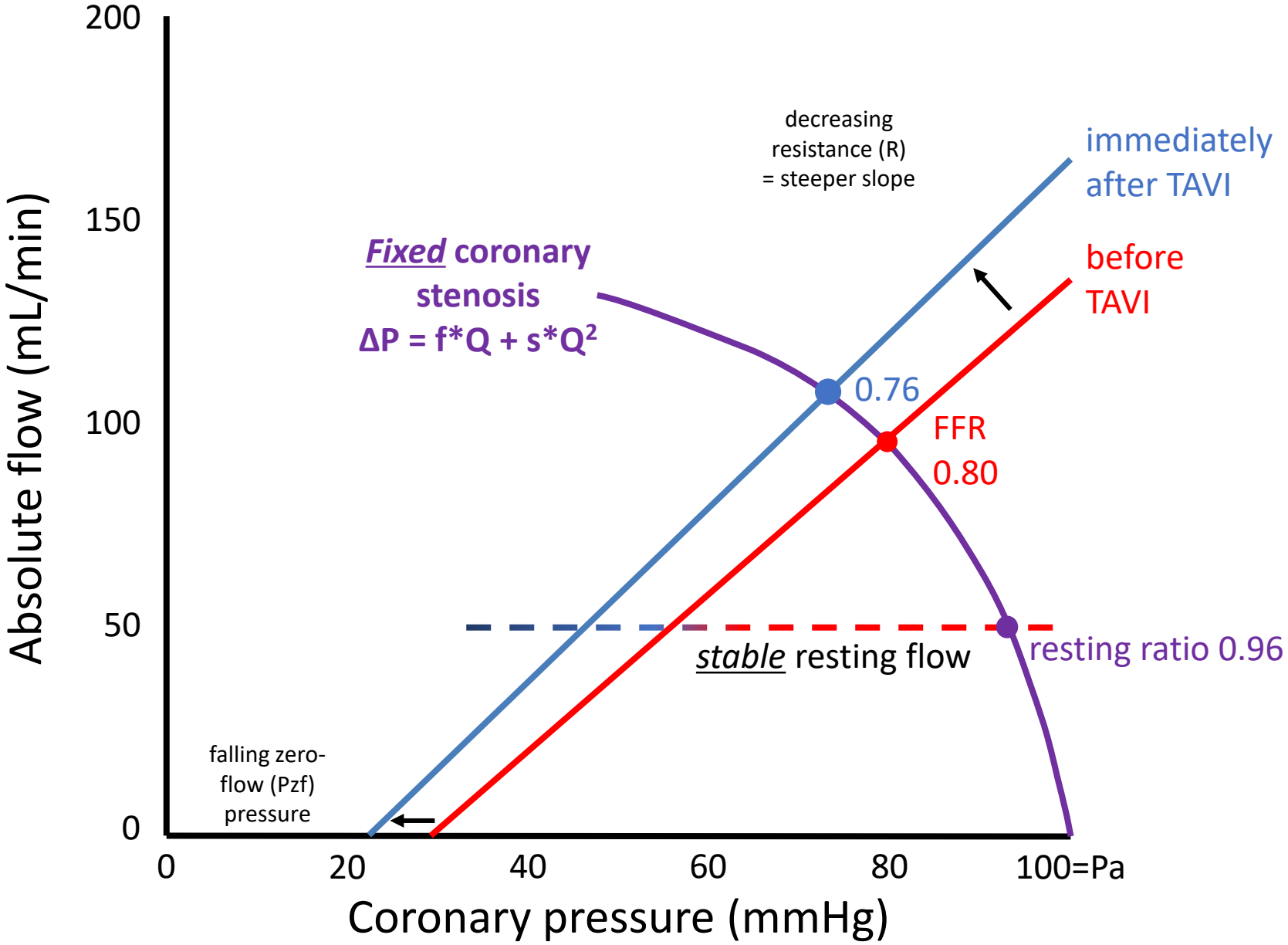

line shifts *rightwards*
(higher backpressure)



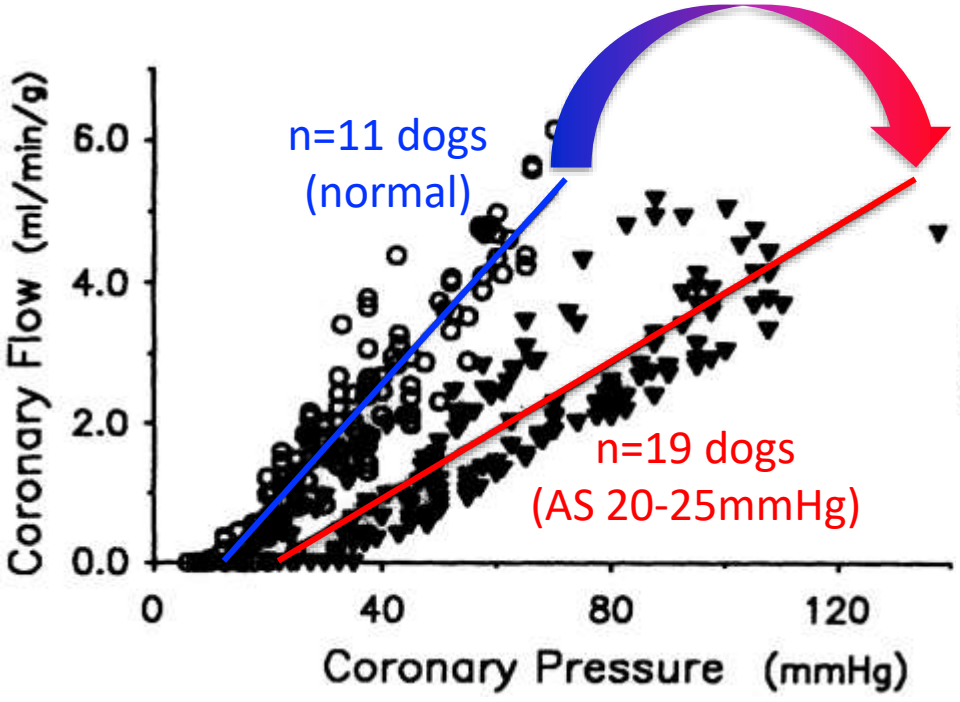

coronary backpressure
relates to ***LV filling pressure***

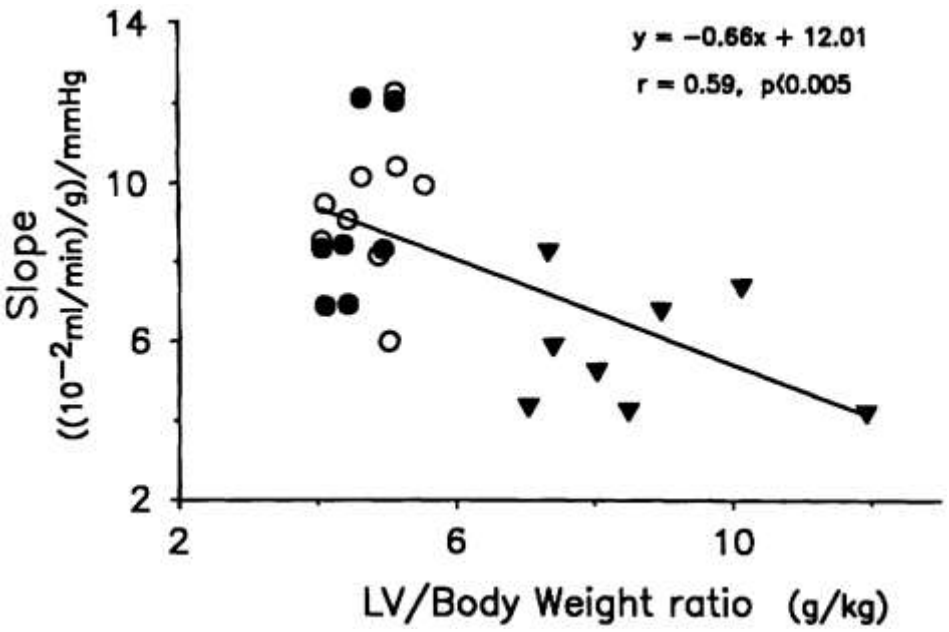
Duncker DJ. *Circ Res*. 1993 Mar;72(3):579-87. (Figures 1 [right panel with annotations] and 2)

# Immediately after TAVI



# How does bed change with AS?



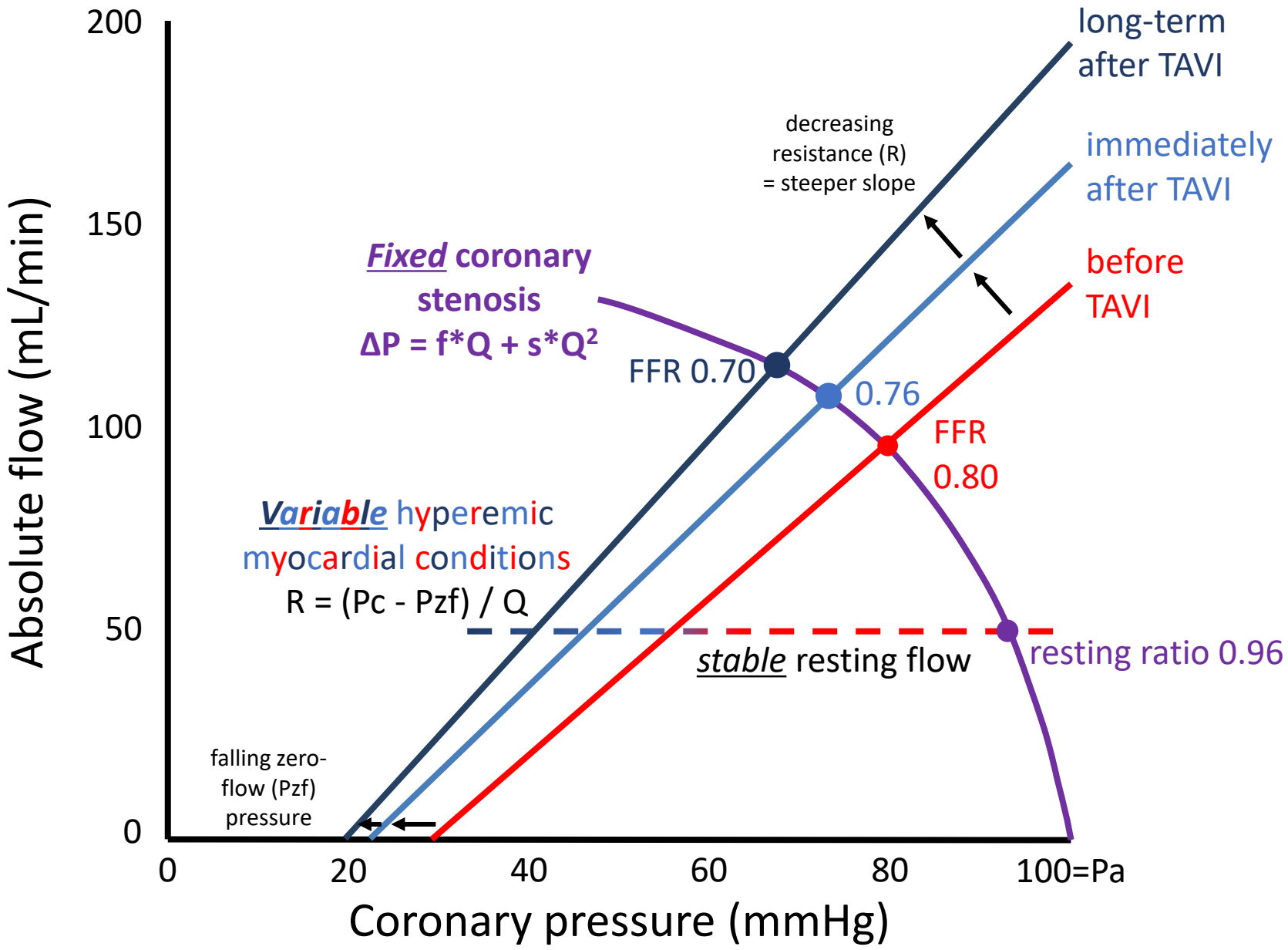




line rotates *clockwise*
(less flow for same pressure)

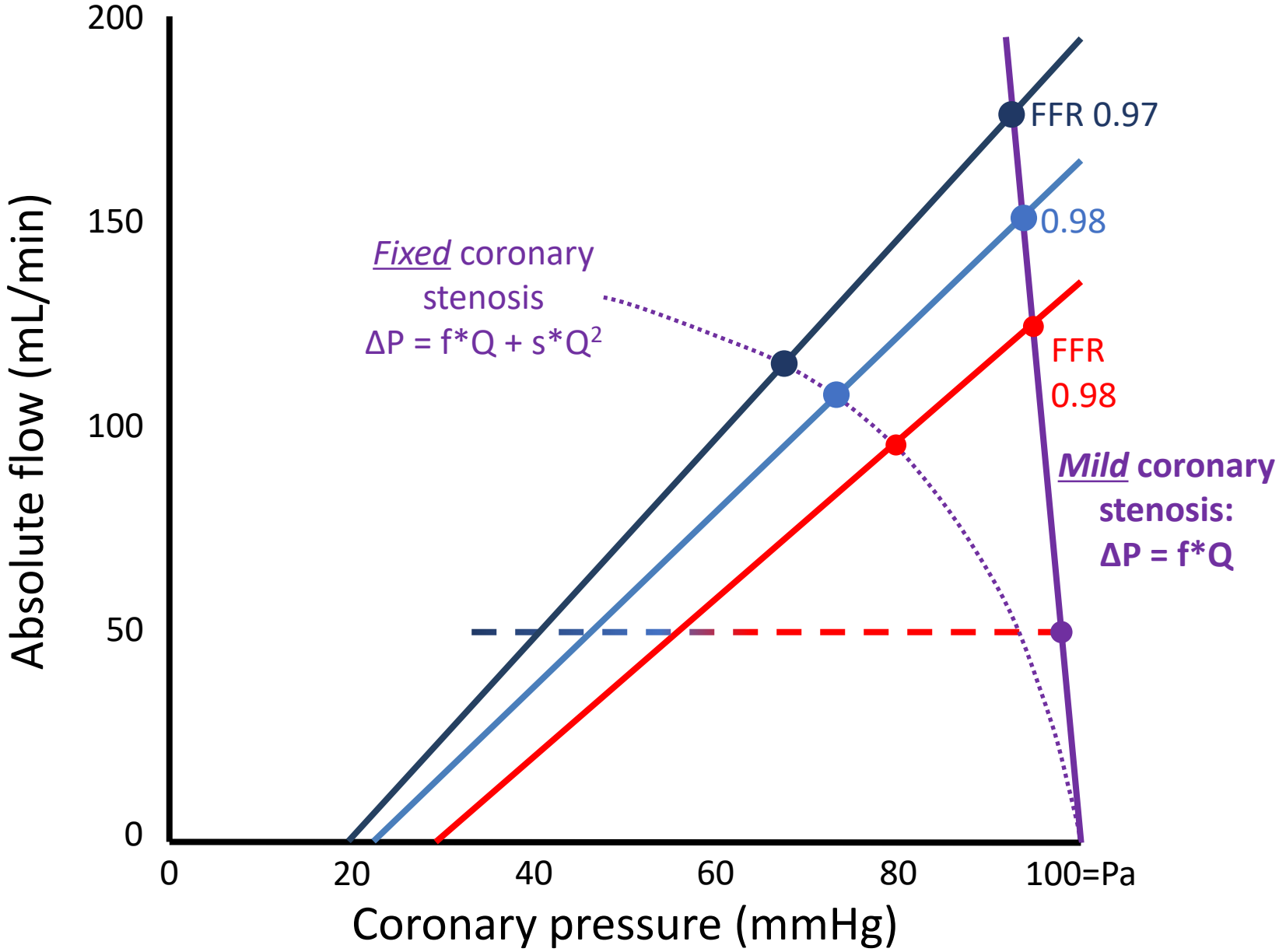
amount of rotation
relates to ***degree of LVH***

Duncker DJ. *Circ Res*. 1993 Mar;72(3):579-87. (Figures 1 [right panel with annotations] and 3)

# Longer-term after TAVI



# But a *mild lesion* does not change!



# Generally hyperemia *improves*

| Author | Citation | N | Baseline | Immediate | p-value | Long-term | p-value | Time | Treatment | Method |
|---|---|---|---|---|---|---|---|---|---|---|
| *Hyperemic perfusion (cc/min/g) or Doppler velocity (cm/sec) or mean transit time (sec)* | | | | | | | | | | |
| Nemes | *Herz 2002;27:780* | 21 | 117 | | | 91.5 | **<0.05** | 15 months | SAVR | echo Doppler (diastolic) |
| Hildick-Smith | *JACC 2000;36:1889* | 27 | 71 | | | 108 | **<0.01** | 6 months | SAVR | echo Doppler (diastolic) |
| Carpeggiani | *J CV Med 2008;9:893* | 8 | 1.68 | | | 1.46 | NS | 12 months | SAVR | PET |
| Rajappan | *Circulation 2003;107:3170* | 22 | 2.17 | | | 2.27 | 0.61 | 12 months | SAVR | PET |
| Camugila | *JACC 2014;63:1808* | 8 | 34 | 29 | NS | 39 | NS | 12 months | TAVI | wire Doppler |
| Vendrik | *JAHA 2020;9:e015133* | 13 | 26.36 | 30.78 | **<0.001** | 40.20 | **<0.001** | 6 months | TAVI | wire Doppler |
| Wiegerinck | *Circ CV Int 2015;8:e002443* | 27 | 44.5 | 51.1 | **0.027** | | | | TAVI | wire Doppler |
| Ahmad | JACC CV Int 2018;11:2019 | 30 | 33.44 | 40.33 | **0.004** | | | | TAVI | wire Doppler |
| Stoller | *EuroIntervention 2018;14:166* | 40 | 0.44 | 0.48 | 0.53 | | | | TAVI | wire thermo |
| *Coronary flow reserve (CFR)* | | | | | | | | | | |
| Nemes | *Herz 2002;27:780* | 21 | 1.96 | | | 2.37 | **<0.05** | 15 months | SAVR | echo Doppler (diastolic) |
| Hildick-Smith | *JACC 2000;36:1889* | 27 | 1.76 | | | 2.61 | **<0.01** | 6 months | SAVR | echo Doppler (diastolic) |
| Carpeggiani | *J CV Med 2008;9:893* | 8 | 1.68 | | | 1.58 | NS | 12 months | SAVR | PET |
| Rajappan | *Circulation 2003;107:3170* | 22 | 2.02 | | | 2.28 | 0.17 | 12 months | SAVR | PET |
| Camugila | *JACC 2014;63:1808* | 8 | 1.53 | 1.58 | 0.41 | 2.18 | **<0.01** | 12 months | TAVI | wire Doppler |
| Vendrik | *JAHA 2020;9:e015133* | 13 | 1.28 | 1.65 | **<0.001** | 1.94 | **<0.001** | 6 months | TAVI | wire Doppler |
| Wiegerinck | *Circ CV Int 2015;8:e002443* | 27 | 1.9 | 2.1 | 0.113 | | | | TAVI | wire Doppler |
| Stoller | *EuroIntervention 2018;14:166* | 40 | 1.9 | 2.0 | 0.72 | | | | TAVI | wire thermo |
| *Fractional flow reserve (FFR)* | | | | | | | | | | |
| Stundl | Clin Res Cardiol 2019;Epub | 13 | 0.77 | | | 0.76 | 0.11 | 2 months | TAVI | |
| Vendrik | *JAHA 2020;9:e015133* | 13 | 0.85 | 0.79 | **<0.001** | 0.71 | **<0.001** | 6 months | TAVI | |
| Ahmad | JACC CV Int 2018;11:2019 | 30 | 0.87 | 0.85 | **0.0008** | | | | TAVI | |
| Stoller | *EuroIntervention 2018;14:166* | 40 | 0.90 | 0.93 | **0.0021** | | | | TAVI | |
| Pesarini | Circ CV Int 2016;9:e004088 | 133 | 0.89 | 0.89 | 0.73 | | | | TAVI | |

N = 342 lesions

11 papers, 21 years

red = hyperemia *increases*

blue = hyperemia *decreases*

Zelis JM, *J Am Heart Assoc*. 2020 Mar 3;9(5):e04905. (Table excerpt and reformatted).

# Generally resting does not change

| Author | Citation | N | Baseline | Immediate | p-value | Long-term | p-value | Time | Treatment | Method |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Resting perfusion (cc/min/g) or Doppler velocity (cm/sec)* | | | | | | | |
| Nemes | *Herz 2002;27:780* | 21 | 62.2 | | | 40.1 | **<0.01** | 15 months | SAVR | echo Doppler (diastolic) |
| Hildick-Smith | *JACC 2000;36:1889* | 27 | 43 | | | 41 | NS | 6 months | SAVR | echo Doppler (diastolic) |
| Carpeggiani | *J CV Med 2008;9:893* | 8 | 1.01 | | | 0.92 | >0.05 | 12 months | SAVR | PET |
| Rajappan | *Circulation 2003;107:3170* | 22 | 1.08 | | | 1.01 | 0.27 | 12 months | SAVR | PET |
| Camugila | *JACC 2014;63:1808* | 8 | 22 | 20 | NS | 18 | NS | 12 months | TAVI | wire Doppler |
| Vendrik | *JAHA 2020;9:e015133* | 13 | 19.98 | 19.70 | NS | 21.44 | 0.397 | 6 months | TAVI | wire Doppler |
| Ahmad | JACC CV Int 2018;11:2019 | 30 | 22.13 | 24.84 | 0.1 | | | | TAVI | wire Doppler |
| Wiegerinck | *Circ CV Int 2015;8:e002443* | 27 | 24.4 | 25.5 | 0.401 | | | | TAVI | wire Doppler |
| | | | *Instantaneous wave-free ratio (iFR)* | | | | | | | |
| Vendrik | *JAHA 2020;9:e015133* | 13 | 0.82 | 0.83 | NS | 0.83 | 0.735 | 6 months | TAVI | |
| Ahmad | JACC CV Int 2018;11:2019 | 30 | 0.88 | 0.88 | 0.94 | | | | TAVI | |
| Scarsini | EuroIntervention 2018;13:1512 | 145 | 0.89 | 0.89 | 0.66 | | | | TAVI | |

N = 301 lesions

9 papers, 19 years

red = resting *increases*

blue = resting *decreases*

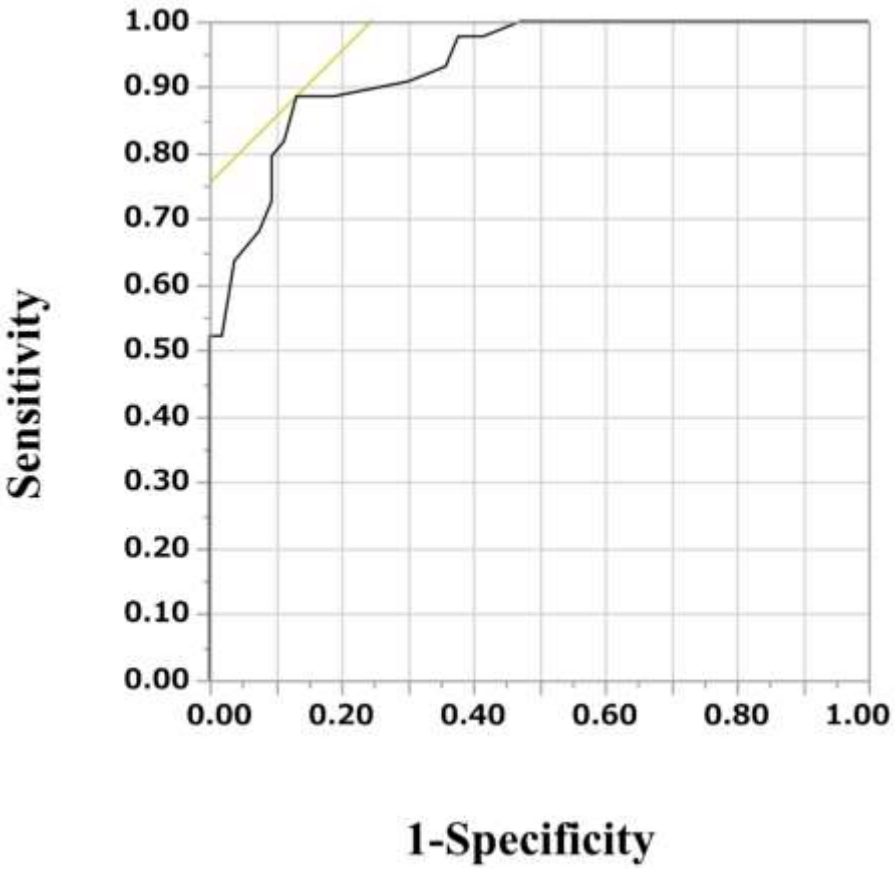
Zelis JM, *J Am Heart Assoc*. 2020 Mar 3;9(5):e04905. (Table excerpt and reformatted).

# Which tool?

Can we substitute?

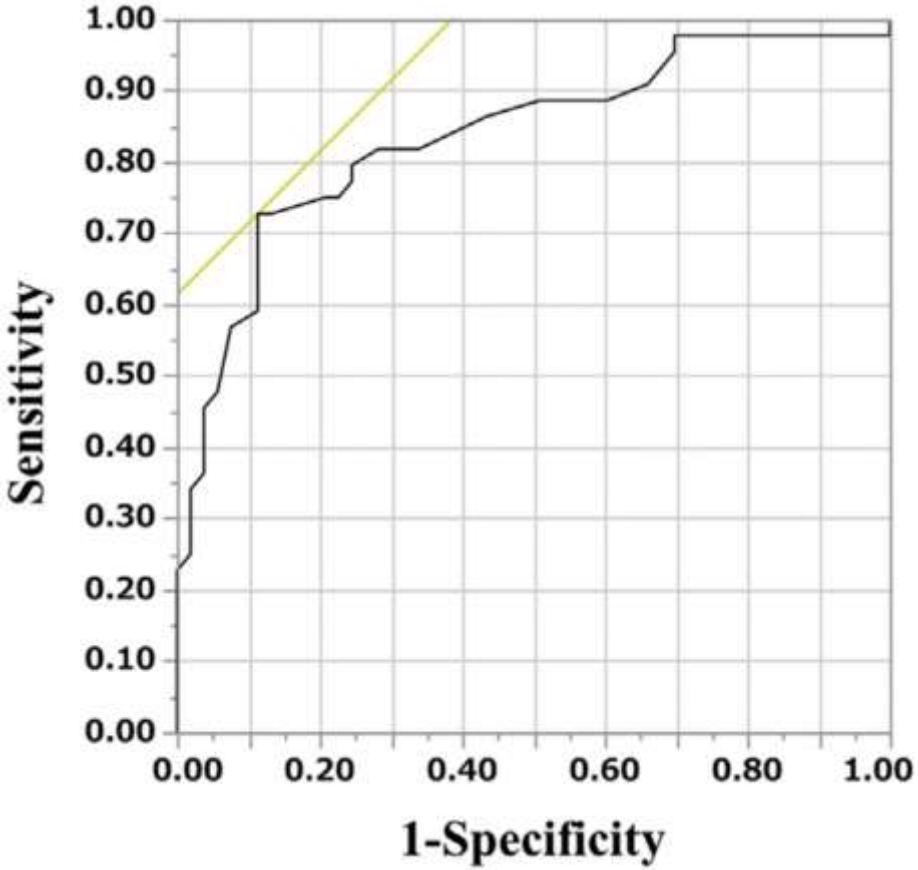
# How do FFR/iFR match SPECT in AS?

FFR vs SPECT




- cutoff FFR=0.83
- AUC 0.93

iFR vs SPECT




- cutoff iFR=0.82
- AUC 0.84

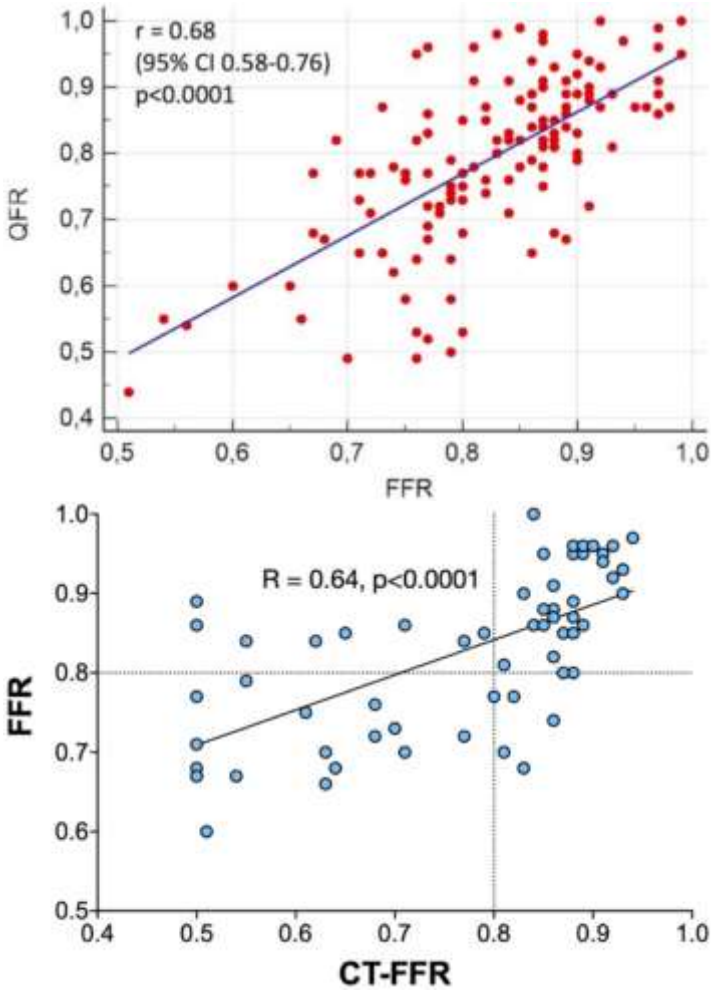
Yamanaka F, *JACC Cardiovasc Interv*. 2018 Oct 22;11(20):2032-2040. (Online Figure 2A and Figure 5A)

# How well can we substitute?

| Method | Condition | Vessels | Bias | Imprecision |
|---|---|---|---|---|
| FFR | general | 953 | <0.005 | 0.018 |
| | AS* | 133 | <0.01 | ? |
| QFR | general | 969 | 0.01 | 0.07 |
| | AS** | 138 | 0.03 | 0.09 |
| | AS*** | 29 | 0.02 | 0.11 |
| $FFR_{CT}$ | general | 908 | 0.03 | 0.09 |
| | AS**** | 68 | 0.06 | 0.11 |

↑ imprecision = QFR/FFRCT models in AS

QFR or $FFR_{CT}$ 0.85 = maybe FFR 0.75




Johnson NP, Tonino PAL. *EuroIntervention*. 2020 Jul 17;16(4):e273-e275. (Based on Table 1 and its associated references)

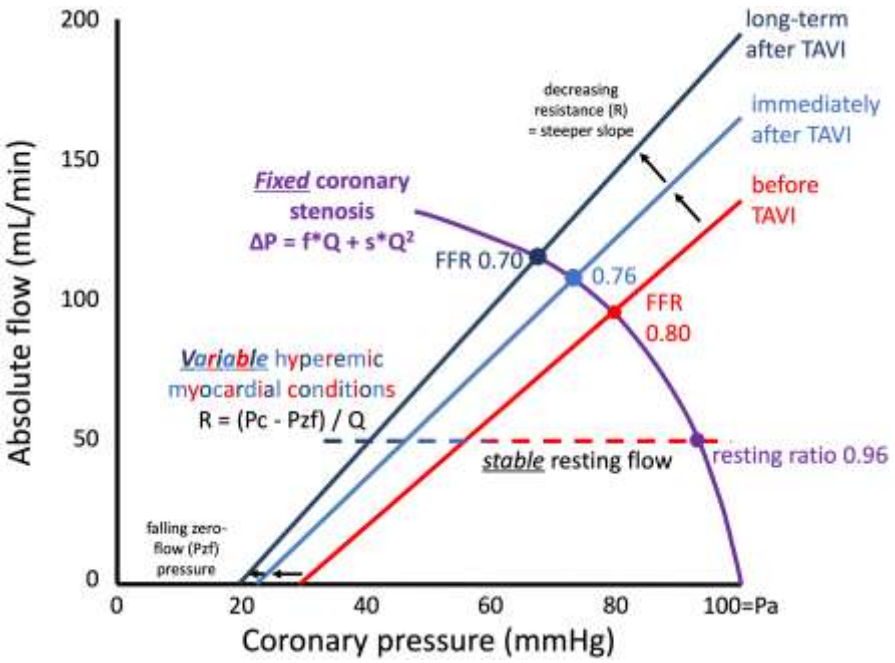
* = Pesarini G, *Circ Cardiovasc Interv*. 2016;9:e004088.

** = Mejía-Rentería H, *EuroIntervention*. 2020 Jul 17;16(4):e285-e292. (Supplementary Figure 2A)

*** = Sejr-Hansen M, Catheter Cardiovasc Interv. [2021 Feb 3. Online ahead of print.] (Figure 2)

**** = Michail M, Circ Cardiovasc Interv. 2021 Jan;14(1):e009586. (Figure 3A)

# Summary: coronary physiology in AS




- Guidelines historically against it
- Emerging RCT data on PCI pre-TAVI
  - ✓ ACTIVATION = avoid PCI
  - ✓ await NOTION-3
  - ✓ await FAITAVI
- Observational FFR outcomes data
- Stress drugs safe for FFR pre-TAVI
- FFR matches better with SPECT
- QFR and $FFR_{CT}$ are $\pm 0.1$ imprecise
- Physiology of AS/coronary coupling
- Due to TAVI impact on myocardium
  - ✓ FFR>0.85 do not drop <0.75
  - ✓ FFR=0.80-0.85 may drop <0.75