Coronary physiology + AS

decision-making in TAVI patients

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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 (chronologic)
• Grant/research support (to *institution*)	• St Jude Medical (CONTRAST, NCT02184117) • Volcano/Philips (DEFINE-FLOW, NCT02328820) • CoreAalst (PPG registry, NCT04789317) • Abiomed (local "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) • K143664 (HeartSee, 2014) • K171303 (HeartSee update, 2017) • K202679 (HeartSee update, 2020)
• Patents filed (USPTO serial numbers 62/597,134 + 62/907,174)	• SAVI and ΔP/Q methods • Correction of fluid-filled catheter signal

Guidelines?

Not much guidance

ESC focuses on anatomy

Recommendations for management of CAD in patients with VHD.

Recommendations	Class[a]	Level[b]
Indications for myocardial revascularization		
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa	C

[e]Stenosis ≥50% can be considered for left main stenosis.

[f]FFR ≤0.8 is a useful cut-off indicating the need for an intervention in patients with mitral or tricuspid diseases, but has not been validated in patients with aortic stenosis.

Assessing the clinical value of systematic PCI in TAVI patients with significant associated CAD is the objective of ongoing RCTs. Patients with severe symptomatic aortic stenosis and diffuse CAD unsuitable for revascularization should receive optimal medical therapy and undergo SAVR or TAVI according to individual characteristics.

Has >70%DS been "validated in patients with aortic stenosis"?

Vahanian A, *EHJ*. 2021 Aug 28:ehab395. (Table from section 3.6.1 and text from section 5.5 with *emphasis*)

ACC/AHA allows %DS, FFR, iFR

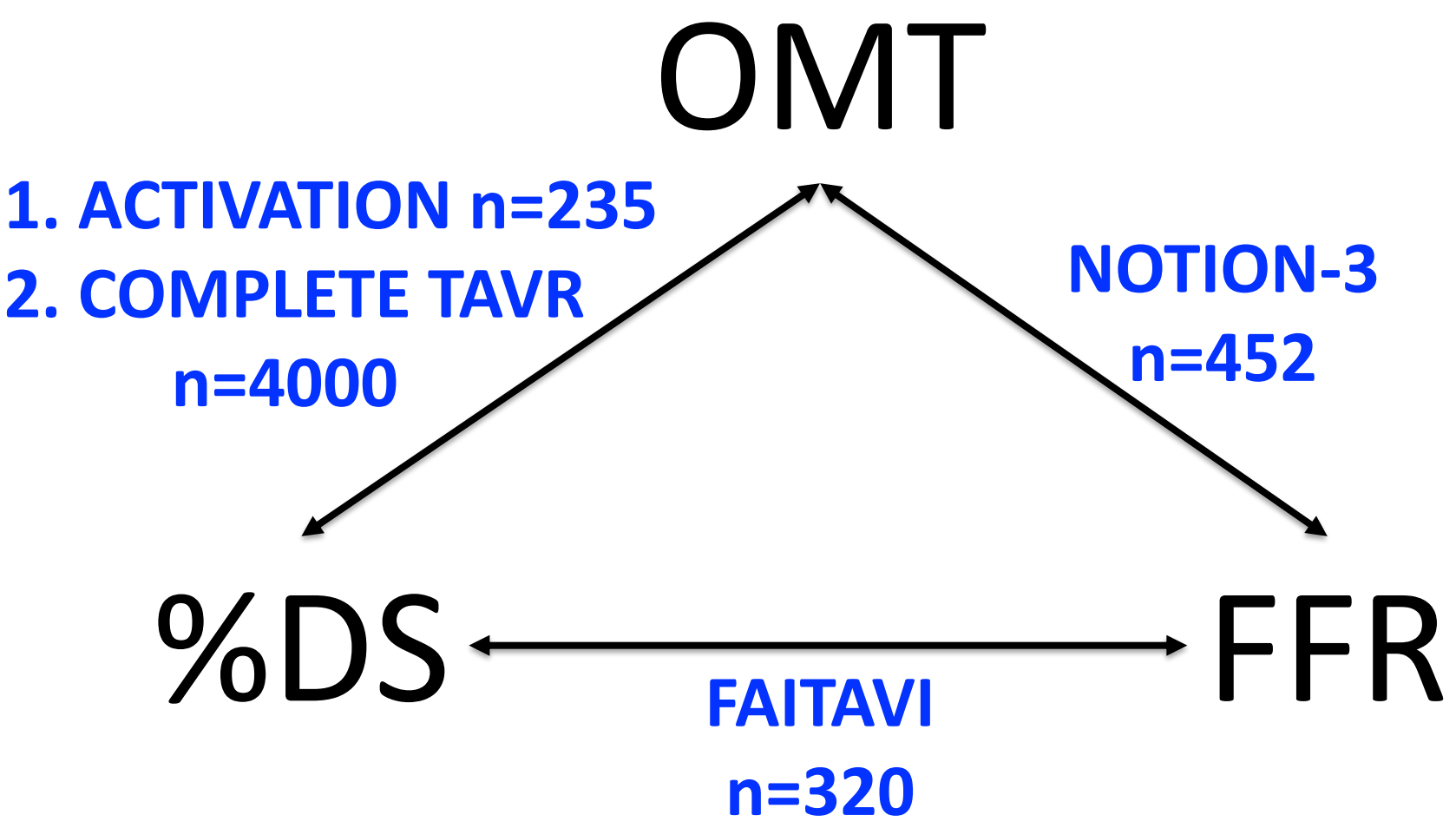
Invasive functional assessment of coronary lesions in TAVI candidates by using fractional flow reserve or instantaneous wave-free ratio is safe and feasible (13-15). Instantaneous wave-free ratio may be particularly attractive because it does not require the administration of a vasodilator and is less 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.

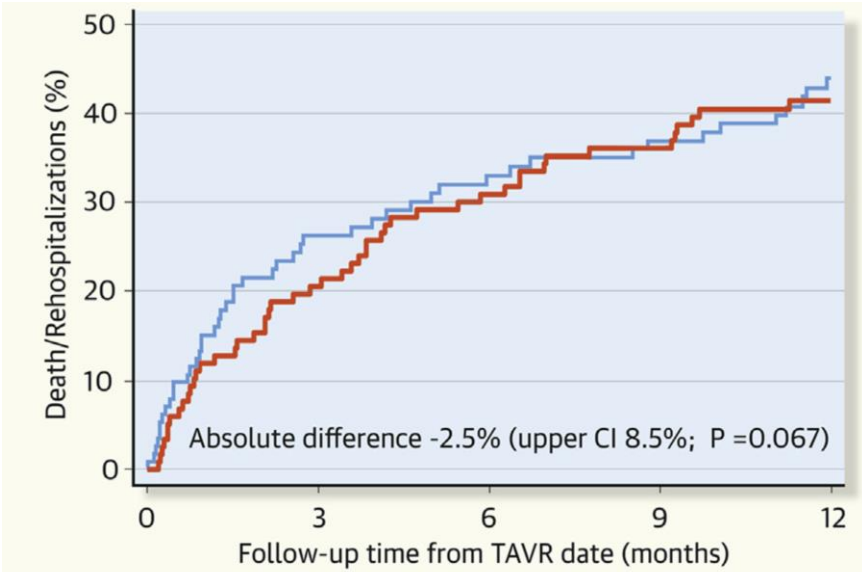
COR	LOE	RECOMMENDATIONS
1	C-EO	1. In patients undergoing TAVI, 1) contrast-enhanced coronary CT angiography (in patients with a low pretest probability for CAD) or 2) an invasive coronary angiogram is recommended to assess coronary anatomy and guide revascularization.
2a	C-LD	2. In patients undergoing 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



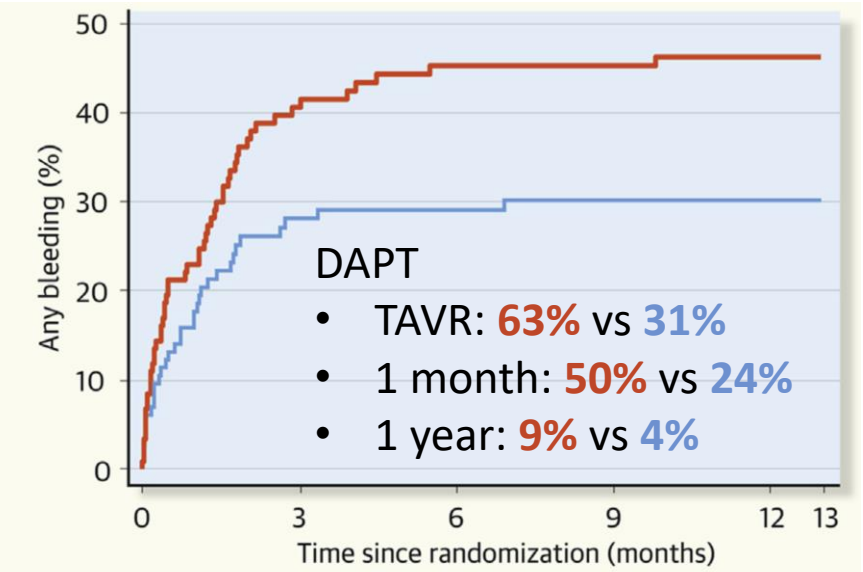


TABLE 1 Baseline Characteristics of the Patient Cohorts

	PCI (n = 119)	No PCI (n = 116)
Angina grade (CCS class)		
0	81 (68.1)	79 (69.3)
I	14 (11.8)	18 (15.8)
II	23 (19.3)	16 (14.0)
III	1 (0.8)	1 (0.9)
IV	0 (0.0)	0 (0.0)

TABLE 2 Angiographic and Procedural Characteristics

	PCI (n = 119)	No PCI (n = 116)
Coronary artery disease		
Left anterior descending artery >70%	73 (61.3)	69 (60.5)
Circumflex artery >70%	42 (35.3)	38 (33.3)
Right coronary artery >70%	47 (39.5)	59 (51.8)
Left main stem coronary artery >70%	3 (2.5)	6 (5.3)
PCI undertaken	116 (97.5)	–
Number of patients	116 (97.5)	
Number of lesions	194	
Lesion length, mm	17.4 ± 6.6	
Number of treated lesions	1 (0-2)	
Number of stents	1 (0-4)	
Pre-PCI stenosis, %	80.3 ± 15.2	
Post-PCI stenosis, %	2.2 ± 7.2	

Patterson T, *JACC Cardiovasc Interv*. 2021 Sep 27;14(18):1965-1974. (Central Illustration and parts of Tables 1 and 2 with *annotations*)

RCT of *%DS vs OMT*: COMPLETE TAVR

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ClinicalTrials.gov

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Staged Complete Revascularization for Coronary Artery Disease vs Medical Management Alone in Patients With AS Undergoing Transcatheter Aortic Valve Replacement (COMPLETE TAVR)

Sponsor:
University of British Columbia

Information provided by (Responsible Party):
David Wood, University of British Columbia

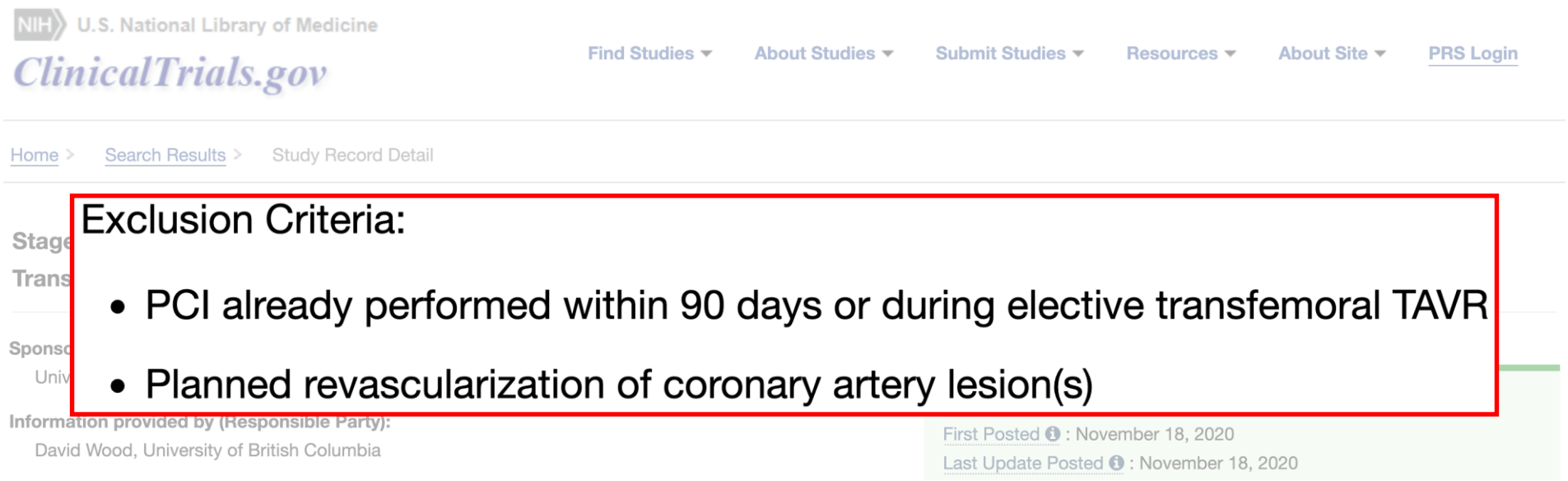
ClinicalTrials.gov Identifier: NCT04634240

Recruitment Status : Not yet recruiting
First Posted : November 18, 2020
Last Update Posted : November 18, 2020

- N = 4000 subjects
- starting soon
- endpoint: 3.5 year CV death, MI, PCI, UA/HF
- randomized 1:1 *after* TAVI
  - ✓medical therapy
  - ✓PCI for >70%DS in ≥2.5mm vessel

URL https://clinicaltrials.gov/ct2/show/NCT04634240, accessed February 12, 2022.

RCT of *%DS vs OMT*: COMPLETE TAVR



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URL https://clinicaltrials.gov/ct2/show/NCT04634240, accessed February 12, 2022.

RCT of *FFR vs OMT*: NOTION-3

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

Sponsor:
Thomas Engstrom

Collaborators:
Rigshospitalet, Denmark
Aarhus University Hospital
Aalborg University Hospital
Odense University Hospital
Lund University Hospital
Karolinska University Hospital
Haukeland University Hospital
Helsinki University Central Hospital
Tampere University Hospital
Oulu University Hospital
Turku University Hospital
Sahlgrenska University Hospital, Sweden
Pauls Stradins Clinical University Hospital

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

ClinicalTrials.gov Identifier: NCT03058627

Recruitment Status : Recruiting
First Posted : February 23, 2017
Last Update Posted : February 10, 2022

See Contacts and Locations

- 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 12, 2022.

RCT of *FFR vs %DS*: FAITAVI

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Home > Search Results > Study Record Detail

Functional Assessment In TAVI: FAITAVI (FAITAVI)

Sponsor:
Universita di Verona

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

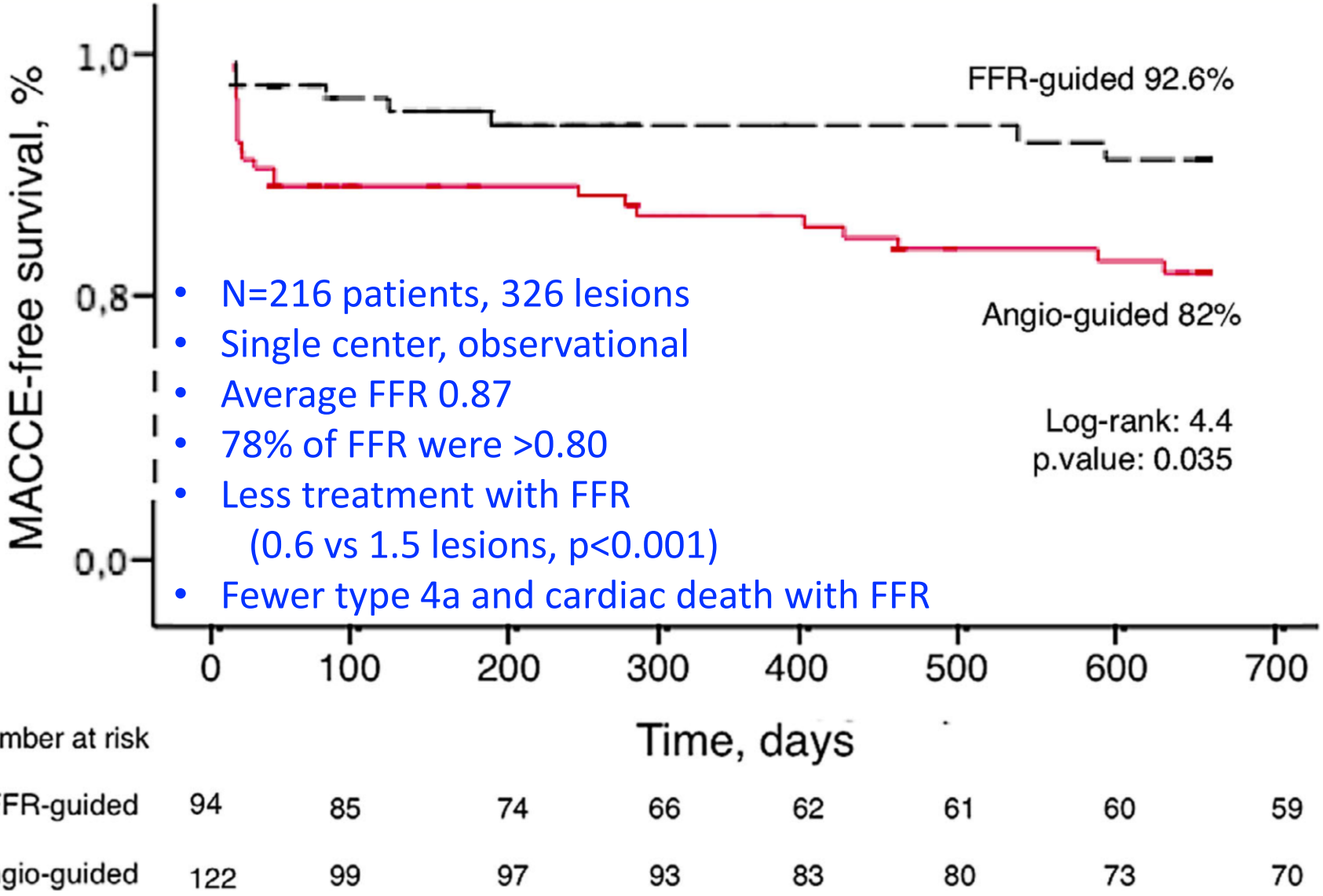
ClinicalTrials.gov Identifier: NCT03360591

Recruitment Status : Recruiting
First Posted : December 4, 2017
Last Update Posted : May 12, 2021

- 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 12, 2022.

Observational: FFR better than %DS



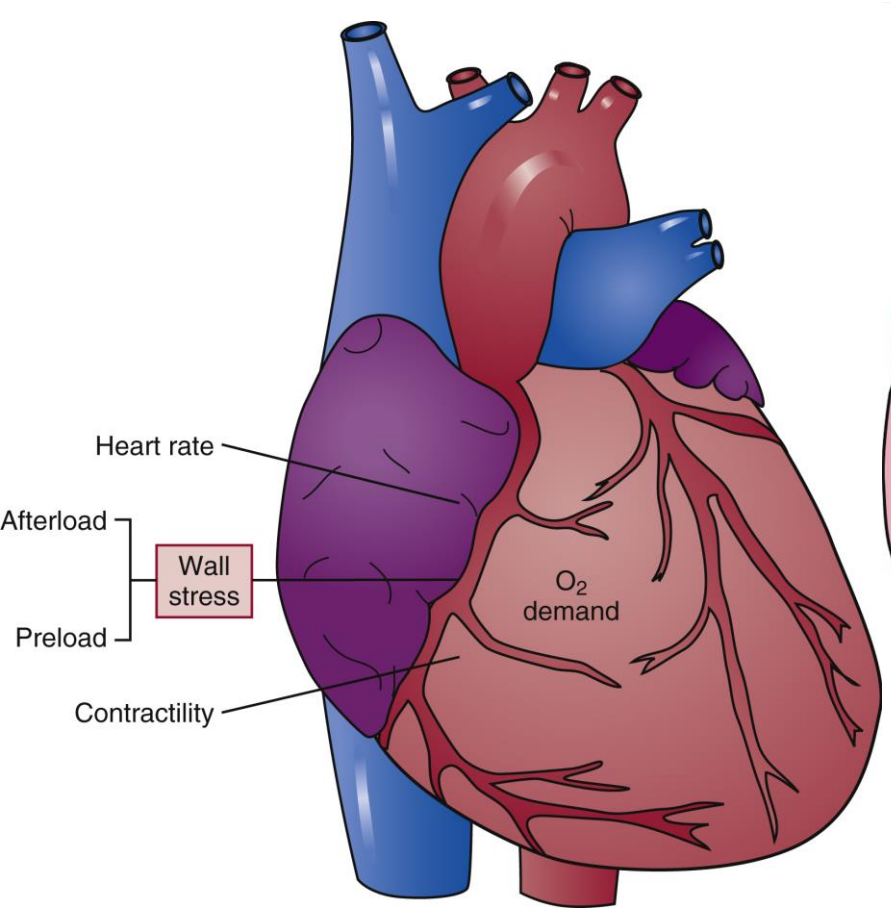
- N=216 patients, 326 lesions
- Single center, observational
- Average FFR 0.87
- 78% of FFR were >0.80
- Less treatment with FFR
  (0.6 vs 1.5 lesions, p<0.001)
- Fewer type 4a and cardiac death with FFR

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

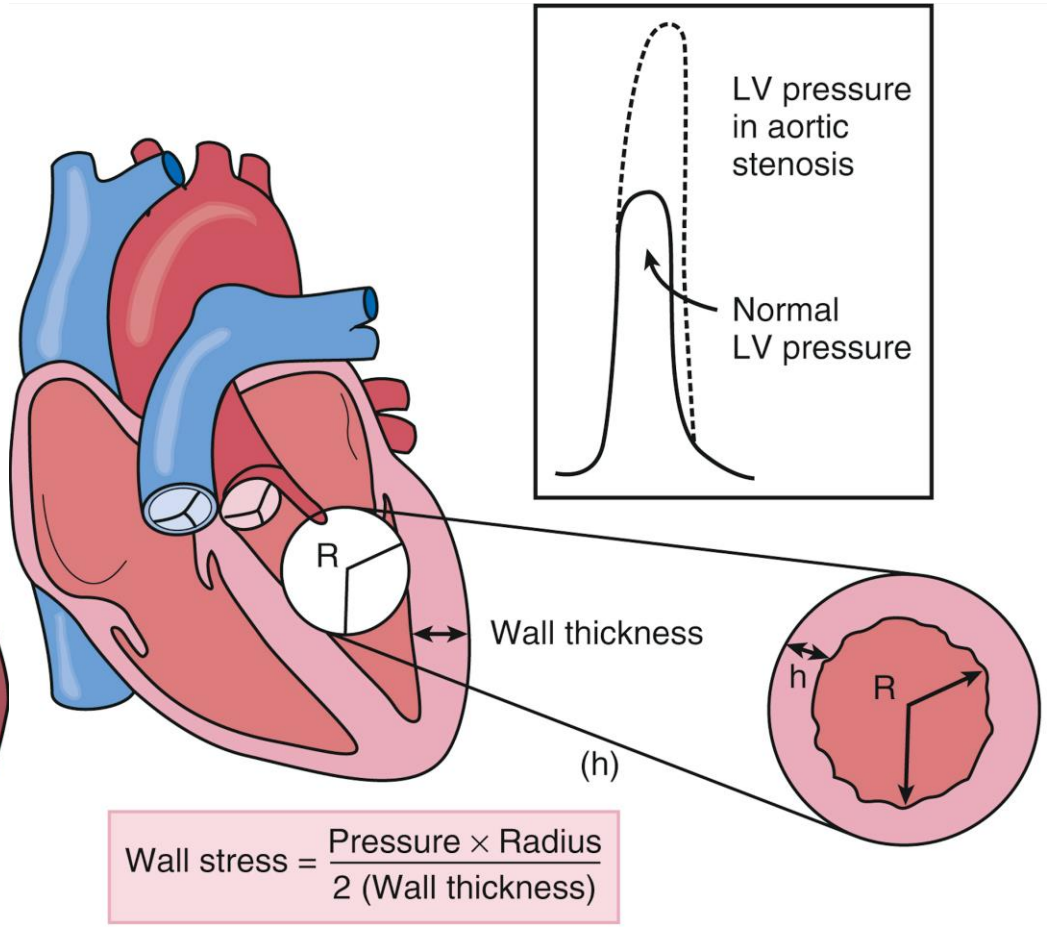
Bigger is worse

LVH and AS

Aortic stenosis -> LV hypertrophy



Major determinants of O_2 demand

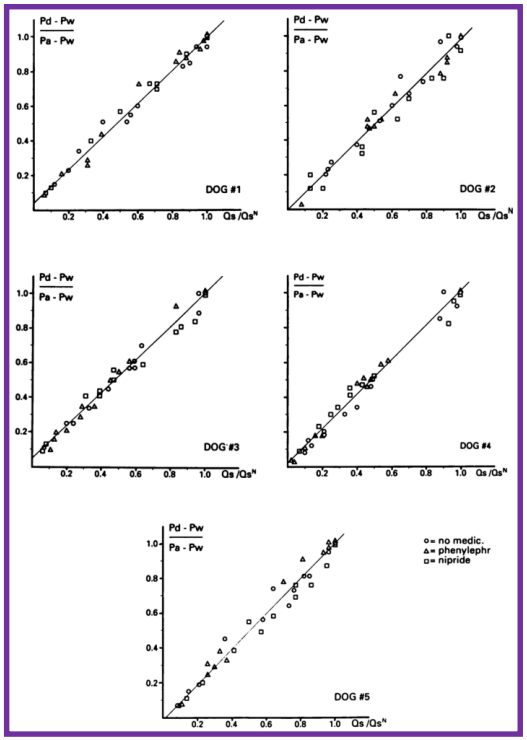


$$\text{Wall stress} = \frac{\text{Pressure} \times \text{Radius}}{2\ (\text{Wall thickness})}$$

(Laplace law)

Figures 46-20 (left) and 46-18A (right) from Bers DM and Borlaug BA, Chapter 46 "Mechanisms of Cardiac Contraction and Relaxation" in *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 12th edition (2022), pages 889-912.

How does LVH affect *bed*?



Pijls NH, *Circulation*. 1993 Apr;87(4):1354-67. (Figure 5)

Absolute flow (mL/min)

200
150
100
50
0

hyperemia

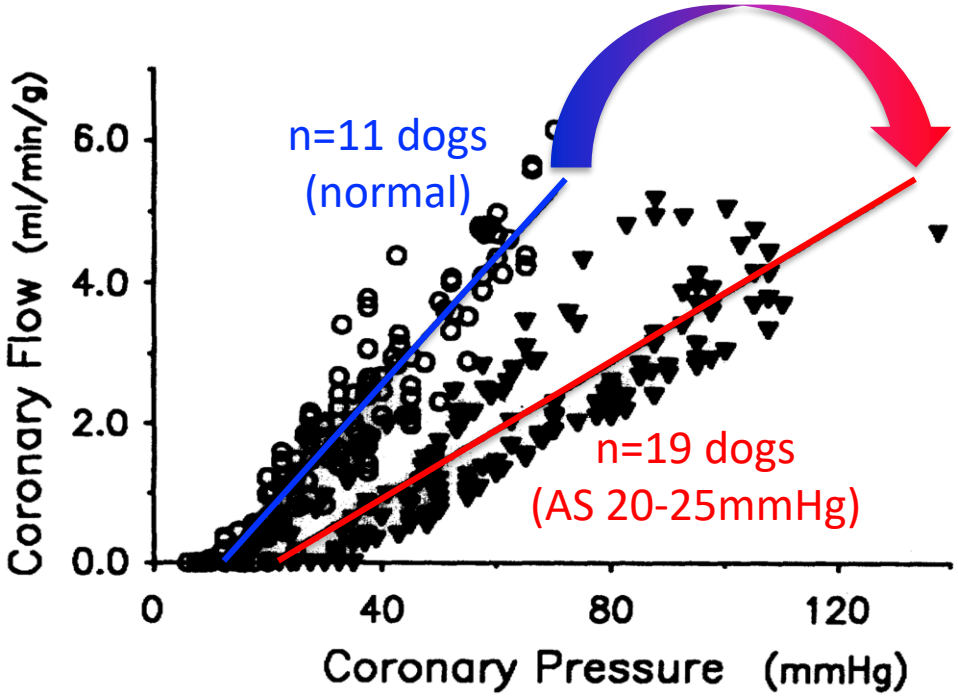
change slope

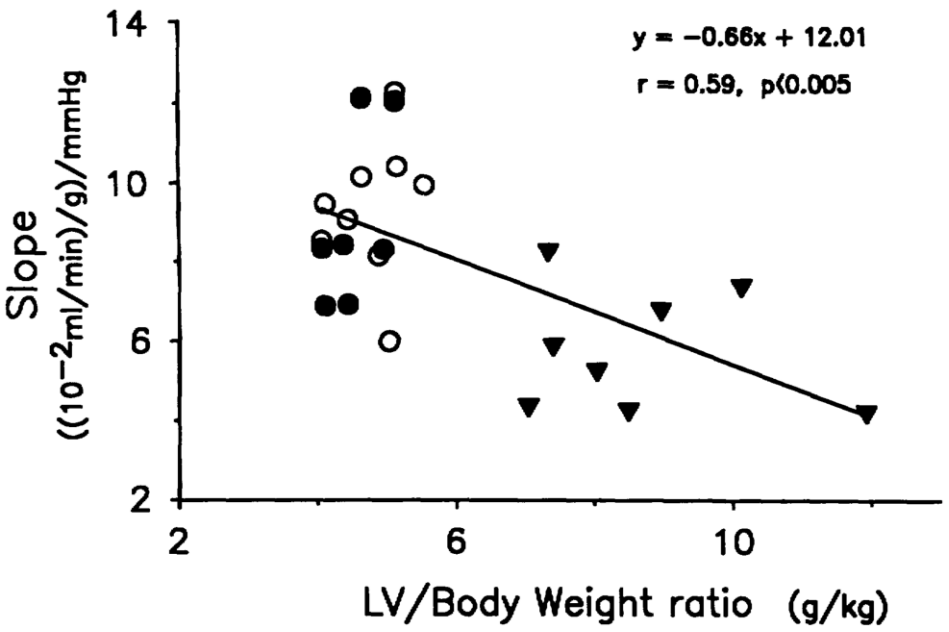
change offset

0 20 40 60 80 100=Pa

Coronary pressure (mmHg)

LVH reduces peak flow



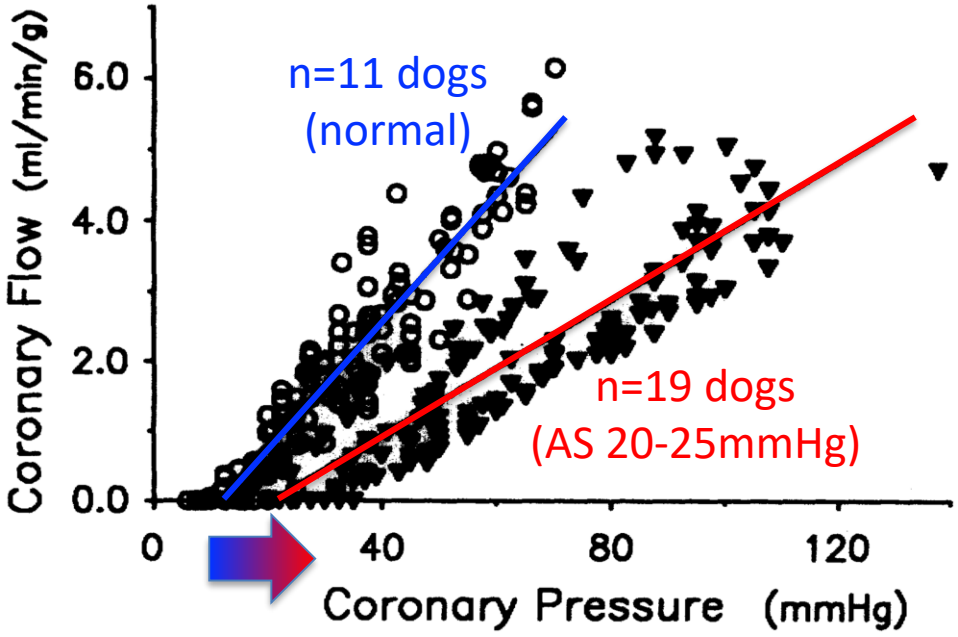


line rotates *clockwise*
(less flow for same pressure)

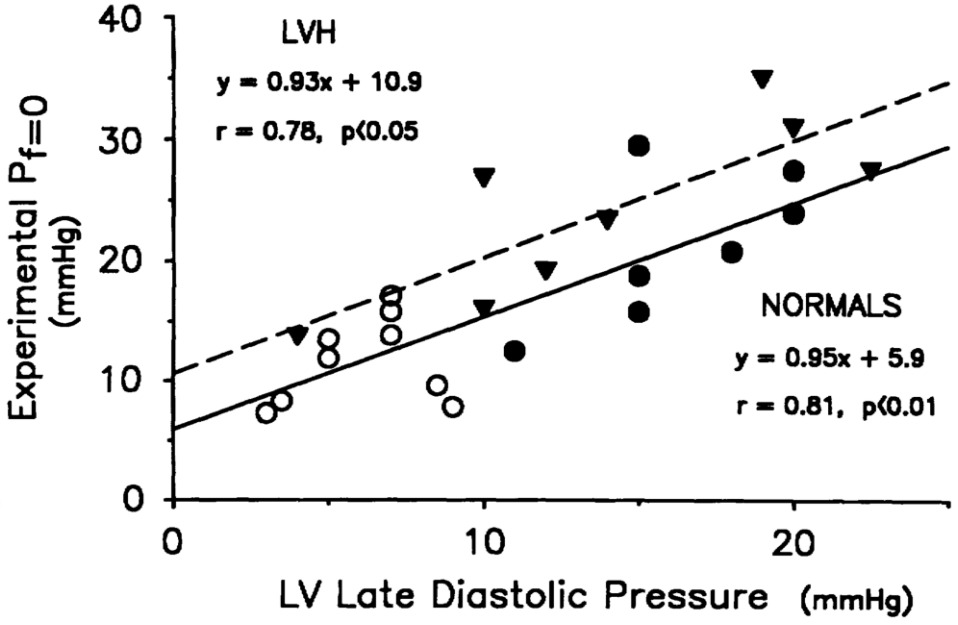
amount of rotation
relates to ***degree of LVH***

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

Backpressure affected by LVedp



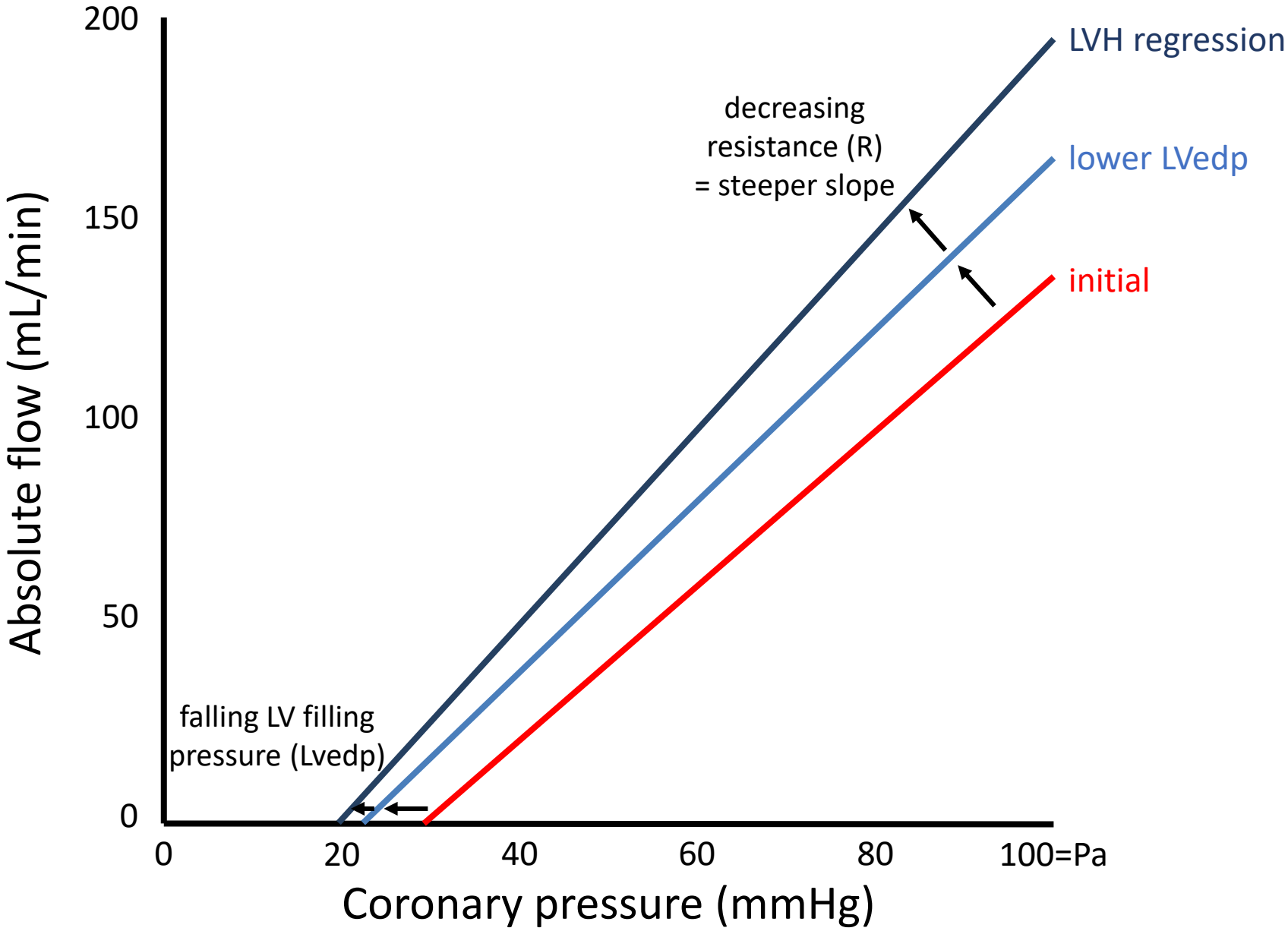
line shifts *rightwards*
(higher backpressure)



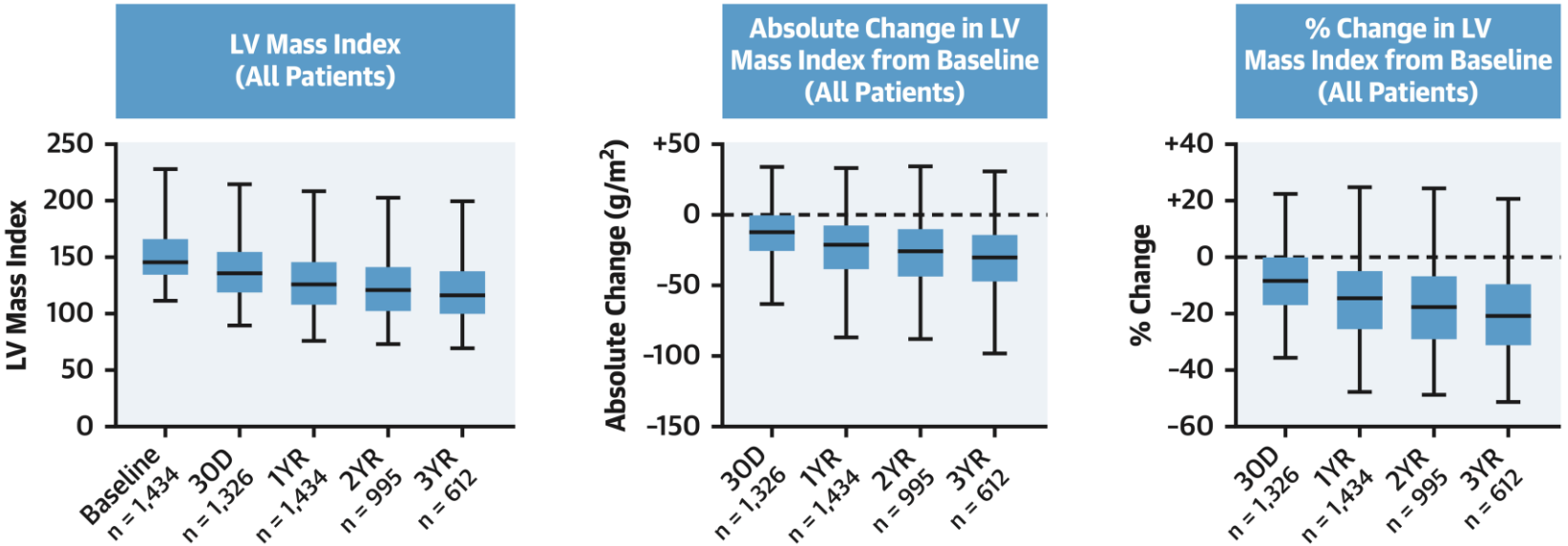
coronary backpressure
relates to ***LV filling pressure***

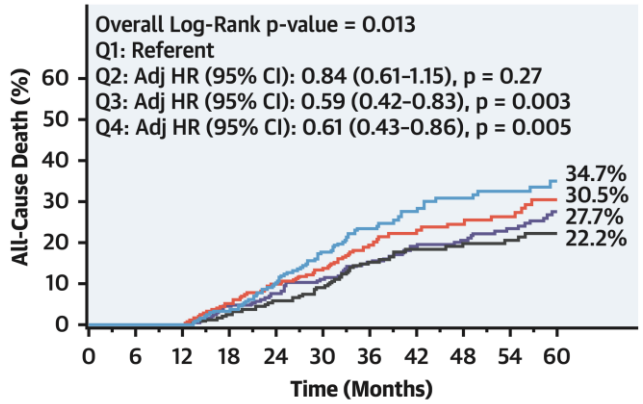
Duncker DJ. *Circ Res*. 1993 Mar;72(3):579-87. (Figures 1 [right panel with annotations] and 2)

Effect of LVH regression



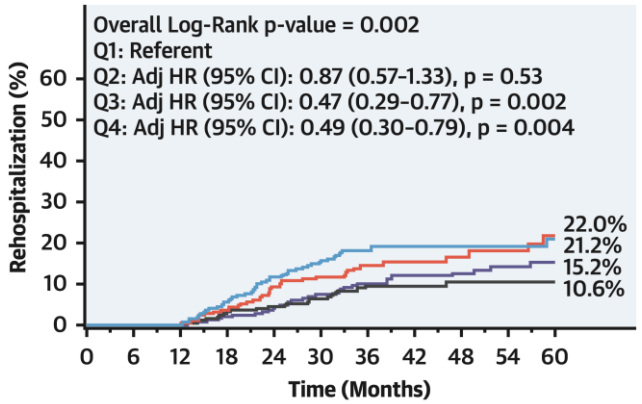
More LVH regression = better!





Number at risk:

Q1	358	358	356	338	326	272	250	160	149	128	63
Q2	359	359	357	346	328	257	231	121	114	99	54
Q3	359	359	358	337	317	217	194	102	89	75	41
Q4	358	358	358	345	317	213	185	97	83	71	41



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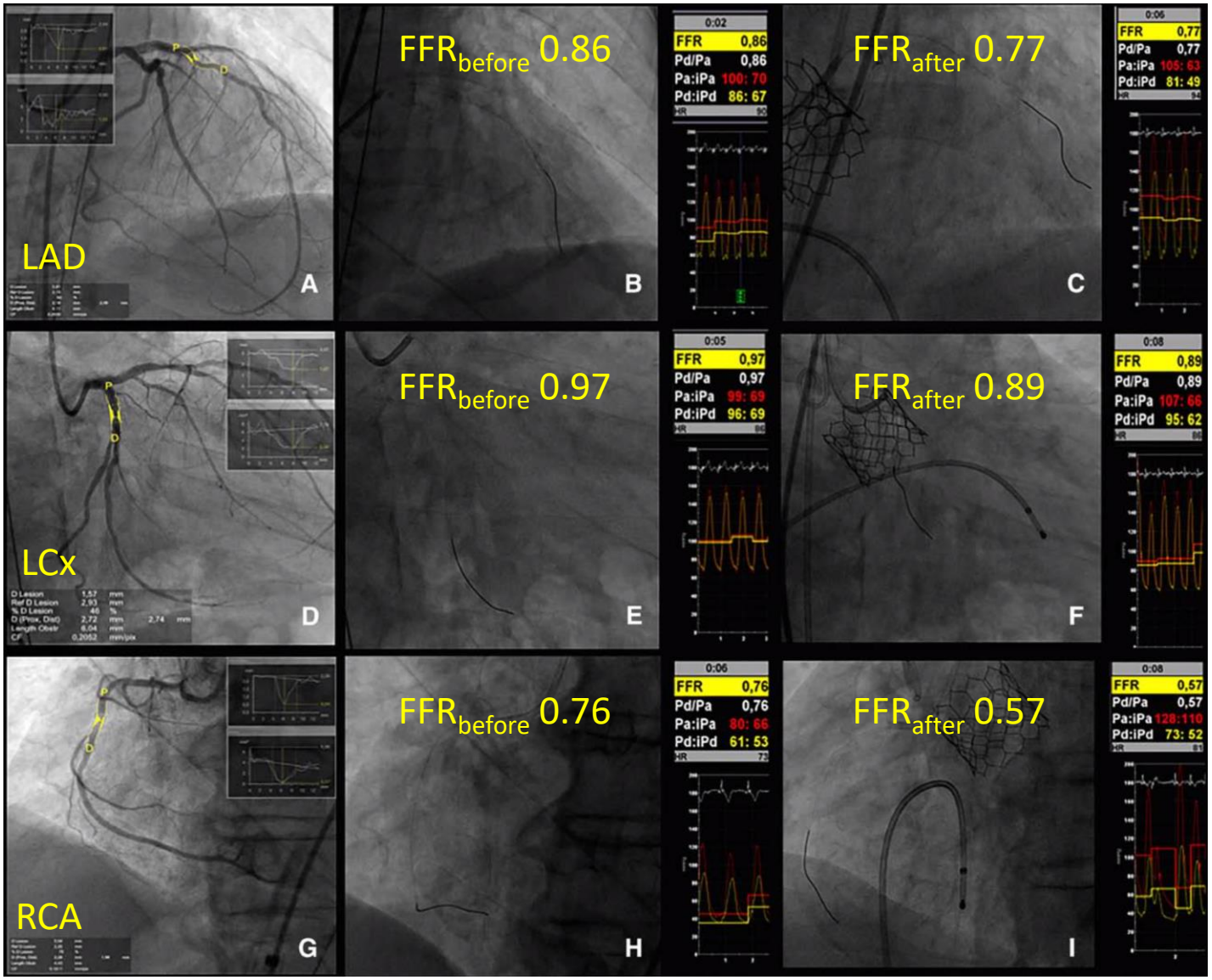
Q3	359	359	358	337	317	217	194	102	89	75	41
Q4	358	358	358	345	317	213	185	97	83	71	41

Chau KH, *JACC*. 2020 May 19;75(19):2446-2458. (Figure 1A-C and Figure 2A+C)

Before vs after

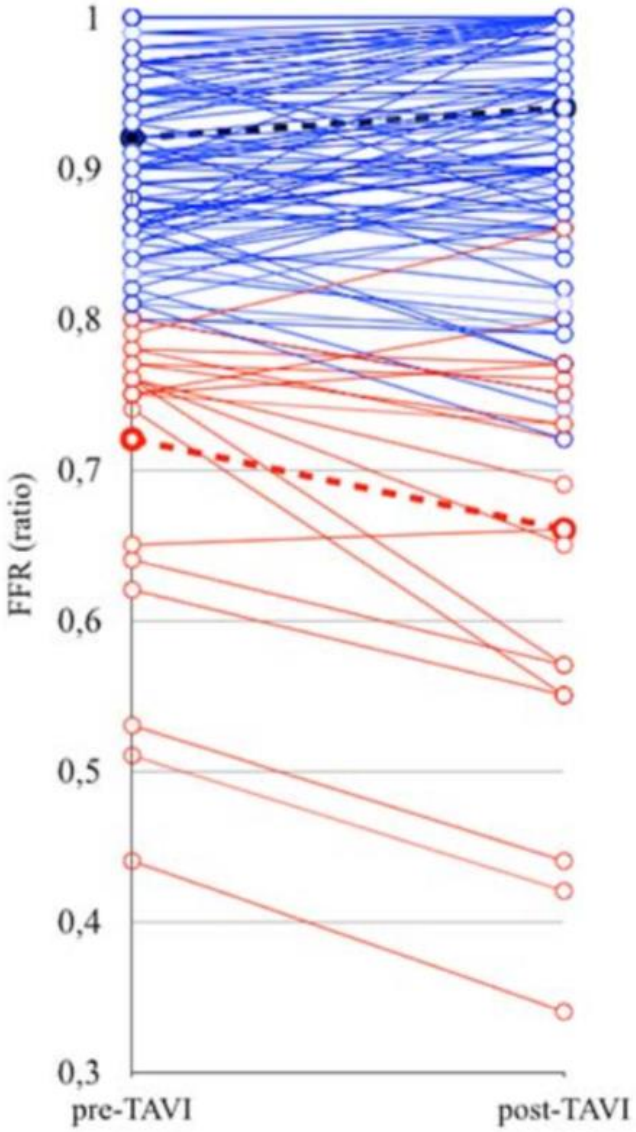
Why does FFR change?

Is FFR stable before/after TAVI?



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

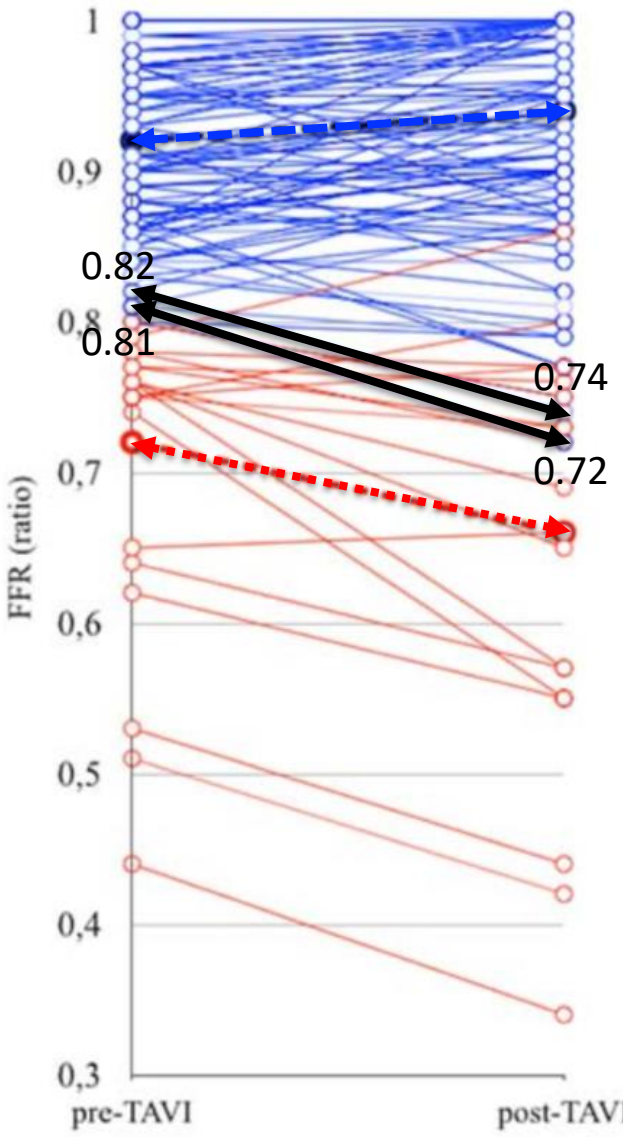
Is FFR stable before/after TAVI?



- 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)

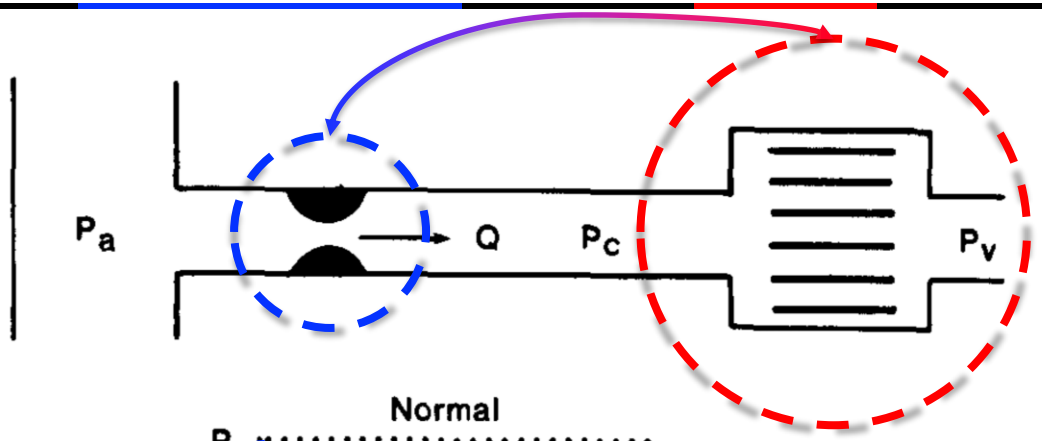
Is FFR stable before/after TAVI?

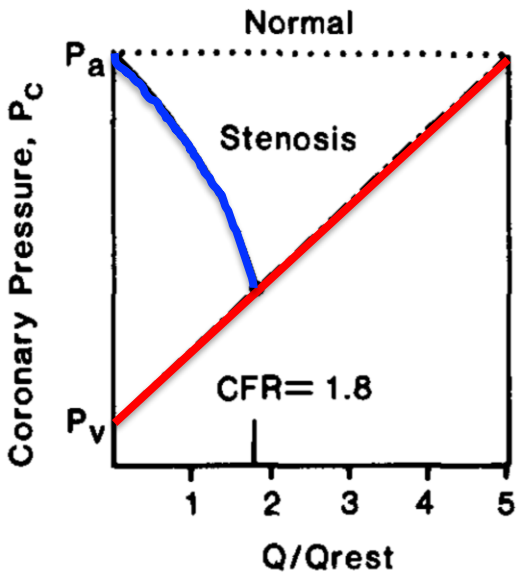


- 133 lesions from 54 patients
- FFR
  - ✓ before 0.89 ± 0.10
  - ✓ after 0.89 ± 0.13
  - ✓ p=0.73 for pairs
- interaction between Δ and FFR=0.8
  - ✓ FFR>0.8 the Δ=+0.01
  - ✓ FFR<0.8 the Δ=-0.05
- 8 lesions crossed FFR=0.80
- 3 lesions switched "grey zone"
  - ✓ 0.83 to 0.75 (LAD)
  - ✓ 0.82 to 0.74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

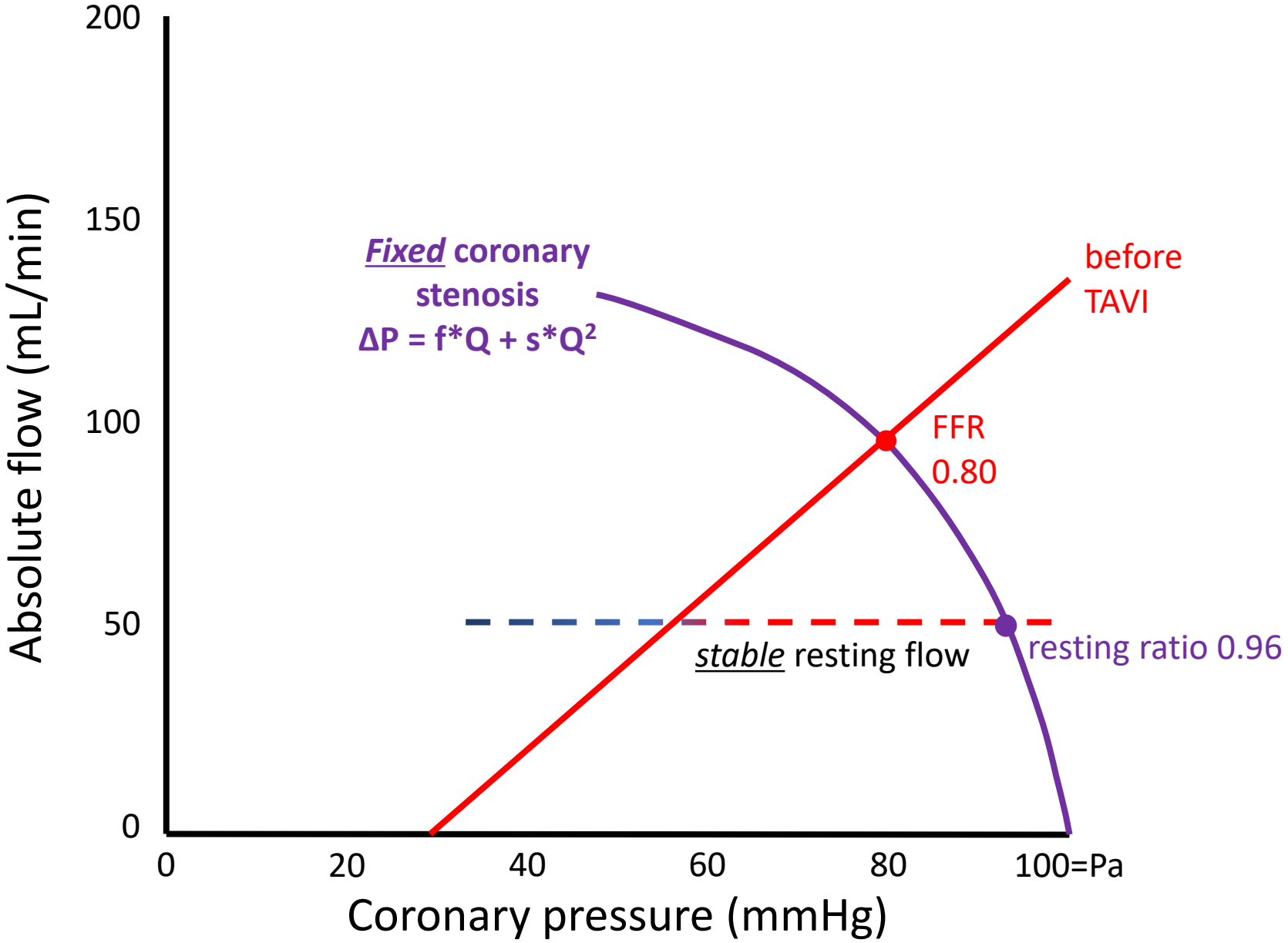




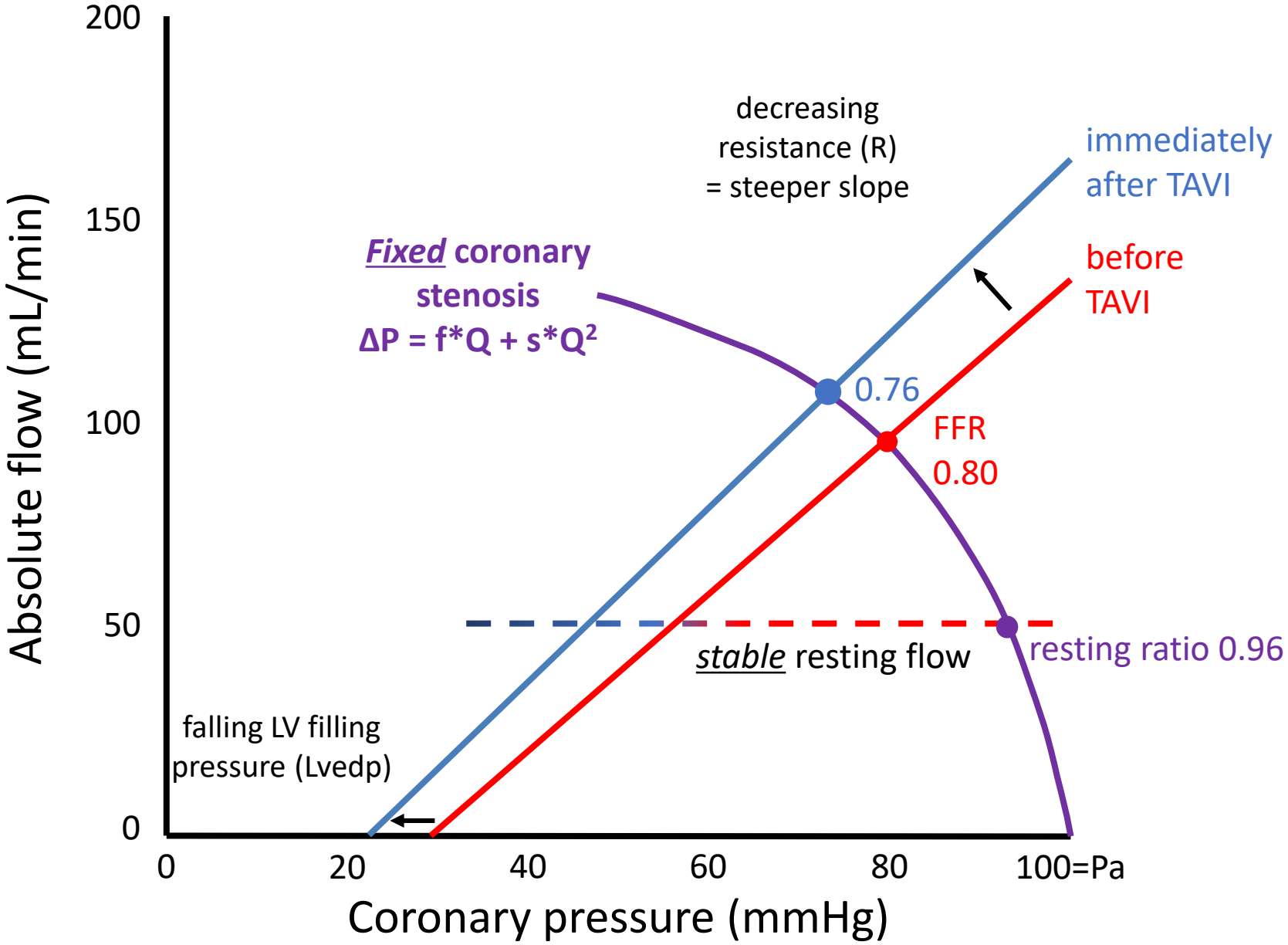
$$Pc = Pa - \underbrace{\left[A(Q/Qrest) + B\,(Q/Qrest)^2\right]}_{\text{Stenosis Pressure Drop}}$$

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

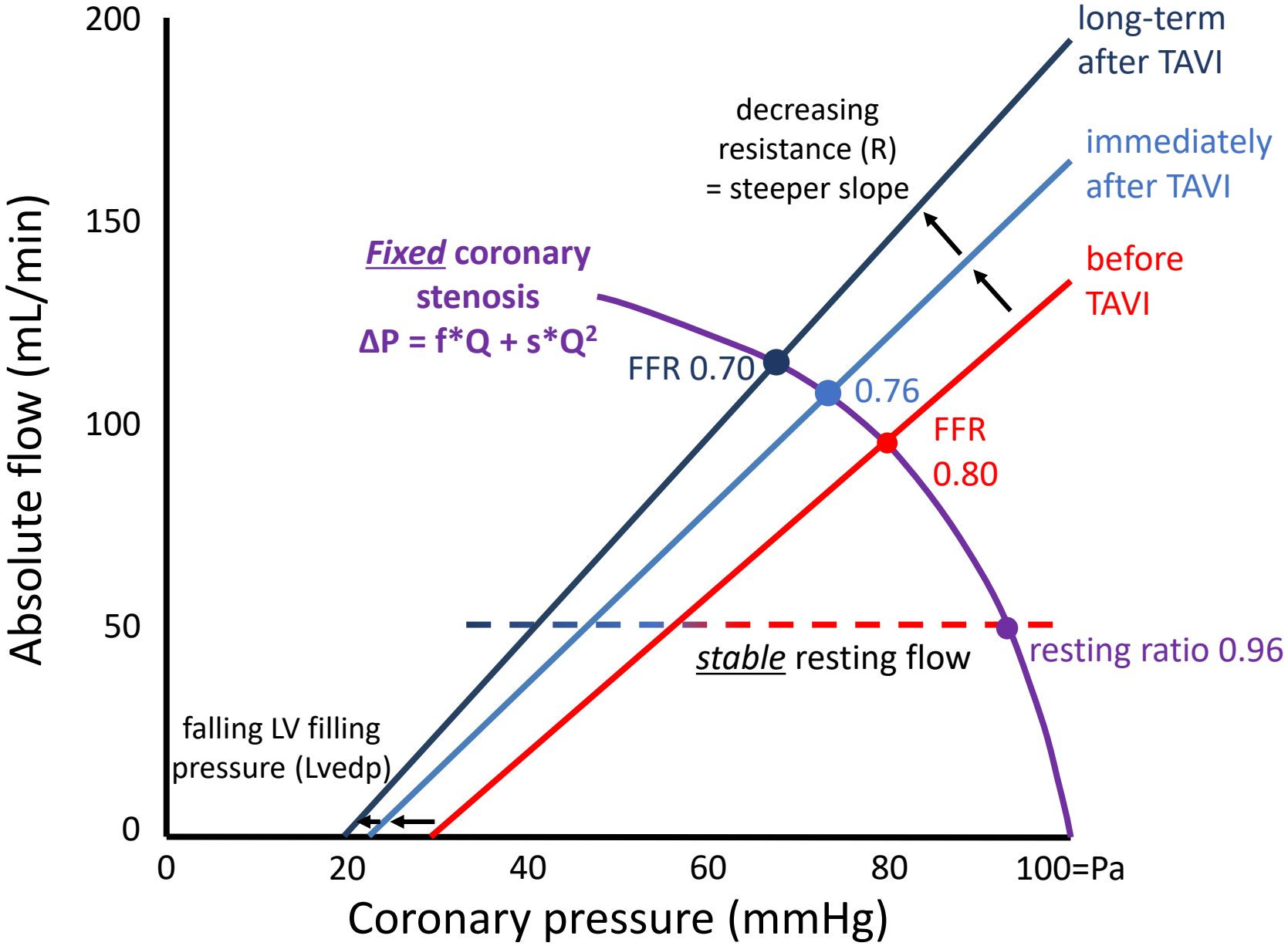
Coronary/valvular coupling for FFR/AS



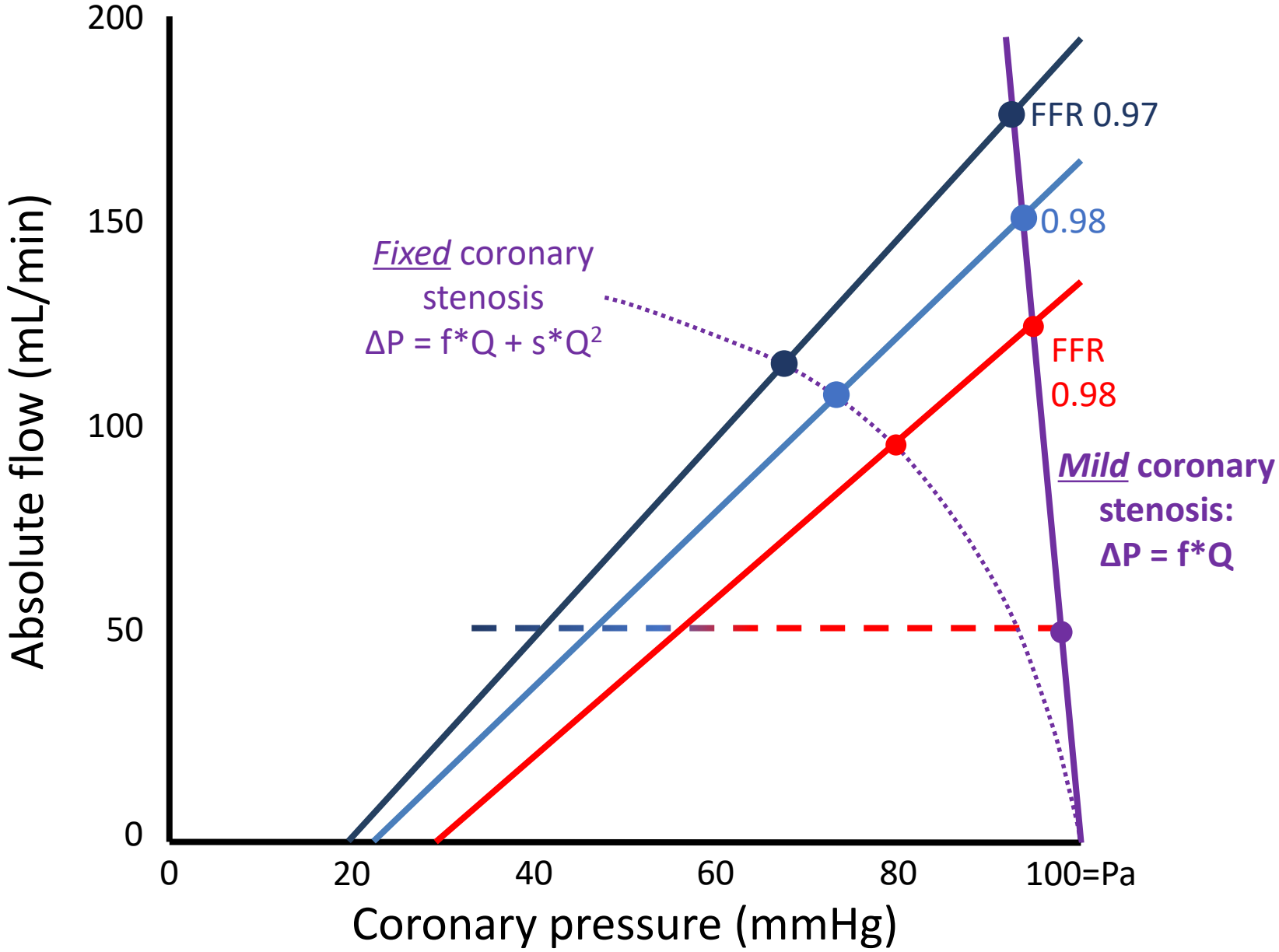
Immediately after TAVI



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	
Sabbah	*Circ CV Interv* 2022;15:e011331	50	0.84			0.86	0.72	6 months	TAVI	
Pesarini	*Circ CV Int* 2016;9:e004088	133	0.89	0.89	0.73				TAVI	

N = 392 vessels

12 papers, 22 years

red = hyperemia *increases*

blue = hyperemia *decreases*

updated table from Zelis JM, *J Am Heart Assoc*. 2020 Mar 3;9(5):e04905.

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	
Sabbah	*Circ CV Interv* 2022;15:e011331	50	0.88			0.92	**0.003**	6 months	TAVI	RFR
Scarsini	*EuroIntervention* 2018;13:1512	145	0.89	0.89	0.66				TAVI	

N = 351 vessels

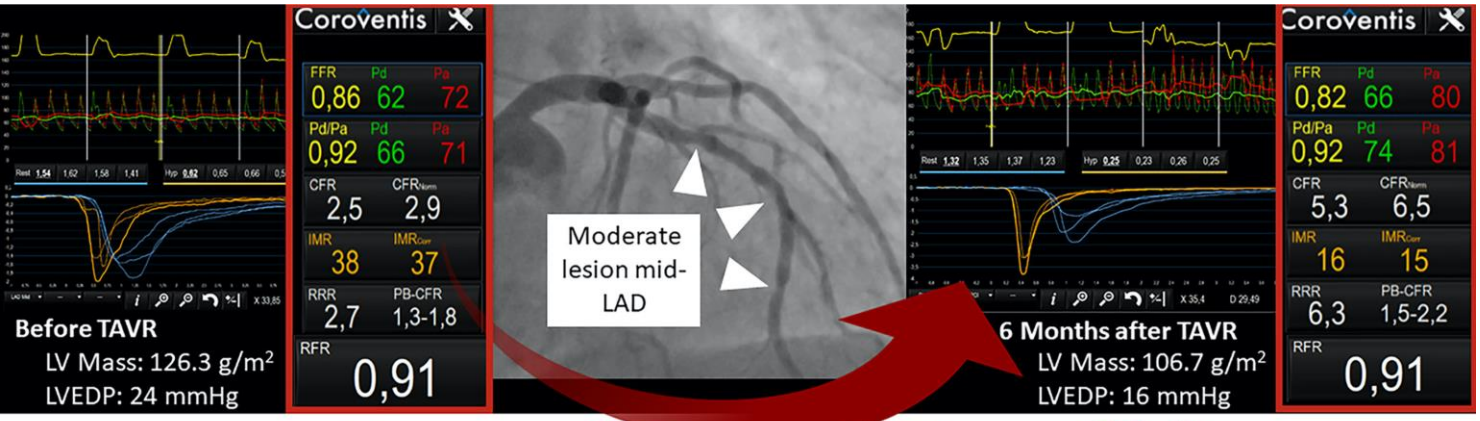
10 papers, 22 years

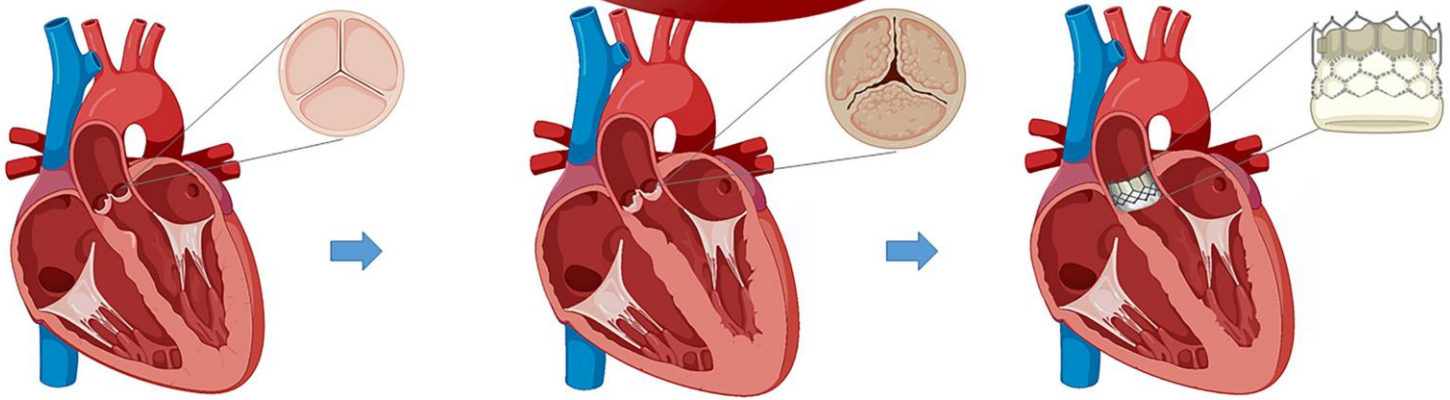
red = resting *increases*

blue = resting *decreases*

updated table from Zelis JM, *J Am Heart Assoc*. 2020 Mar 3;9(5):e04905.

Remodeling in COMIC-AS





- observational (NCT04420325)
- n=100 severe AS
- n=80 after TAVI
- n=60 at 6 months
- SPECT
- FFR, IMR, RFR

before TAVI

- FFR 0.86
- LV mass 126 g/m²
- LVedp 24mmHg

6 months later

- FFR 0.82
- LV mass 107 g/m²
- LVedp 16mmHg

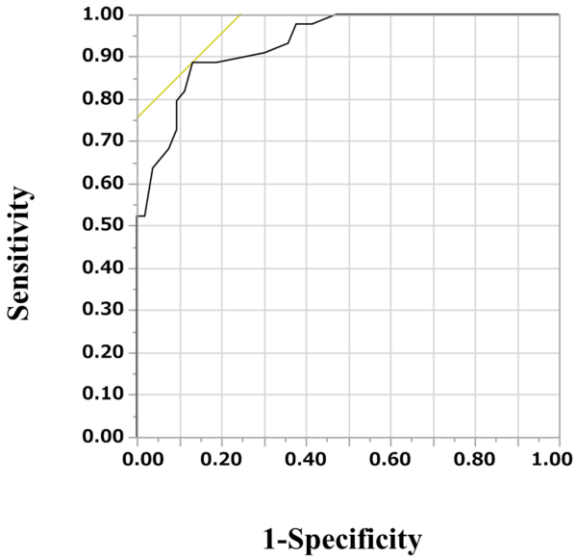
Minten L, *AJP Heart Circ Physiol*. 2021 Dec 1;321(6):H1106-H1116. (Figure 5)

Which tool?

Choose your adventure

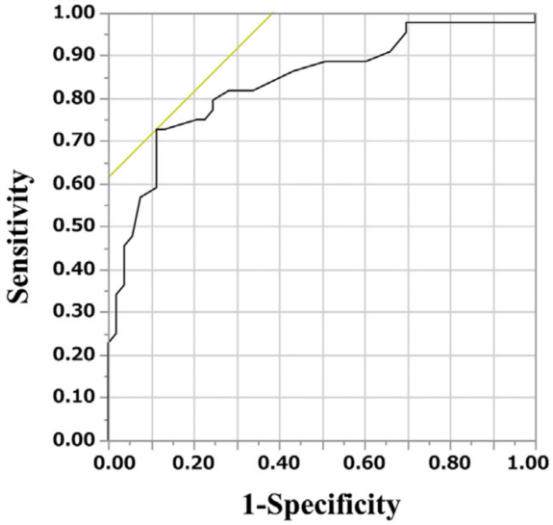
Two lessons for FFR vs NHPR

FFR vs SPECT



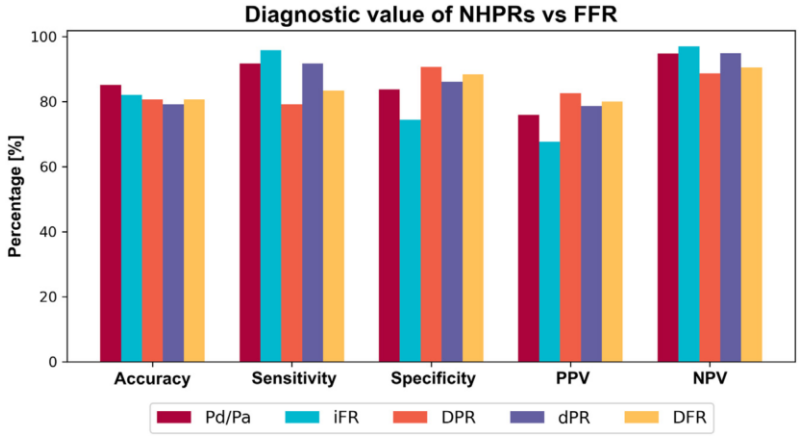
- cutoff FFR=0.83
- AUC 0.93

iFR vs SPECT



- cutoff iFR=0.82
- AUC 0.84

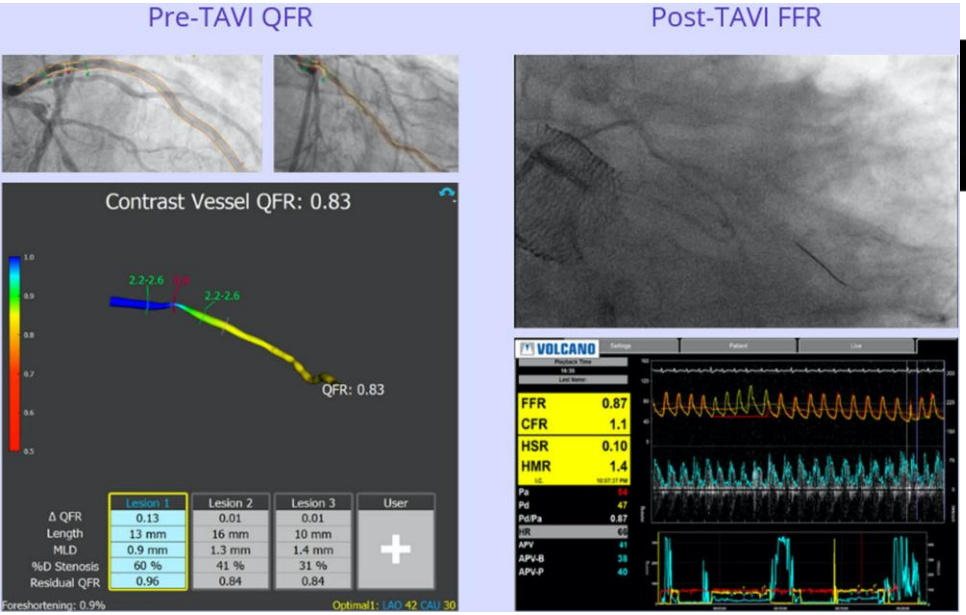
NHPR vs FFR

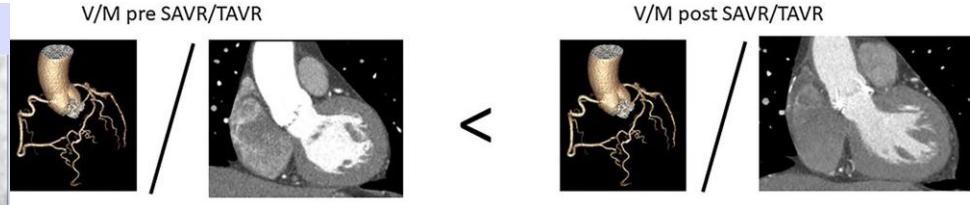


- 67 lesions from CAST-FFR
- AUC>0.97 to predict iFR
- similar to predict FFR

left = Yamanaka F, *JACC Cardiovasc Interv*. 2018 Oct 22;11(20):2032-2040. (Online Figure 2A and Figure 5A)
right = Comella A, *Cardiovasc Revasc Med*. 2022 Jan 19:S1553-8389(22)00011-2. (Figure 5)

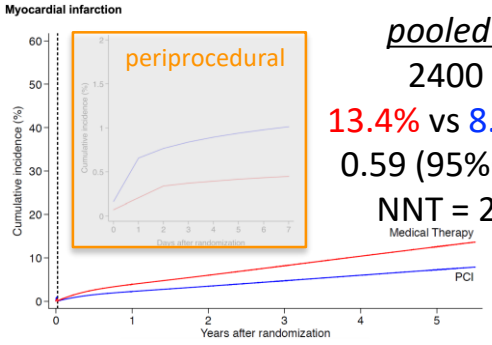
QFR and FFR_{CT}?



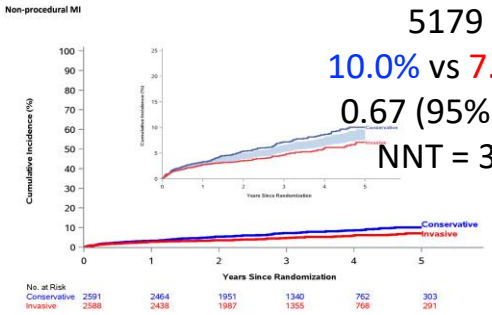


left = Sejr-Hansen M, *Catheter Cardiovasc Interv*. 2022 Jan 1;99(1):68-73. (Figure 1)
right = Michiels V, *Int J Cardiovasc Imaging*. 2021 Sep 8. doi: 10.1007/s10554-021-02401-1. Online ahead of print. (Figure 1)

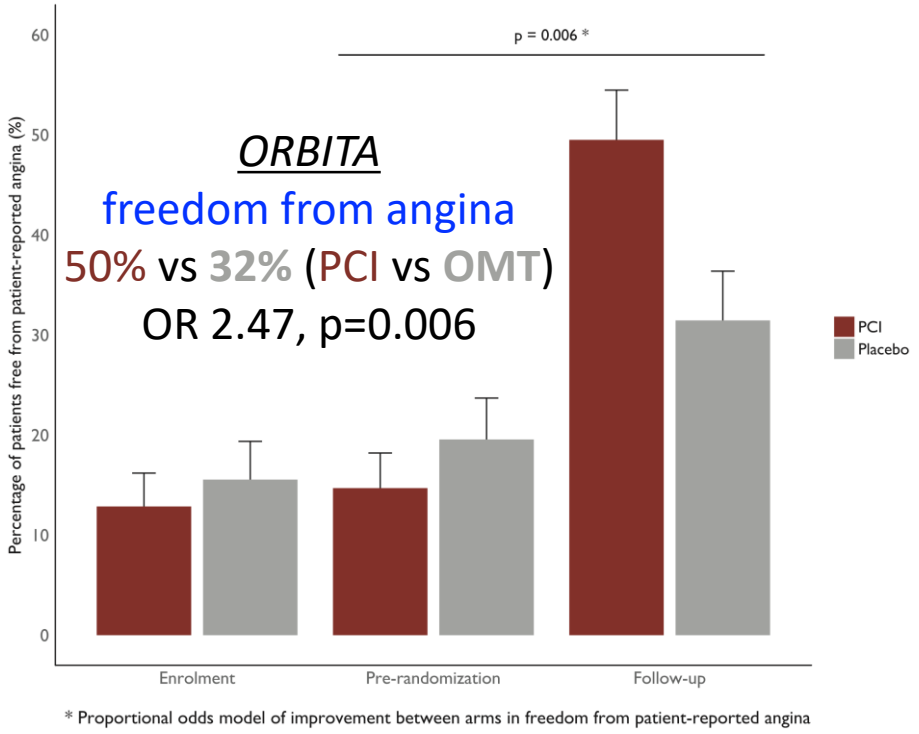
Does PCI have similar benefits in AS?



pooled FFR trials
2400 subjects
13.4% vs 8.5% at 5 years
0.59 (95%CI 0.42-0.83)
NNT = 20 patients



ISCHEMIA
5179 subjects
10.0% vs 7.1% at 5 years
0.67 (95%CI 0.53-0.83)
NNT = 34 patients



ORBITA
freedom from angina
50% vs 32% (PCI vs OMT)
OR 2.47, p=0.006

left (pooled FFR trials) = Zimmermann FM, *Eur Heart J*. 2019 Jan 7;40(2):180-186. (Figure S2, subpanel MI with *inset labeled and muted*)
left (ISCHEMIA) = Maron DJ, *NEJM*. 2020 Apr 9;382(15):1395-1407. (Figure S8, subpanel non-procedural MI)
right (ORBITA) = Al-Lamee R, *Circulation*. 2018 Oct 23;138(17):1780-1792. (Figure 4 with *annotations*)

RCT completed or in progress