Moderate AS physiology

the ongoing SAVI-AoS trial

Nils Johnson
MD, MS, FACC, FESC

Professor of Medicine
Weatherhead Distinguished Chair of Heart Disease
Division of Cardiology, Department of Medicine
and the Weatherhead PET Imaging Center
McGovern Medical School at UTHealth (Houston)
Memorial Hermann Hospital – Texas Medical Center
United States of America

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 (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

Concepts

the big picture

Concept 1: measure when *symptoms* are *gone*?

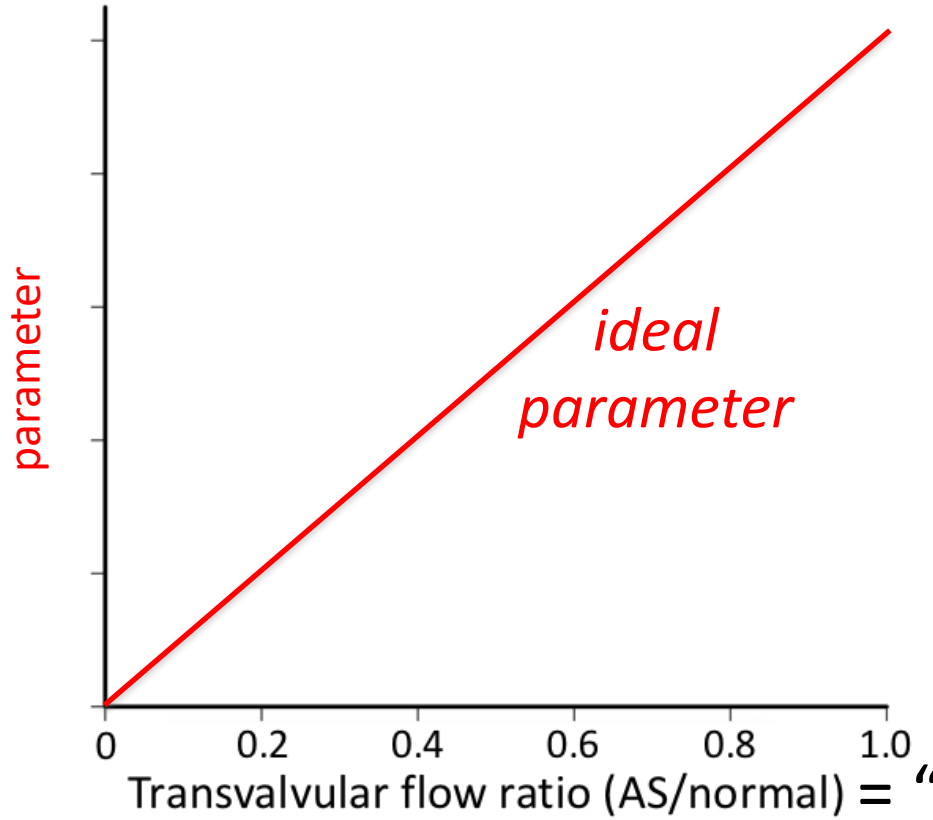
SYMPTOMS
(? hemodynamics)

HEMODYNAMICS
(*no* symptoms)

contradiction!

left = URL https://rehabilitateyourheart.wordpress.com/2013/01/16/exercise-induced-angina/, accessed May 1, 2023 (but can be found at may sites).
right = URL https://www.capitalradiology.com.au/services/echocardiography, last accessed May 1, 2023 (but can be found at many sites).

Concept 2: how much does valve limit peak flow?

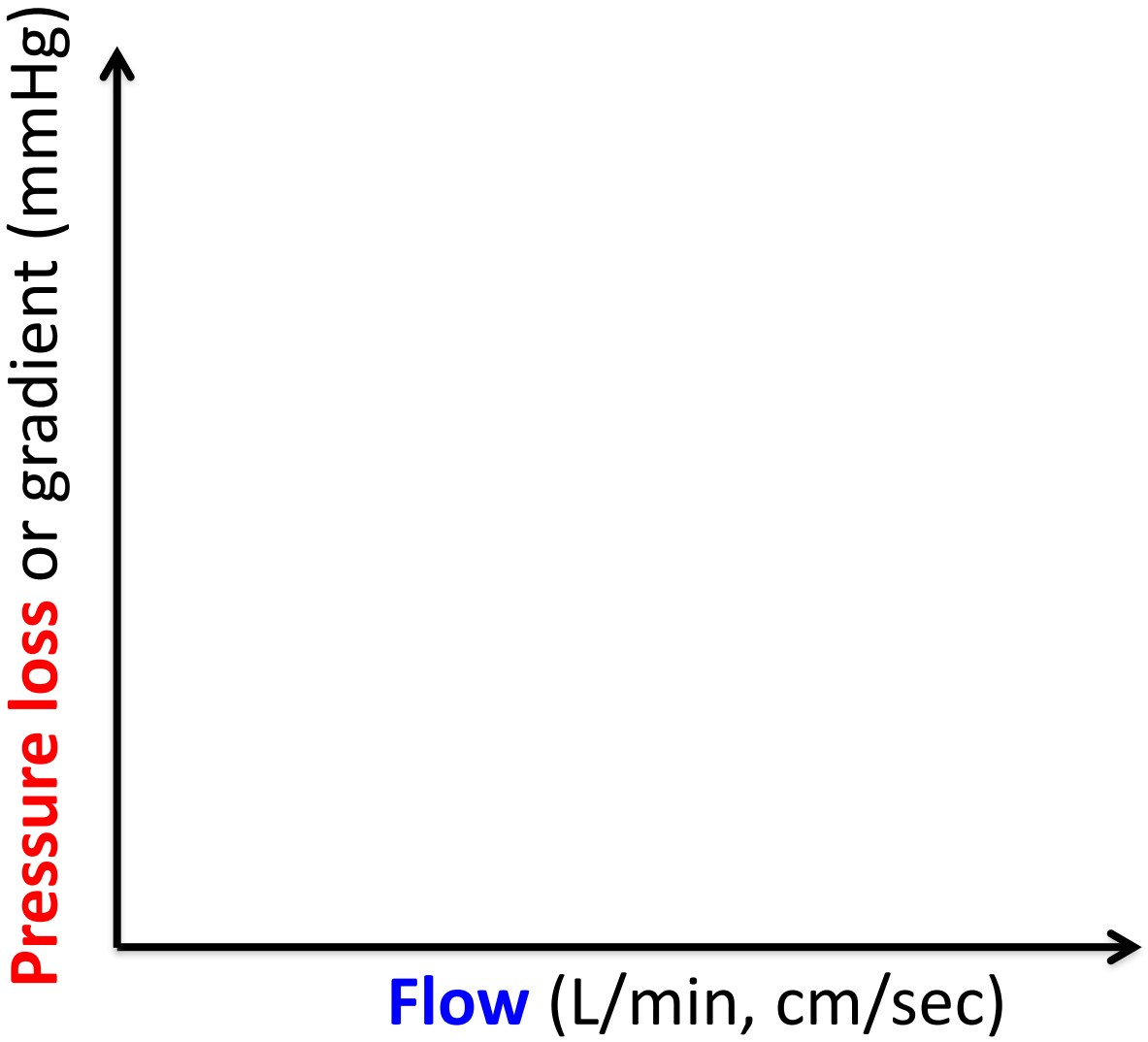


$$\frac{\text{FLOW}_{\textit{stenotic}\ \text{valve}}}{\text{FLOW}_{\textit{normal}\ \text{valve}}}$$

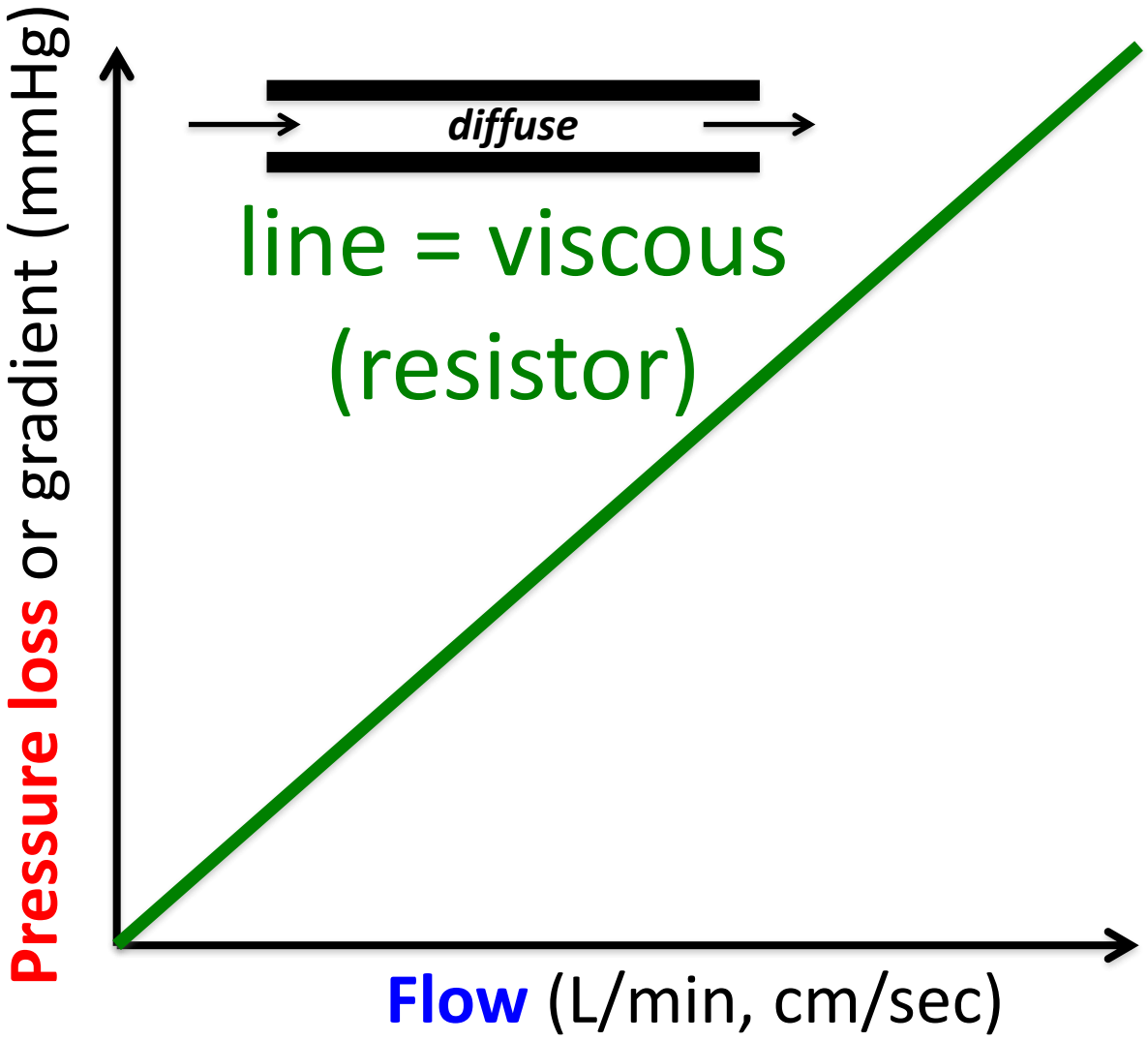
Physiology

of a stenosis

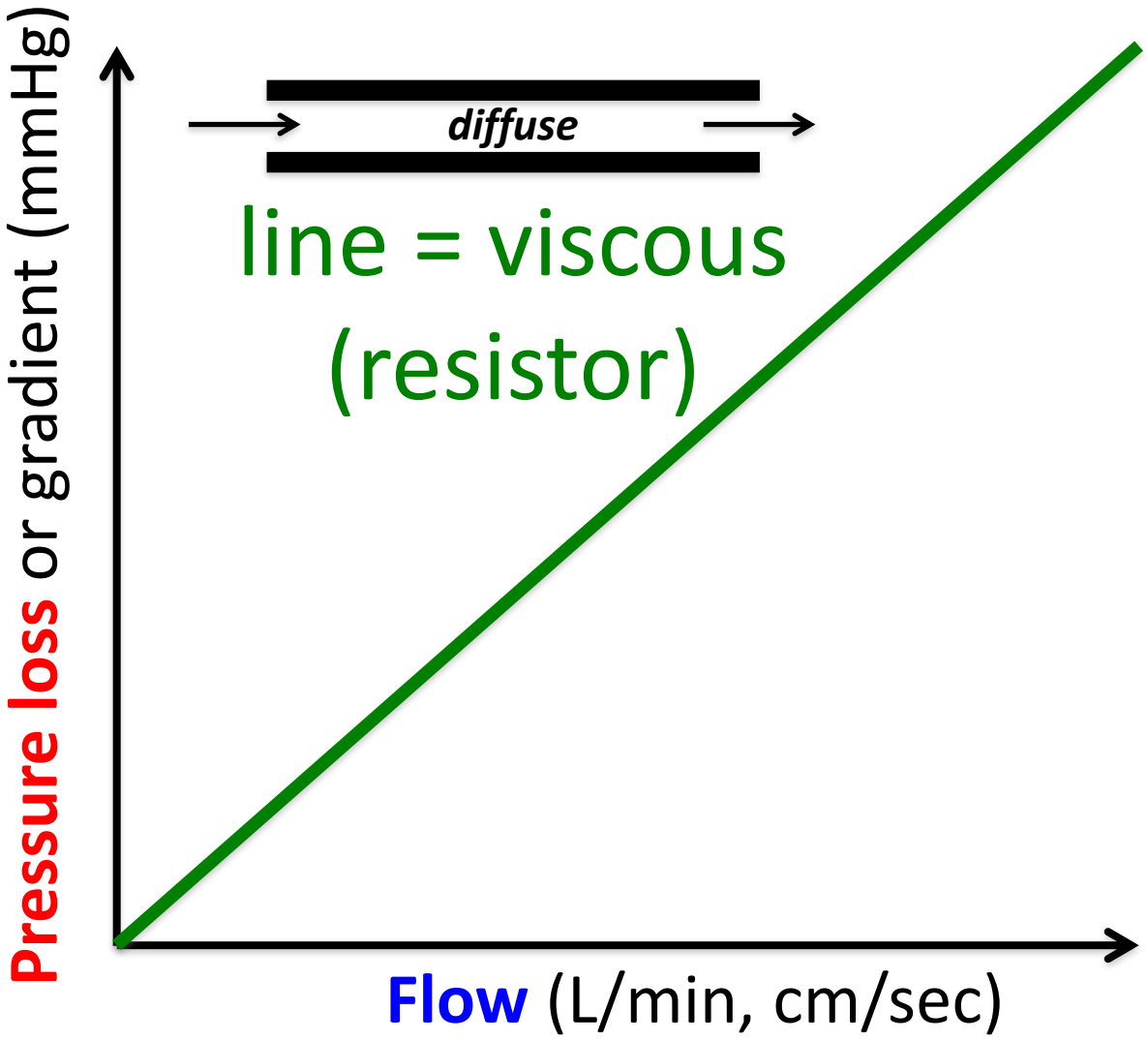
How to describe a stenosis?

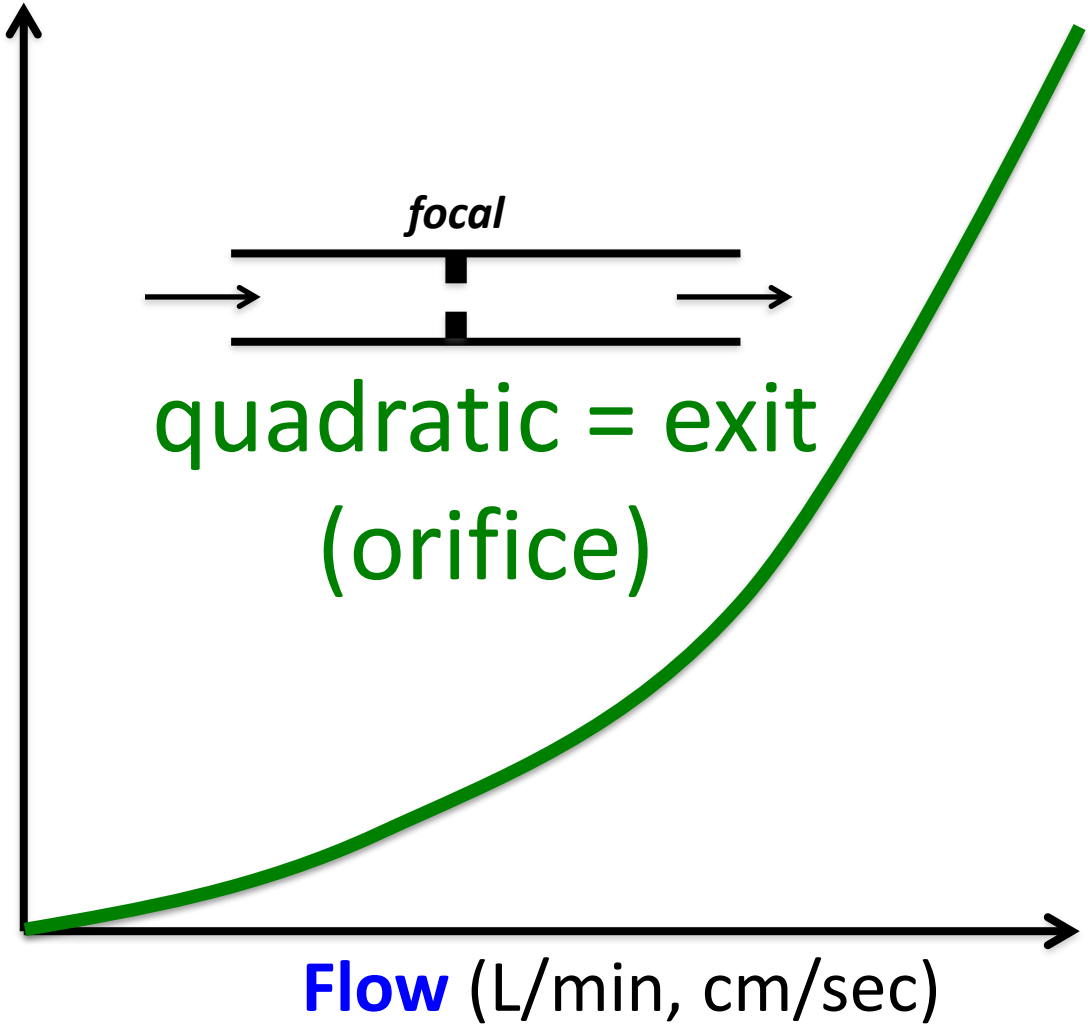


How to describe a stenosis?



How to describe a stenosis?





Gorlin model for valve area

American Heart Journal

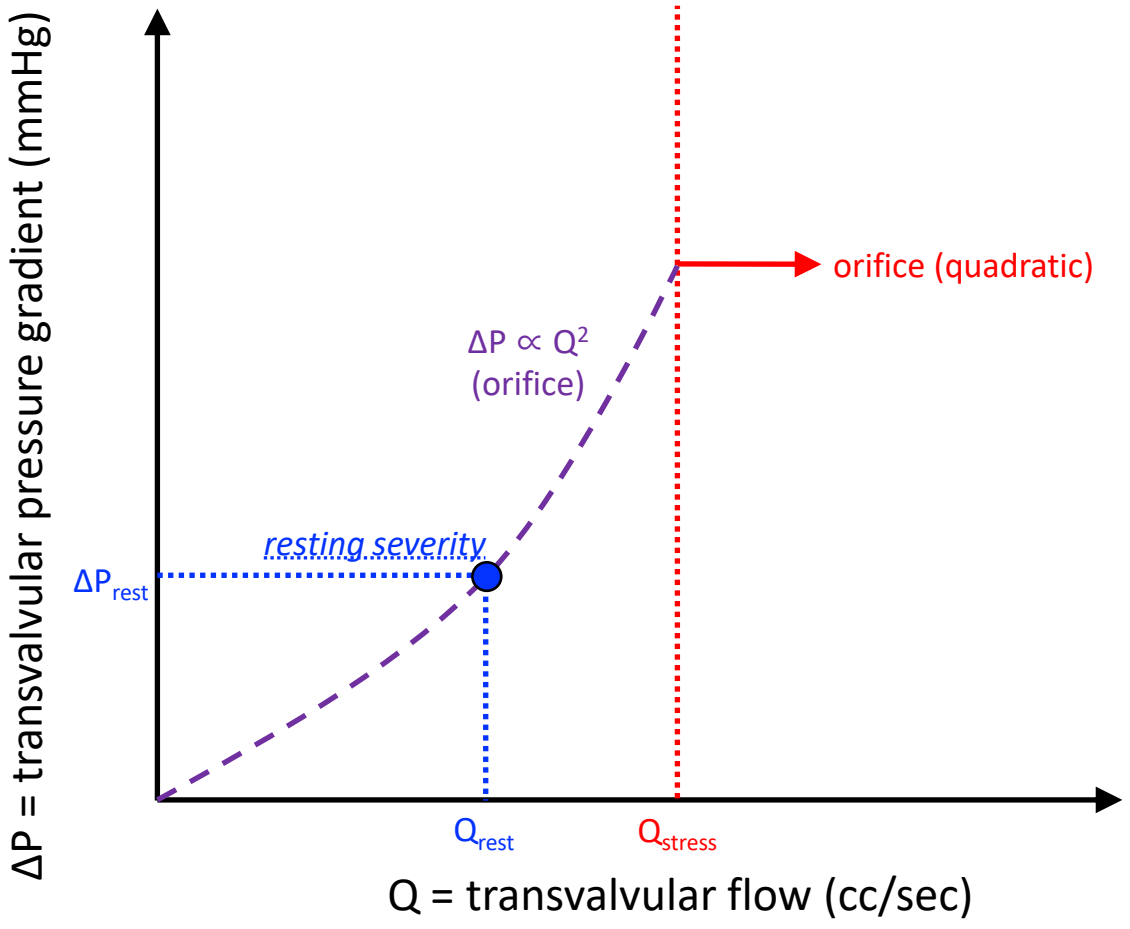
VOL. 41 JANUARY, 1951 No. 1

Original Communications

HYDRAULIC FORMULA FOR CALCULATION OF THE AREA OF THE STENOTIC MITRAL VALVE, OTHER CARDIAC VALVES, AND CENTRAL CIRCULATORY SHUNTS. I.

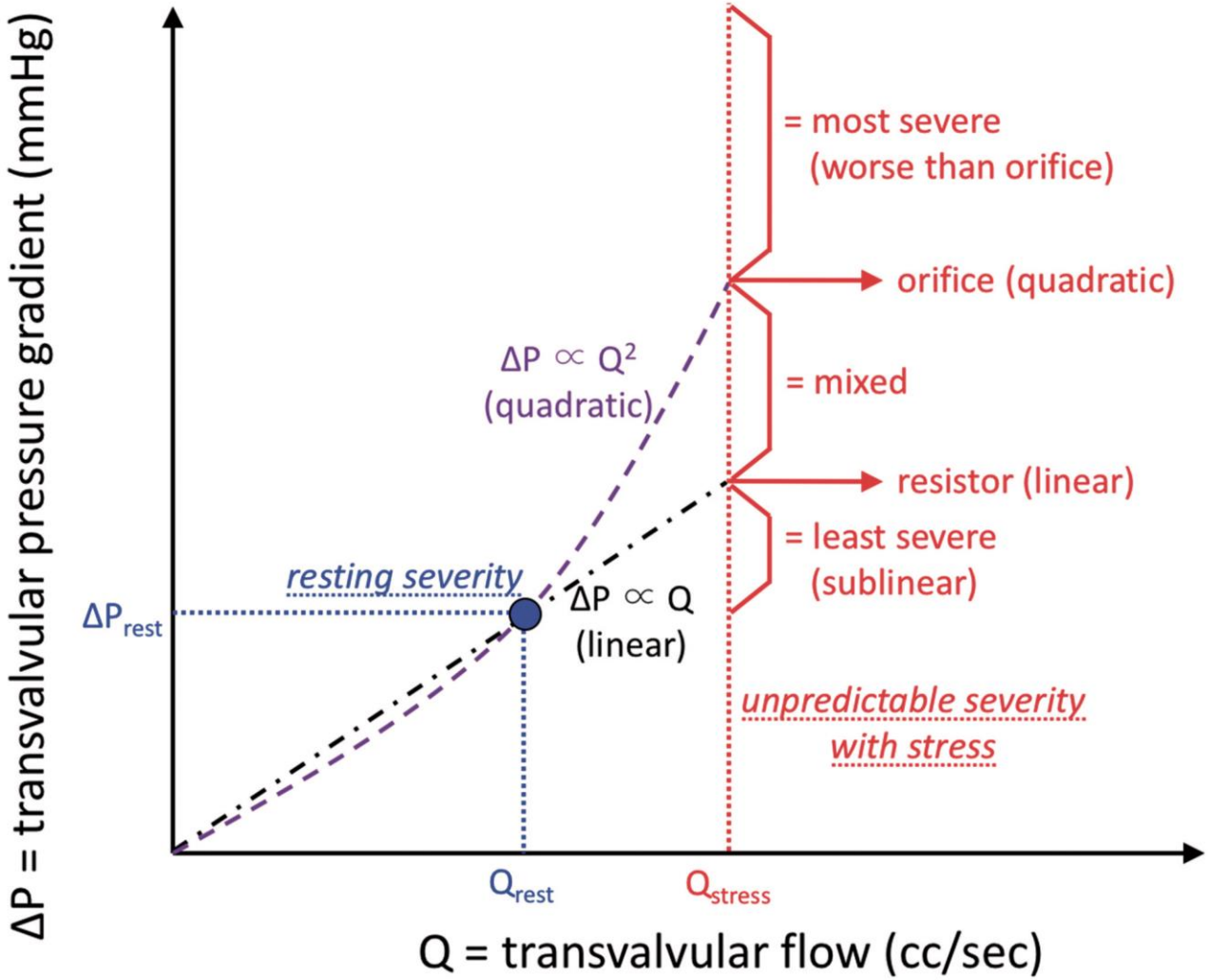
R. GORLIN, M.D.,* AND S. G. GORLIN, M.E.

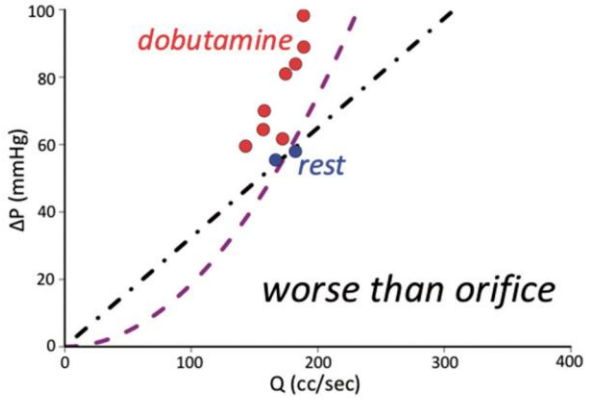
He earned an international reputation when, in collaboration with his father, a mechanical engineer who designed hydraulic systems for gasoline engines at the beginning of the century, he developed a formula to calculate the area of stenotic cardiac valves and congenital heart chamber defects. The "Gorlin formula," still considered the "gold standard" for diagnosis of critical heart valve obstruction, was crucial to the evolution of cardiac surgery because it allowed proper case selection and contributed greatly to the design of artificial valves.

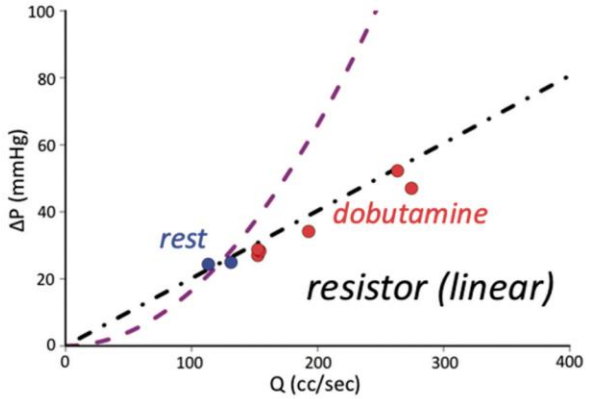


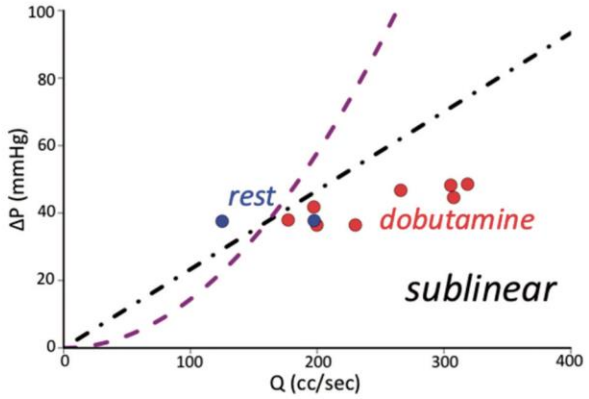
top = Gorlin R, *Am Heart J*. 1951 Jan;41(1):1-29.
bottom = Fuster V, *Circulation*. 1998 Mar 3;97(8):715. (Figure portion and text excerpt)

Severe AS can have a variety of ΔP/Q curves





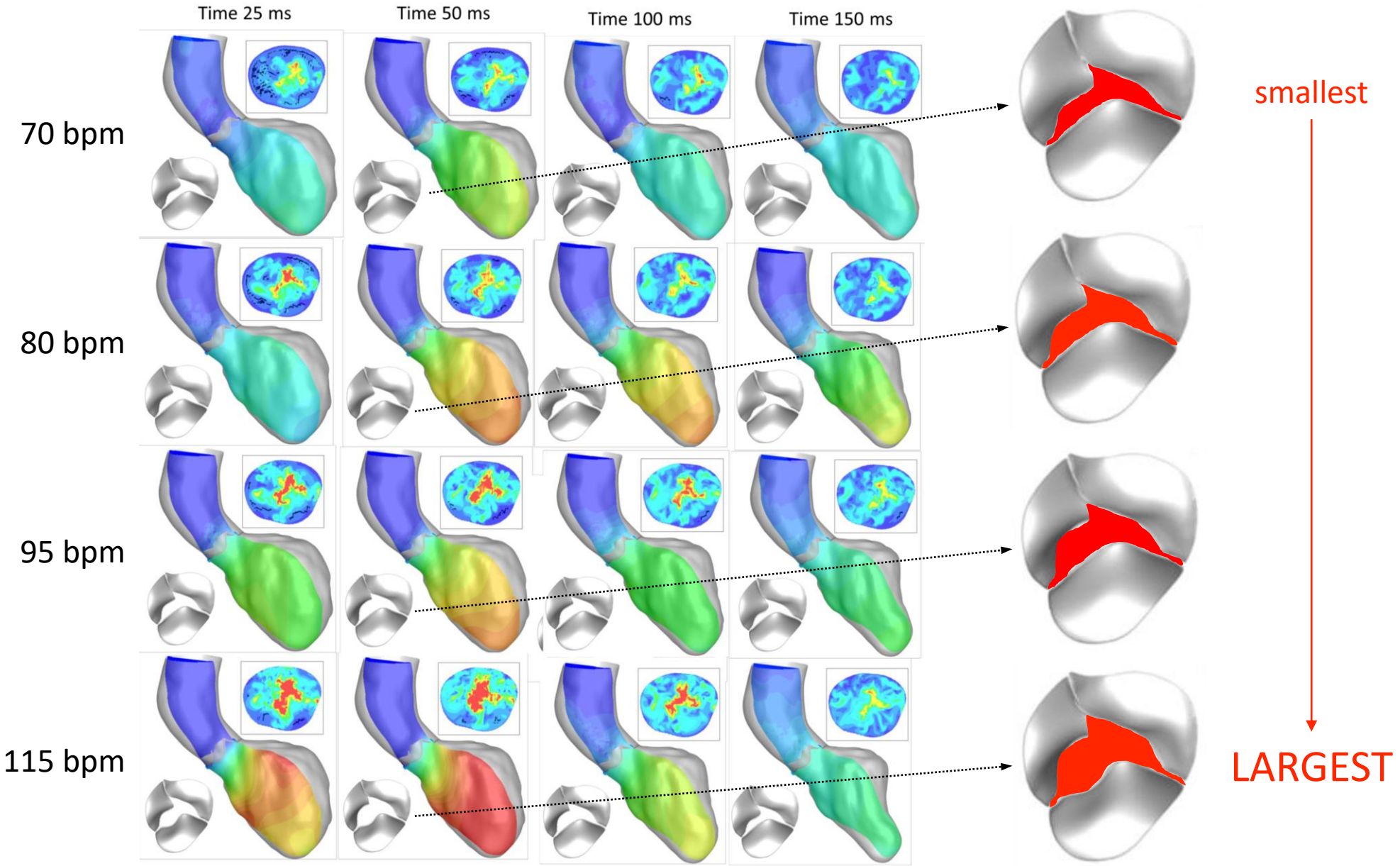




"mean transvalvular pressure loss (DP) did not display a consistent relationship with transvalvular flow (Q) ... Whereas *few cases (3, or 20%) behaved like an orifice* or worse, a *large majority of cases (10, or 67%) fit a linear or sublinear pattern*."

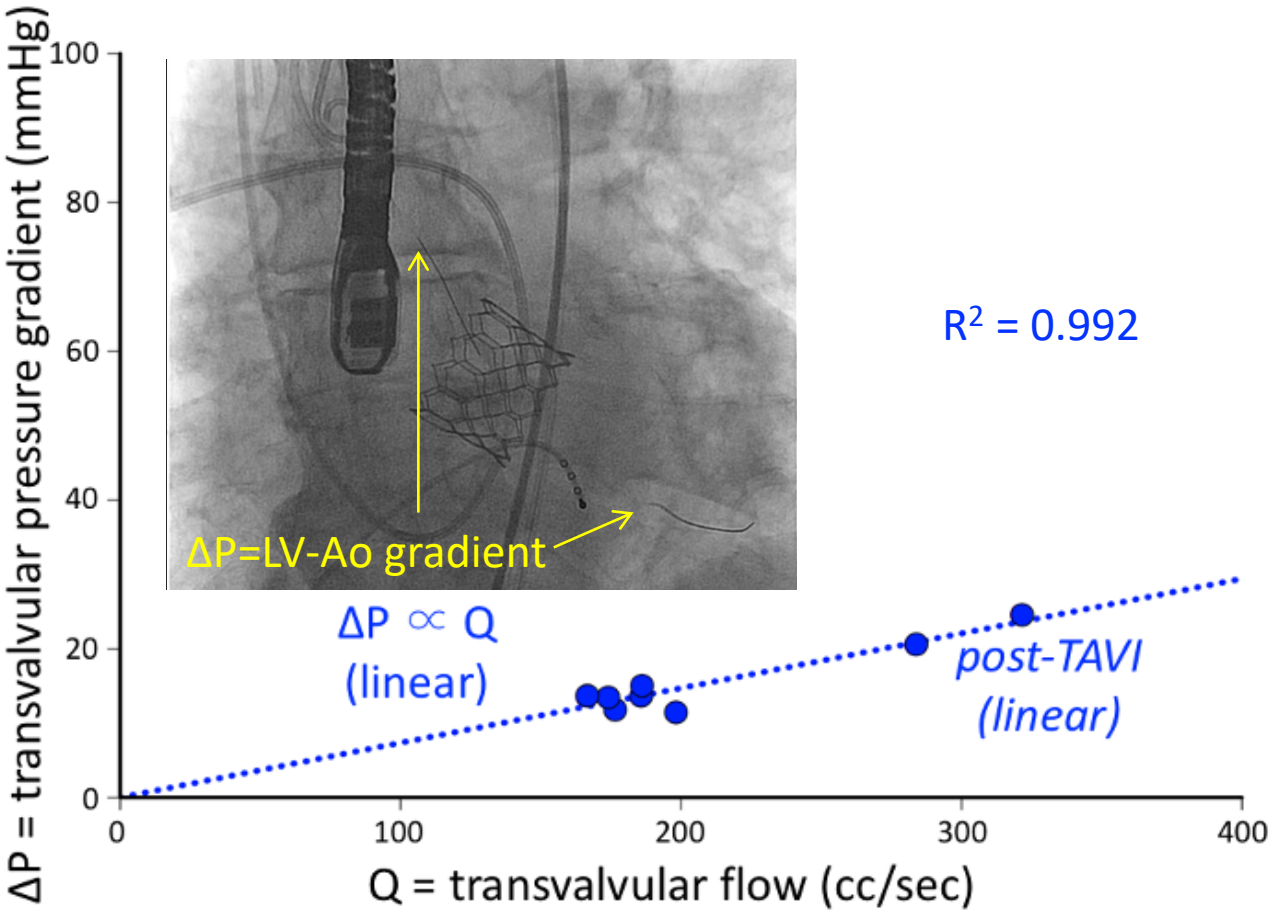
Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Central Illustration with quote from results plus my emphasis)

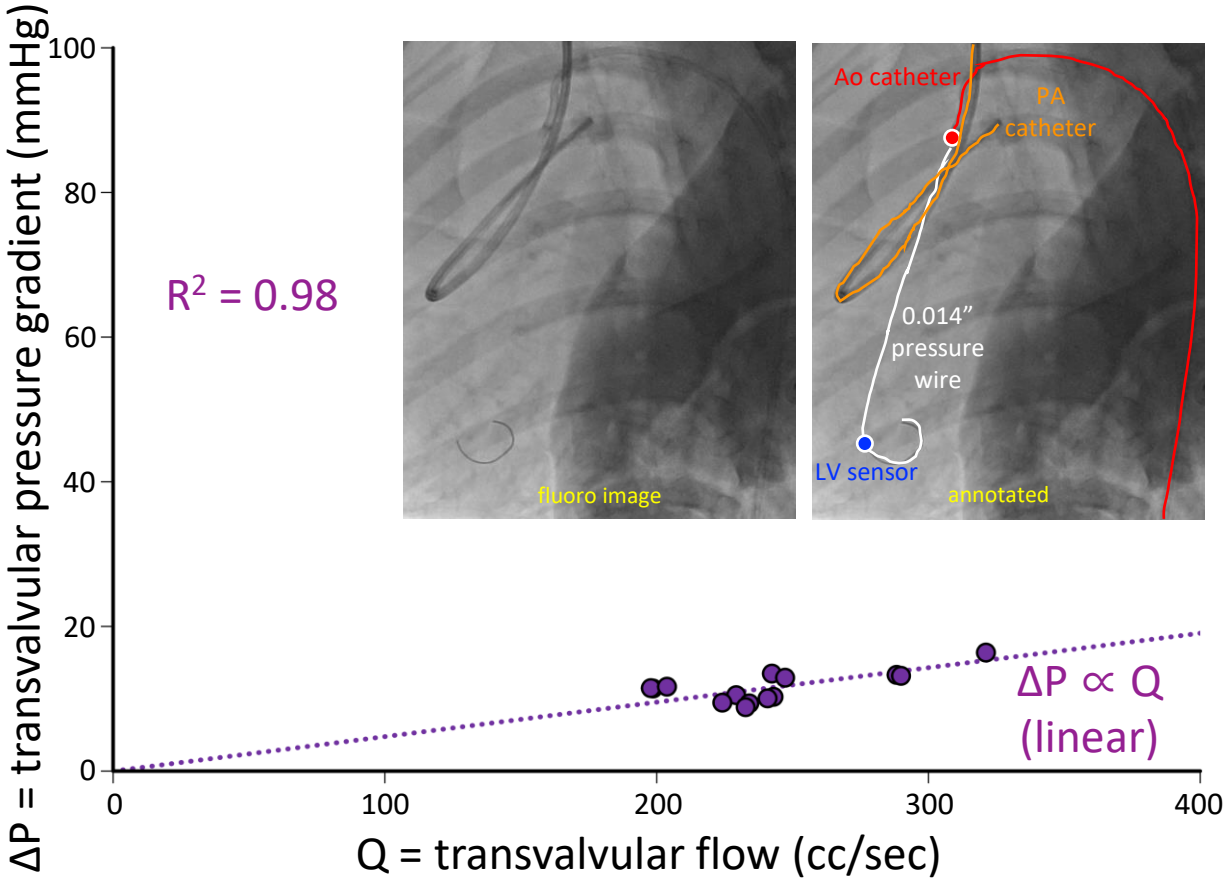
Valve changes geometry with stress



Preliminary, unpublished data courtesy of Dr. Vijay Govindarajan, Houston, Texas.

TAVI and normal AV = resistor





Linear relationship is an excellent description
(median *R^2 = 0.96 for linear model*)
Hence *valid TAVI "resistance"* physiology
Median resistance 0.65 Woods units

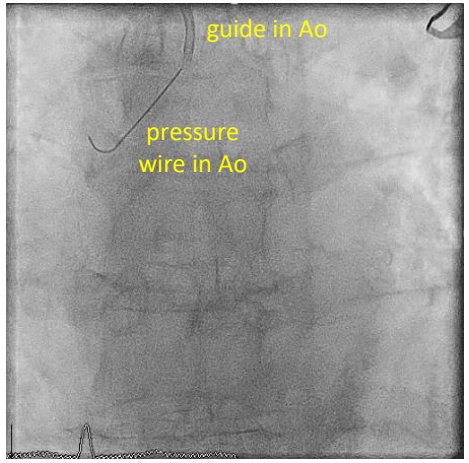
swine model
normal aortic valve
highly linear ΔP/Q relationship

left = Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Figure 2"B" case but post-TAVI only plus fluoro inset), right = unpublished personal data

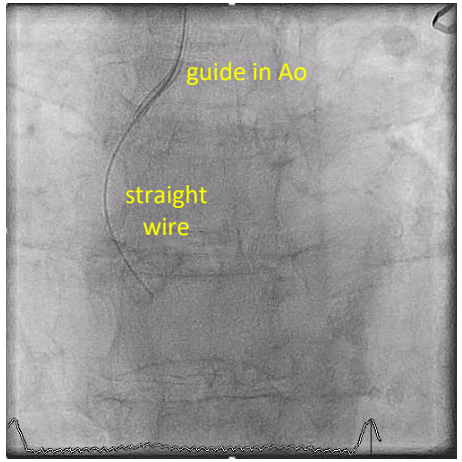
SAVI

"FFR for AS"

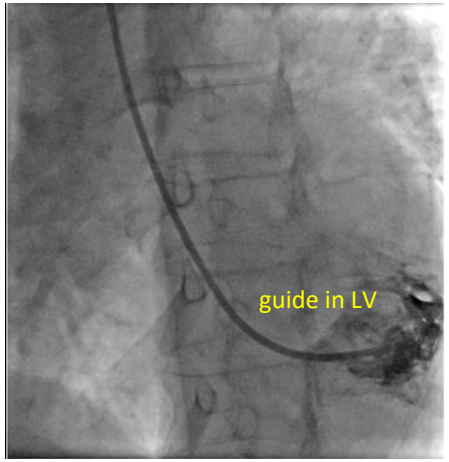
SAVI in cath lab = procedure like FFR



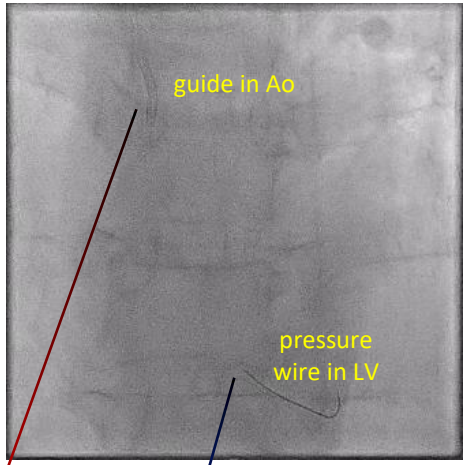
1. equalize wire in aorta



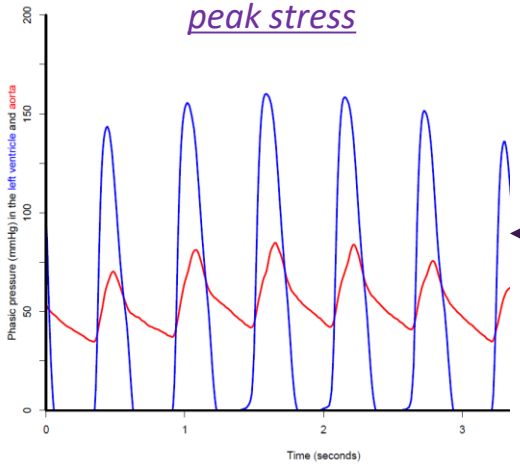
2. cross aortic valve using straight wire



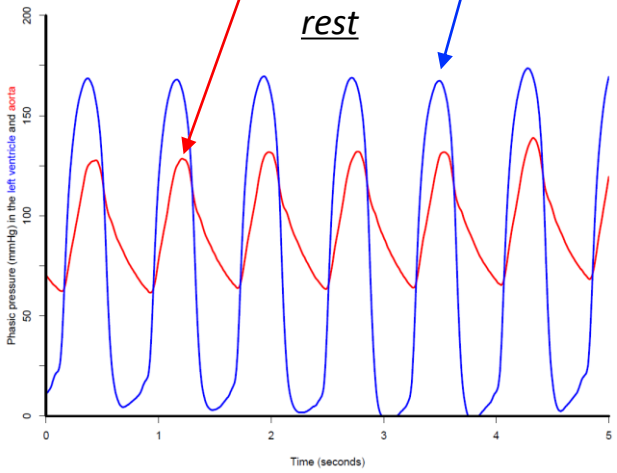
3. bring guide into LV over wire



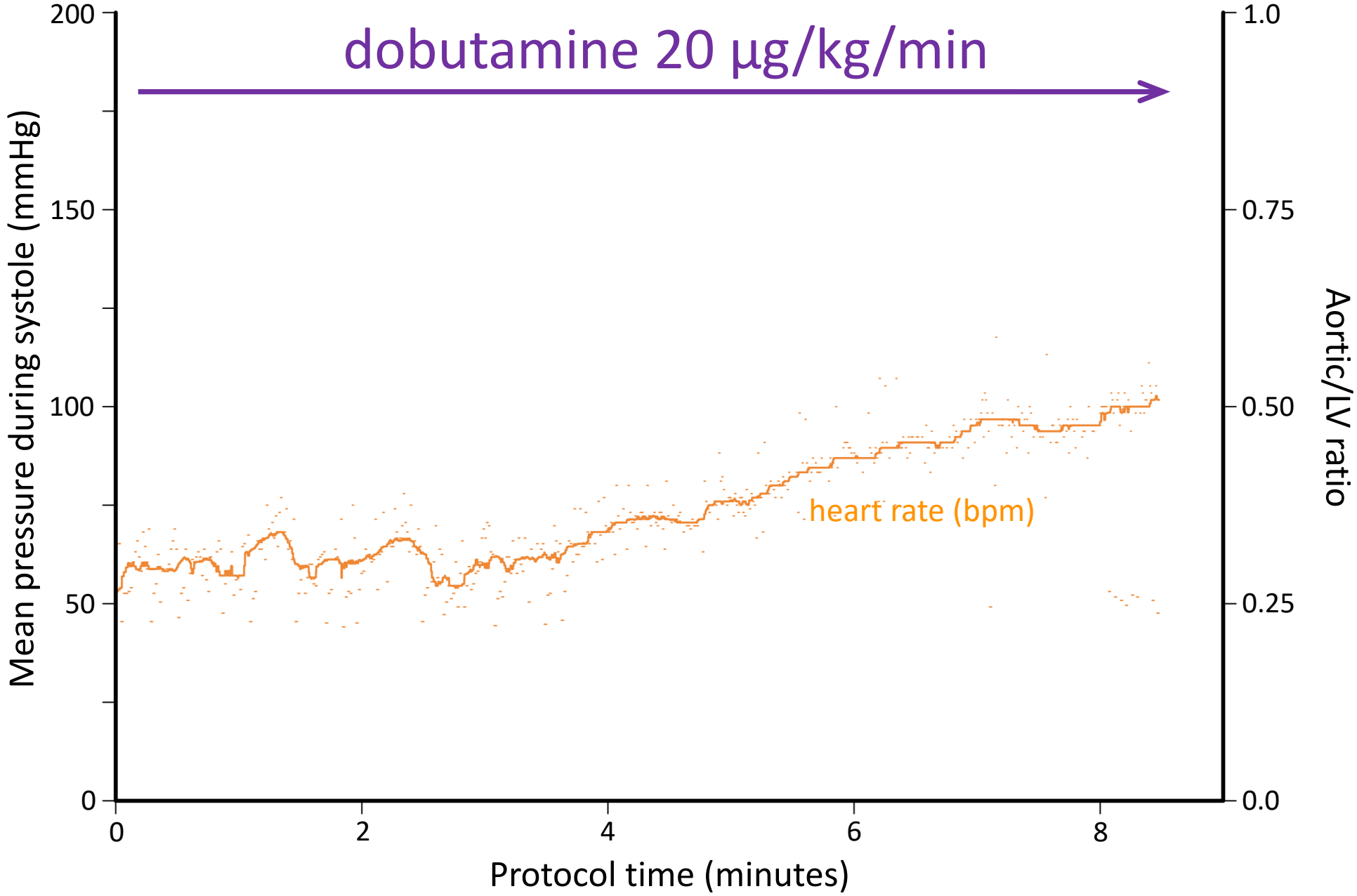
4. exchange for pressure wire and pull guide into aorta



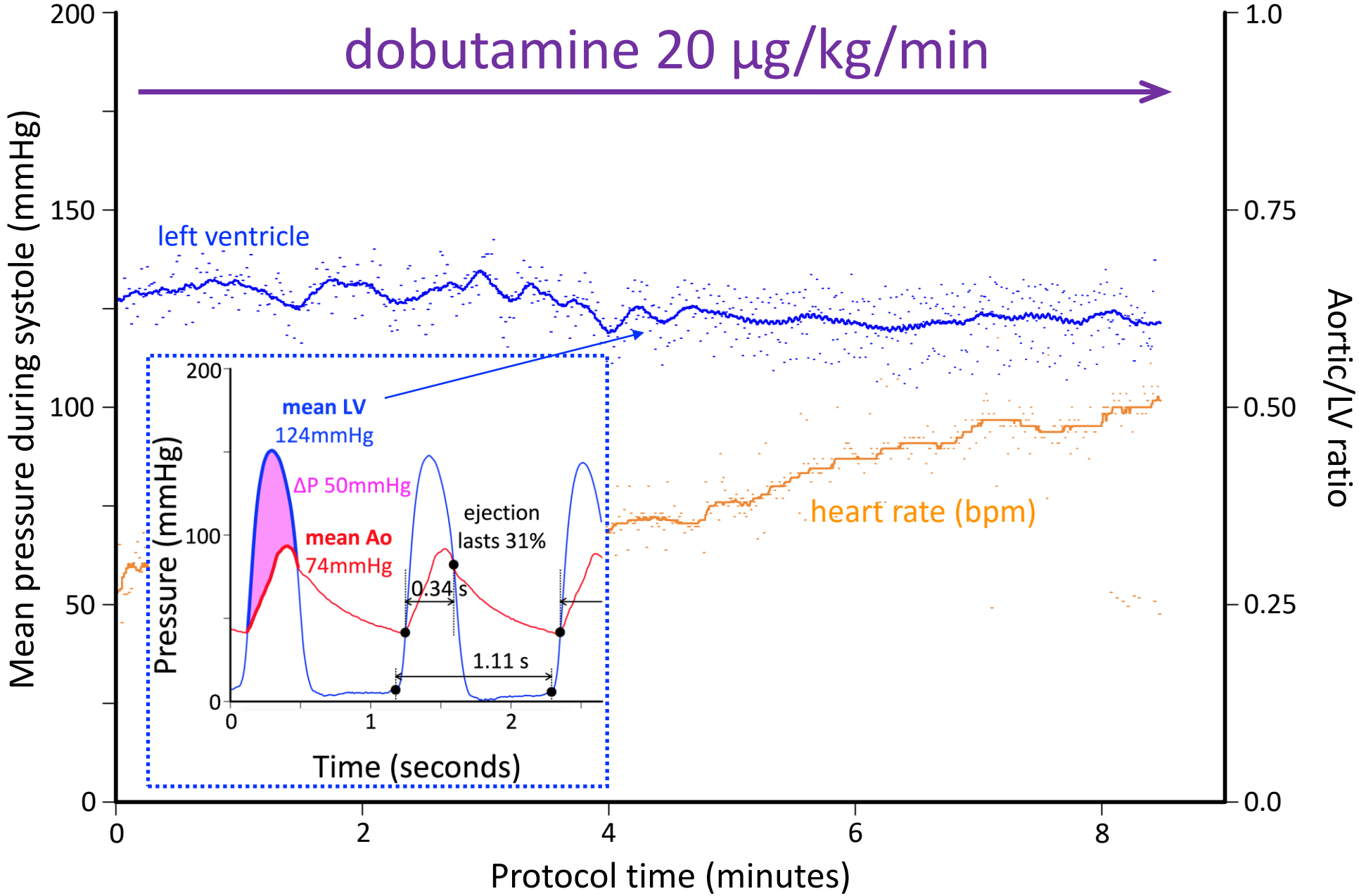
IV dobutamine
20 to 40 μg/kg/min
for 10 minutes



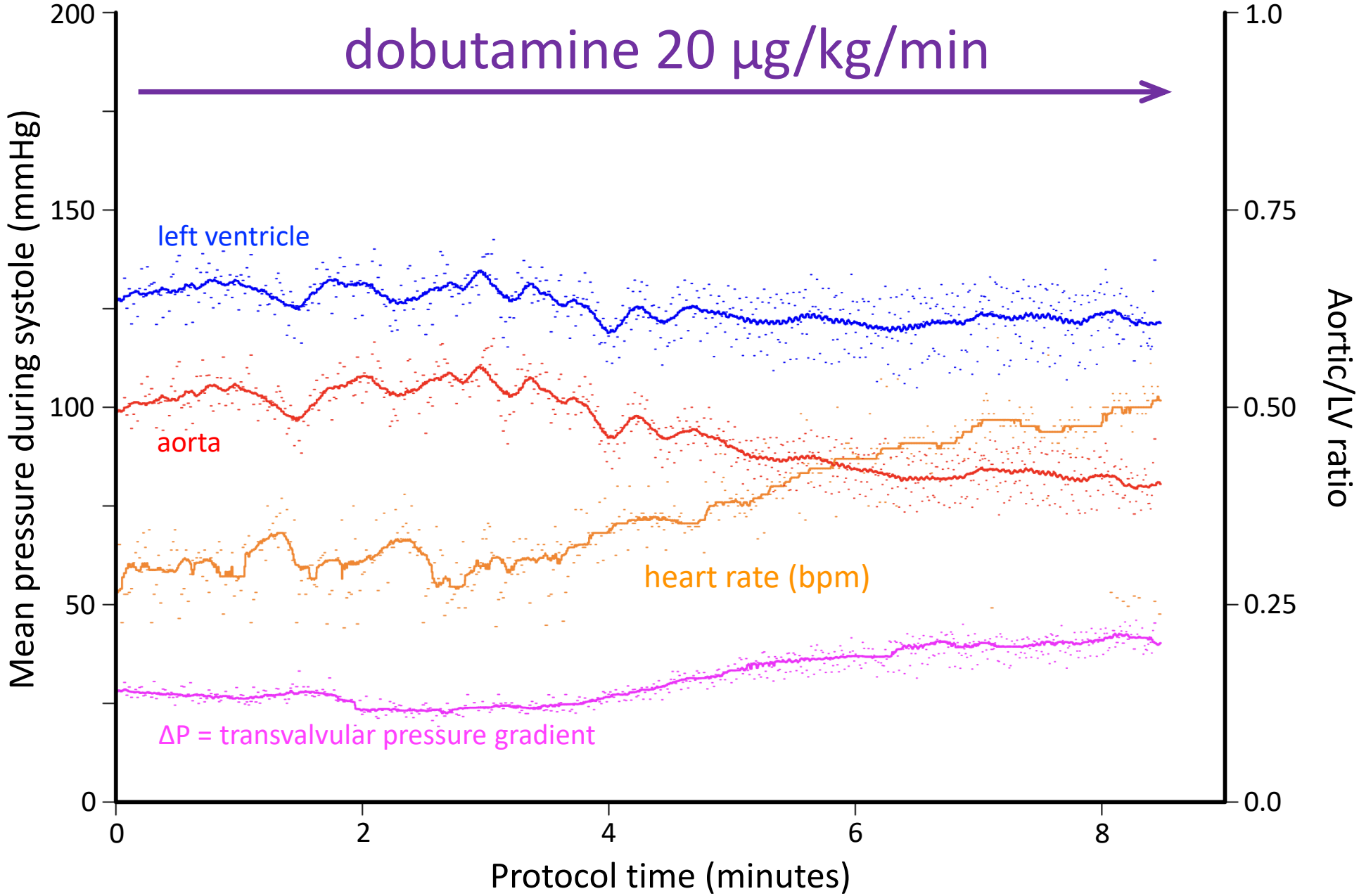
What is a typical SAVI case?



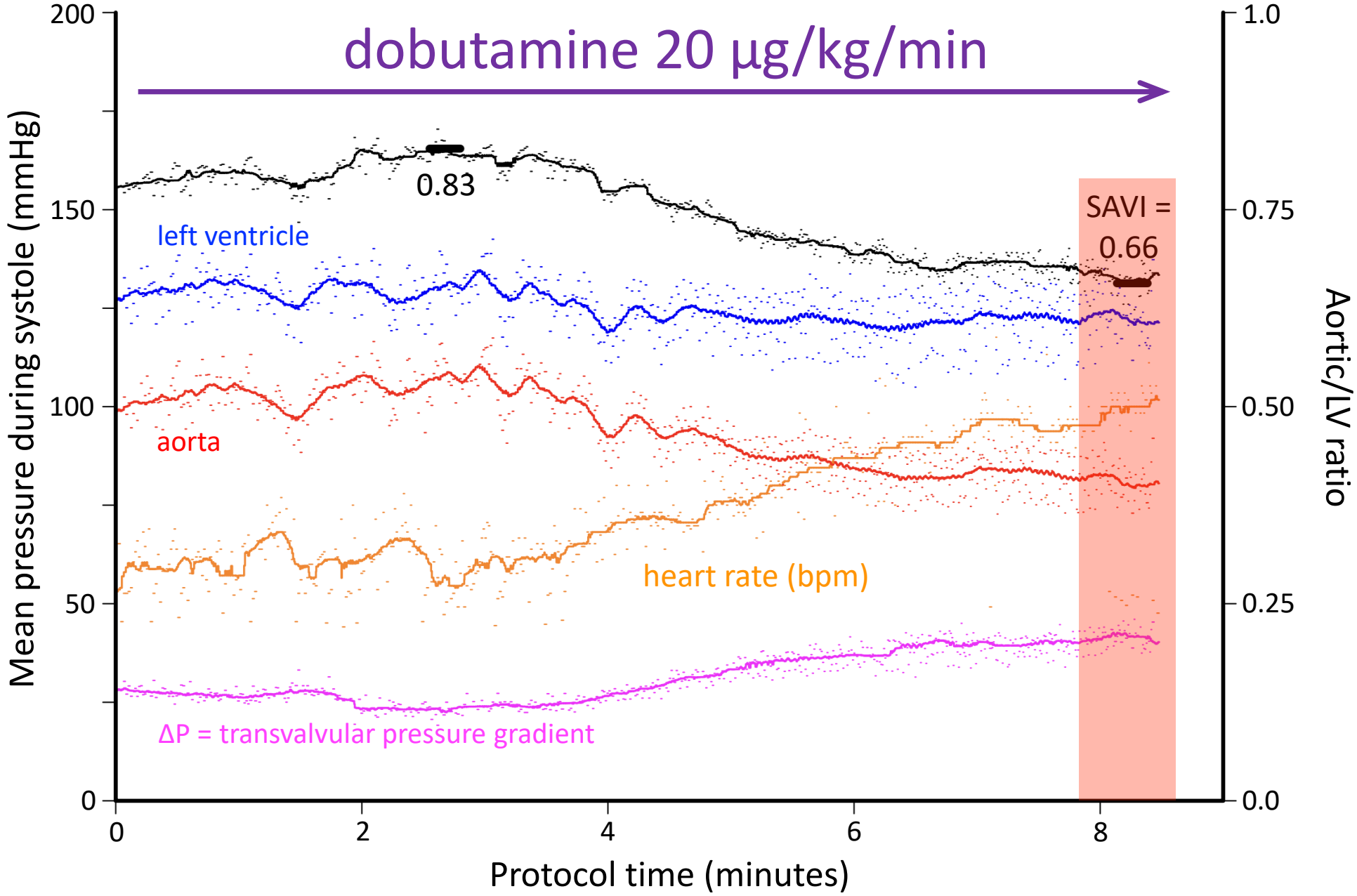
What is a typical SAVI case?



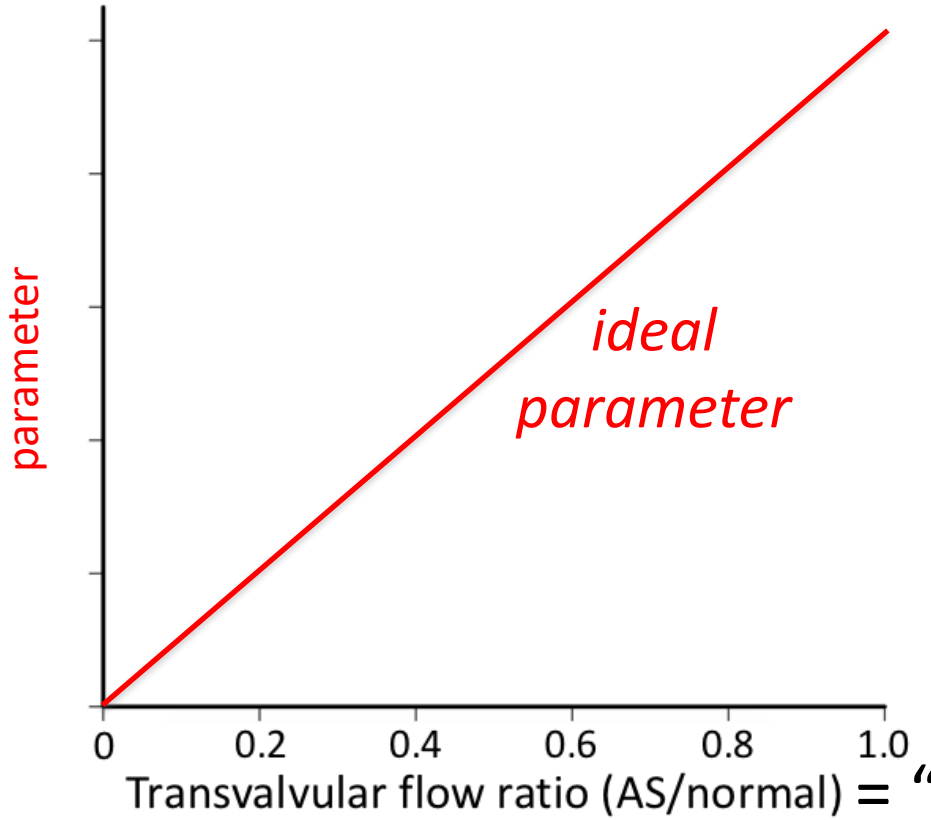
What is a typical SAVI case?



What is a typical *SAVI* case?

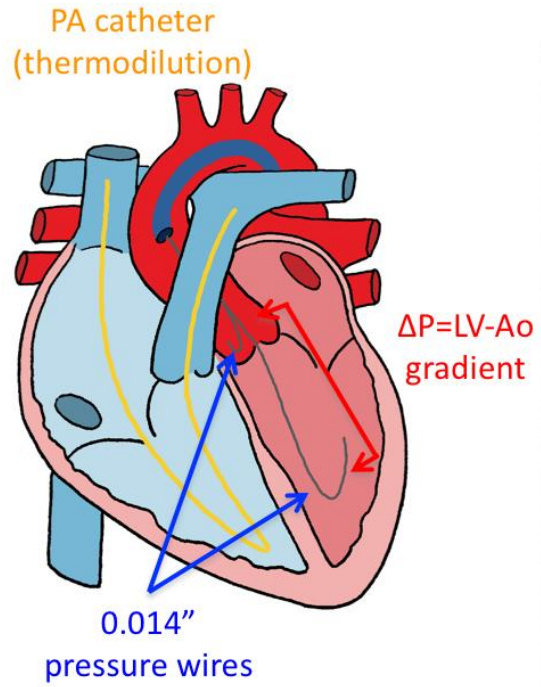


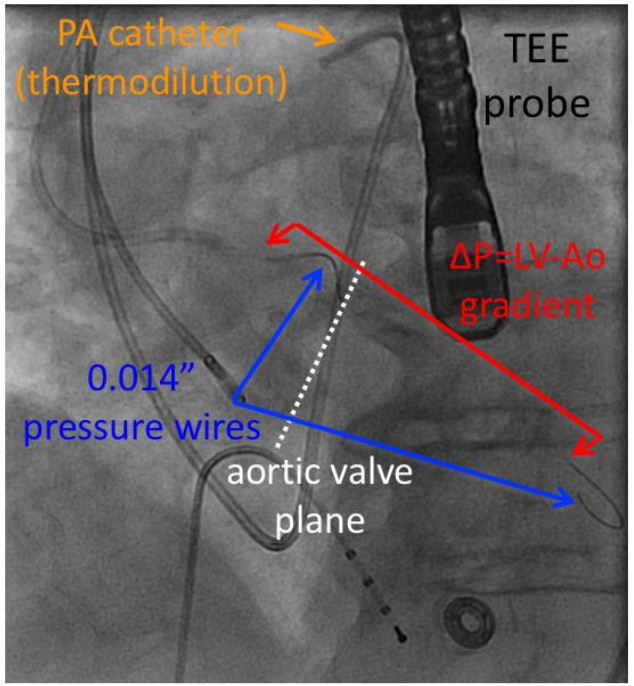
How much does valve limit peak flow?

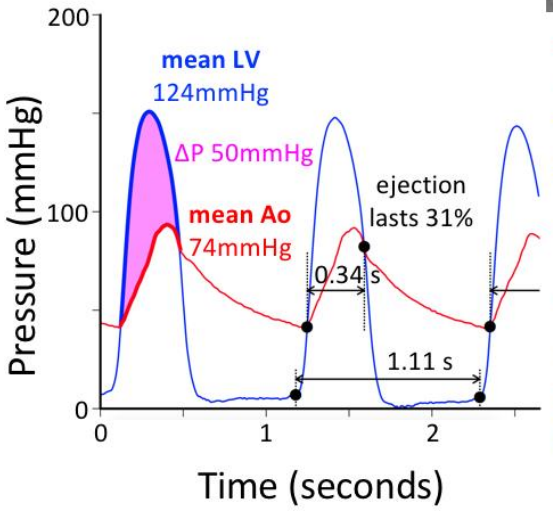


$$\frac{\text{FLOW}_{\textit{stenotic}\ \text{valve}}}{\text{FLOW}_{\textit{normal}\ \text{valve}}}$$

Patients with severe AS pre/post TAVI







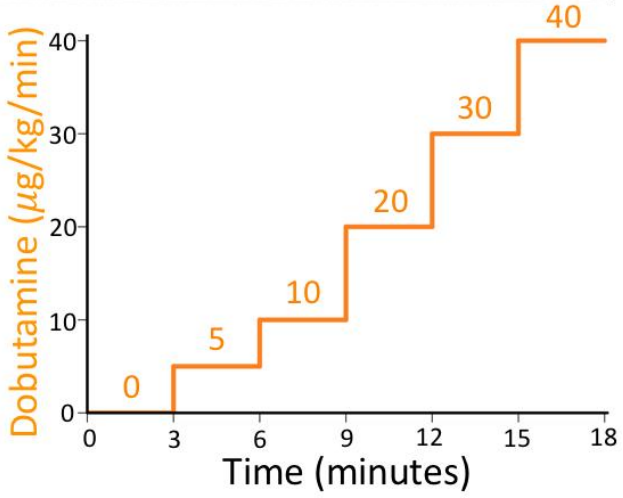


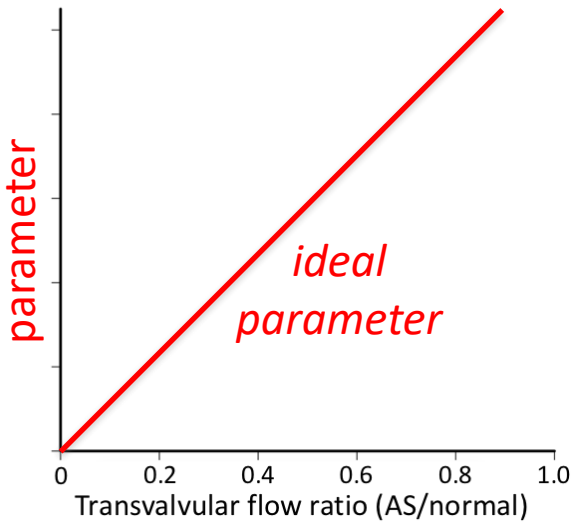
Table 1 Baseline and procedural characteristics

Characteristics	Summary (n = 16)
Age (years)	82.3 ± 4.2
Male	8 (50)
Logistic EuroSCORE	12.3 ± 6.7
Risk factors	
Hypertension	11 (69)
Dyslipidaemia	4 (25)
Diabetes mellitus	6 (38)
Active smoking	1 (6)
Major cardiac events	
Prior myocardial infarction	5 (31)
Prior PCI	2 (12)
Prior CABG	4 (25)
Cardiac and vascular disease	
Cerebral vascular disease	2 (12)
Peripheral vascular disease	3 (19)
COPD	3 (19)
Atrial fibrillation	9 (56)
Permanent pacemaker	2 (12)
Laboratory values	
hs-cTnT (ng/L)	20 (18–28)
NT-proBNP (pmol/L)	165 (84–322)
Creatinine (mg/dL)	0.99 (0.82–1.28)
Transcatheter valve[a]	
Medtronic CoreValve Evolut (mm)	8 (53)
26	1
29	7
Edwards SAPIEN 3 (mm)	7 (47)
23	1
26	3
29	3

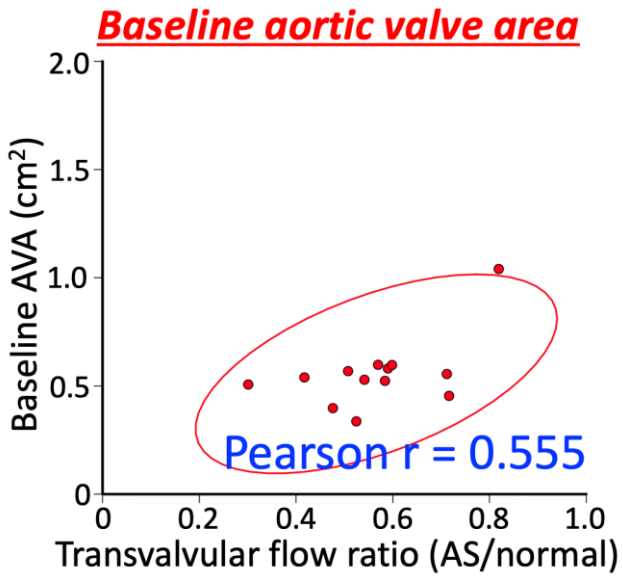
Summary values represent n (%), mean ± standard deviation, or median (IQR). CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention.
[a]Only 15 valves implanted.

Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Figure 1 and Table 1)

AVA *weakly related* to reduced flow



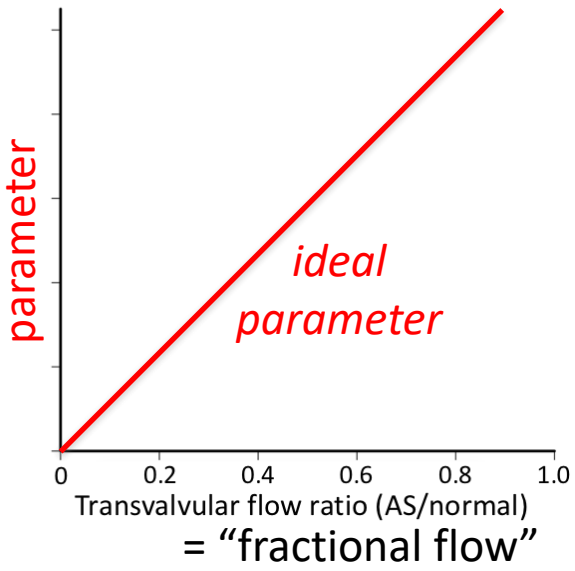
= "fractional flow"



$$\frac{\text{FLOW}_{\textit{stenotic}\ \text{valve}}}{\text{FLOW}_{\textit{normal}\ \text{valve}}}$$

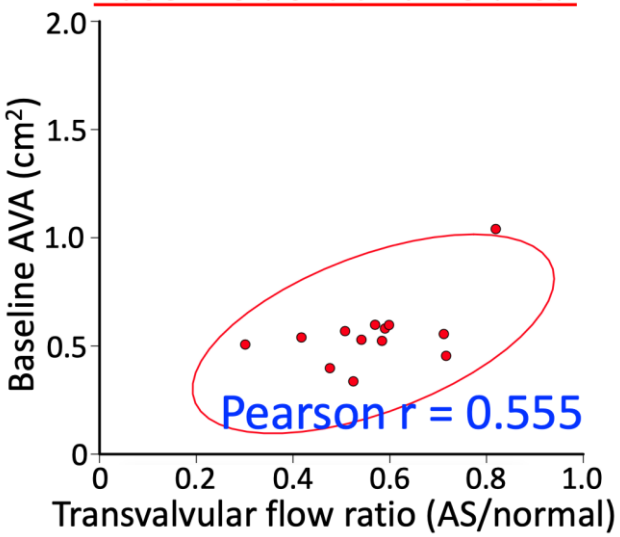
top middle = Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Figure 3 excerpt)

SAVI ≈ "FFR of aortic valve"

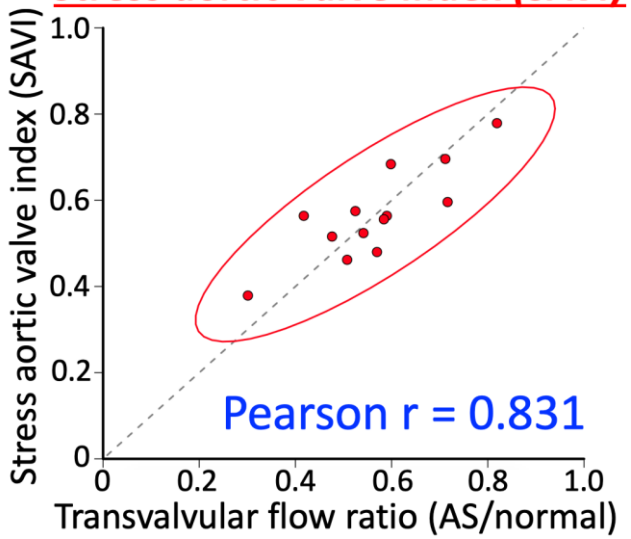


= "fractional flow"

Baseline aortic valve area



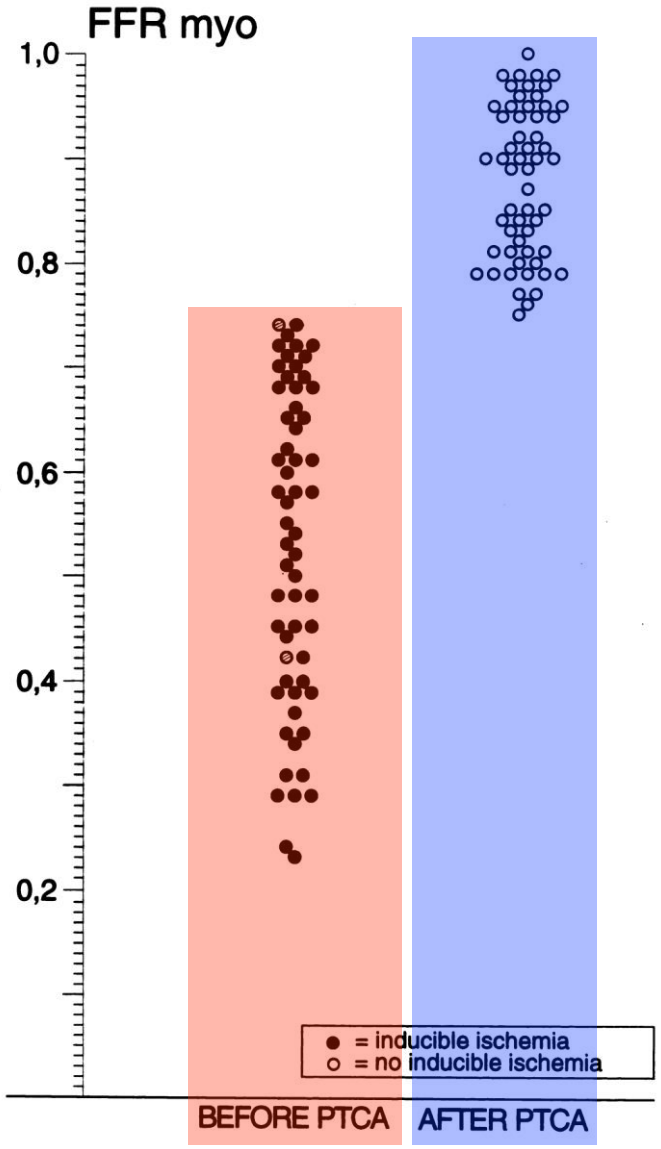
Stress aortic valve index (SAVI)



$$\frac{\text{FLOW}_{\textit{stenotic}\ \text{valve}}}{\text{FLOW}_{\textit{normal}\ \text{valve}}}$$

top right two = Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Figure 3 excerpt)

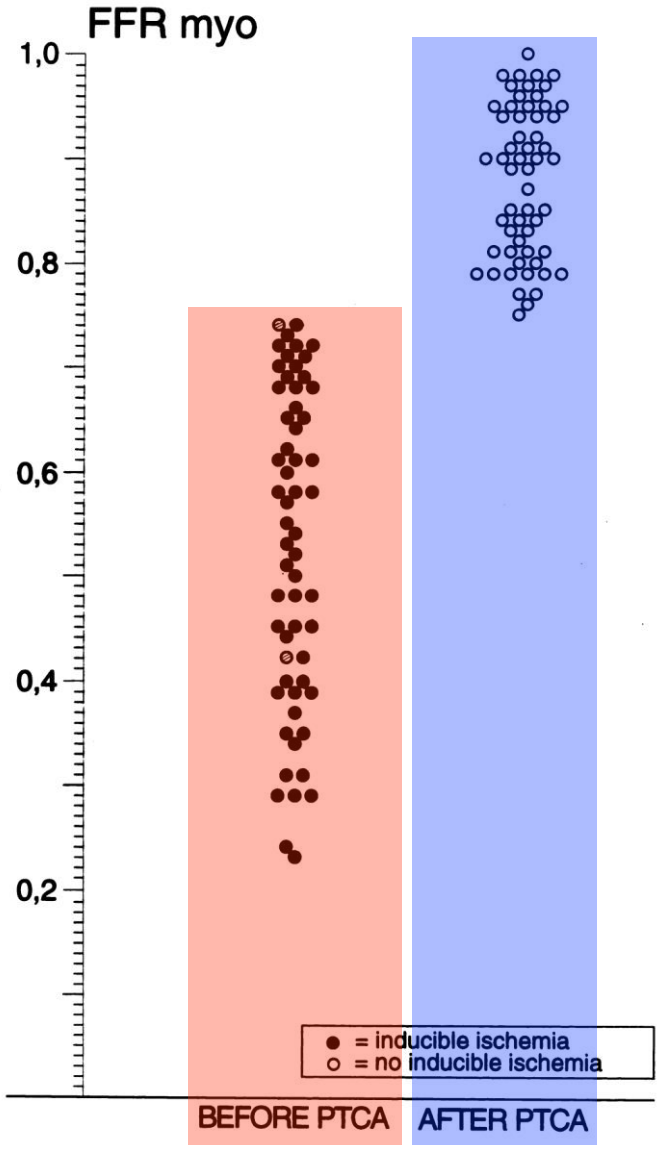
How to define a threshold for device therapy?

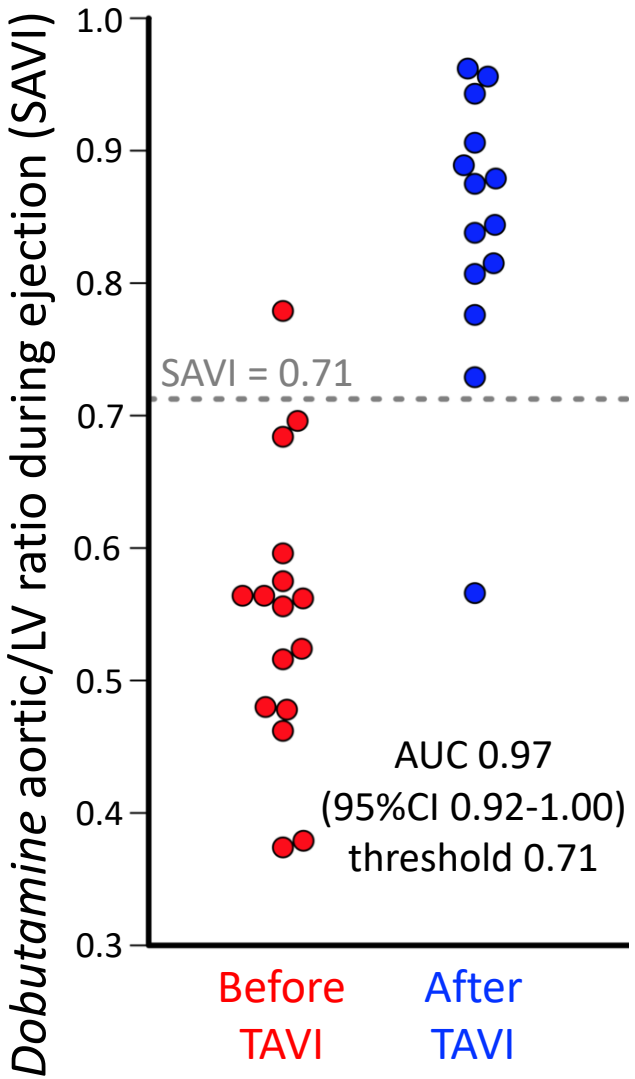


"In all PTCA patients,
FFR_{myo} before PTCA was ≤0.74.
After successful PTCA (as assessed by the reversal of a positive [exercise test] result),
FFR_{myo} was always >0.74"
-December 1995

Pijls NH, *Circulation*. 1995 Dec 1;92(11):3183-93. (Figure 4 with annotations and quote)

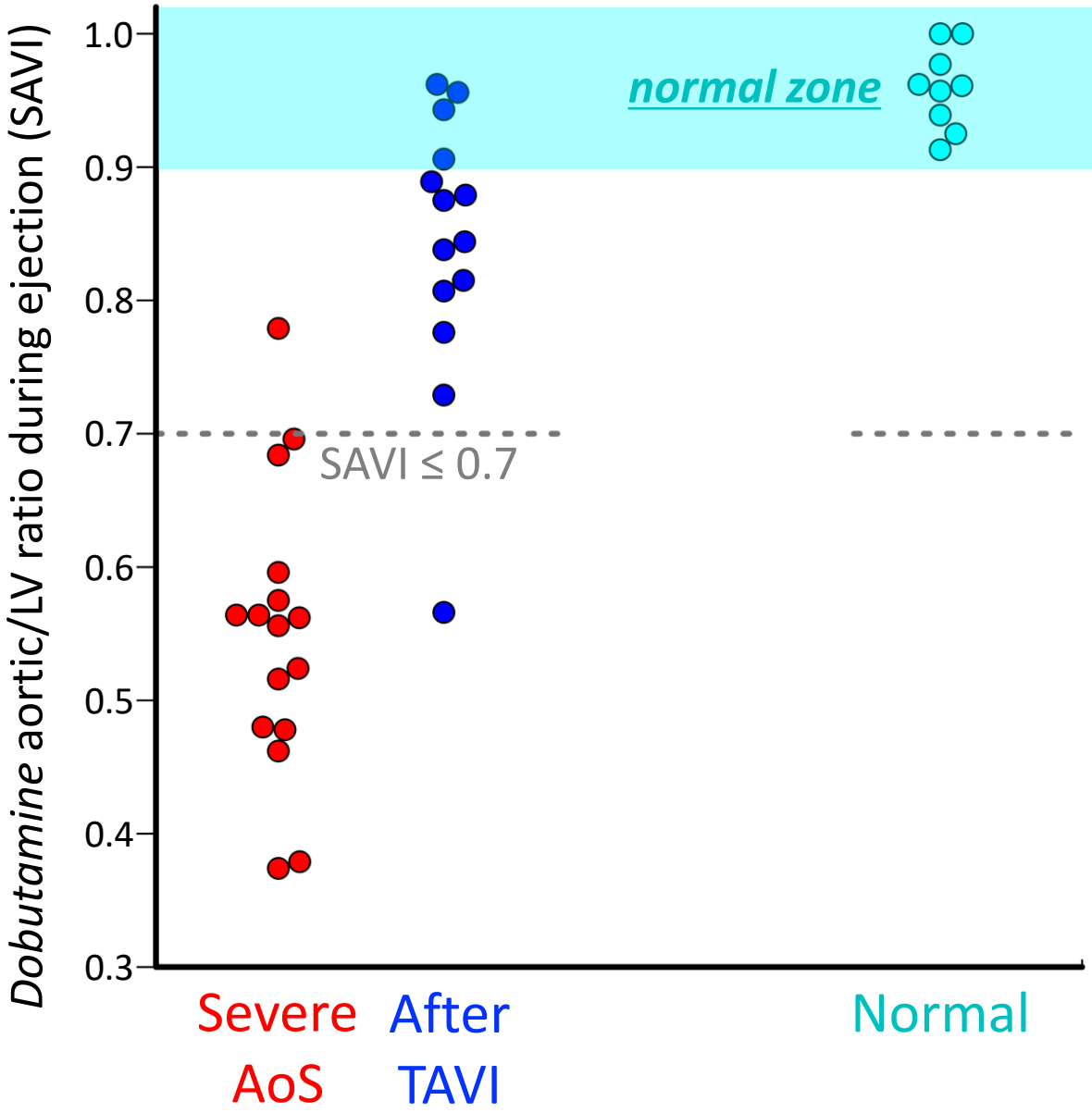
SAVI=0.7 defines AS suitable for TAVI





left = Pijls NH, *Circulation*. 1995 Dec 1;92(11):3183-93. (Figure 4 with annotations)
right = Johnson NP, *EHJ*. 2018 Jul 21;39(28):2646-2655. (Figure 4 right-hand portion)

SAVI=0.9 indicates normal valve function



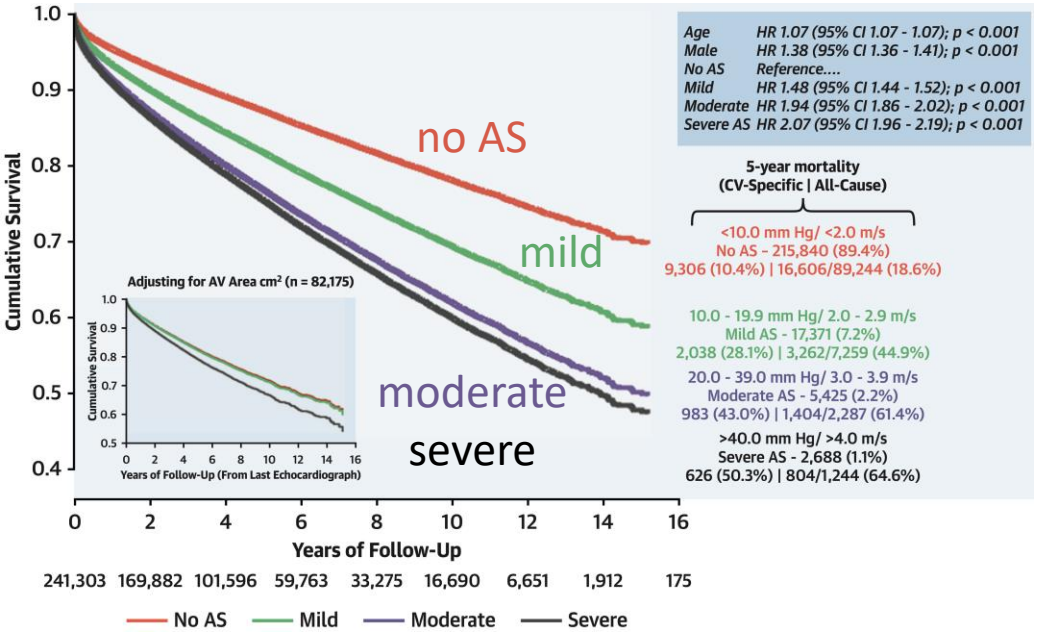
- 9 subjects
- normal aortic valves
- dobutamine stress

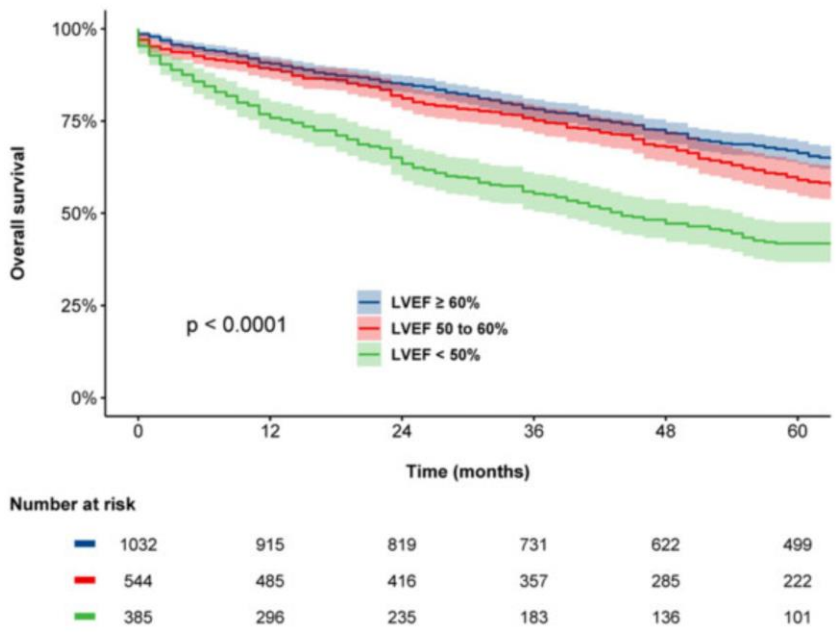
Preliminary, unpublished data courtesy of Dr. Rob Eerdekens, Eindhoven, Netherlands.

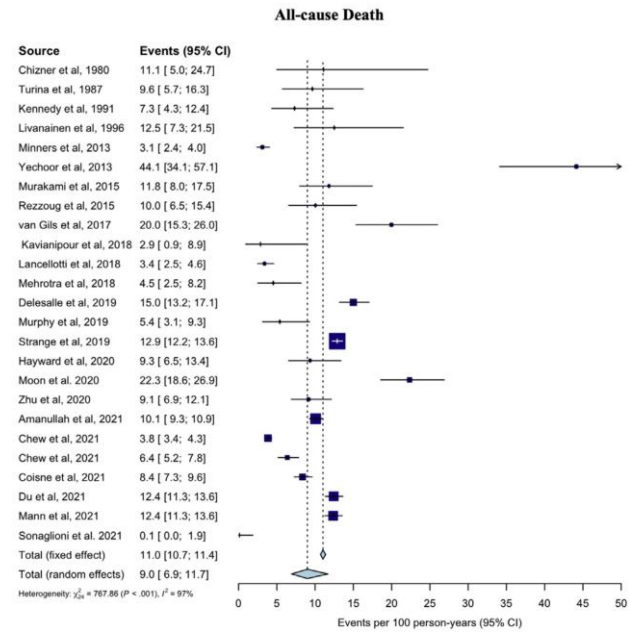
SAVI-AoS

360° of moderate AS

Moderate AS has high risk of *death*







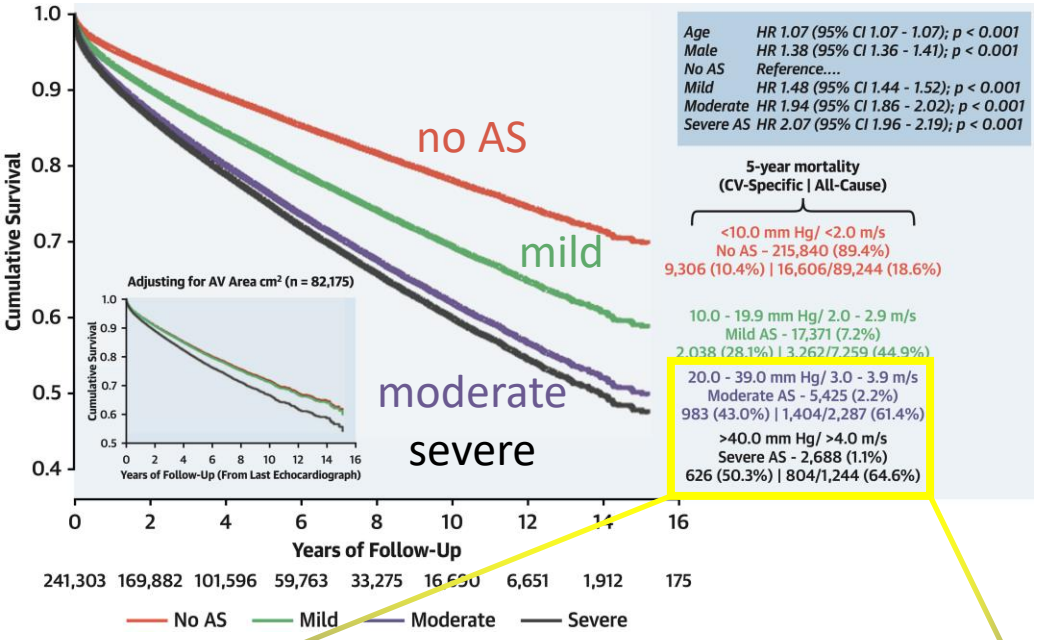
National Australian database
N = 3315 moderate AS
total 241303 subjects
median 3.3 years follow-up
25% dead after 5 years, moderate AS

3 academic hospitals
N = 1961 moderate AS
median 4.2 years follow-up
20% dead after 5 years, EF>50%

25 study-level papers
N = 12143 moderate AS
mean 3.8 years follow-up
10 deaths/100 person-years

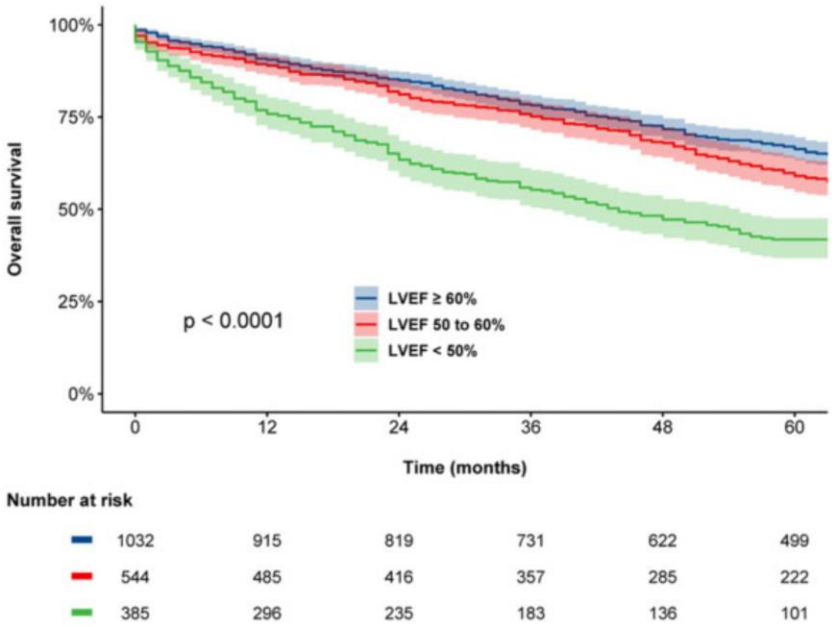
left = Strange G, *JACC*. 2019 Oct 15;74(15):1851-1863. (Figures 3 with *colors* and Central Illustration)
middle = Stassen J, *EHJ Cardiovasc Imaging*. 2022 Jun 1;23(6):790-799. (Figure 2A)
right = Coisne A, *JACC Cardiovasc Interv*. 2022 Aug 22;15(16):1664-1674. (Figure 1A)

Moderate AS has high risk of *death*



National Australian database

N = 3315 moderate AS

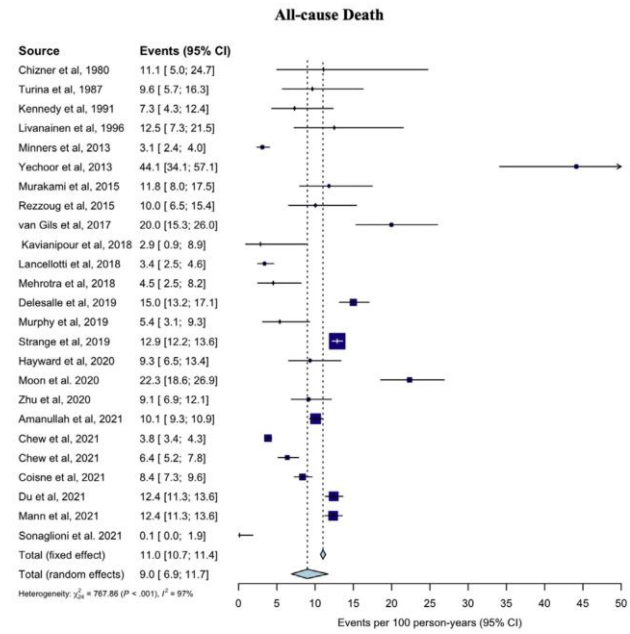


3 academic hospitals

N = 1961 moderate AS

median 4.2 years follow-up

20% dead after 5 years, EF>50%



25 study-level papers

N = 12143 moderate AS

mean 3.8 years follow-up

10 deaths/100 person-years

prevalence

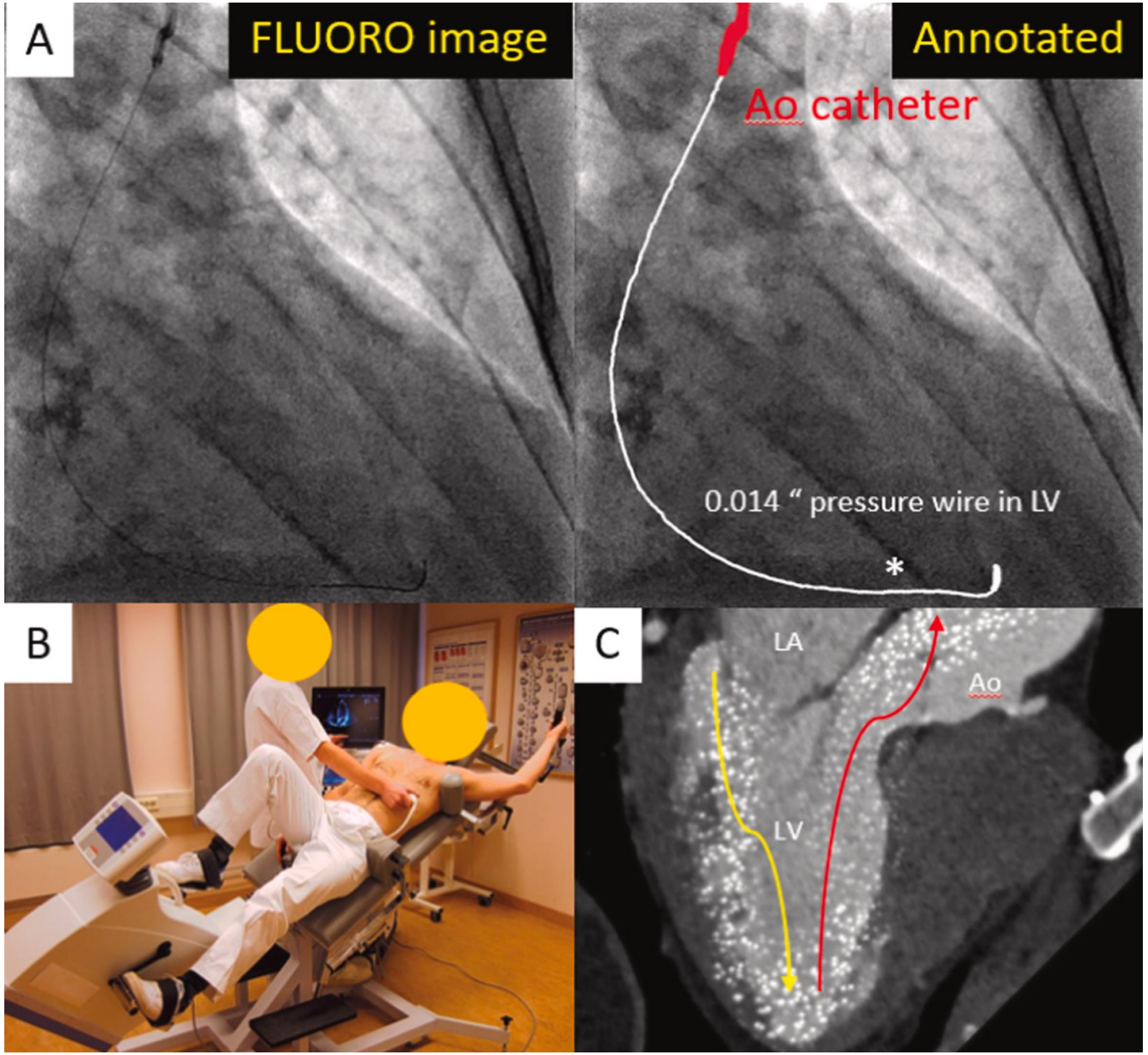
- severe AS = 1.1%
- moderate AS = 2.2%

left = Strange G, *JACC*. 2019 Oct 15;74(15):1851-1863. (Figures 3 with *colors* and Central Illustration)

middle = Stassen J, *EHJ Cardiovasc Imaging*. 2022 Jun 1;23(6):790-799. (Figure 2A)

right = Coisne A, *JACC Cardiovasc Interv*. 2022 Aug 22;15(16):1664-1674. (Figure 1A)

SAVI-AoS = “valve stress test”



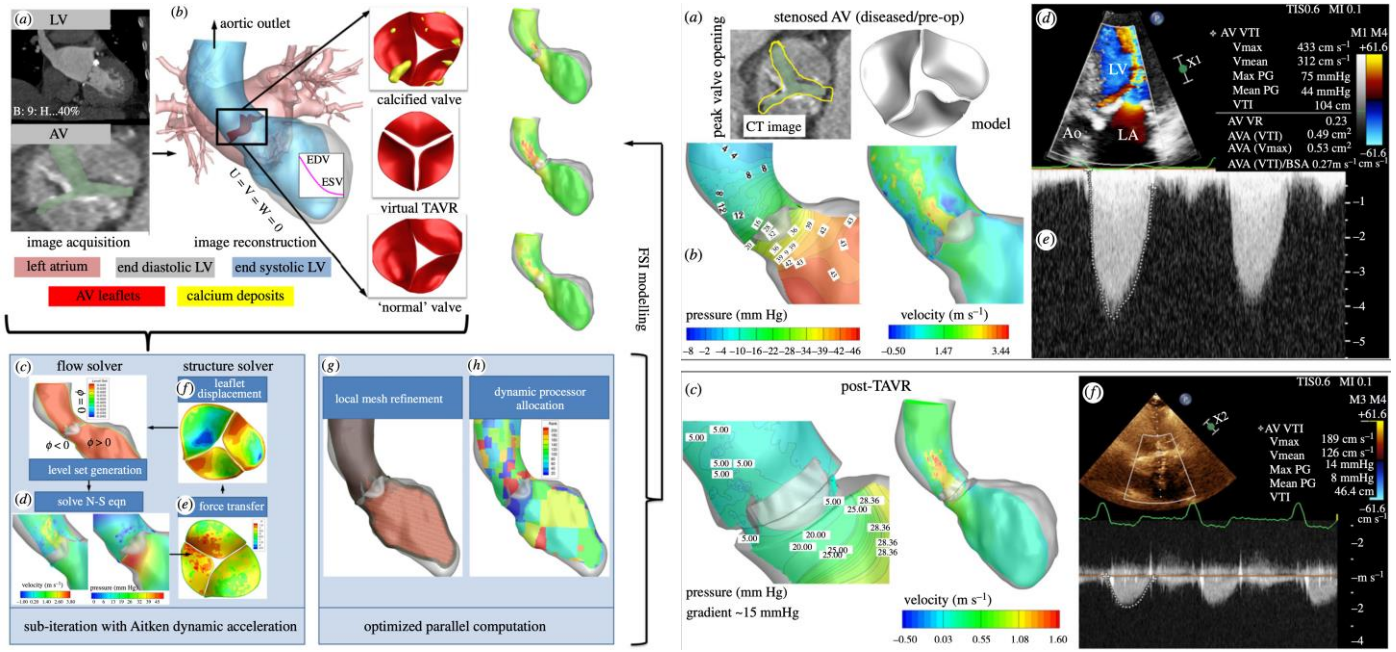
- moderate AS (rest)
  - ✓ AVA >1.0 cm^2
  - ✓ ΔP 15-39 mmHg
    or velocity 2.5-3.9 m/s
- EF>50%
- age > 50 years
- able to exercise
- no bad CAD, COPD, CKD, …

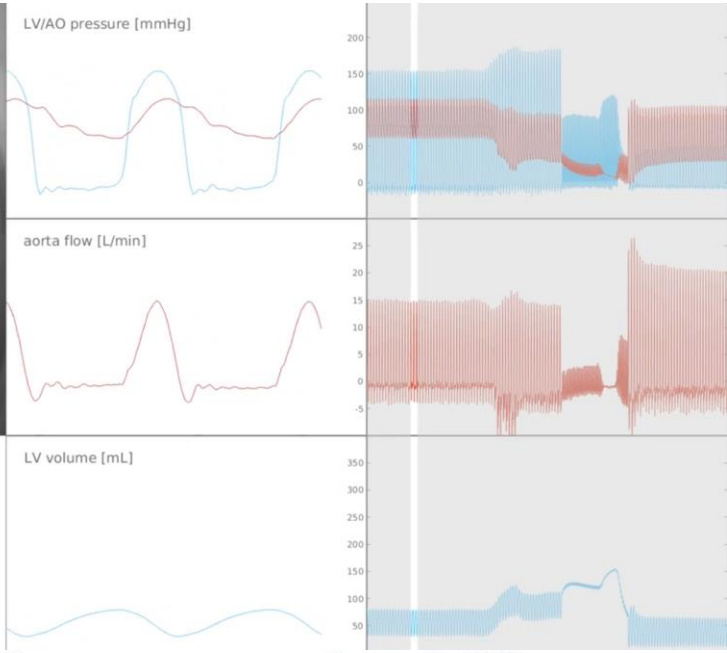
observational design

- 100 subjects
- 6-minute walk test
- KCCQ quality of life
- biomarkers (BNP, troponin)
- valve calcium score
- clinical events
- follow-up for 5 years

Eerdekens R, *Int J Cardiol Heart Vasc*. 2022 May 27;41:101063. (Figure 1) and clinicaltrials.gov (NCT04514250)

CFD and printed valves to understand mechanism





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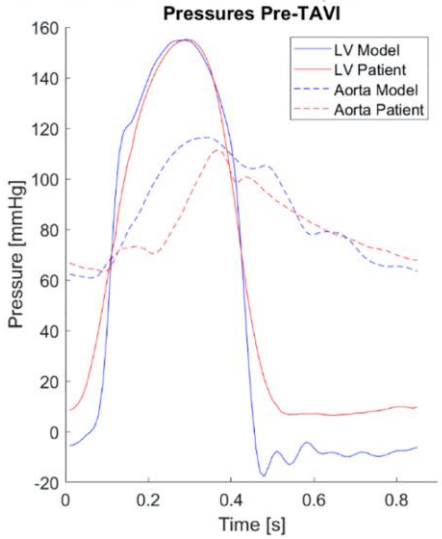
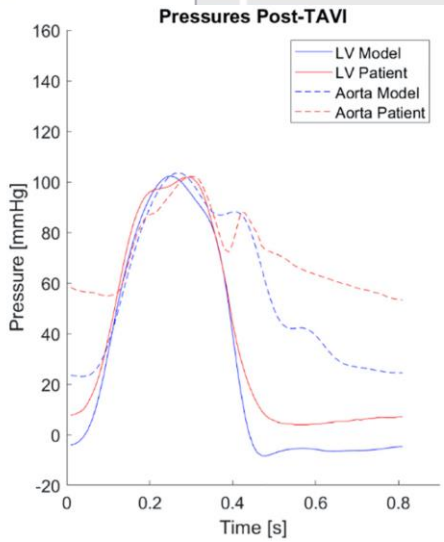
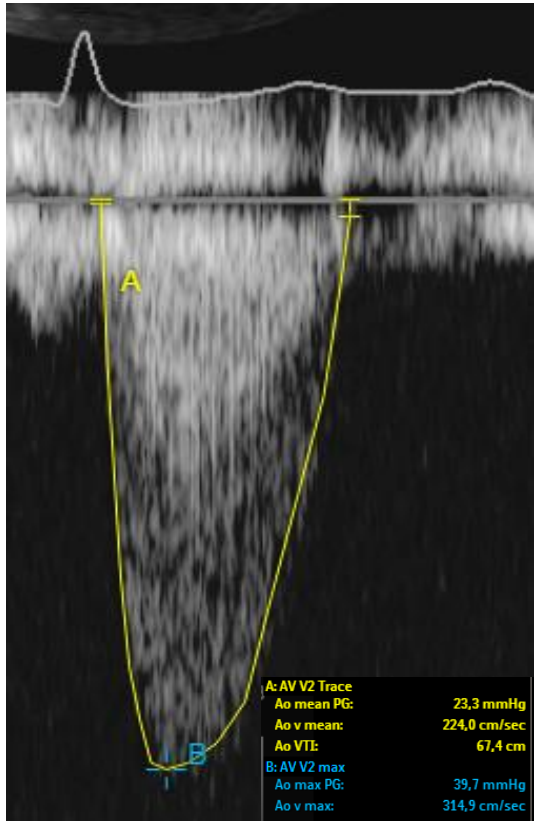
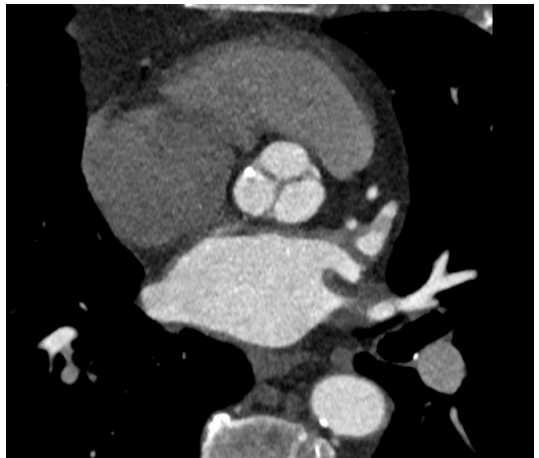




left, middle = Govindarajan V, *R Soc Open Sci*. 2022 Feb 9;9(2):211694. (Figures 1 and 2)
right top and bottom = Zelis JM, *Int J Cardiol*. 2020 Aug 15;313:32-34. (On-line video frame and Figure 1)

A symptomatic *patient*





Demographics

- 81-year-old woman
- angina, CCS class II
- BMI 30 kg/m^2

Laboratory

- hs-cTnT 15 ng/L
- NT-proBNP 213 pg/mL
- 6MWT = 205 meters

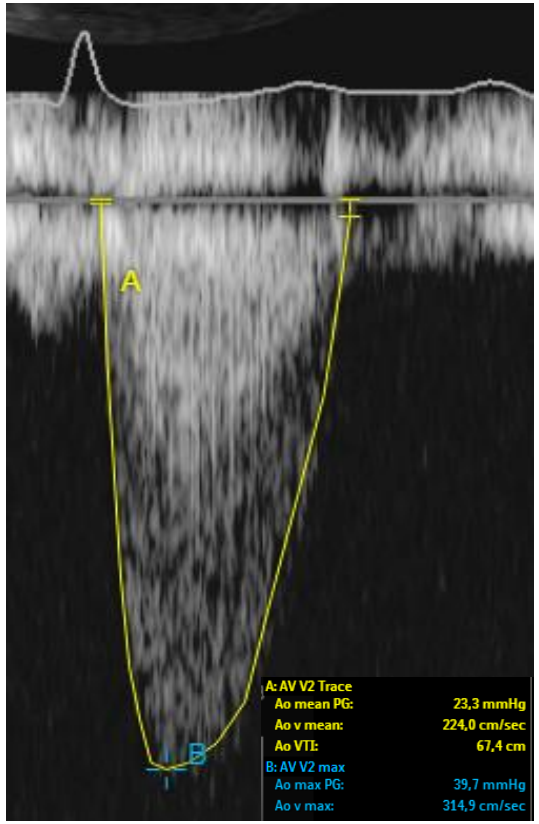
Echocardiography

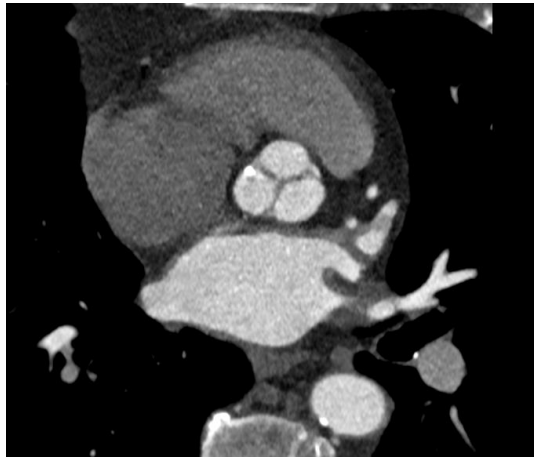
- V_{max} 3.2 m/s
- mean ΔP 23 mmHg
- AVA 1.3 cm^2

Valve CT

- 700 AU

Two symptomatic *patients*





Demographics

- 81-year-old woman
- angina, CCS class II
- BMI 30 kg/m^2

Laboratory

- hs-cTnT 15 ng/L
- NT-proBNP 213 pg/mL
- 6MWT = 205 meters

Echocardiography

- V_{max} 3.2 m/s
- mean ΔP 23 mmHg
- AVA 1.3 cm^2

Valve CT

- 700 AU

Demographics

- 83-year-old man
- dyspnea, NYHA class II
- BMI 24 kg/m^2

Laboratory

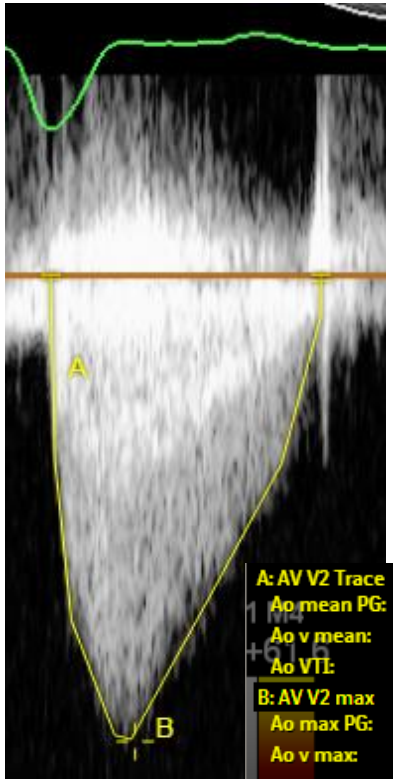
- hs-cTnT 10 ng/L
- NT-proBNP 98 pg/mL
- 6MWT = 370 meters

Echocardiography

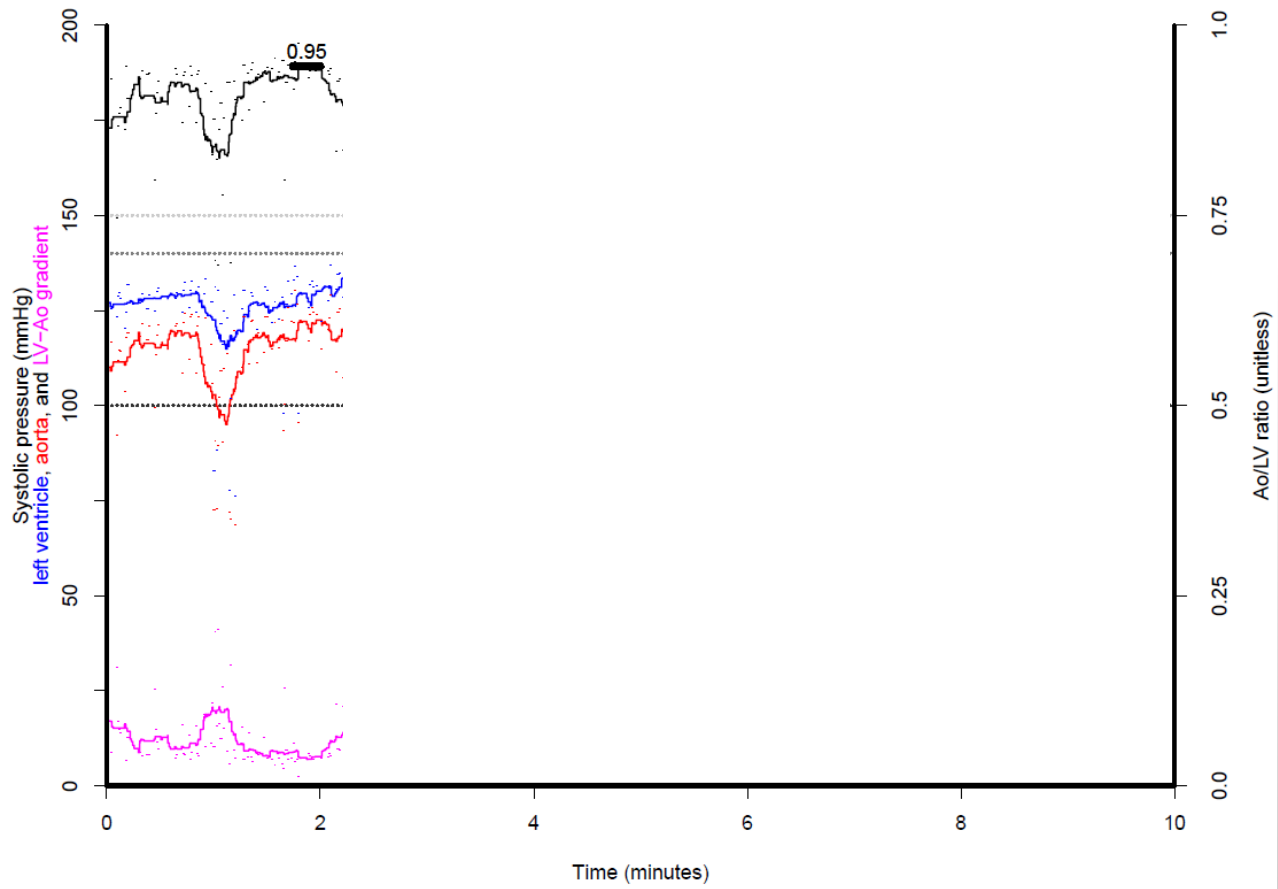
- V_{max} 3.1 m/s
- mean ΔP 19 mmHg
- AVA 1.3 cm^2

Valve CT

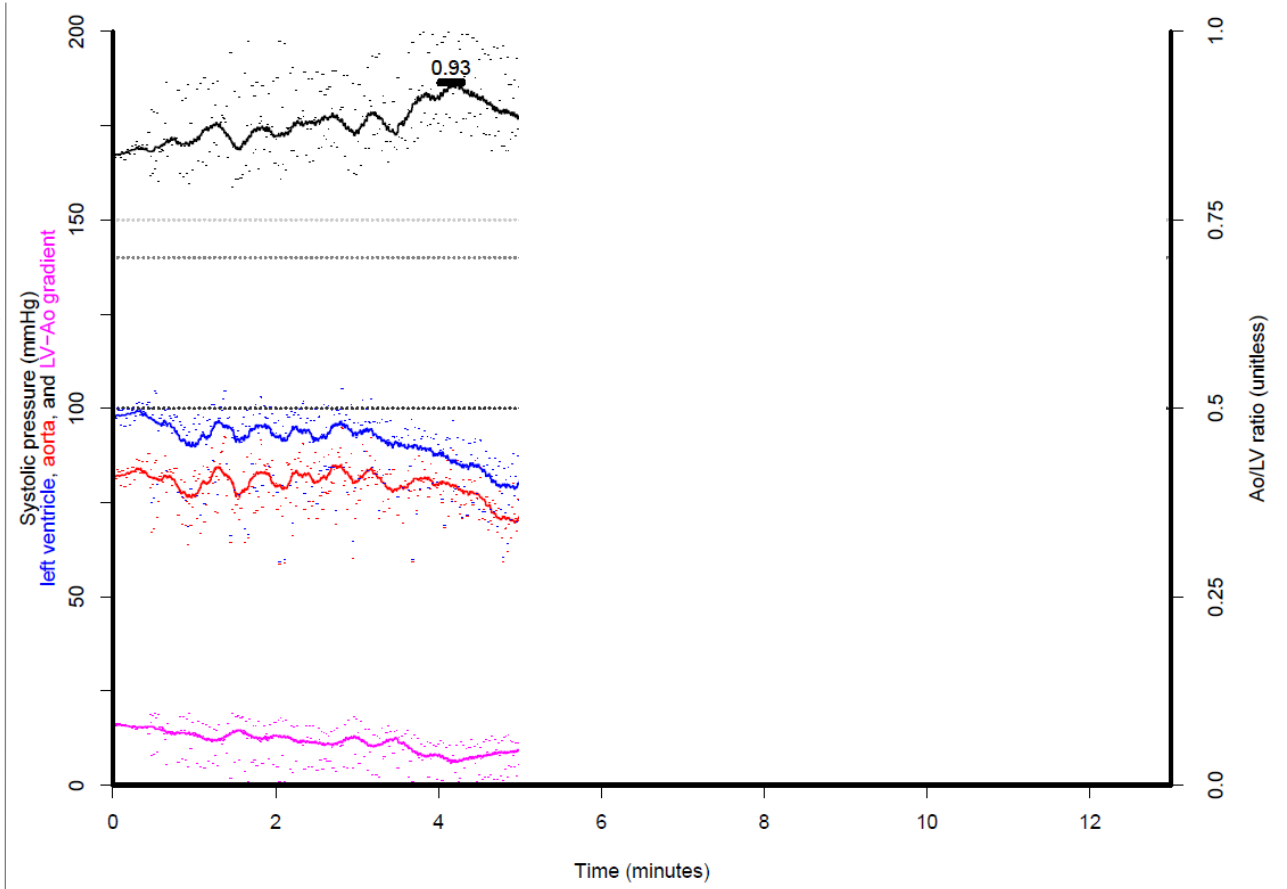
- 1096 AU



Both appear the same at rest…

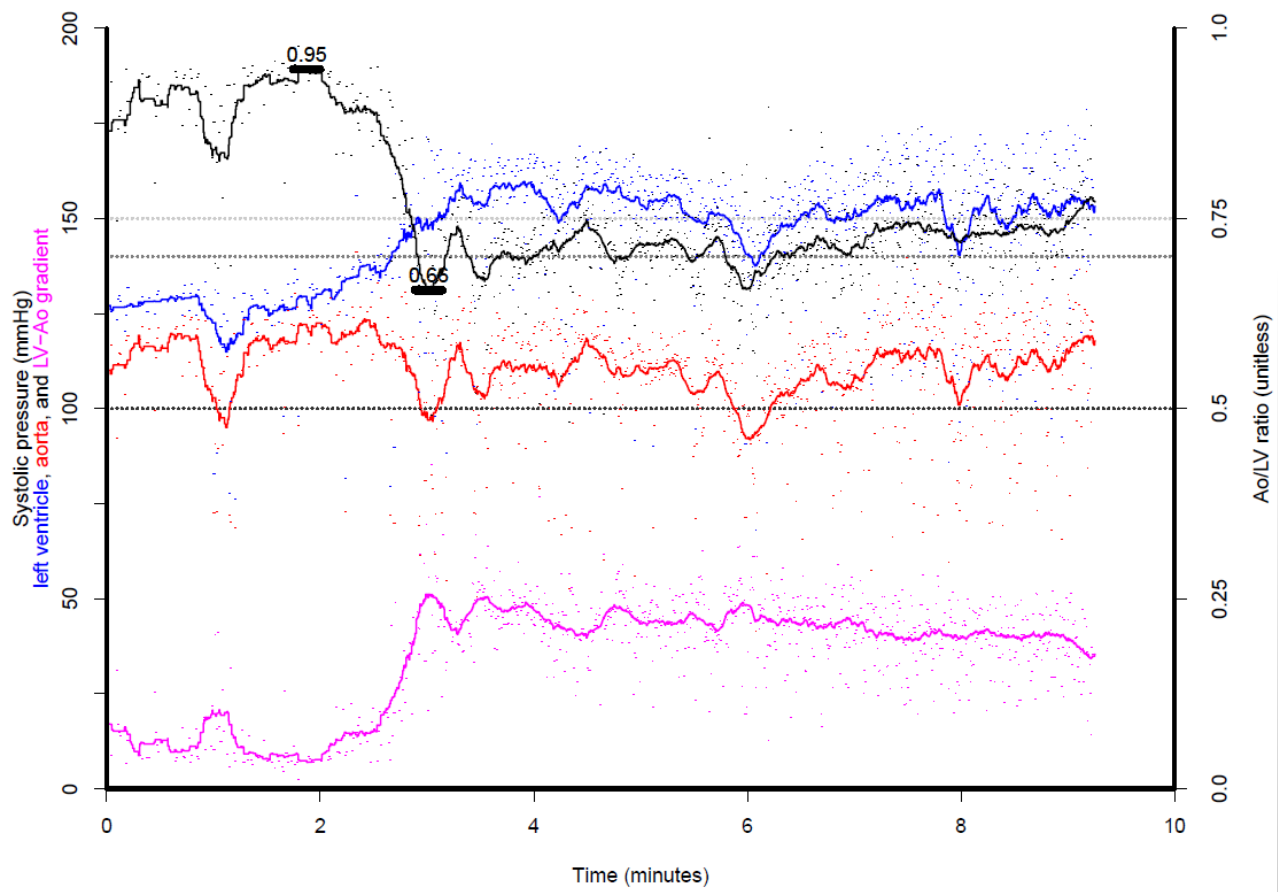


Ao/LV = 0.95



Ao/LV = 0.93

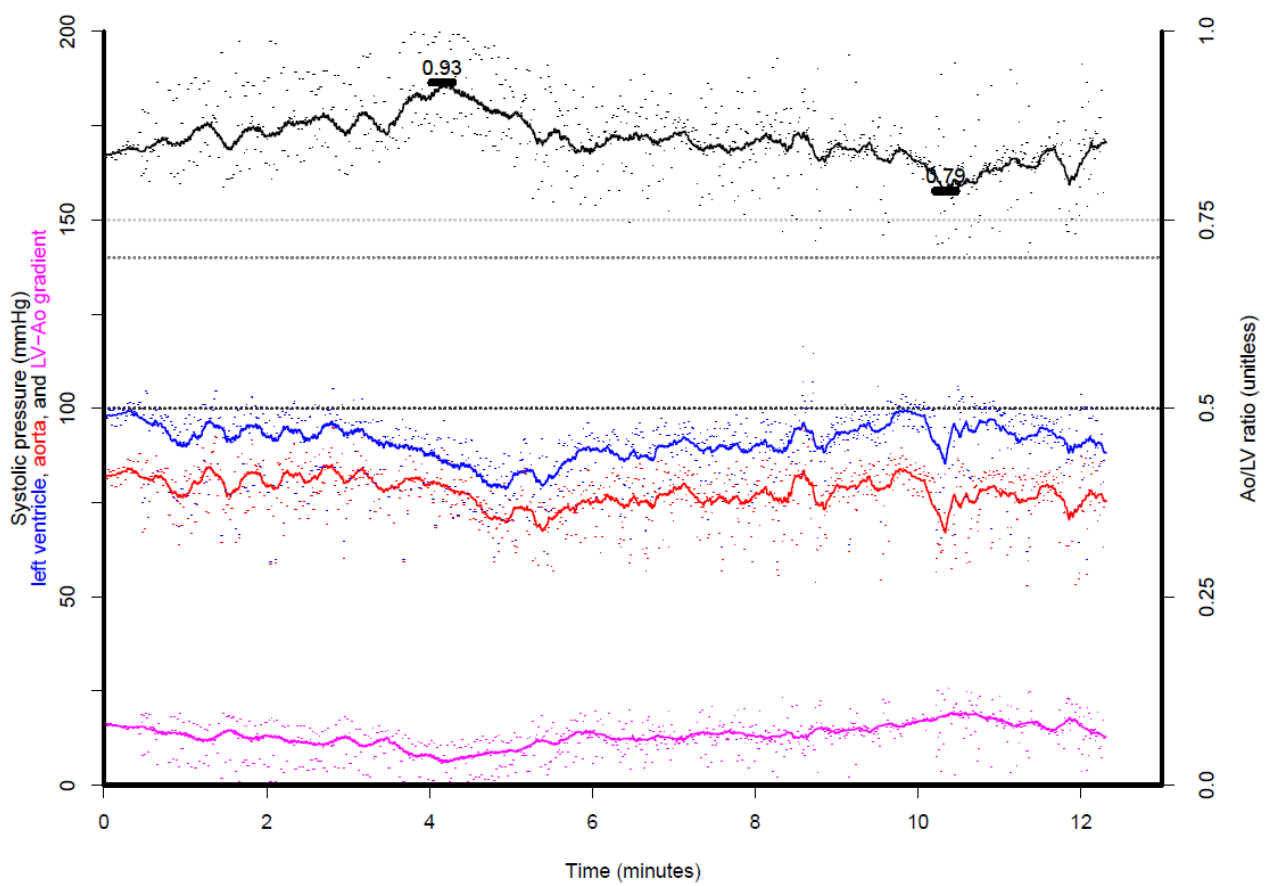
But only one becomes severe during stress!



Ao/LV = 0.95

SAVI = 0.65

(benefit from TAVI?)

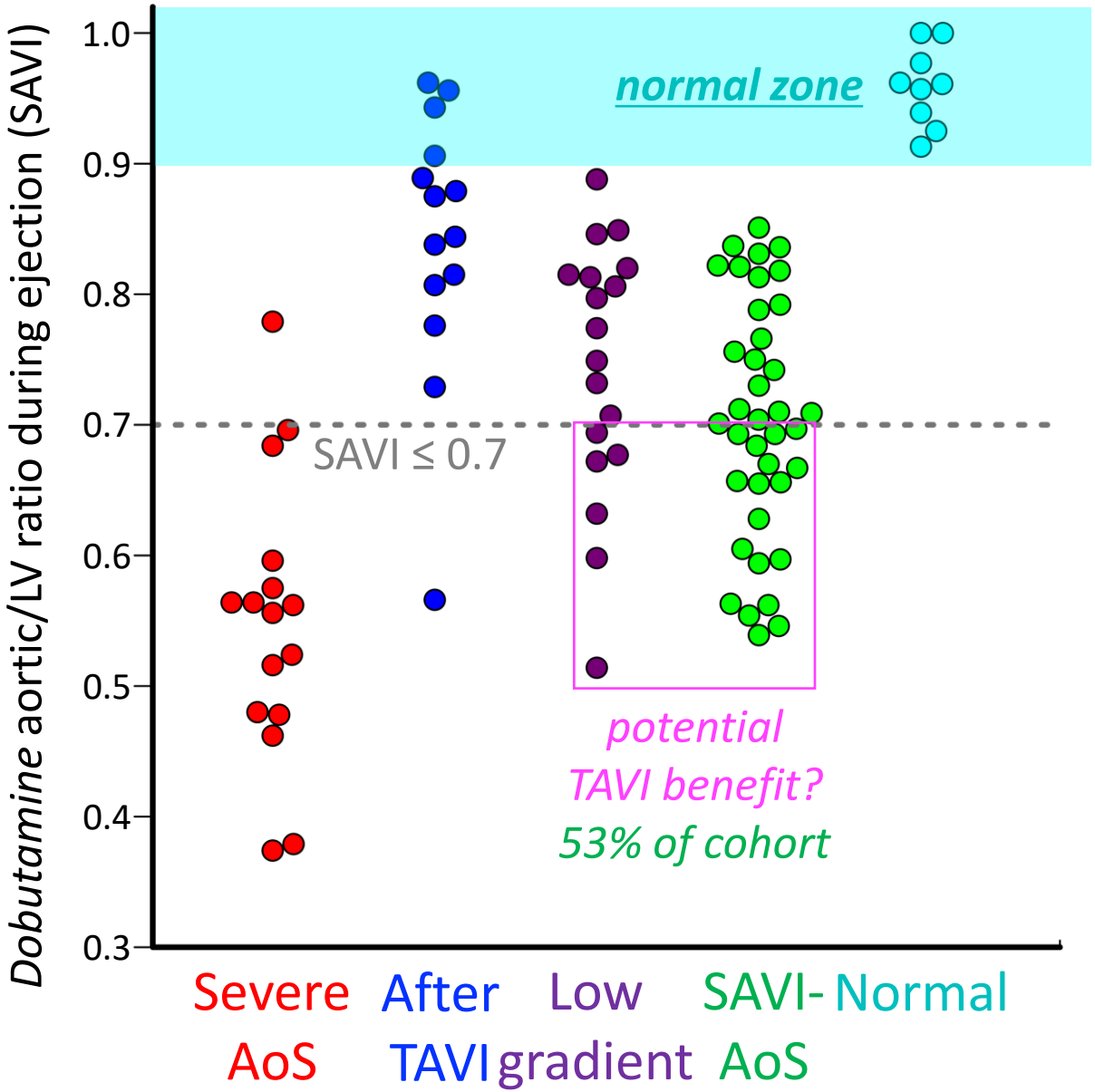


Ao/LV = 0.93

SAVI = 0.79

(does not need TAVI)

Half of moderate = severe with stress

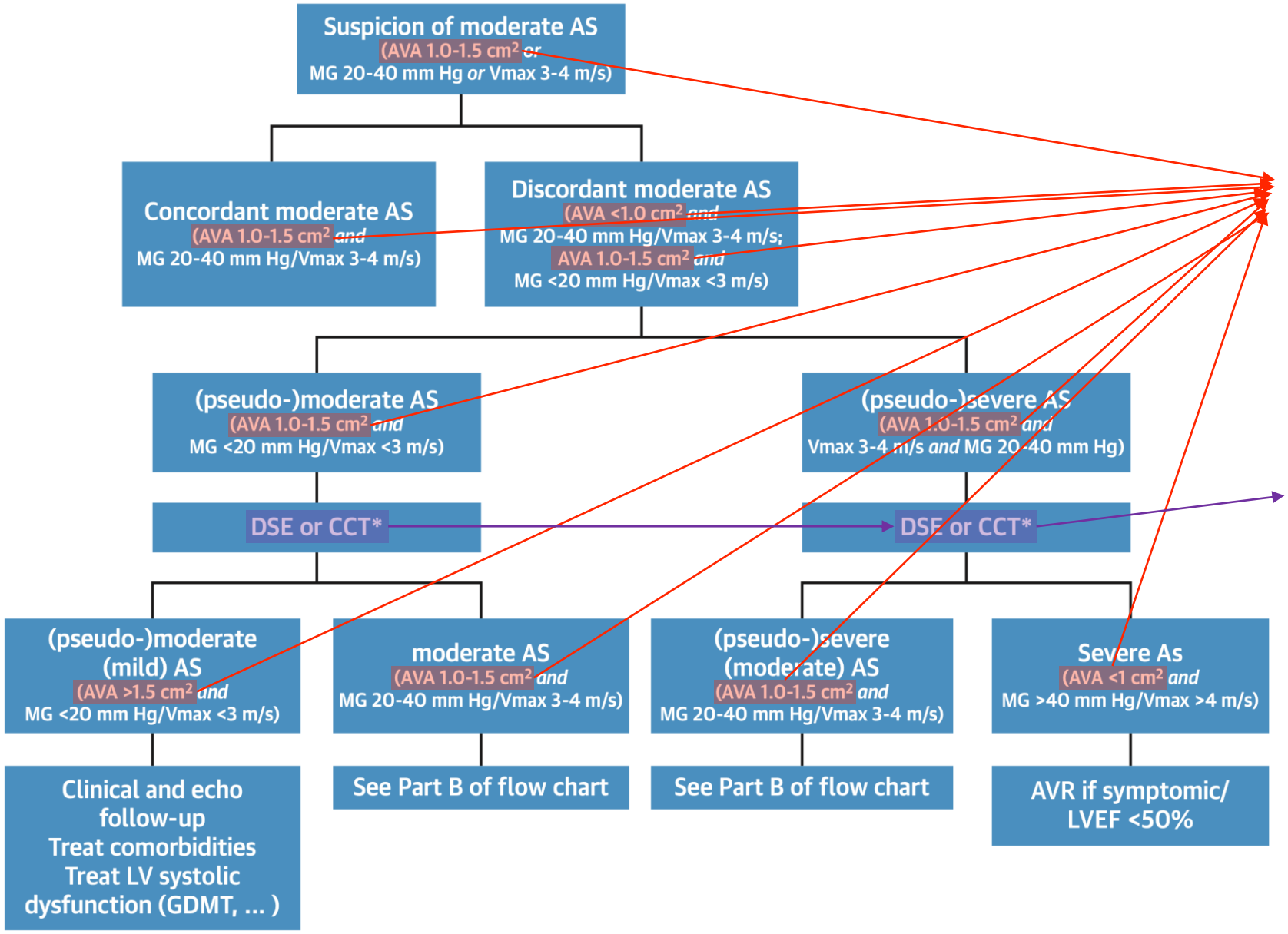


Preliminary, unpublished data courtesy of Dr. Rob Eerdekens, Eindhoven, Netherlands.

Summary

and in conclusion…

Where does *SAVI* fit?



emphasis on AVA

- anatomic (not physiologic)
- changes with stress

DSE = stress test

CCT = anatomic metric (calcium)

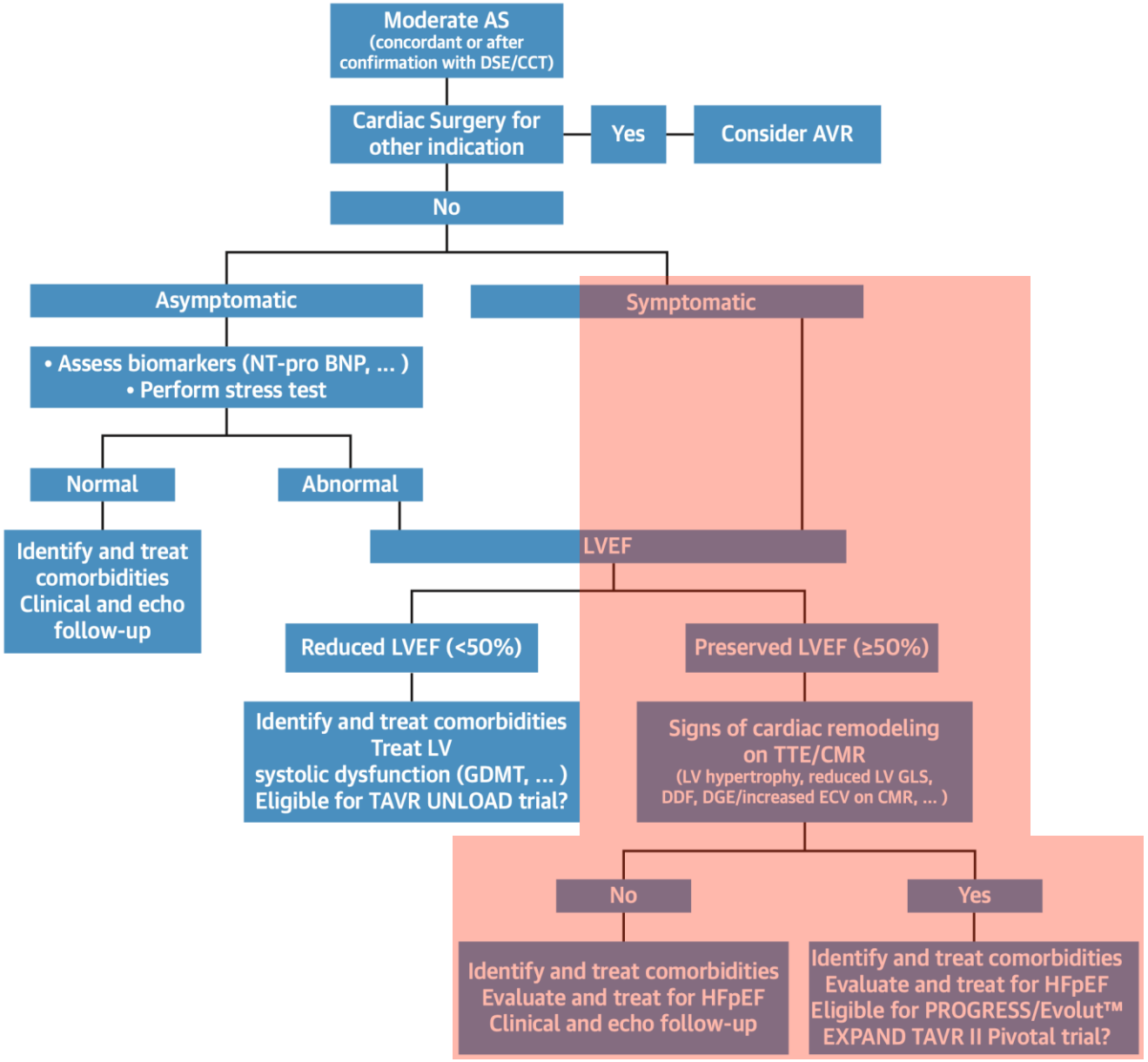
just measure SAVI?!

Stassen J, *JACC Cardiovasc Imaging*. 2023 Jan 14:S1936-878X(22)00741-0. (Central Illustration part A with *annotations*)

Potential *limitations* to SAVI

1. *Invasive* but greater precision.
   - Can echo/CMR enrich 50% further?
2. Maybe *fractional flow is less/not important*.
   - Most of body can increase O_2 extraction.
3. *Dobutamine versus exercise* stress.
   - Might dobutamine overestimate daily life?
4. Chronic injury from AS may happen at rest.
   - We spend most of our lives at rest.
5. Even if we improve symptoms with TAVI, are risks of procedure worth it?
   - PARTNER 3 with 1% CVA and 7% pacemaker.
   - But it also had 0.4% TAVI-related death.

Where does *SAVI-AoS* fit?



- symptomatic
- intact EF

SAVI-AoS
- observational
- mechanistic
- stress testing

PROGRESS and EXPAND TAVR II
- randomized
- outcomes
- rest testing

Stassen J, *JACC Cardiovasc Imaging*. 2023 Jan 14:S1936-878X(22)00741-0. (Central Illustration part B with *annotations*)