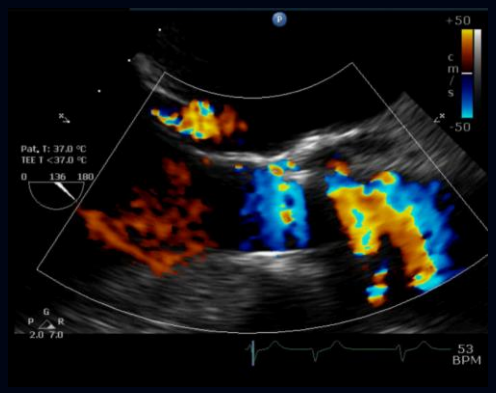

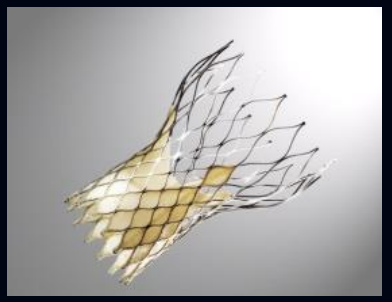

Mild paravalvular regurgitation is not an independent predictor of mortality following TAVI

Philippe Pibarot, DVM, PhD, FACC, FAHA, FASE

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DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC

Université
LAVAL

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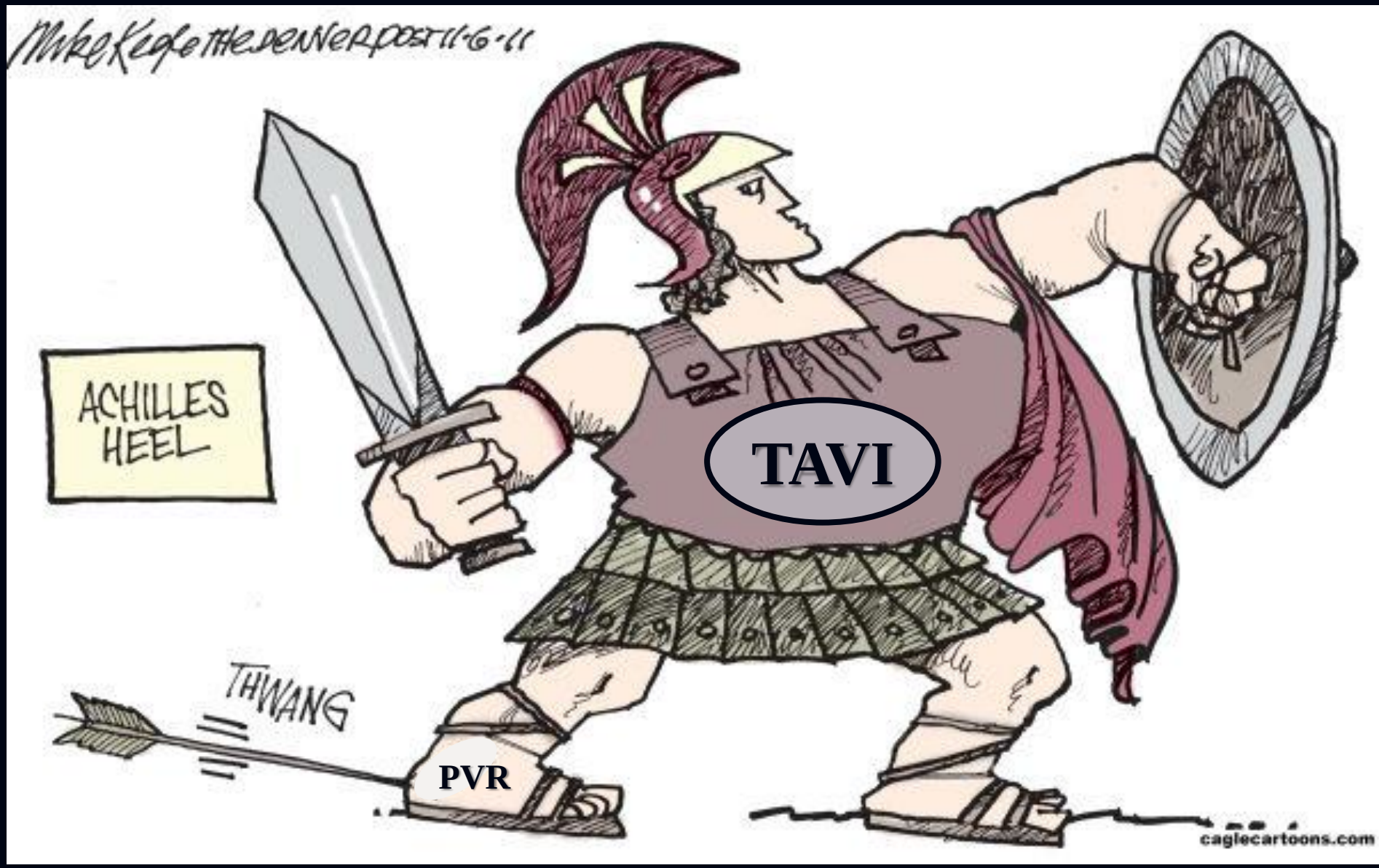
- Heart and Stroke Foundation of Canada

Industry:

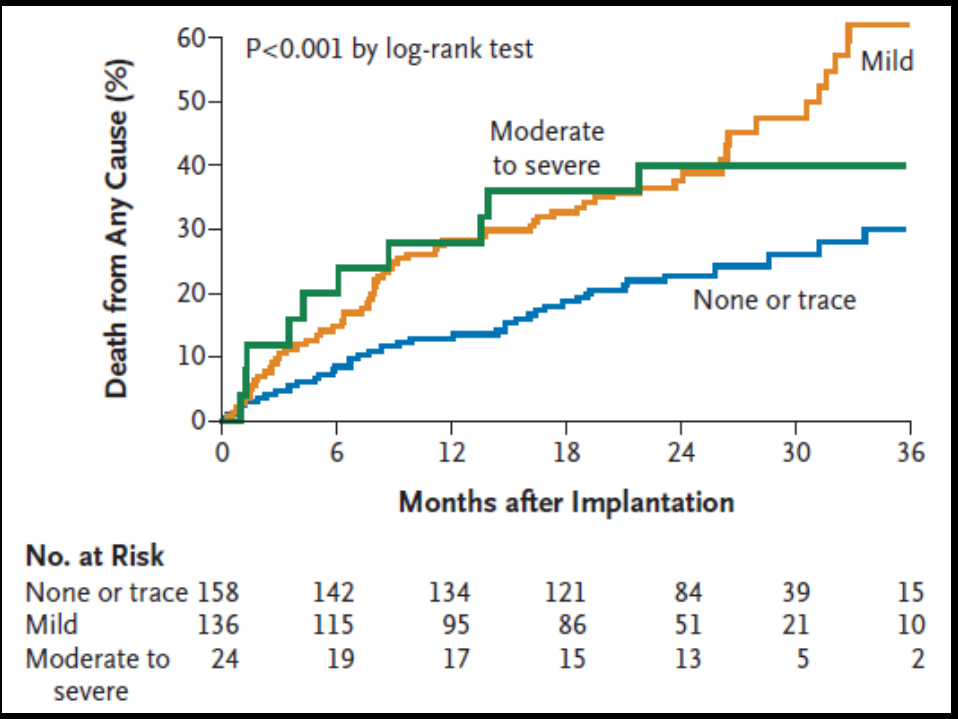
- Edwards Life Science: Research grant
Echo Core Lab – TAVI

- V-Wave Ltd. Research grant
Echo Core Lab Heart failure

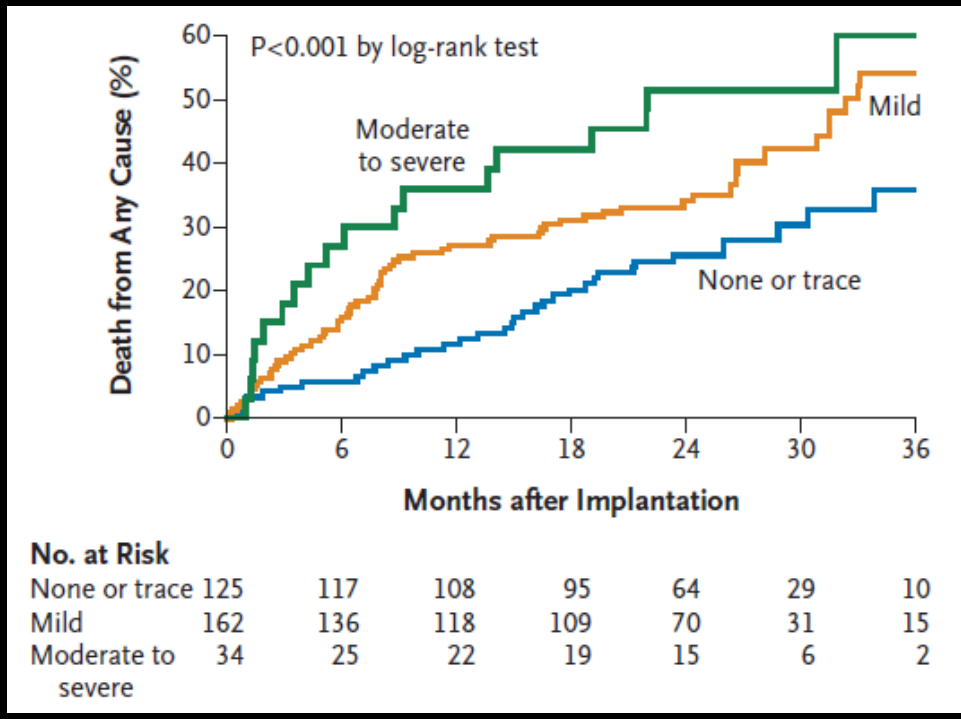

Mike Keefe the DENVER POST 11-6-11
ACHILLES HEEL
TAVI
THWANG
PVR
caglecartoons.com

Impact of Paravalvular Regurgitation on 2-Year Outcomes: PARTNER-I A Trial

Paravalvular Regurgitation



Total (Paravalvular+Central) Regurgitation



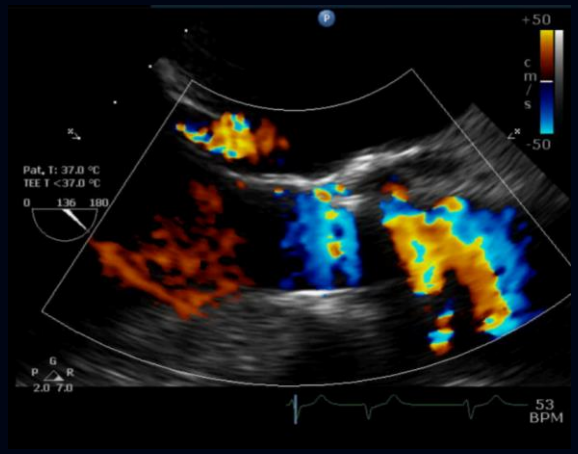
Kodali et al.; NEJM 2012

3 Main Questions:

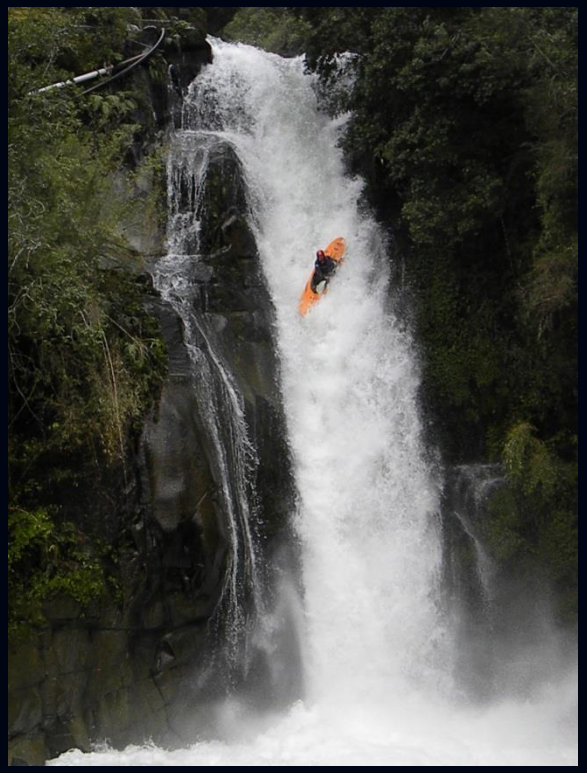
1- Is it really mild PVR?

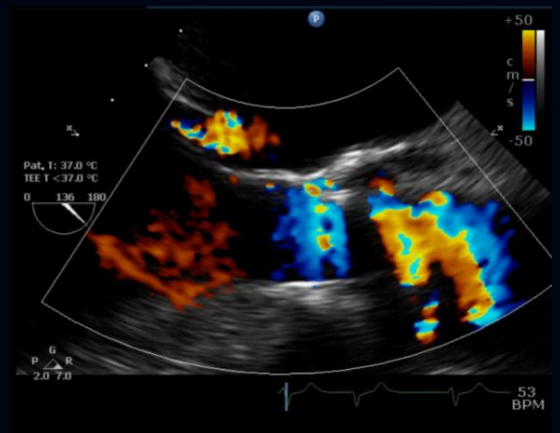
2- Is Mild PVR an actor or a marker?

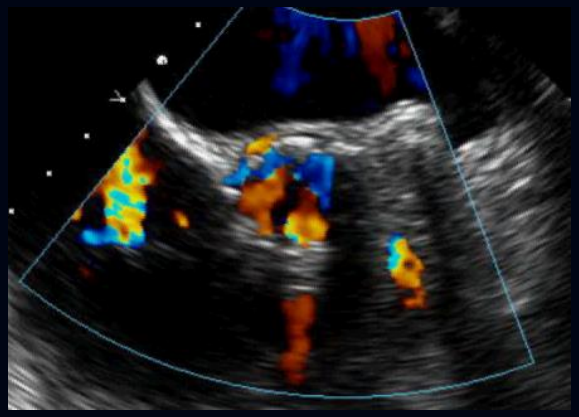
3- Does mild PVR have a significant and independent impact on survival?



Question #1: Is it really mild PVR?







Quantification of Transcatheter Valve Regurgitation

Table 3 Doppler echocardiographic criteria for severity of prosthetic aortic valve regurgitation (central and paravalvular)

	Mild	Moderate	Severe
Valve structure and motion			
Mechanical or bioprosthesis	Usually normal	Usually abnormal†	Usually abnormal†
Doppler parameters (qualitative or semi-quantitative)			
Vena contracta width (mm)*	<3	3–6	>6
Jet width in central jets (% LVOT diameter): colour Doppler*	Narrow (≤25)	Intermediate (26–64)	Large (>65)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): CW Doppler‡	Slow (>500)	Variable (200–500)	Steep (<200)
LV outflow versus RV outflow ratio: PW Doppler (ratio of stroke volumes or time–velocity integrals)	Slightly increased (>1.2)	Intermediate (>1.5)	Greatly increased (>1.8)
Diastolic flow reversal in the ascending aorta: PW Doppler	Absent or brief early diastolic	Intermediate	Prominent holodiastolic (end-diastolic velocity >18 cm/s)
Circumferential extent of paravalvular regurgitation (%)¶	<10	10–20	>20
Doppler parameters (quantitative)			
Regurgitant volume (ml/beat)	<30	30–59**	>60
Regurgitant fraction (%)	<30	30–50	>50
Indirect signs			
LV size§	Normal	Normal/mildly dilated	Dilated

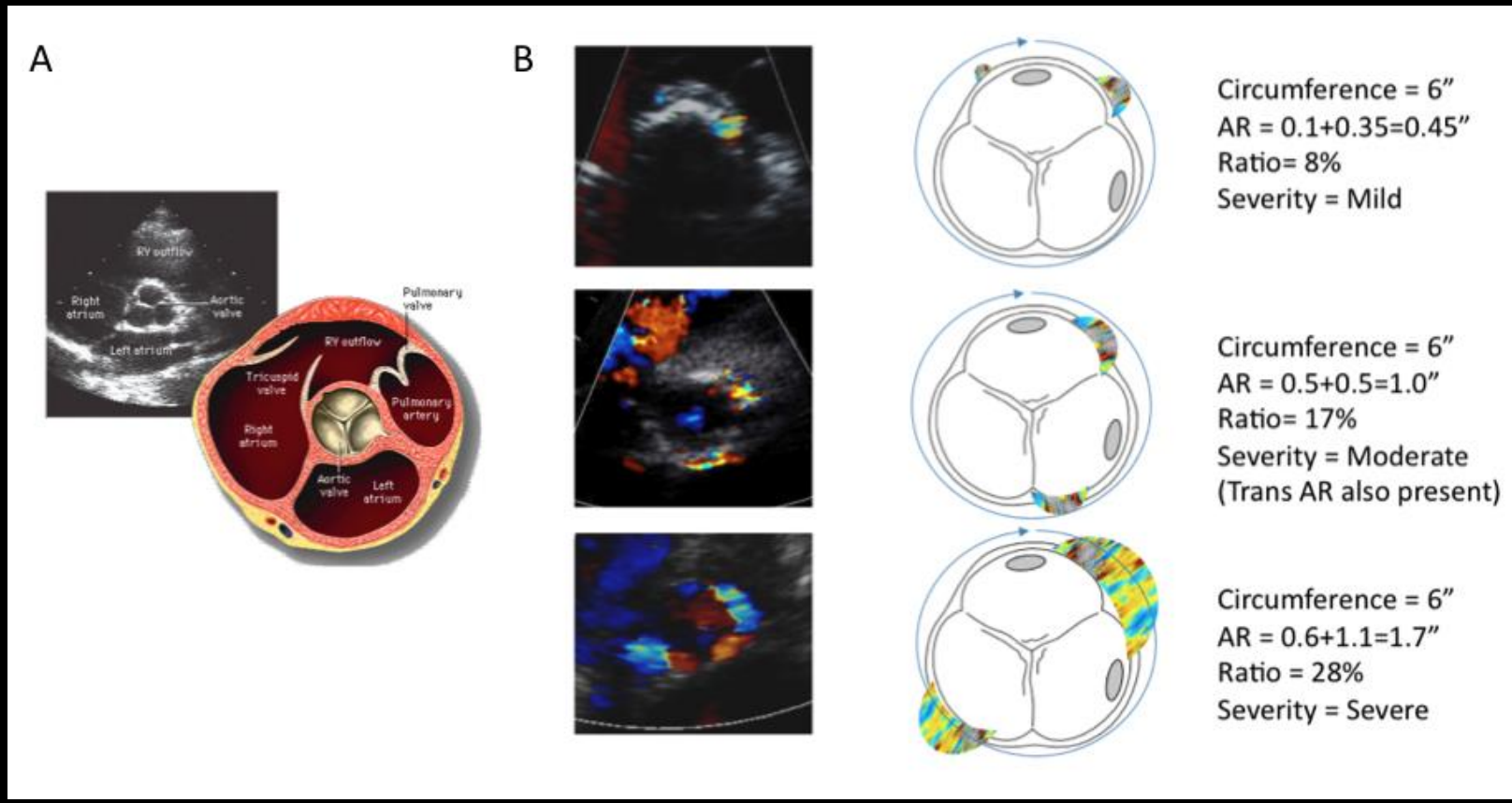
Zoghbi et al. J Am Soc Echocardiogr, 22:975-1014, 2009
Pibarot & Dumesnil, Heart, 98:69-78, 2012

European Heart Journal (2012) **33**, 2403–2418
doi:10.1093/eurheartj/ehs255

Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document†

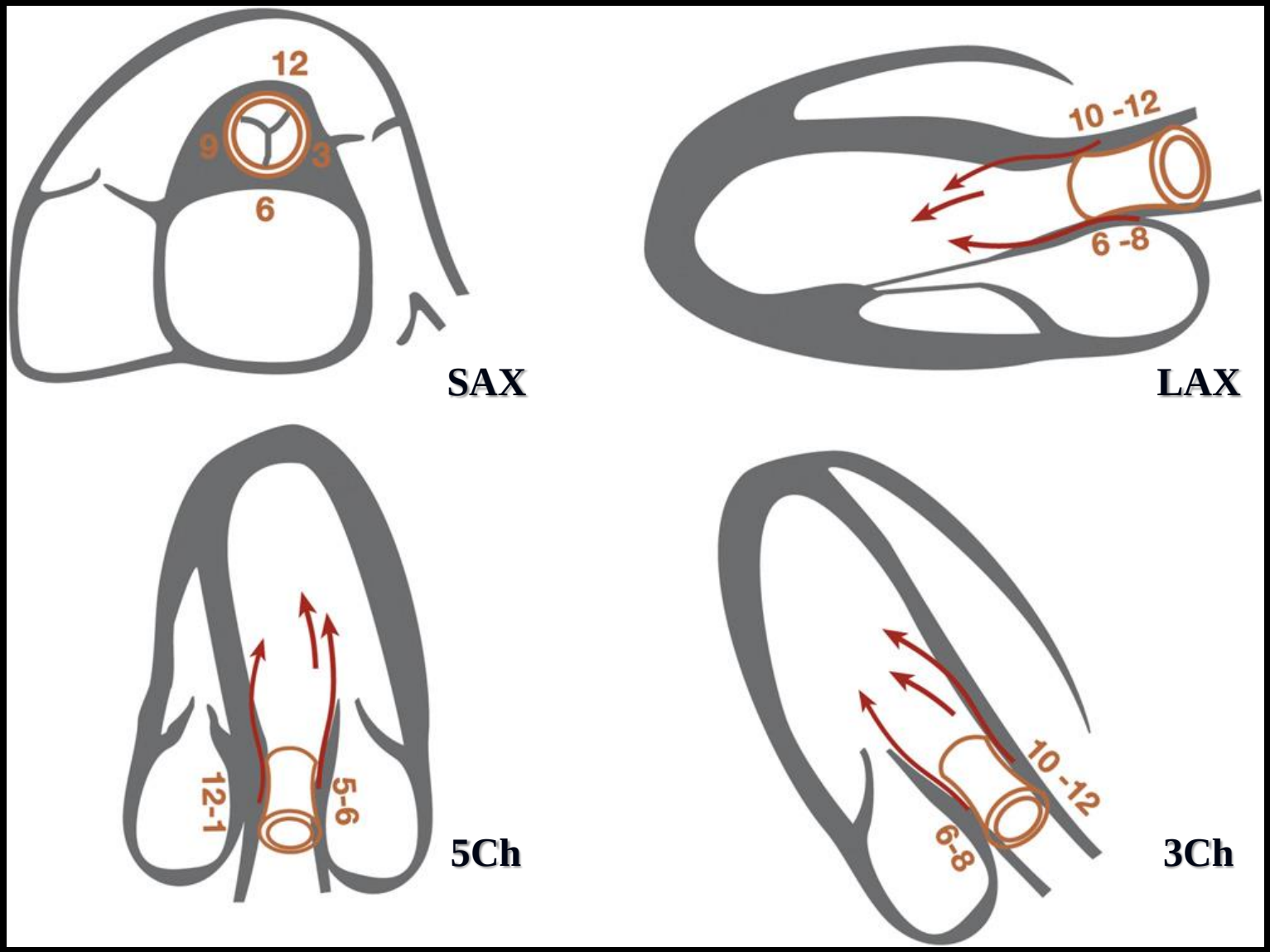
	Prosthetic aortic valve regurgitation		
	Mild	**Moderate**	**Severe**
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)[h]	< 10%	10–29%	≥ 30%
Quantitative parameters[c]			
Regurgitant volume (mL/beat)	< 30 mL	30–59 mL	≥ 60 mL
Regurgitant fraction (%)	< 30%	30–49%	≥ 50%
EROA (cm^2)	0.10 cm^2	0.10–0.29 cm^2	≥ 0.30 cm^2

Grading Severity of Paravalvular Regurgitation



Bloomfield; JACC Img; 5:441–55, 2012

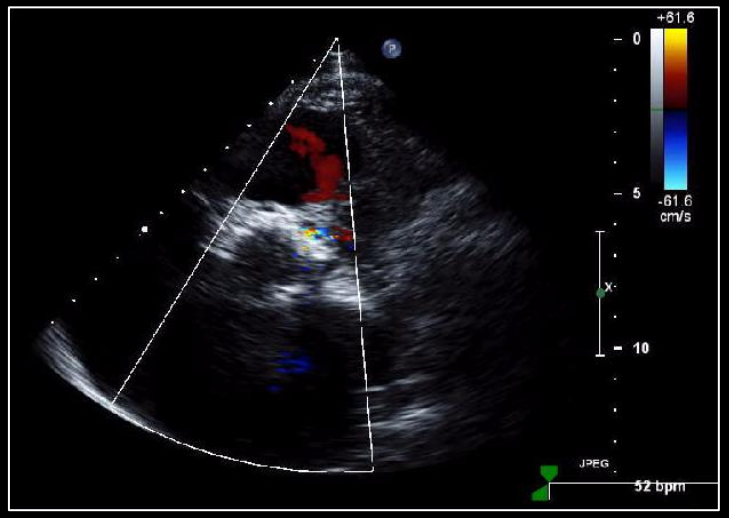
Multi-window Imaging is Key!



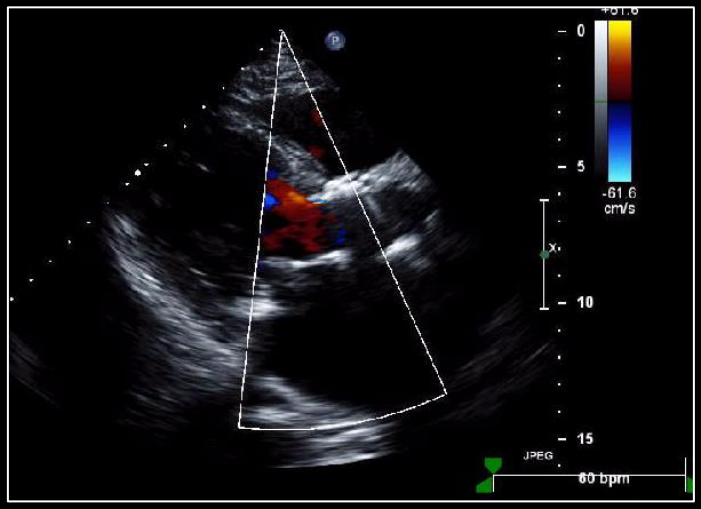
Gonçalves et al. J Am Soc Echocardiogr 2012;25:47-55

Multi-window Imaging is Key!

SAX View

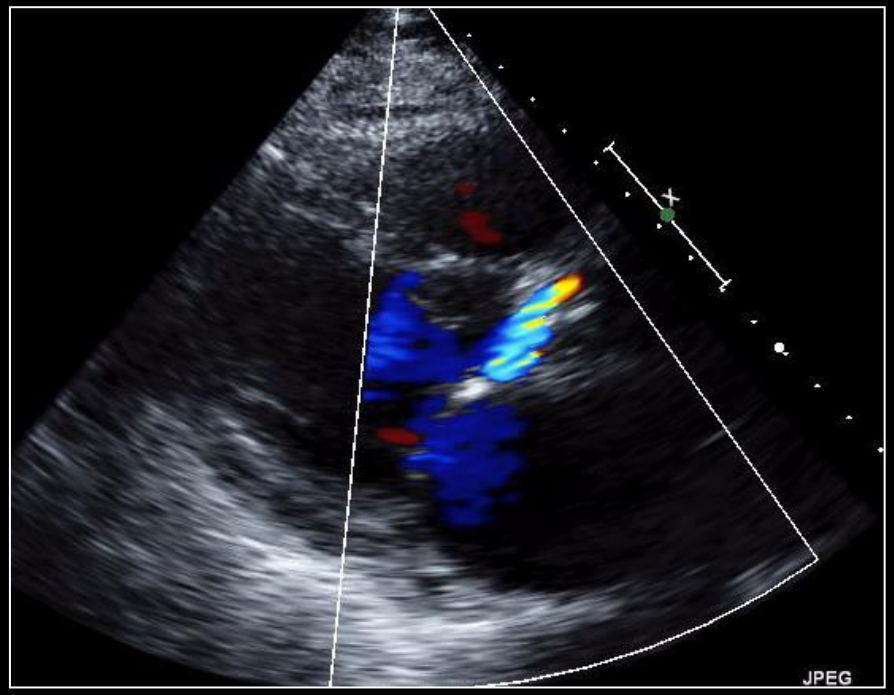


LAX View

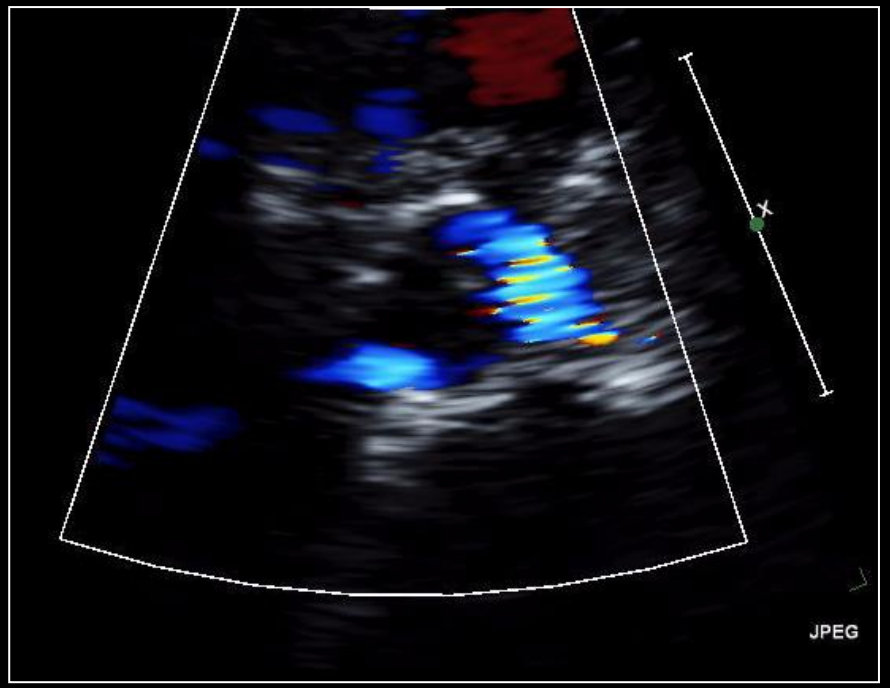


Overestimation of Circumferential Extent with Eccentric Jets

LAX View

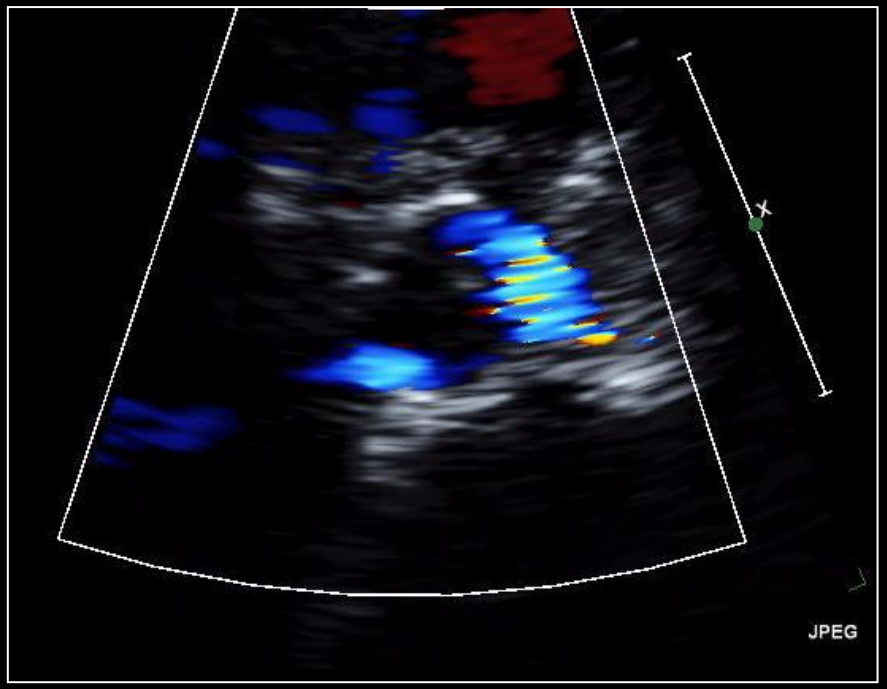


SAX View

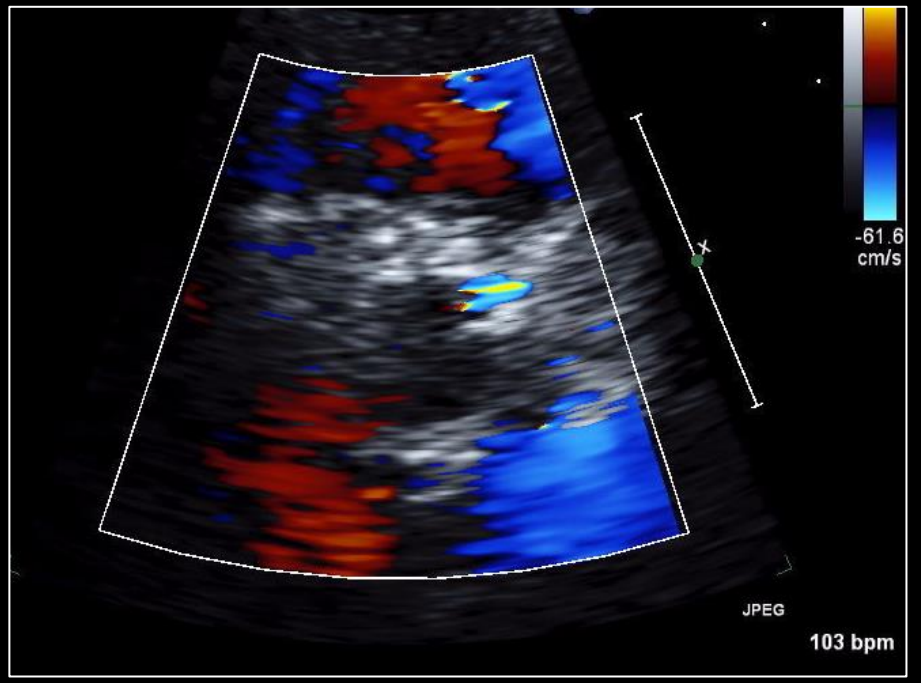


Overestimation of Circumferential Extent with Eccentric Jets

SAX View



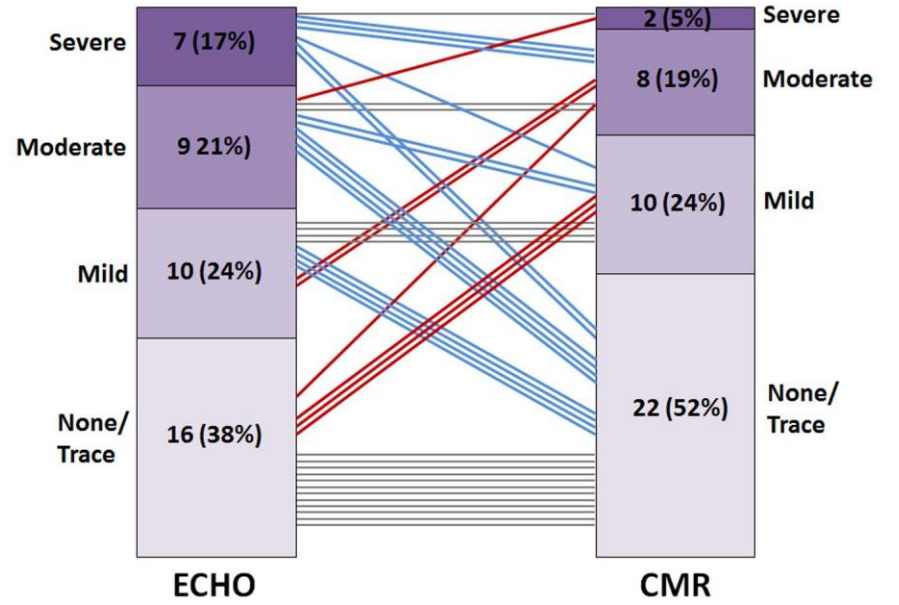
SAX View



Circumferencial Extent of PVR versus CMR to Assess AR Following TAVR

POST

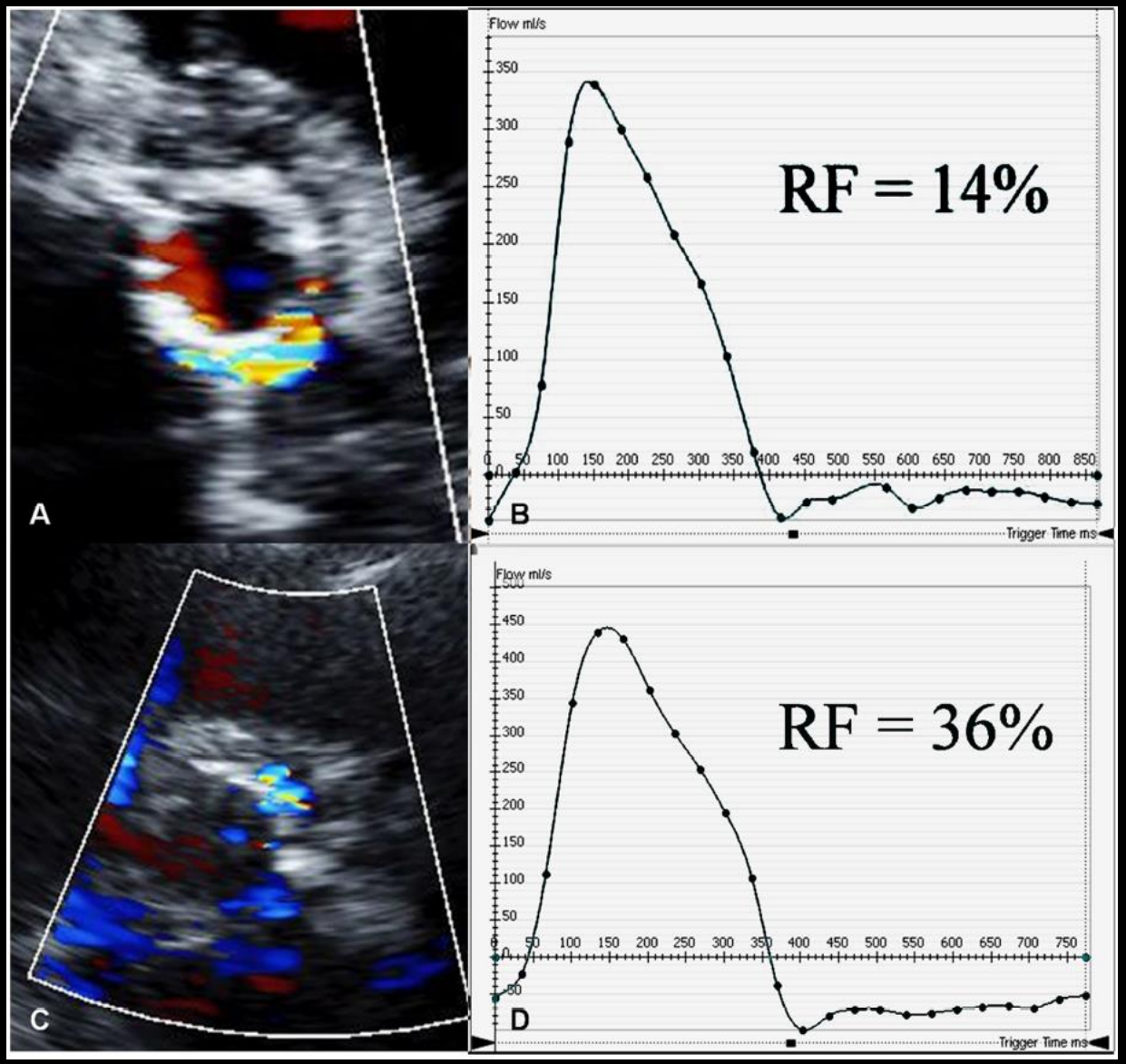
A



B

ECHO / CMR	None/ Trace	Mild	Moderate	Severe	Total
None/ Trace	12 (75)	4 (40)	4 (44)	2 (29)	22
Mild	3 (19)	4 (40)	2 (22)	1 (14)	10
Moderate	1 (6)	2 (20)	2 (22)	3 (43)	8
Severe	-	-	1 (11)	1 (14)	2
Total	16	10	9	7	19/42 (45)

Ribeiro HB, et al. Heart, 2014

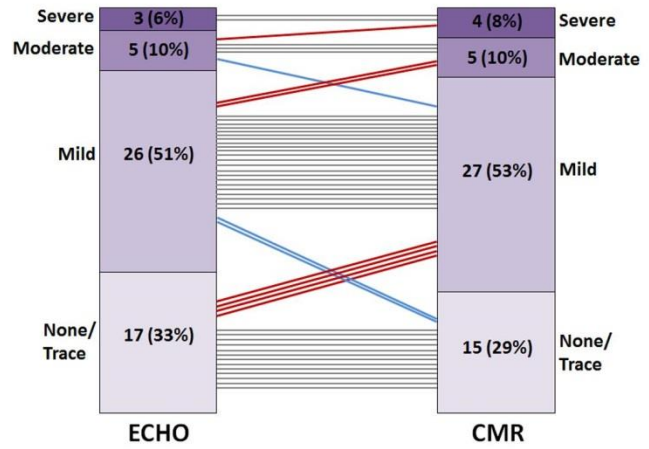


Ribeiro HB, et al. Heart, 2014

Multi-View/Multi Parametric TTE versus CMR to Assess AR Following TAVR

PRE

A

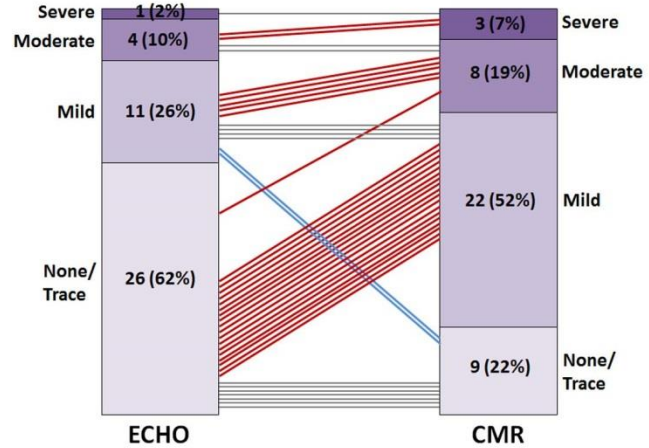


B

ECHO / CMR	None/ Trace	Mild	Moderate	Severe	Total
None/ Trace	13 (76)	2 (8)	-	-	15
Mild	4 (24)	22 (84)	1 (20)	-	27
Moderate	-	2 (8)	3 (60)	-	5
Severe	-	-	1 (20)	2 (100)	3
Total	17	26	5	2	40/50 (80)

POST

C

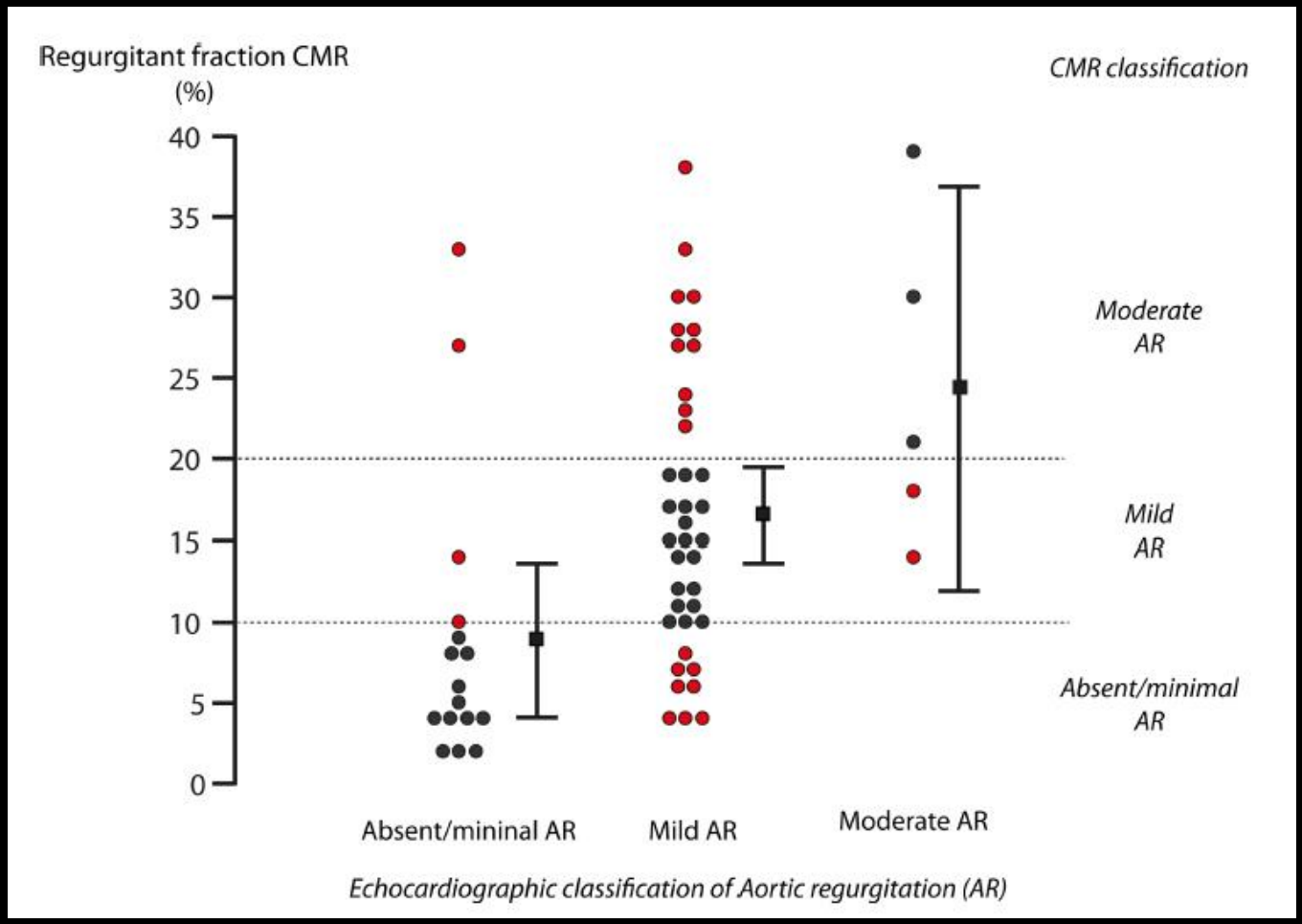


D

ECHO / CMR	None/ Trace	Mild	Moderate	Severe	Total
None/ Trace	7 (27)	2 (18)	-	-	9
Mild	18 (69)	4 (36)	-	-	22
Moderate	1 (4)	5 (46)	2 (50)	-	8
Severe	-	-	2 (50)	1 (100)	3
Total	26	11	4	1	14/42 (33)

Ribeiro HB, et al. Heart, 2014

Echo versus CMR to Assess AR Following TAVR



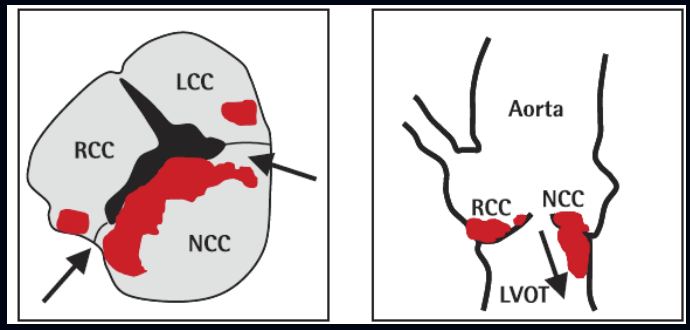
Orwat et al. Heart 2014

Question #2: Is Mild PVR Marker or an Actor?

Gilbreath C. Opt. Eng. 51(2) March 2012

Predictors of Paravalvular Regurgitation following TAVI

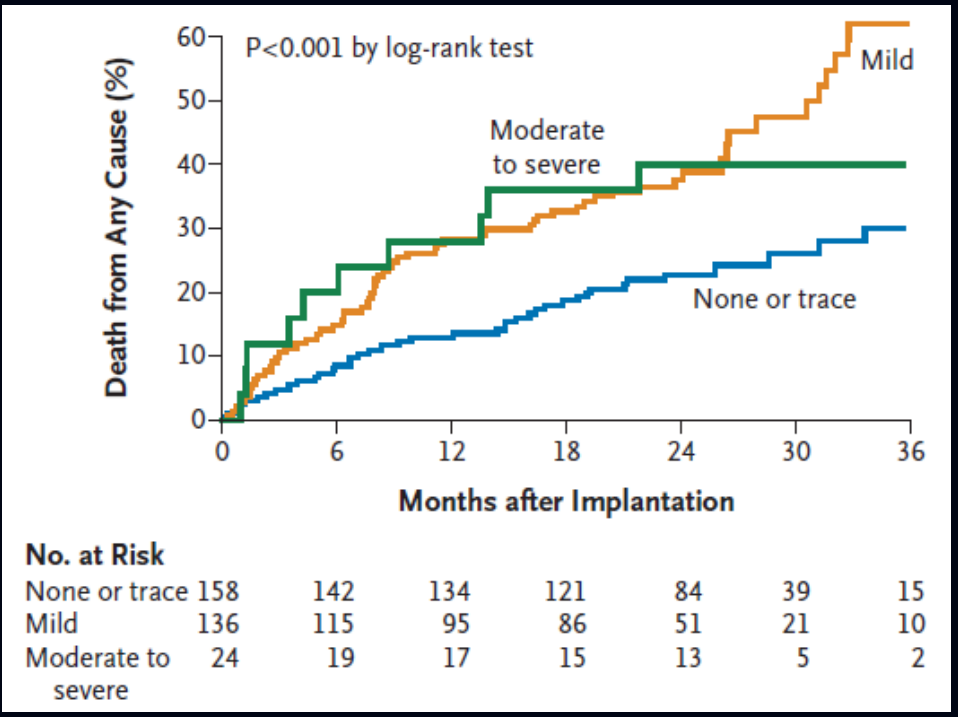
- **Male gender**
- **NYHA Class IV**
- **Atrial fibrillation**
- **AR at baseline**
- **MR at baseline**



- **Severity and distribution of valve calcification**
- **Larger aortic annulus**
- **Smaller cover index**
- **Inadequate valve positioning**
- **Self expending valve**

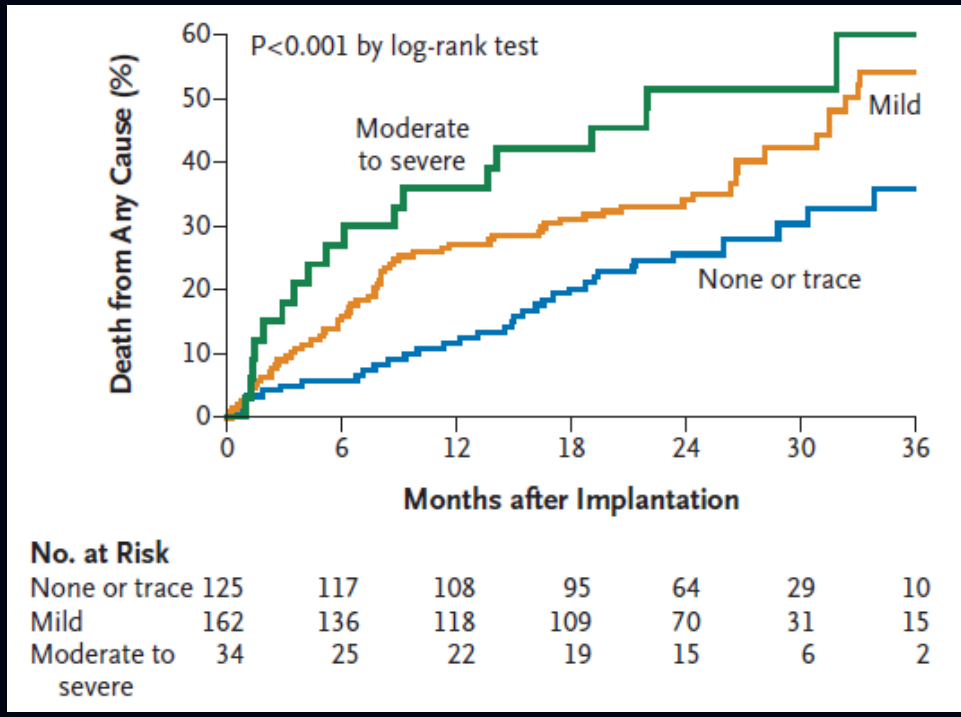
Sinning et al. JACC, 2012
Haensig M, EJCTS, 2012
Ewe et al. Am J Cardiol 2011
Ubehaum et al. JACC, 2012
Sinning et al. JACC 2013

Are patients with mild PVR the same as those with none/trace PVR?



No. at Risk

None or trace	158	142	134	121	84	39	15
Mild	136	115	95	86	51	21	10
Moderate to severe	24	19	17	15	13	5	2



No. at Risk

None or trace	125	117	108	95	64	29	10
Mild	162	136	118	109	70	31	15
Moderate to severe	34	25	22	19	15	6	2

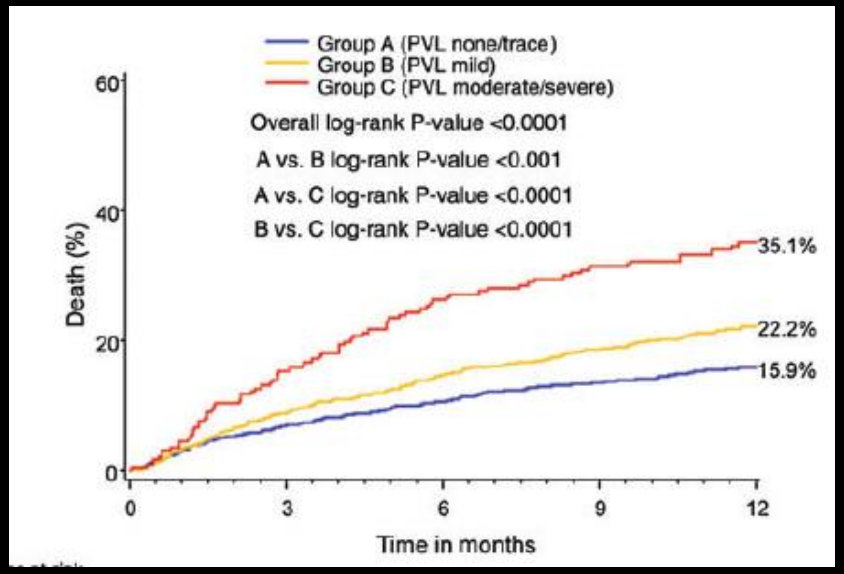
Baseline Characteristics of TAVR Patients with Paravalvular Regurgitation in the PARTNER Trial

Table 2 Baseline echocardiographic characteristics of patients by severity of paravalvular regurgitation

Baseline parameters	Severity of paravalvular regurgitation			*P*-value (all groups)[a]
	(a) None/trace (*n* = 1288)	(b) Mild (*n* = 925)	(c) Moderate/severe (*n* = 221)	
LVEDD (cm)	4.41 ± 0.74	4.60 ± 0.77	4.68 ± 0.74	<0.0001
LVESD (cm)	3.20 ± 0.92	3.35 ± 0.94	3.51 ± 0.92	<0.0001
Stroke volume (cc)	64.2 ± 19.6	68.5 ± 21.4	67.6 ± 25.0	0.01
Cardiac output	4.38 ± 1.41	4.62 ± 1.54	4.57 ± 1.59	0.08
LV EF (%)	53.7 ± 12.4	51.4 ± 13.2	50.2 ± 13.9	<0.0001
LV mass (g)	238.7 ± 74.1	260.3 ± 78.3	267.2 ± 73.6	<0.0001
LVOT diameter (cm)	1.98 ± 0.18	2.04 ± 0.18	2.06 ± 0.19	<0.0001
Annulus diameter (cm)	21.27 ± 1.86	21.64 ± 1.83	21.91 ± 1.88	<0.001
EOA (cm^2)	0.65 ± 0.19	0.66 ± 0.19	0.65 ± 0.19	0.25
Aortic regurgitation				
None/trace	44.7%	42.8%	34.2%	0.02
Mild	46.5%	46.8%	41.2%	0.36
Moderate/severe	8.6%	10.3%	24.4%	<0.0001
Mitral regurgitation				
None/trace	29.9%	25.8%	17.8%	0.001
Mild	50.7%	51.7%	46.1%	0.37
Moderate/severe	19.5%	22.5%	36.1%	<0.0001

Kodali et al. Eur Heart J 2014

Impact of PVR on Mortality in the PARTNER Trial



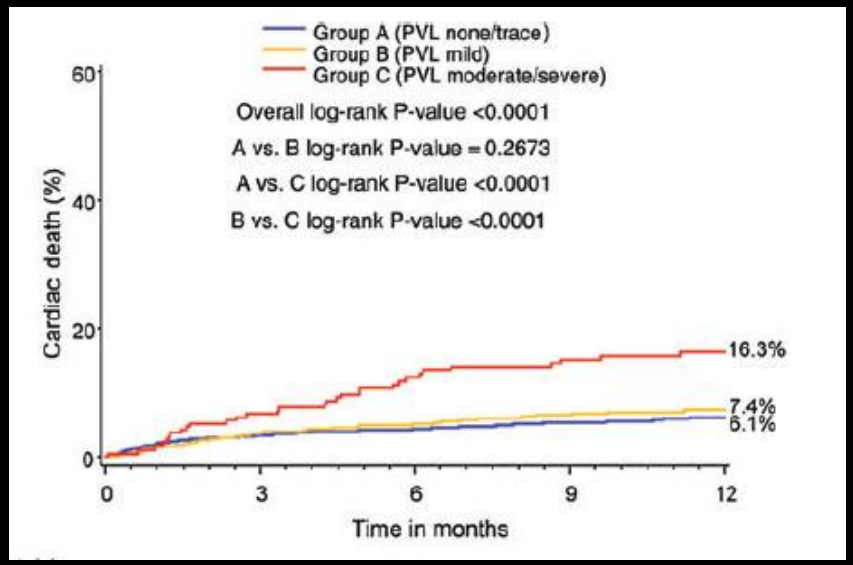


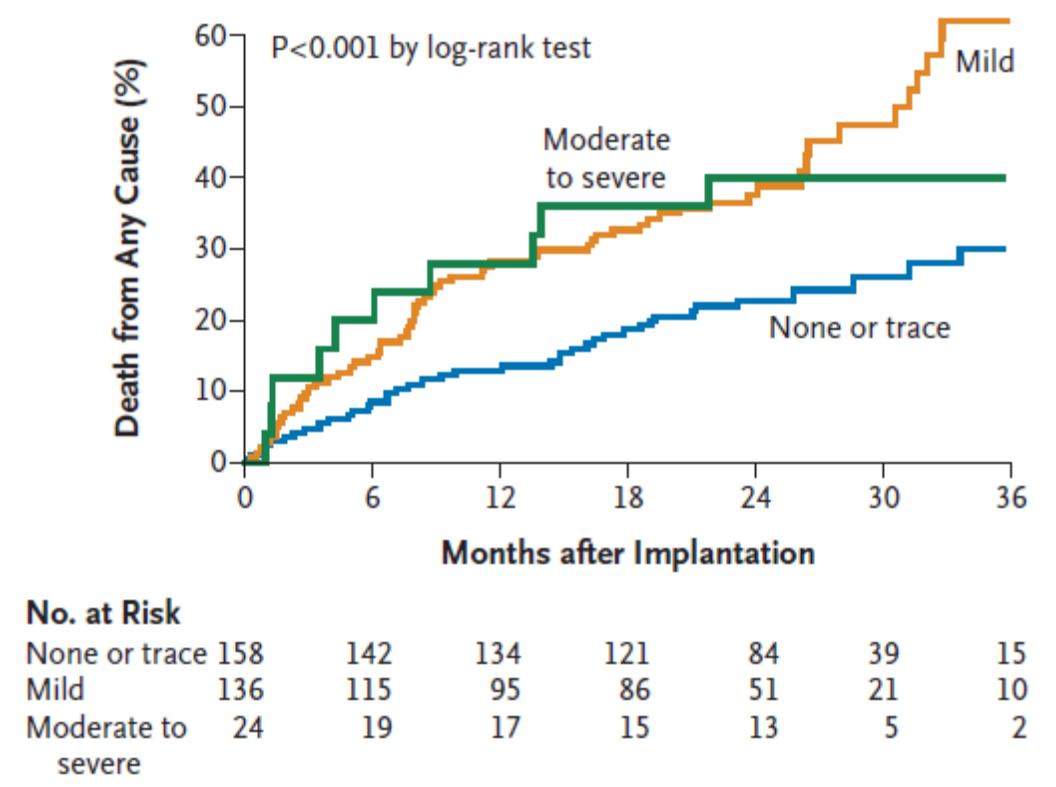
Table 4 Multivariable predictors of all-cause 1-year mortality

Multivariable analysis: baseline and procedural predictors of 1-year mortality

Variable	Hazard ratio	95% Confidence interval	*P*-value[a]
Major arrhythmia	1.41	1.14–1.75	0.002
TF vs. TA	0.73	0.59–0.91	0.005
AV annulus diameter (per 1 mm increase)	1.07	1.03–1.11	0.001
BMI (per 1 kg/m^2 increase)	0.95	0.93–0.97	<0.0001
Total distance walked (per 10 m increase)	0.97	0.96–0.98	<0.0001
AV mean gradient (per 1 mmHg)	0.98	0.97–0.99	<0.0001
Paravalvular regurgitation			
None/trace	Referent	–	–
Mild	1.35	1.07–1.72	0.013
Moderate/severe	2.20	1.60–3.03	<0.0001
Renal disease (CR ≥2)	1.35	1.04–1.74	0.023

Kodali et al. Eur Heart J 2014

Question #3: Does Mild PVR have a signifiant impact on survival?

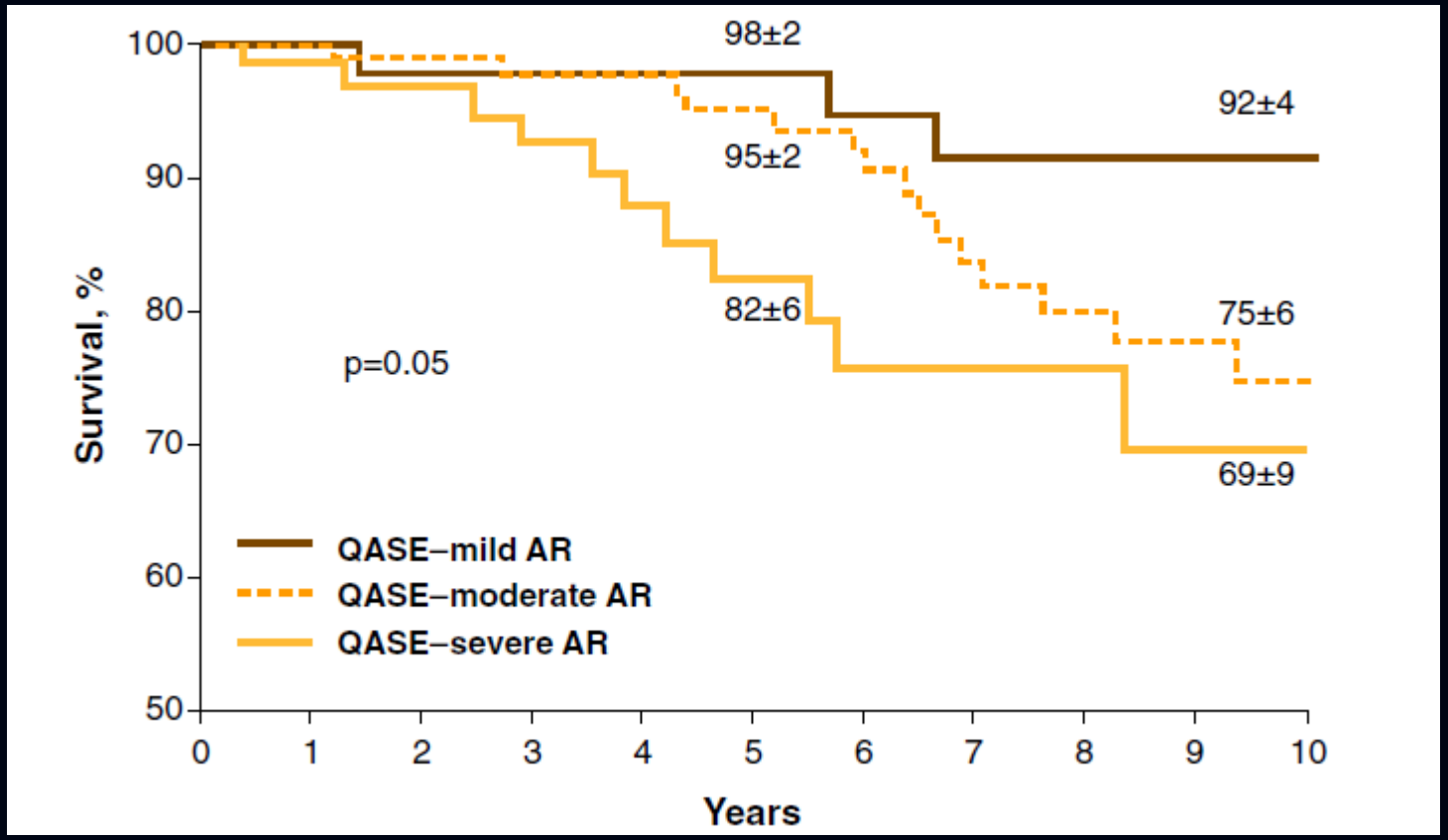


No. at Risk

None or trace	158	142	134	121	84	39	15
Mild	136	115	95	86	51	21	10
Moderate to severe	24	19	17	15	13	5	2

Kodali et al.; NEJM 2012

Survival Under Conservative Management After Diagnosis of Native AR



Detaint D et al. J Am Coll Cardiol Img 2008;1:1–11

Mild PVR post-SAVR

Natural history of early aortic paraprosthetic regurgitation: A five-year follow-up

Loukianos S. Rallidis, MD, Ioannis E. Moyssakis, MD, Ignatios Ikonomidis, MD, and Petros Nihoyannopoulos, MD, FACC, FESC *London, United Kingdom*

Objectives To assess the incidence and natural course of paravalvular leaks detected early after aortic valve replacement.

Background Although the use of echocardiography has simplified the postoperative assessment of patients with aortic valve replacement, there are no data regarding the natural history of early detected paravalvular aortic leaks.

Methods Eighty-four consecutive patients with aortic valve replacement were prospectively followed clinically every 6 months and by echocardiography early (11 ± 7 days), at midterm (27 ± 3 months), and late (63 ± 4 months) after aortic valve replacement. The competence of artificial valves was assessed by Doppler color flow mapping.

Results Paraprosthetic leaks were detected in 40 (47.6%) aortic prostheses during the early study; the majority (90%) were small. All leaks remained unchanged during the follow-up period. Left ventricular dimensions and function did not differ between patients with or without paravalvular leak during the follow-up. Left ventricular fractional shortening, however, increased during the intermediate study in both subgroups, indicating improved left ventricular function overall. Three patients had severe paravalvular regurgitation suddenly develop from late infective endocarditis, and 1 patient had a degenerative tissue valve failure 4 years after implantation.

Conclusions Paraprosthetic aortic leaks detected early after surgery, in the absence of valve infection, are common, are usually small, and have a benign course. However, the development of new, usually severe, regurgitation should raise the suspicion of prosthetic valve endocarditis or bioprosthetic valve failure. (Am Heart J 1999;138:351-7.)

Mild PVR post-SAVR

Outcome of Mild Periprosthetic Regurgitation Detected by Intraoperative Transesophageal Echocardiography

Daniel J. O'Rourke, MD, MS, FACC,* Robert T. Palac, MD, MS, FACC,†
David J. Malenka, MD, FACC,† Charles A. S. Marrin, MB, BS,‡ Brenda E. Arbuckle, BA,†
Jonathan F. Plehn, MD, FACC§

White River Junction, Vermont; Lebanon, New Hampshire; and Roslyn, New York

OBJECTIVES The goal of this study was to determine the outcome of trivial or mild periprosthetic regurgitation (PPR) identified by intraoperative transesophageal echocardiography (TEE).

BACKGROUND The clinical significance, natural history and correlates of trivial or mild PPR detected early after surgery are unknown.

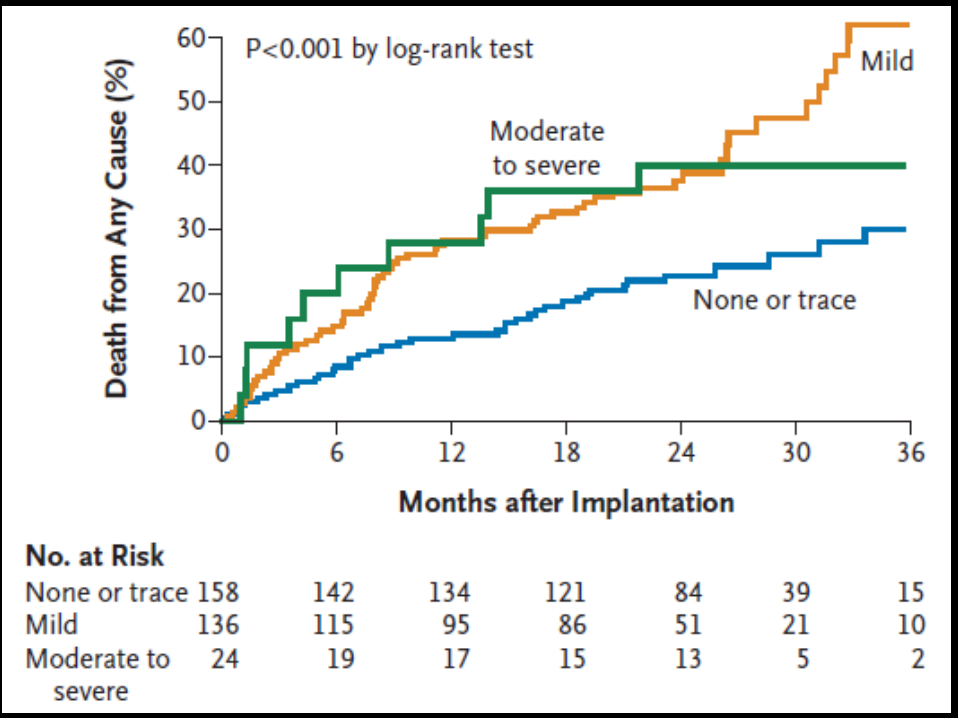
METHODS Between 1992 and 1997, 608 consecutive patients underwent isolated aortic valve replacement or mitral valve replacement at Dartmouth-Hitchcock Medical Center. Of these, 113 patients (18.3%) were found to have trivial or mild PPR at surgery by TEE. Follow-up transthoracic echocardiograms (early TTEs) were obtained within six weeks of surgery in 99.0% of patients and late TTEs (mean 2.1 years) in 54.3%. Clinical, intraoperative and outcome variables associated with PPR were identified using *t* test, chi-square and logistic regression analyses.

RESULTS By univariate analysis, compared with patients without PPR, patients with PPR were older, of smaller body surface area (BSA), had degenerative valve disease more often and were more likely to receive a bioprosthetic valve. By multivariate analysis, smaller BSA and the use of a bioprosthesis were the strongest predictors of PPR ($p < 0.01$). At early TTE, PPR was not observed ($n = 56$) or remained unchanged ($n = 44$) in all patients. At late TTE, four patients were found to have progression of their PPR. All four patients had bioprosthetic valves. Two of these patients had endocarditis, and one had primary valvular degeneration. The fourth patient had progressive PPR.

CONCLUSIONS Trivial or mild PPR is a frequent finding on intraoperative TEE. Smaller body size and the use of a bioprosthetic valve are significantly associated with PPR. The clinical significance and natural history of PPR is benign in most cases. (J Am Coll Cardiol 2001;38:163–6)

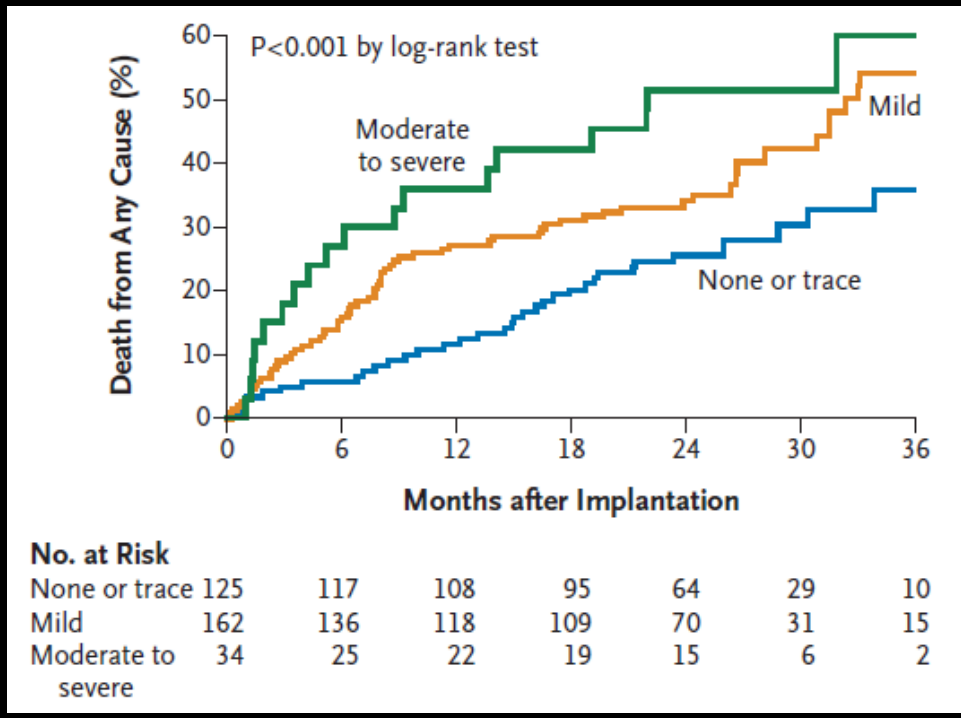
Impact of Paravalvular Regurgitation on 2-Year Outcomes: PARTNER-I A Trial

Paravalvular Regurgitation



No. at Risk							
None or trace	158	142	134	121	84	39	15
Mild	136	115	95	86	51	21	10
Moderate to severe	24	19	17	15	13	5	2

Total (Paravalvular+Central) Regurgitation

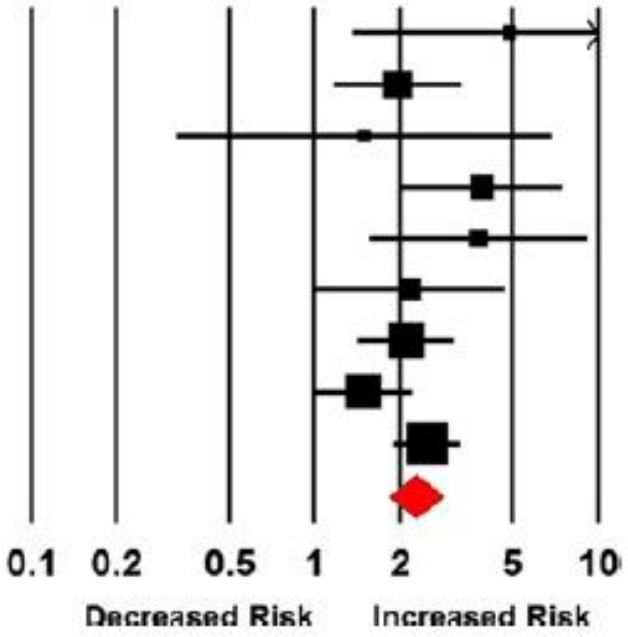


No. at Risk							
None or trace	125	117	108	95	64	29	10
Mild	162	136	118	109	70	31	15
Moderate to severe	34	25	22	19	15	6	2

Kodali et al.; NEJM 2012

Impact of Moderate-Severe AR on Mortality after TAVI: A Meta-analysis

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Lemos*	4.900	1.367	17.570	2.439	0.015
Hayashida	1.970	1.187	3.271	2.621	0.009
Amabile	1.500	0.329	6.829	0.524	0.600
Sinning	3.890	2.020	7.491	4.063	0.000
Tamburino	3.785	1.572	9.112	2.969	0.003
Fraccaro	2.190	1.023	4.686	2.020	0.043
Kodali	2.110	1.433	3.107	3.783	0.000
Moat	1.490	1.002	2.215	1.971	0.049
Gilard	2.490	1.909	3.248	6.728	0.000
All (N=4791)	2.273	1.840	2.808	7.609	0.000



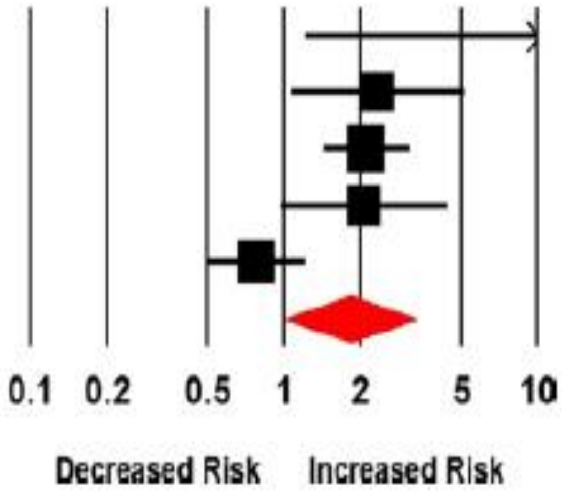
Athapan et al. JACC 2013

Impact of Mild AR on Mortality after TAVI: A Meta-analysis

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Lemos	10.080	1.229	82.673	2.152	0.031
Sinning	2.342	1.066	5.145	2.119	0.034
Kodali	2.110	1.433	3.107	3.782	0.000
Fraccaro	2.064	0.968	4.400	1.876	0.061
Tamburino	0.780	0.499	1.218	-1.092	0.275
All (N=1620)	**1.829**	**1.005**	**3.329**	**1.975**	**0.048**

Statistics for each study

Hazard ratio and 95% CI



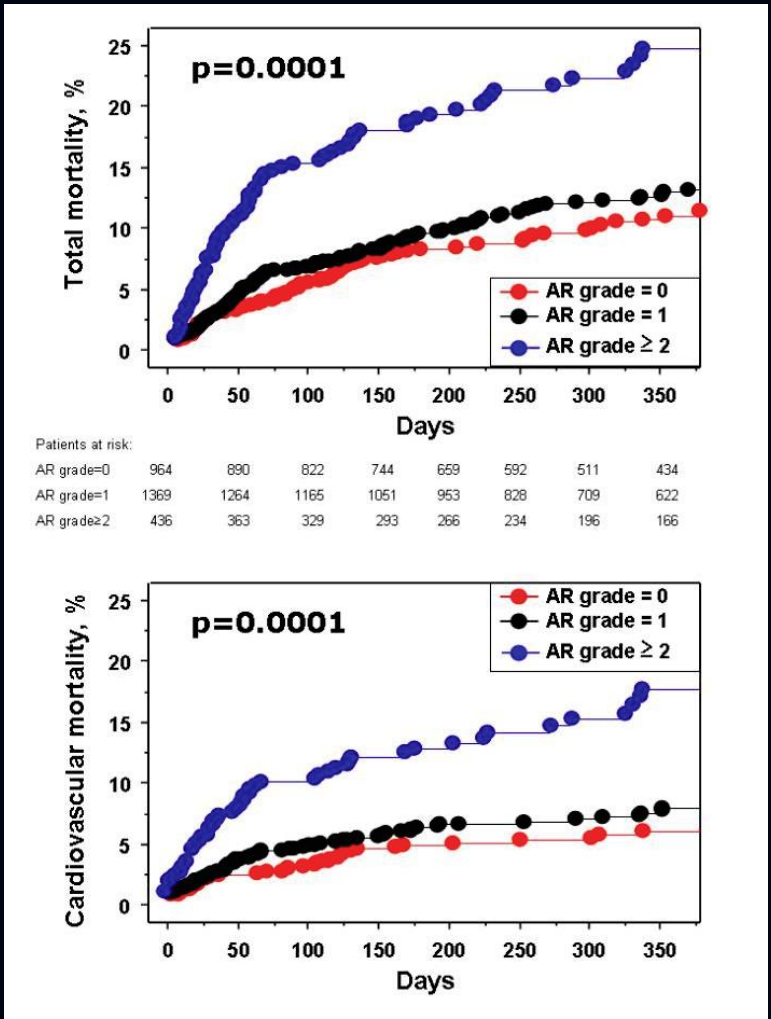
High Heterogeneity (I^2: 75.28)

Sensitivity Analysis: negative results after removing 1 single study

Athapan et al. JACC 2013

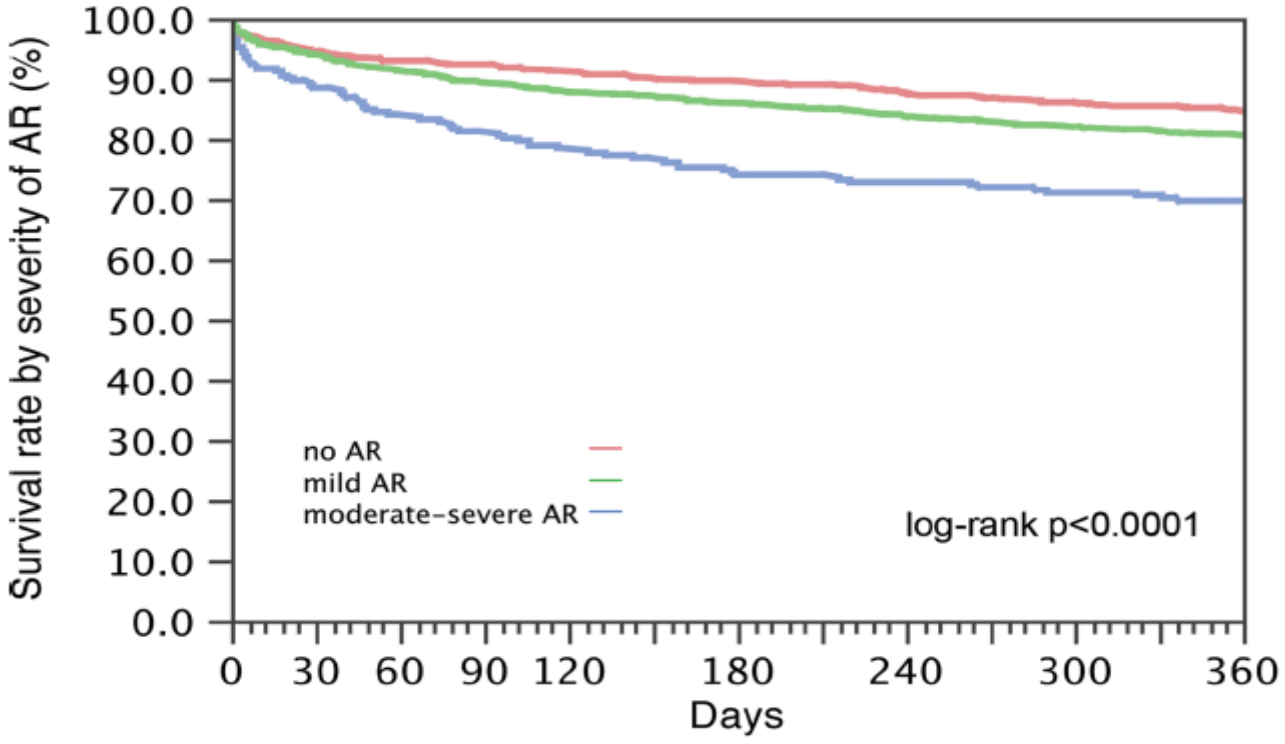
Impact of AR Post-TAVI / France-2 Registry

n= 2769



Van Belle et al. Circulation 2014

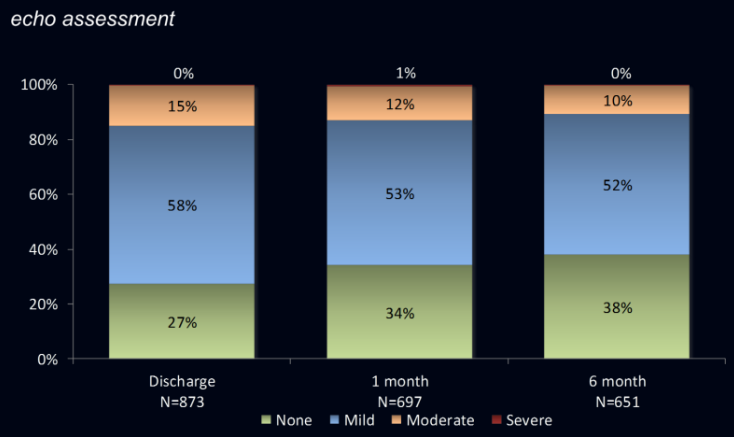
Impact AR Post-TAVI / UK Registry



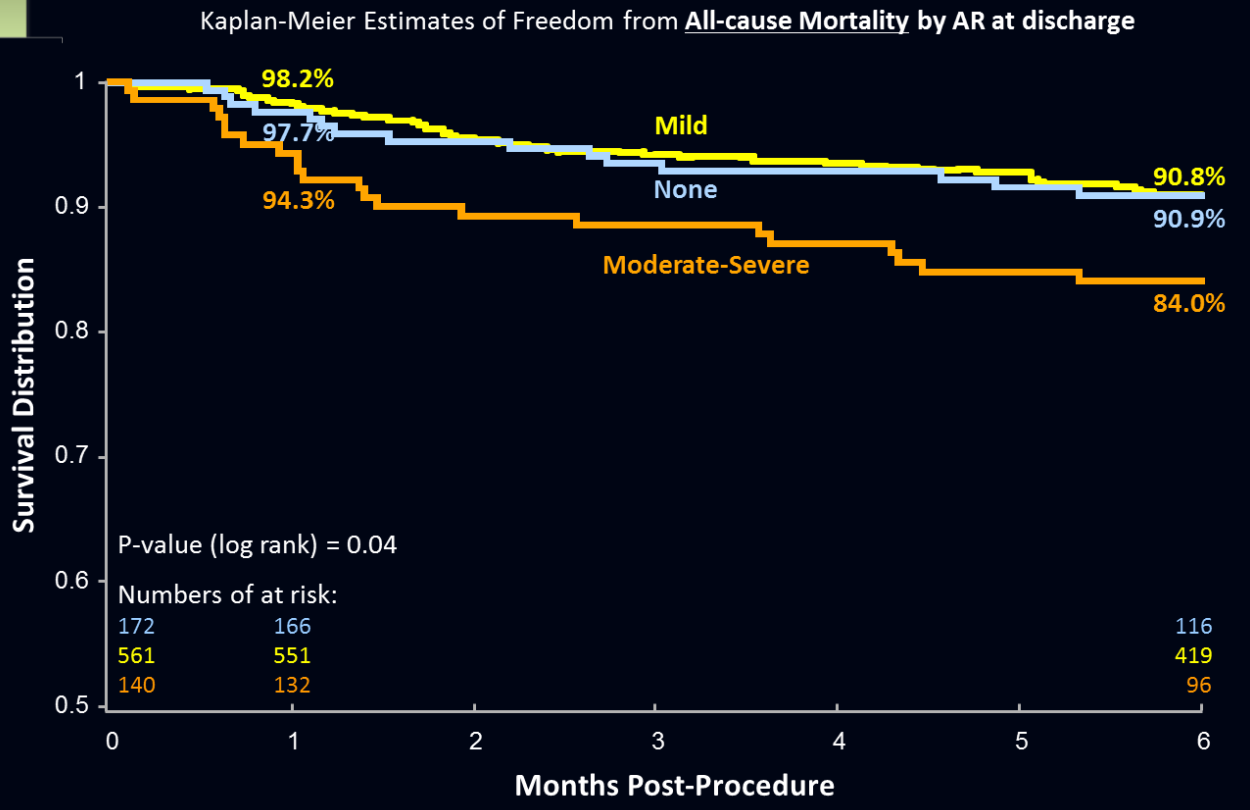
No at risk	Baseline	90 days	180 days	270 days	360 days
Total	2434	2150	2064	1795	1540
No AR	783	714	692	604	525
mild AR	1398	1233	1186	1026	874
moderate-severe AR	253	203	186	165	141

Dworakowski R, et al. Heart 2014

Impact of AR on Mortality:
Medtronic CoreValve ADVANCE Registry

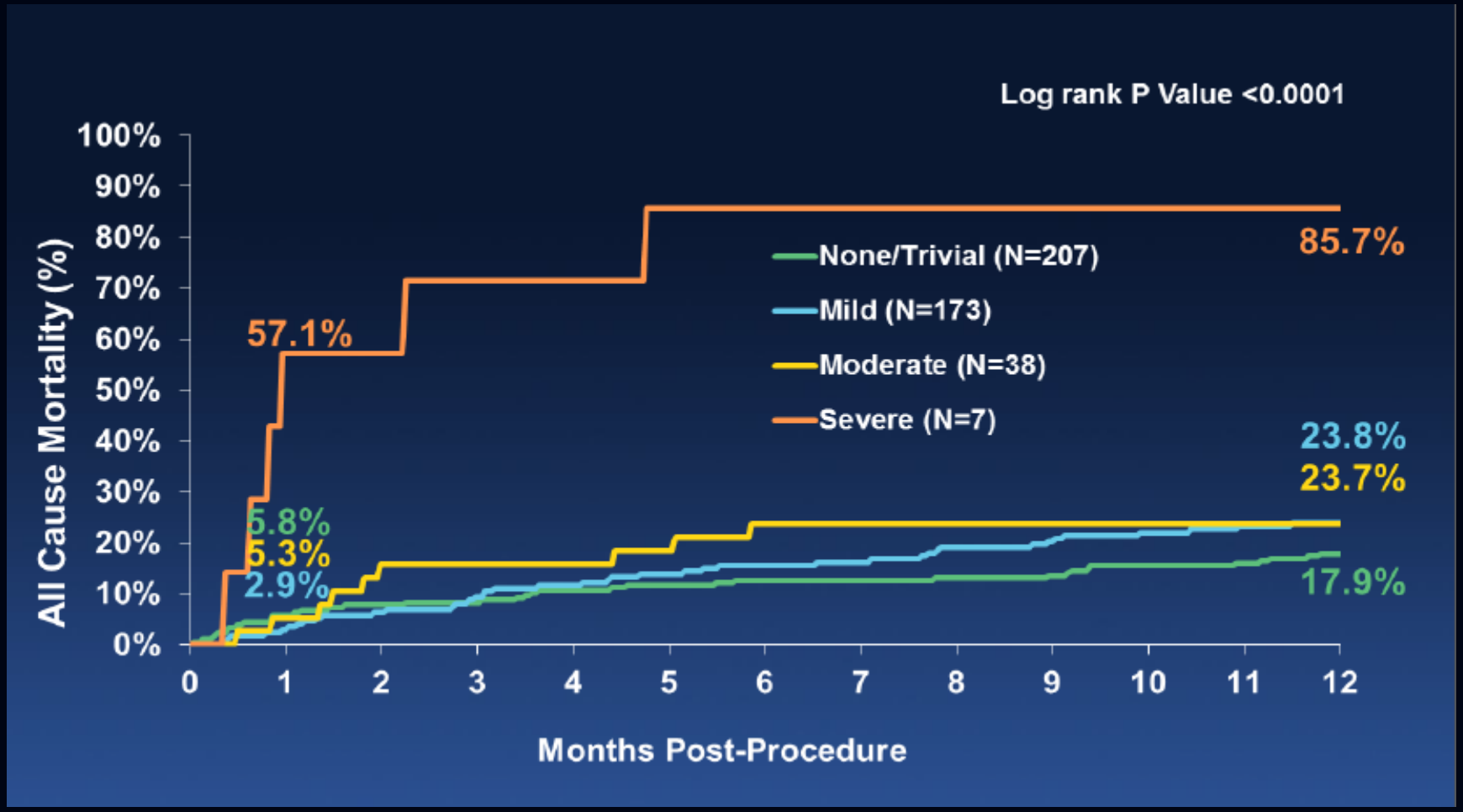


1,015 patients enrolled from March 2010 to July 2011 in 44 centers – 12 countries



Linke A et al. TCT 2012

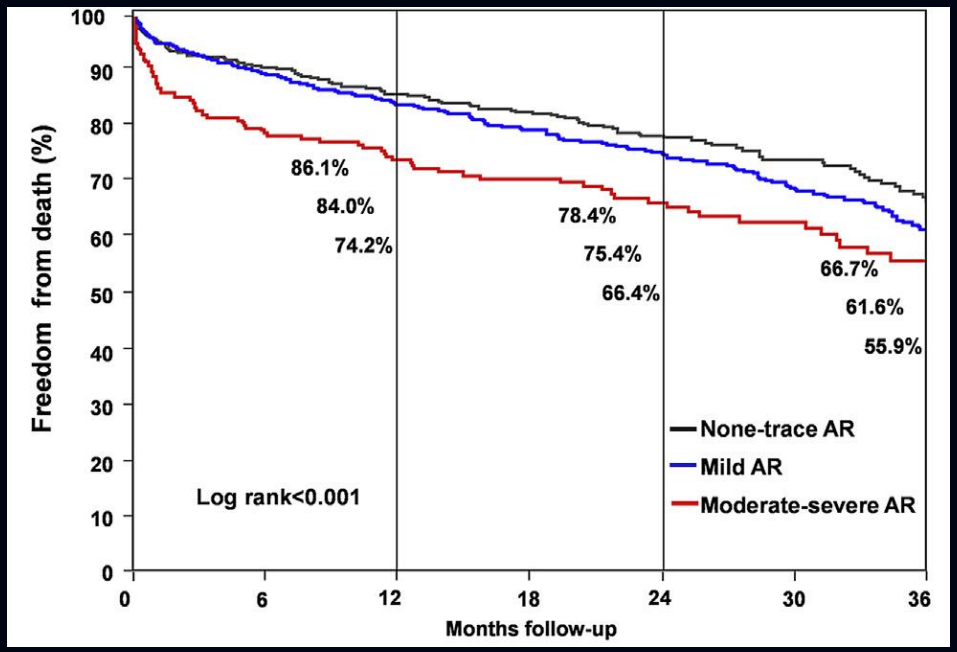
Impact of AR on Mortality CoreValve Pivotal Trial

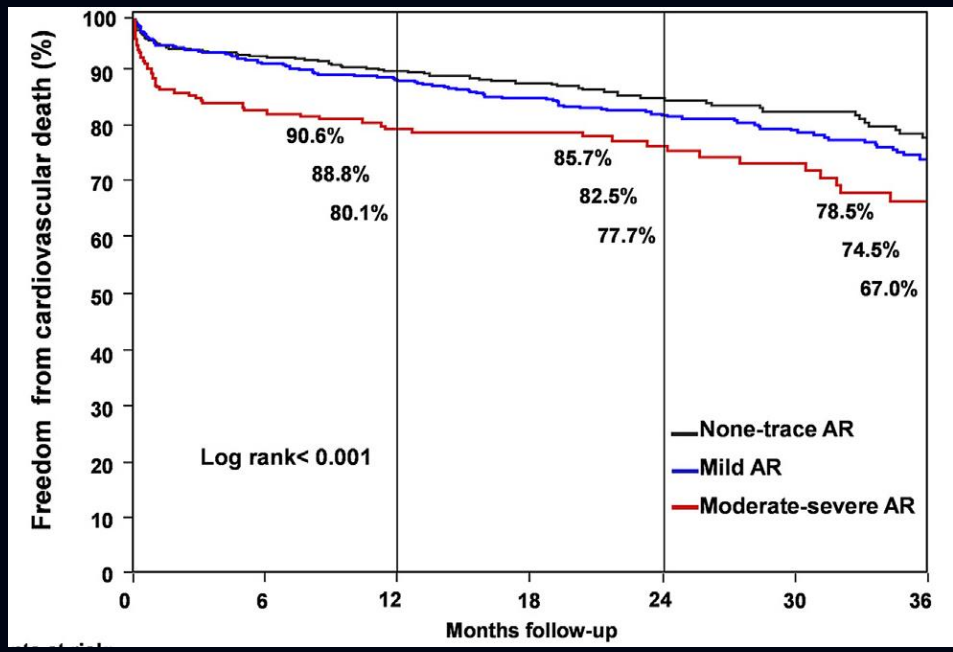


Popma et al. JACC 2014

Impact of AR on Mortality after TAVI:

Multicenter Study (1735 Patients)

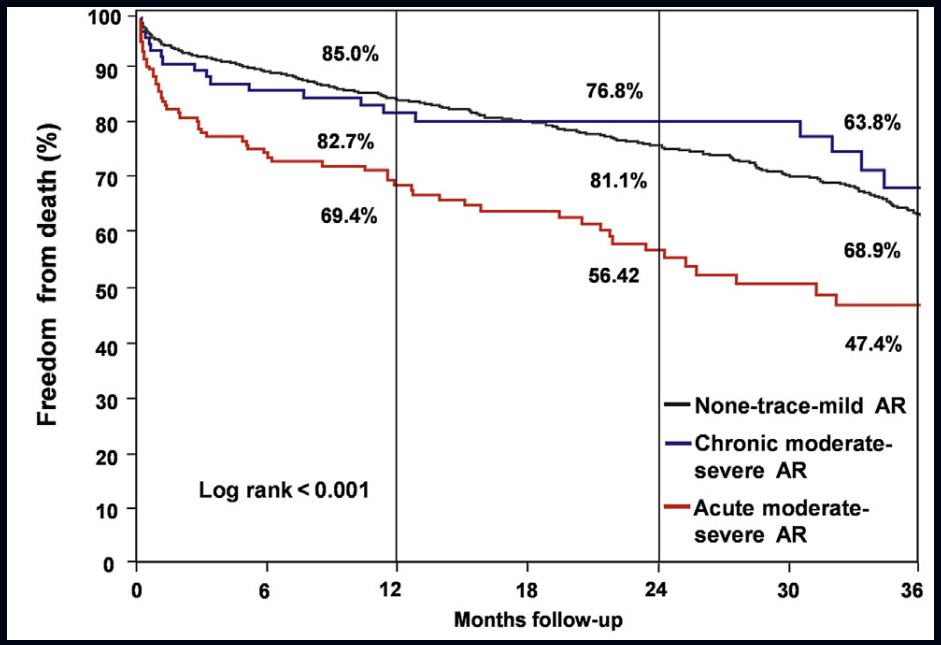


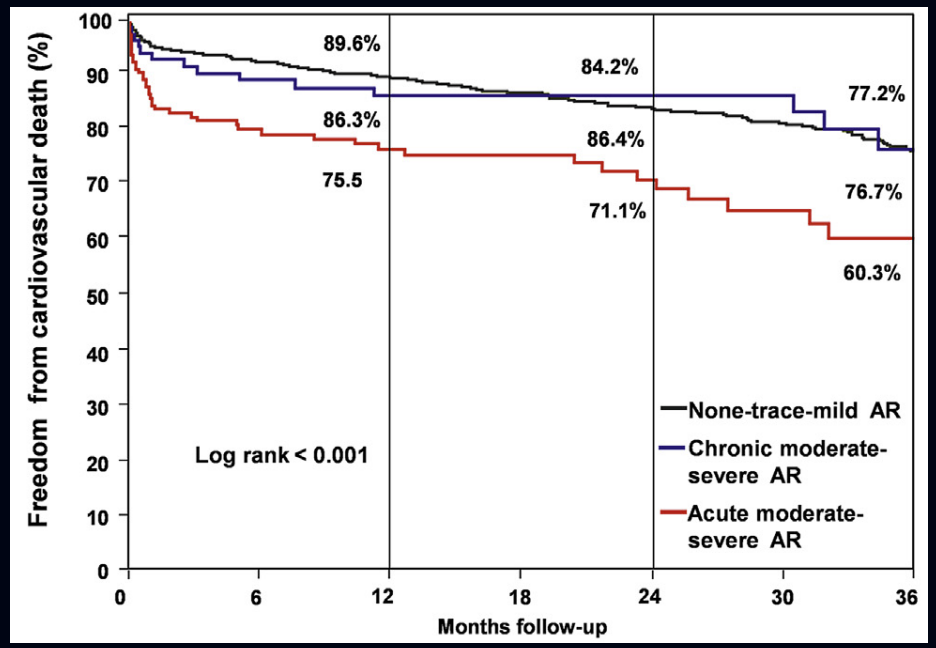


Jerez-Valero et al. J Am Coll Cardiol Intv 2014;7:1022–32

Effect of Acuteness of AR on Mortality After TAVI:

Multicenter Study (1735 Patients)

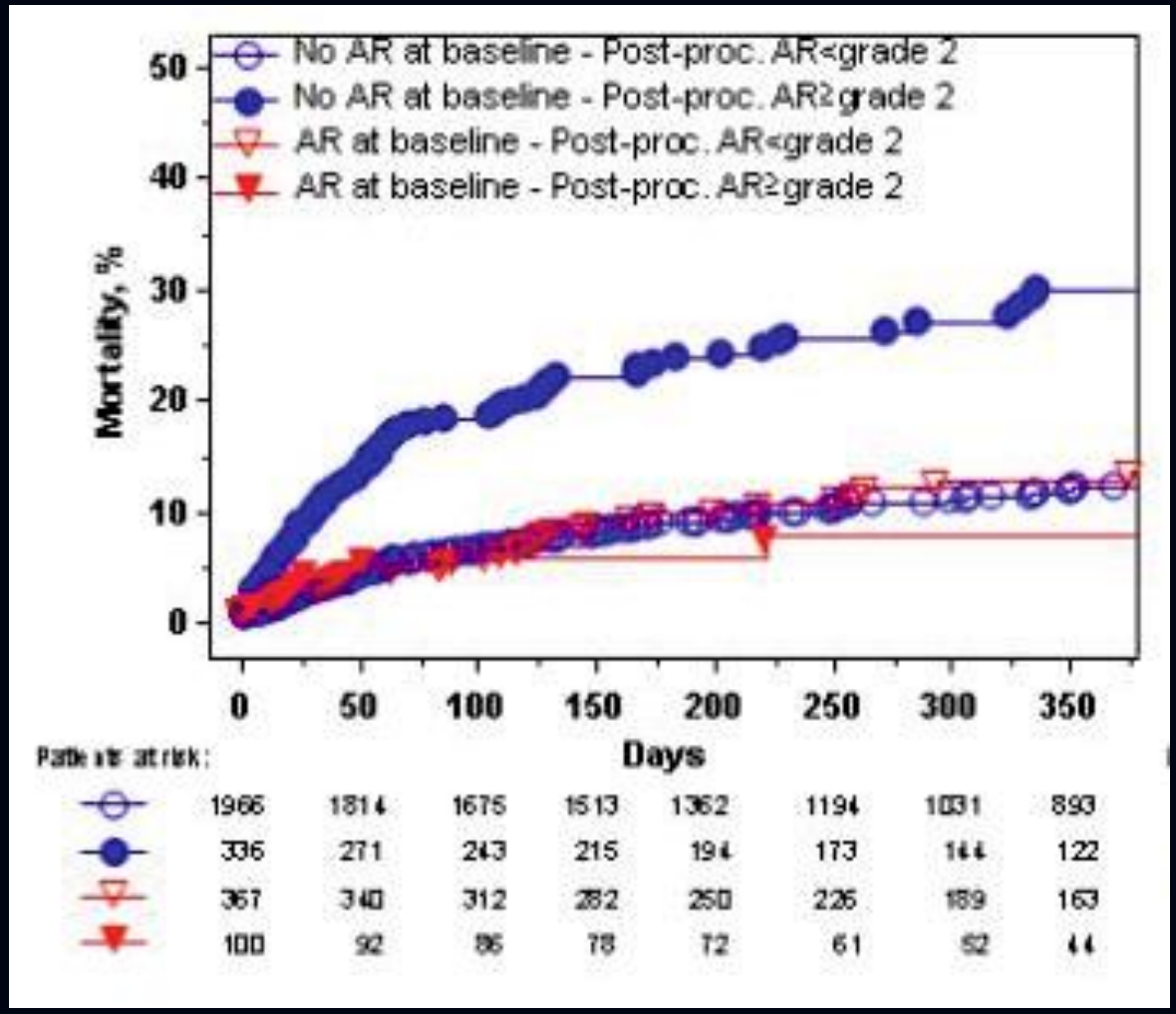




Jerez-Valero et al. J Am Coll Cardiol Intv 2014;7:1022–32

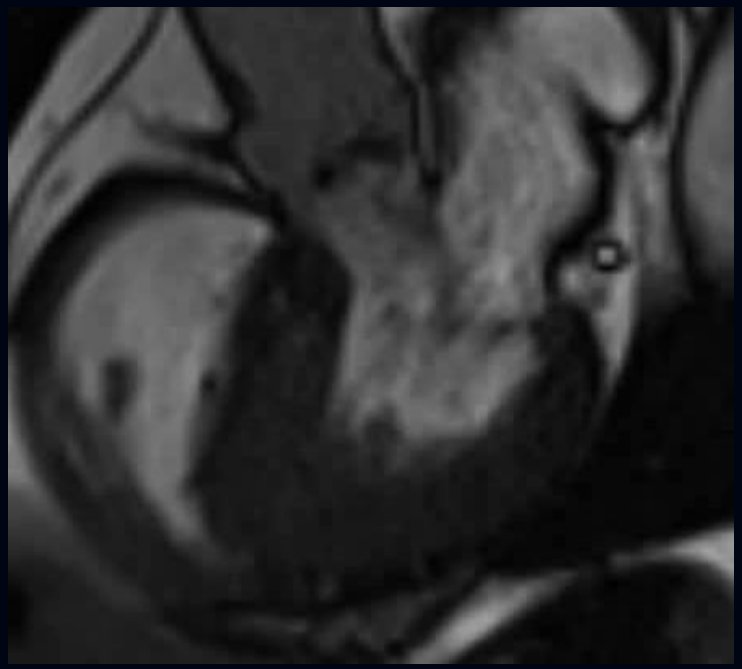
Effect of Acuteness of AR on Mortality After TAVI:

France 2 Registry



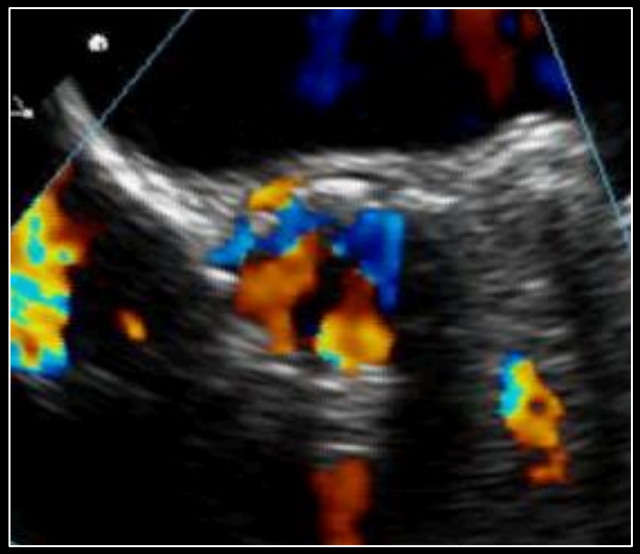
Van Belle et al. Circulation 2014

An acute mild PVR could be harmful in patients with small non-compliant LV?

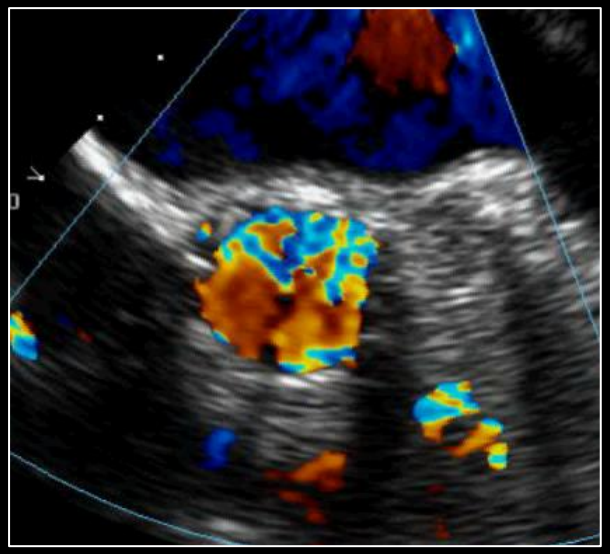


Impact of Balloon Post-dilation on PVR And Outcomes

Pre-BPD



Post-BPD



Impact of Balloon Post-dilation on PVR And Outcomes

PD: 2.5-fold increase in the risk of early cerebrovascular events

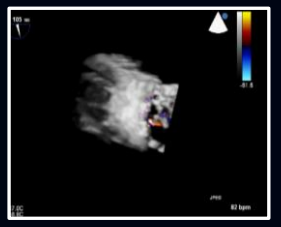
Nombela-Franco et al. JACC CV Intervention 2012
Nombela-Franco et al. Circulation 2012

Conclusions

- **Moderate/severe PVR occurs in 2-25% of patients and is an independent predictor of mortality**
- **Mild PVR is frequent (7-70%) following TAVR**
- **The association between mild PVR and increased mortality is in large part related to worse baseline risk profile**
- **Mild PVR may have an impact on mortality if:**
  - **It is underestimated**
  - **It occurs in a patient with no pre-existing AR and/or restrictive LV physiology**

Clinical Implications

- **Current data do not justify additional measures (balloon post-dilation, valve-in-valve, leak closure, SAVR) in patients with mild PVR post-TAVI**
- **Need to develop Doppler-echo methods to improve quantitation of PVR**



- **Need to improve transcatheter heart valves and procedures to minimize/eliminate PVR**
  - **Optimize Sizing with 3D imaging of annulus**
  - **Balloon post-dilation, V-inV**
  - **New valve models with better sealing**