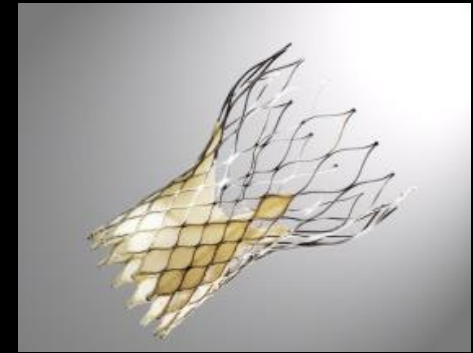
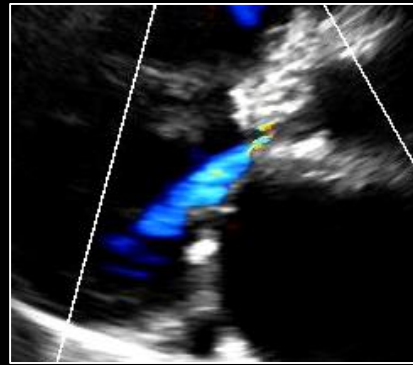




Paravalvular regurgitation: did we fix it or is this still an issue in ~~2016~~ 2017?

Philippe Pibarot, DVM, PhD, FACC, FESC, FASE
Canada Research Chair in Valvular Heart Disease



INSTITUT
UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC



**Université
LAVAL**

Disclosure

Philippe Pibarot

Financial relationship with industry:

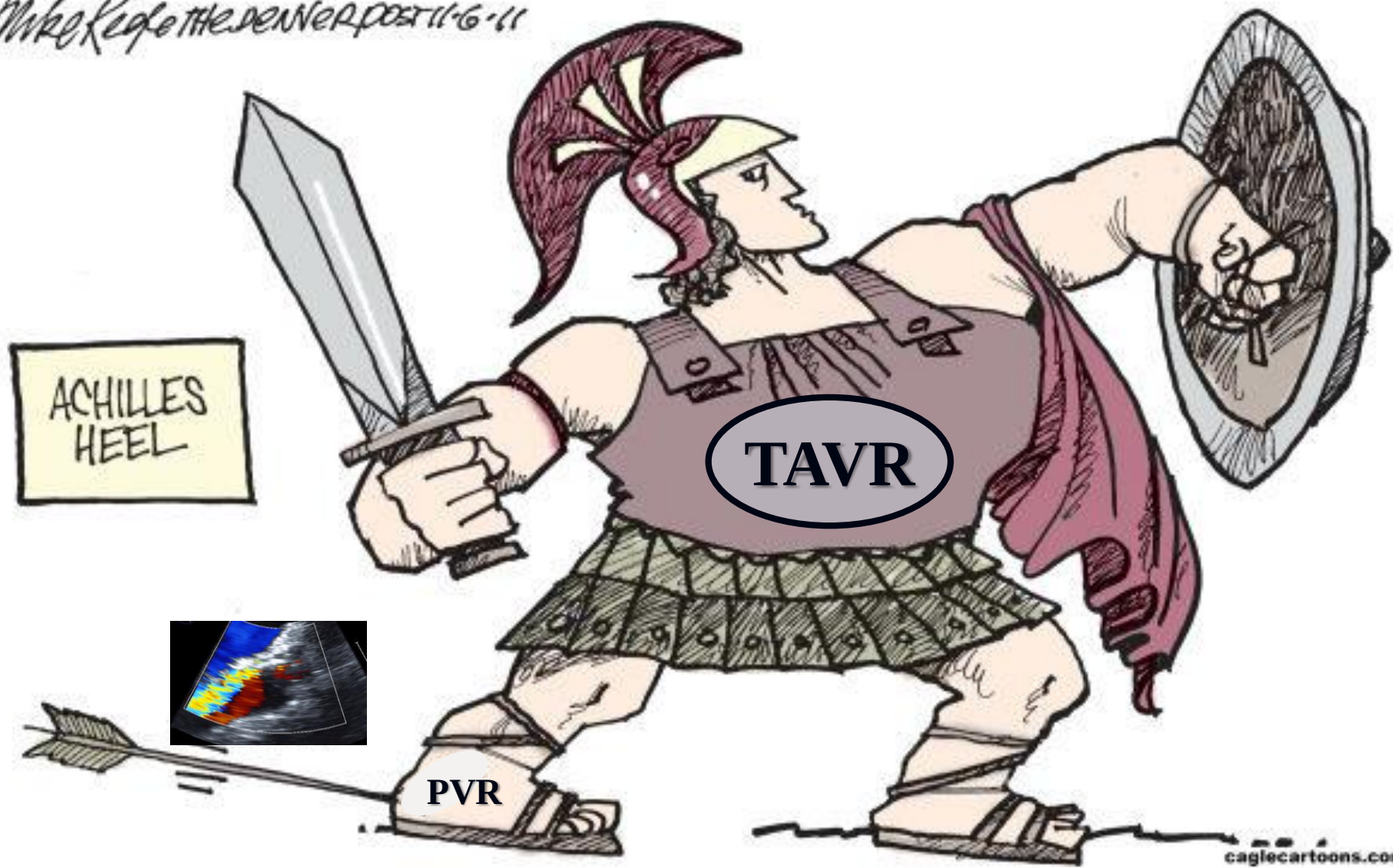
- **Edwards Lifesciences: Echo CoreLab for PARTNER 2 - SAPIEN 3 Registry, PARTNER 3 and TAVR-UNLOAD**
- **Medtronic: Echo CoreLab Evolut R 2.0**
- **V-Wave: Echo CoreLab**
- **Cardiac Pheonix: Echo CoreLab**

Other financial disclosure:

- **Research Grants from Canadian Institutes of Health**
- **Research and Heart & Stroke Foundation of Quebec**

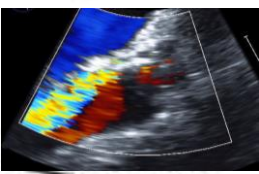
Off label Use: None

Mike Kagle THE DENVER POST 11-6-11



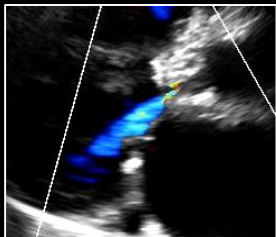
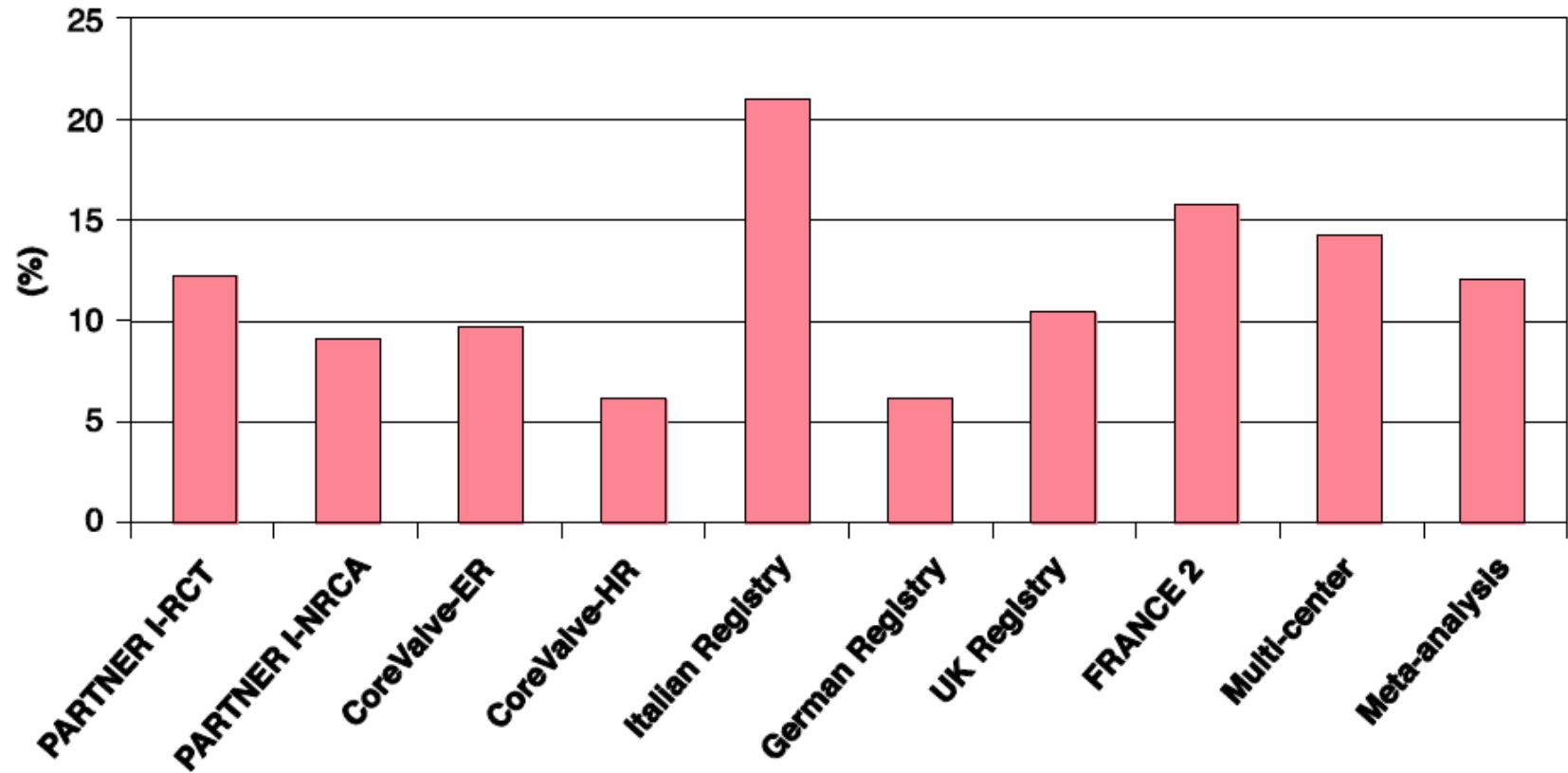
ACHILLES
HEEL

TAVR



PVR

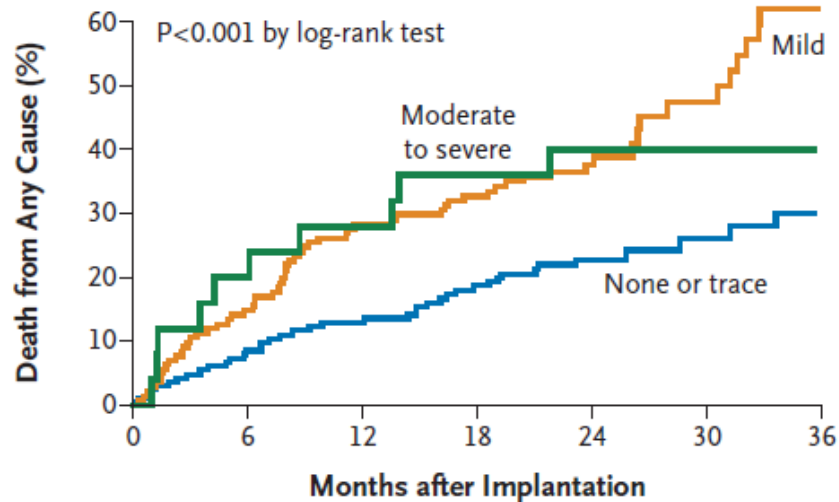
Incidence of Moderate/Severe PVR in TAVR With First Generations of THVs



Pibarot et al. JACC CV Imaging; 8:340-360, 2015

Impact of Paravalvular Regurgitation on 2-Year Outcomes: PARTNER 1A Trial (SAPIEN valve)

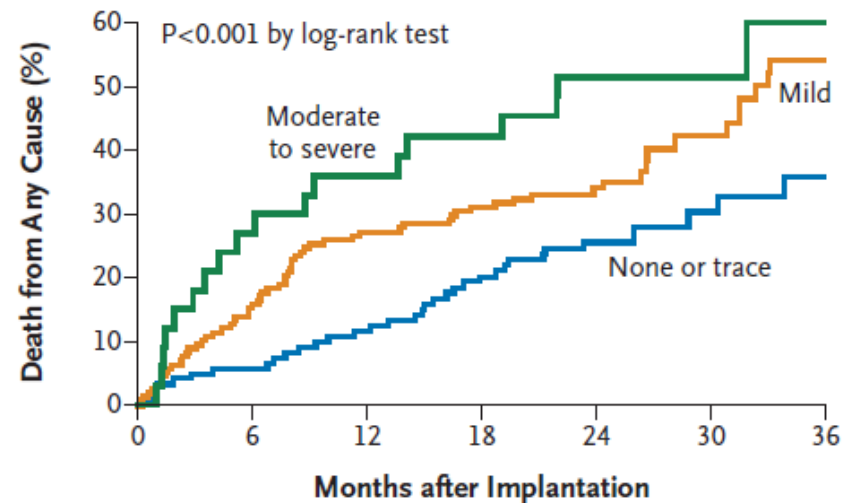
Paravalvular Regurgitation



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

Impact of PVR on Mortality in the PARTNER 1 Trial

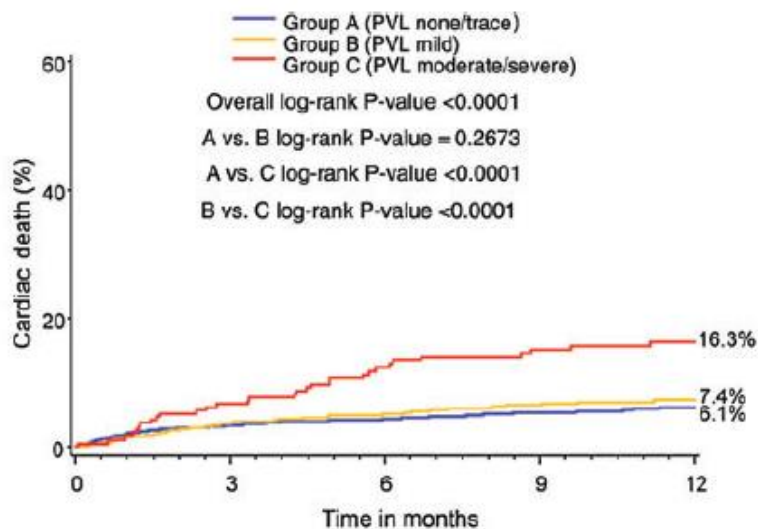
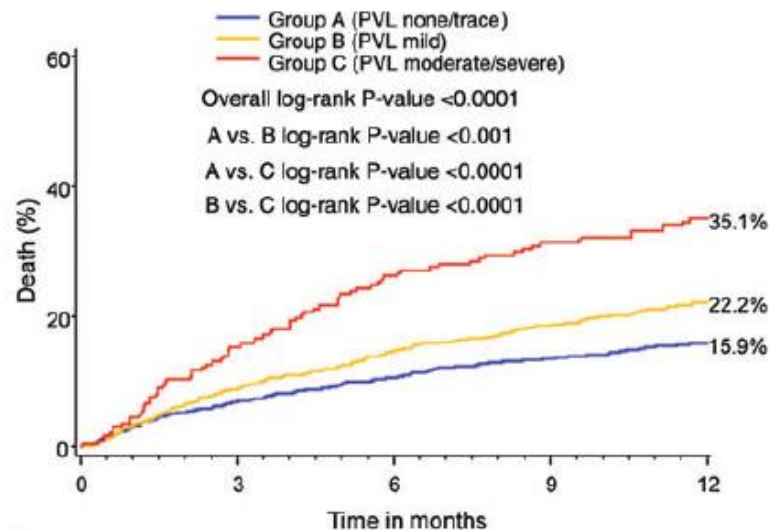


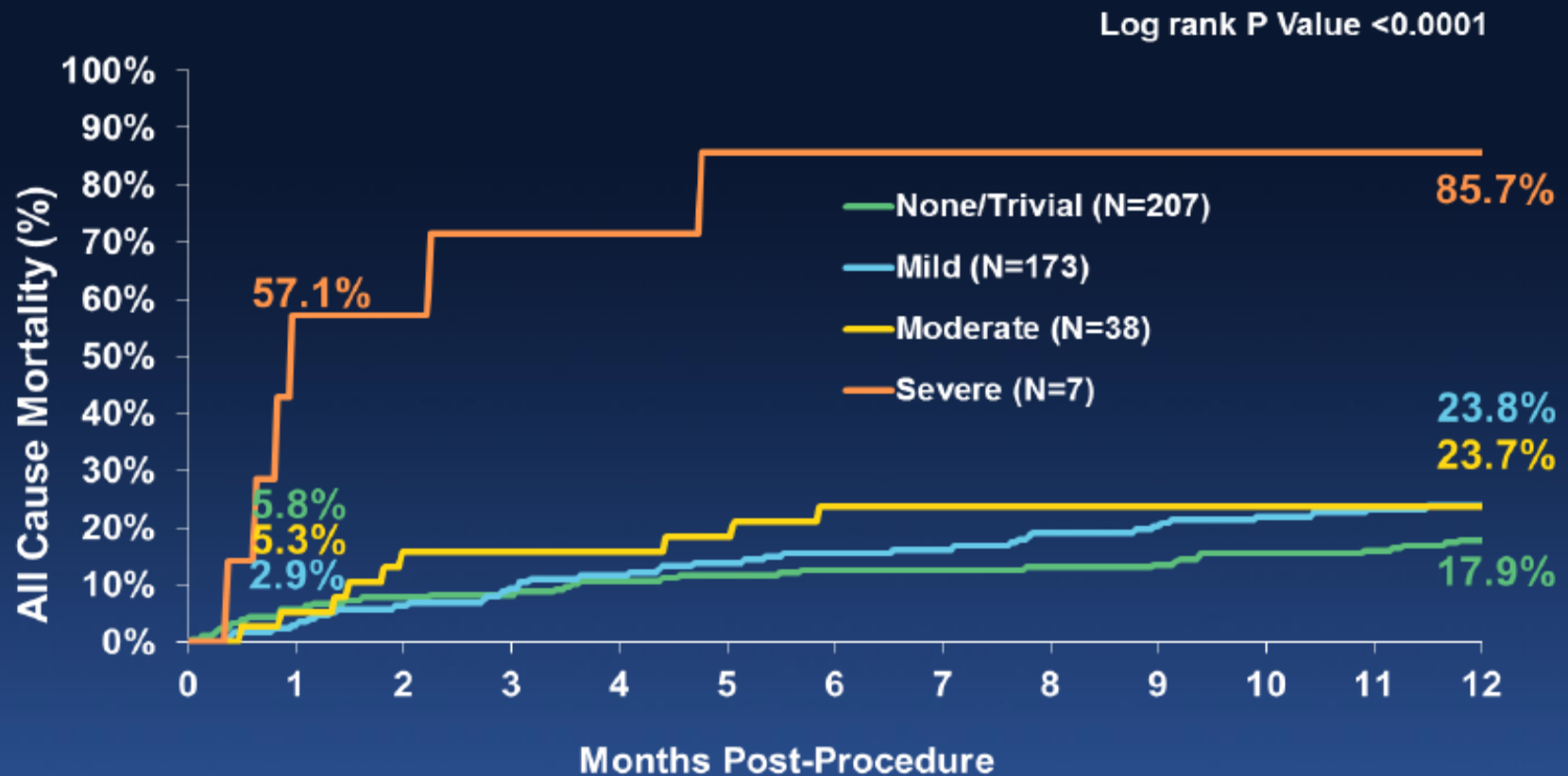
Table 4 Multivariable predictors of all-cause 1-year mortality

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

Impact of AR on Mortality

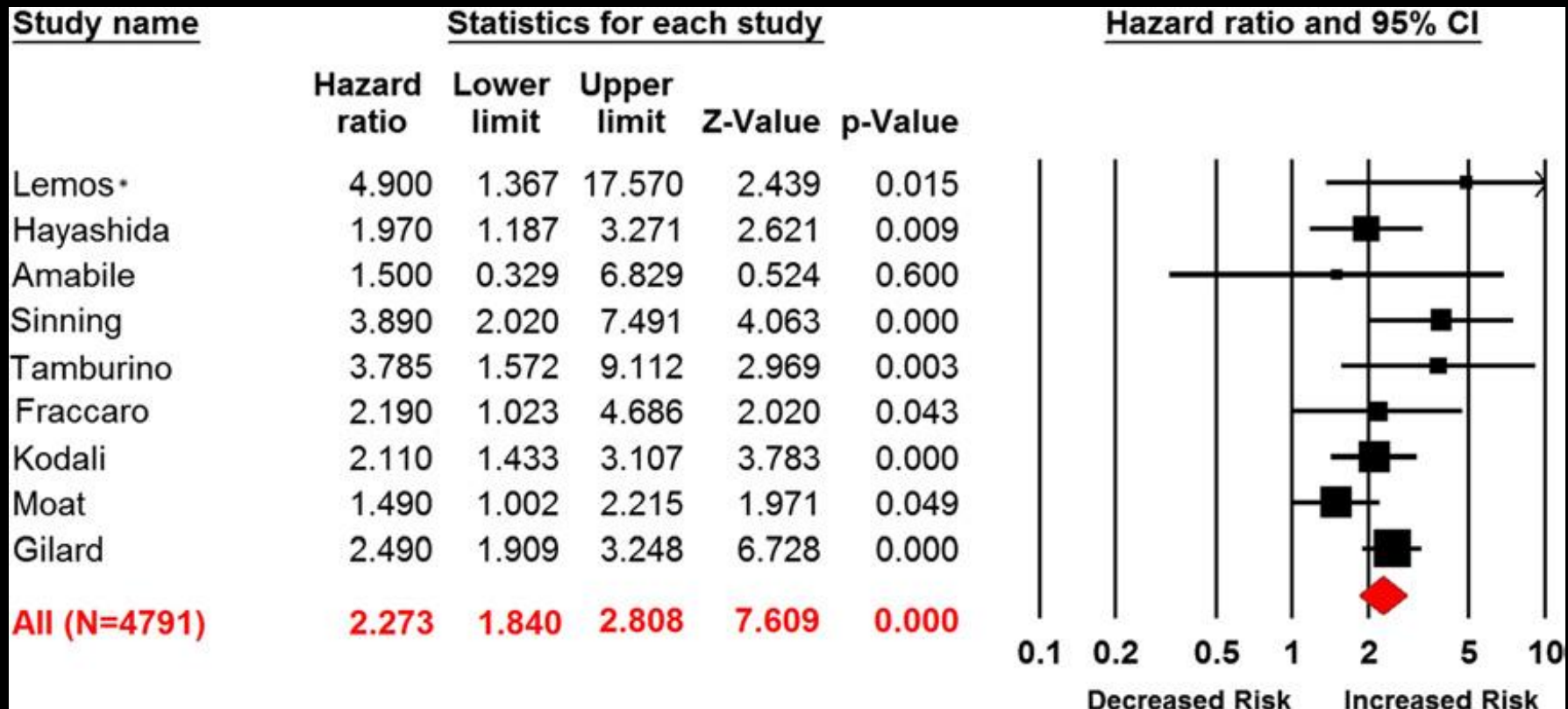
CoreValve Pivotal Trial



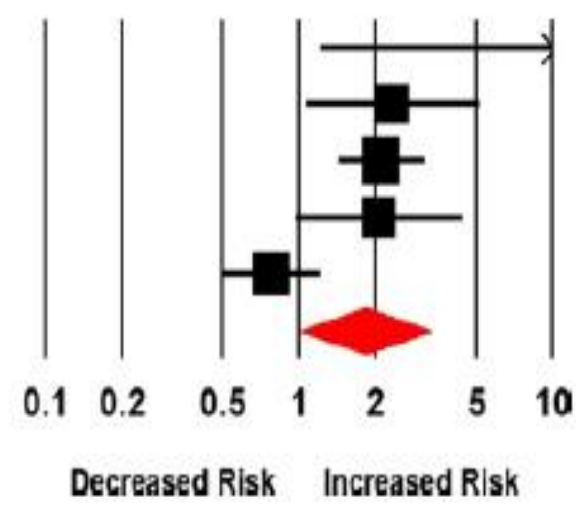
Impact of Moderate / Severe Aortic Regurgitation After TAVR

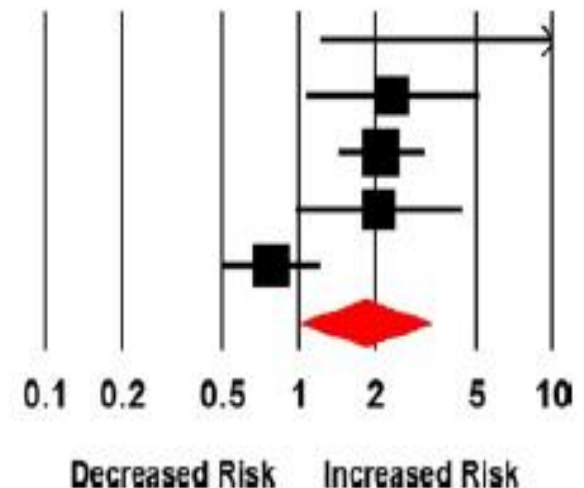
Meta-Analysis and Systematic Review of Literature

Impact of Moderate-Severe AR on Mortality



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

<u>Study name</u>	<u>Statistics for each study</u>					<u>Hazard ratio and 95% CI</u>
	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	



Incidence of Moderate/Severe PVR in TAVR

Balloon expandable vs. Self-expanding Valves

Table 1 Incidence of Moderate/Severe PAR After TAVR

First Author (Ref. #)	Patients	EuroSCORE	Access Route	THV Type	PAR Rate	Assessed by	Mortality for More Than Mild PAR
Abdel-Wahab et al. (8)	690	20.4 ± 13.1	92.4% TF, 3.5% TA	84.3% CV (Medtronic Inc., Minneapolis, Minnesota), 15.7% ES (Edwards Lifesciences Corporation, Irvine, California)	17.2%	Angiography	NA
Leon et al. (1)	179	26.4 ± 17.2	100% TF	100% ES	15.2%	Echocardiography	NA
Tamburino et al. (9)	663	23.0 ± 13.7	90.3% TF, 9.7% TS	100% CV	21.0%	Echocardiography	NA
Smith et al. (2)	348	29.3 ± 16.5	70.1% TF, 29.9% TA	100% ES	13.1%	Echocardiography	NA
Moat et al. (12)	870	18.5 (11.7–27.9)	68.9% TF, 26.4% TA	52.0% CV, 48.0% ES	13.6%	Angiography	NA
Sinning et al. (6)	146	30.2 ± 18.0	91.8% TF, 8.2% TS	100% CV	15.1%	Echocardiography, angiography, hemodynamics	30-day: 22.7%, 1-yr: 63.6%
Gilard et al. (11)	1,915*	21.9 ± 14.3	73.9% TF, 17.7% TA	66.9% ES, 33.1% CV	16.5%	Echocardiography	NA
Gotzmann et al. (16)	198	22.0 ± 16.0	97.5% TF, 2.5% TS	100% CV	14.1%	Echocardiography, hemodynamics	30-day: 21.0%, 1-yr: 57.0%
Vasa-Nicotera et al. (34)	122	22.4 ± 13.0	97.5% TF, 1.7% TA	79.5% CV, 20.5% ES	16.4%	Echocardiography, angiography, hemodynamics	30-day: 30.0%, 1-yr: 60.0%
Hayashida et al. (15)	400	22.3 (17.1–30.3)	NA	86.8% ES, 13.2% CV	3.0%	Echocardiography	30-day: 16.7%, 1-yr: 60.0%

*In 1,915/3,195 patients, PAR was assessed after the TAVR procedure.

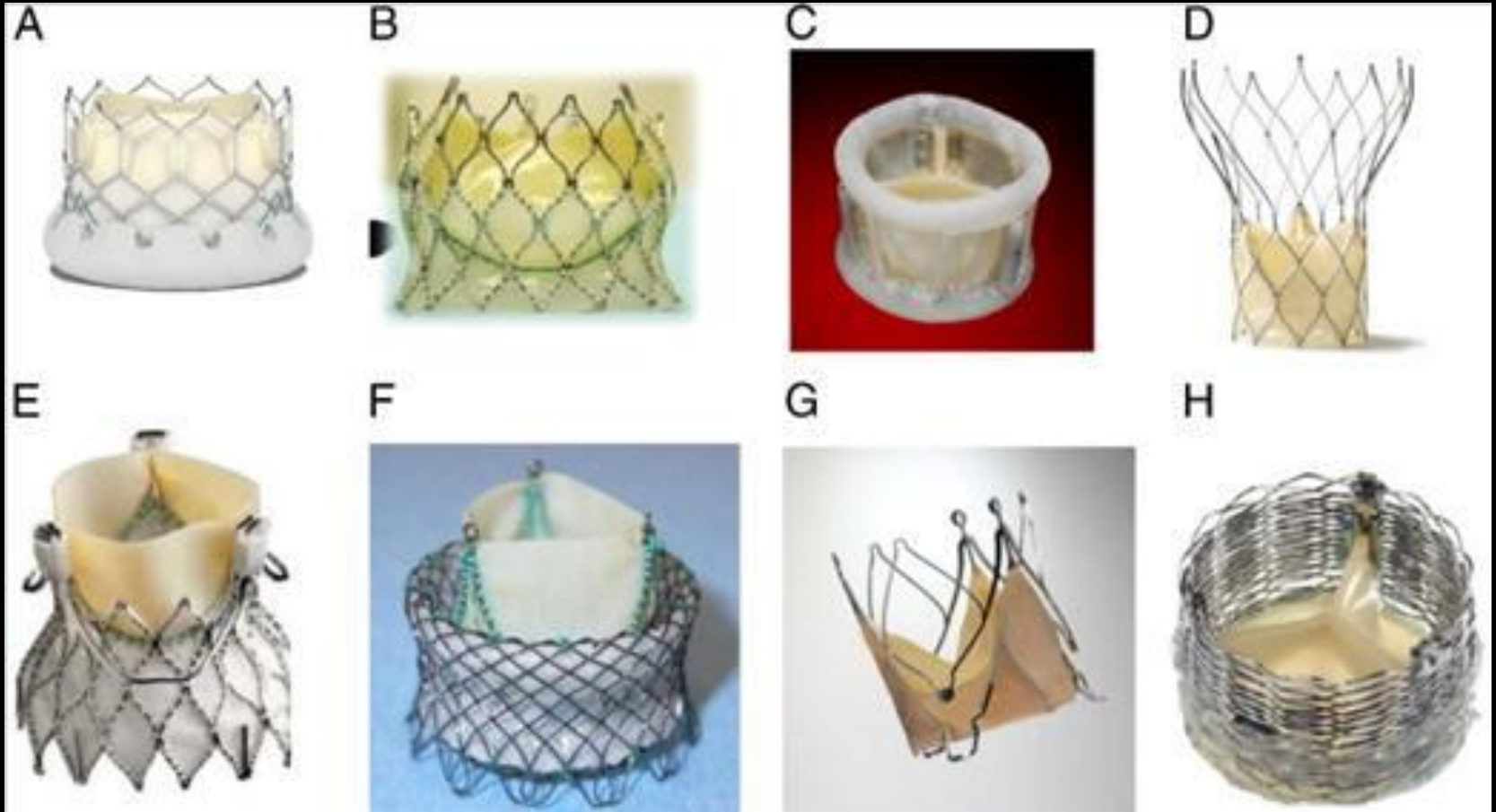
euroSCORE = European System for Cardiac Operative Risk Evaluation; CV = CoreValve; ES = Edwards SAPIEN; NA = not available; PAR = paravalvular aortic regurgitation; TA = transapical; TF = transfemoral; THV = transcatheter heart valve; TS = trans-subclavian.

Sinning et al. JACC; 2013;62:11-20

Moderate-severe AR more common with self-exp vs. balloon-exp. valves (16% vs. 9%, p 0.005)

Athappan et al. JACC 2013;61:1585–95

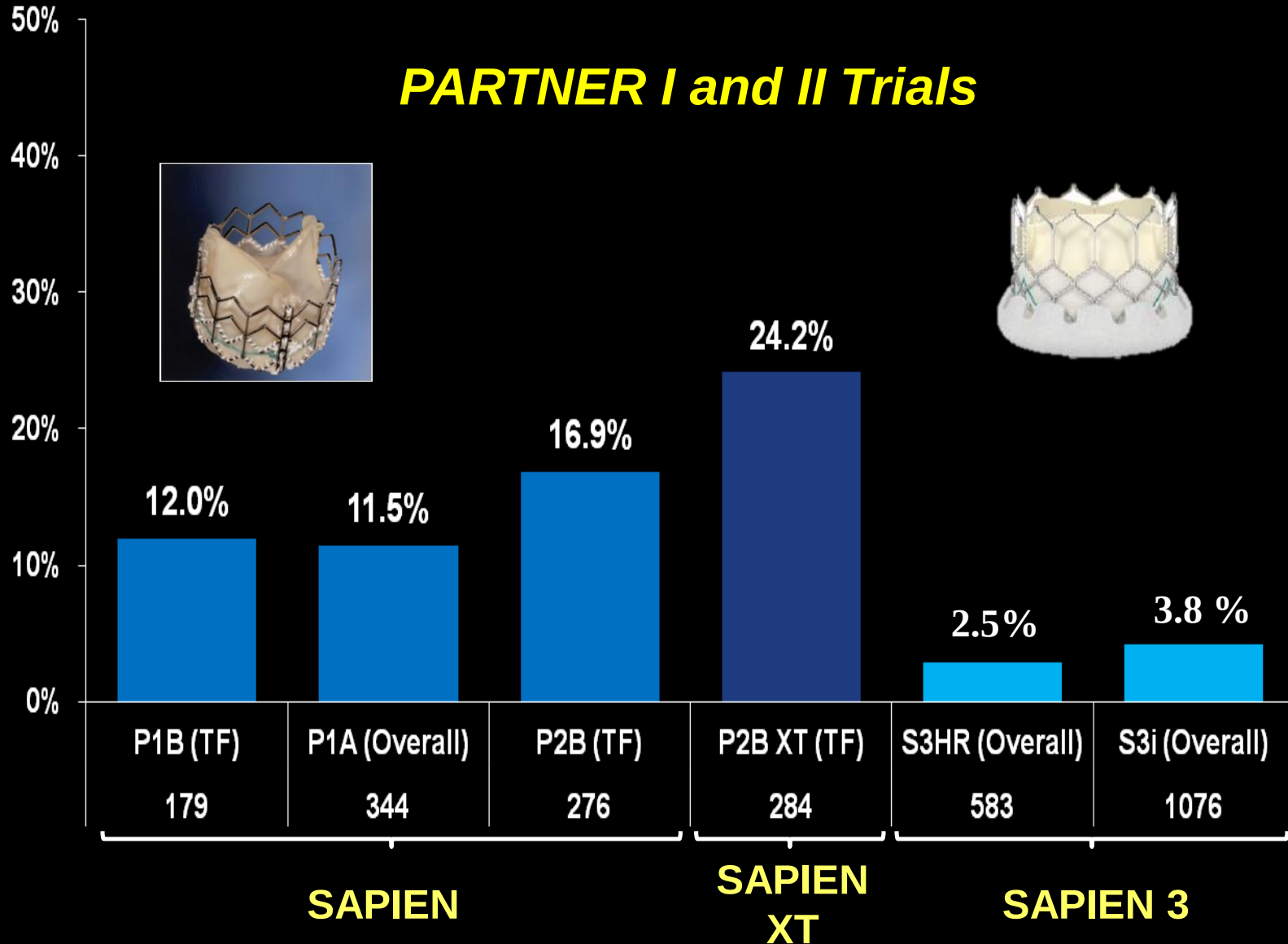
New Generations of Transcatheter Heart Valves to Prevent PVR



Moderate/Severe PVR at 30 Days

Edwards SAPIEN Valves

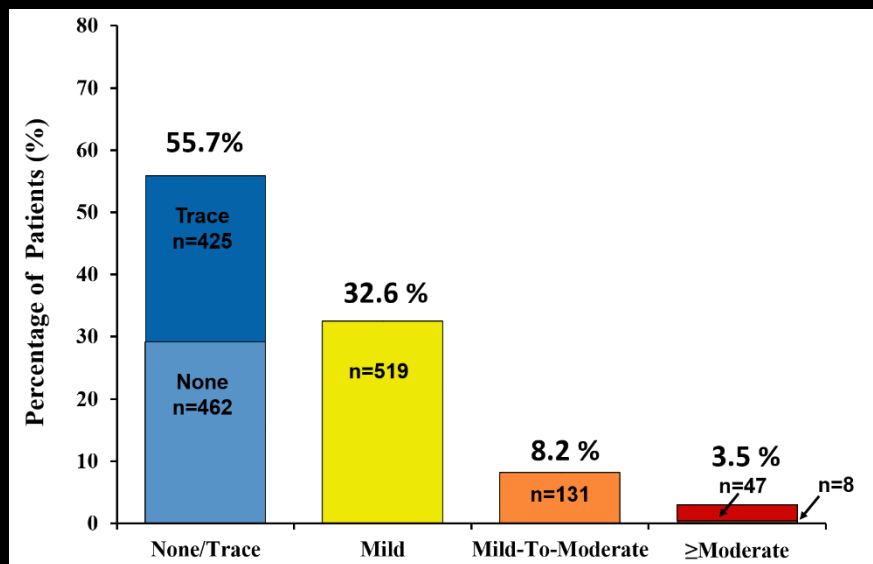
PARTNER I and II Trials



Prevalence of Paravalvular Regurgitation with the SAPIEN 3



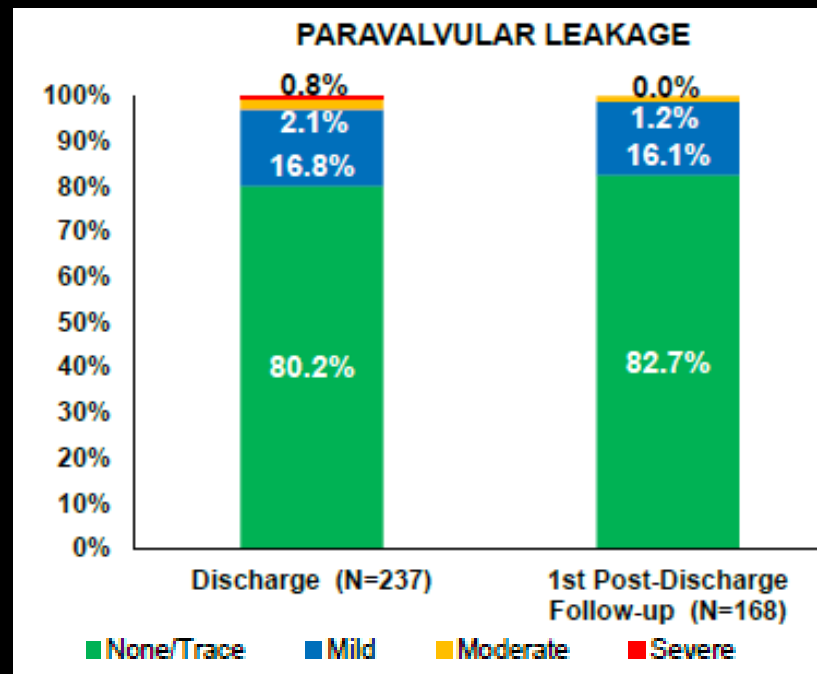
PARTNER 2 – SAPIEN 3 Registry



3.5 % ≥ Moderate PVR

Pibarot et al. TCT 2016

SOURCE 3 Registry



2.9 % ≥ Moderate PVR

Zamorano et al. EuroPCR 2016

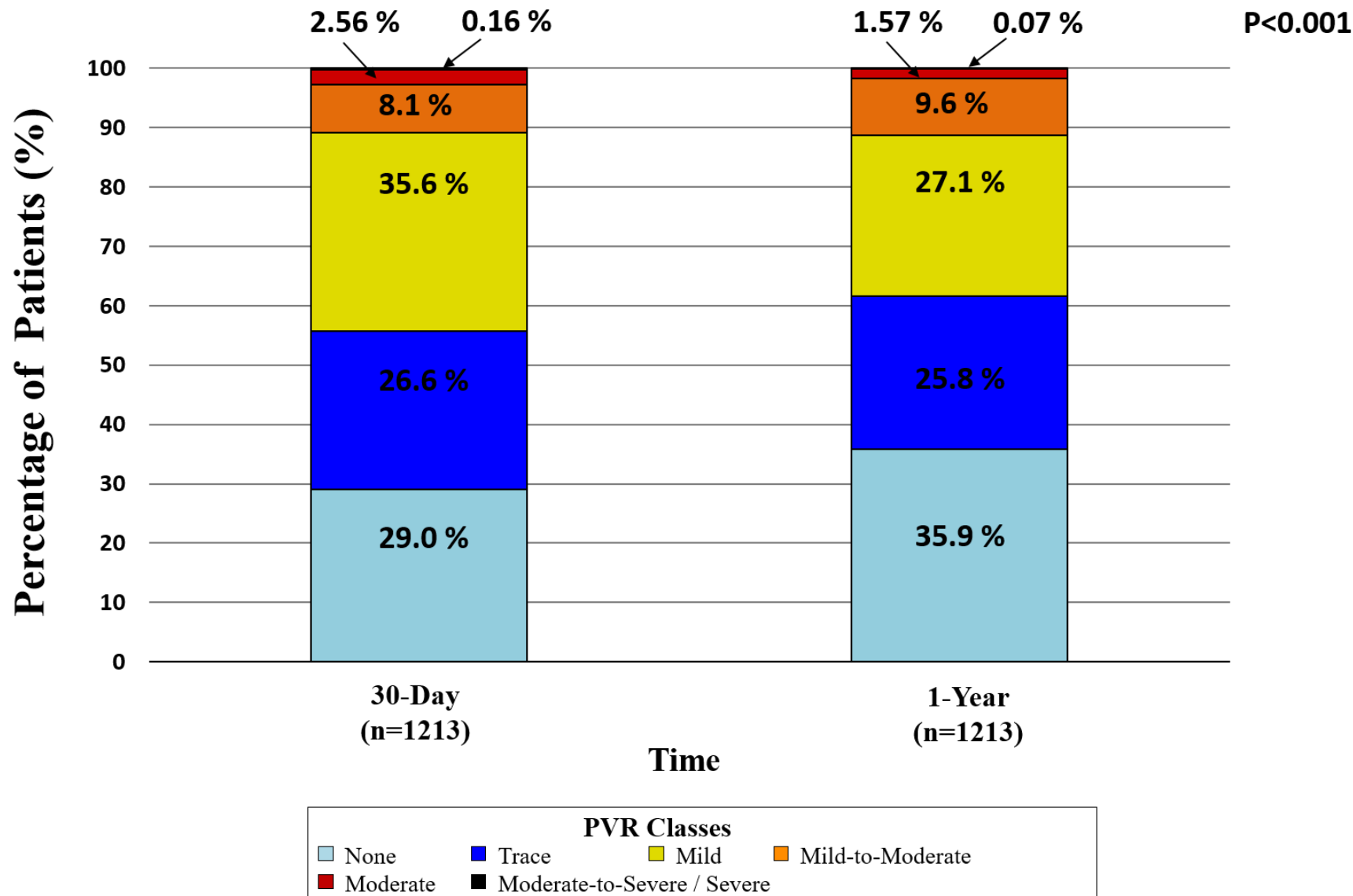
Paired comparison of PVR grade at 30 days vs. 1 year in the PARTNER 2 – SAPIEN 3 Registry



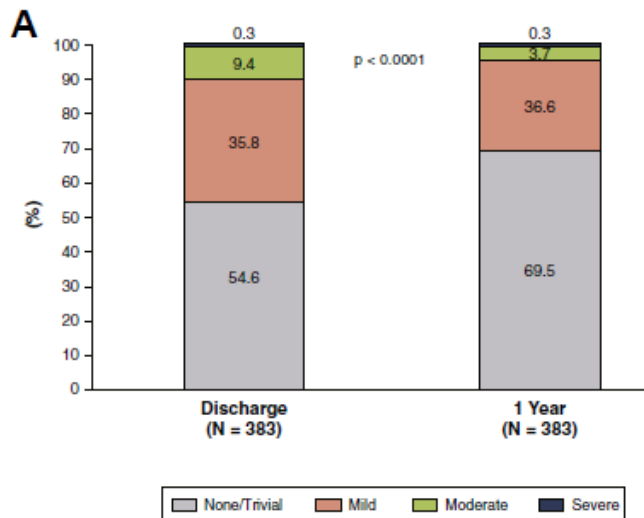
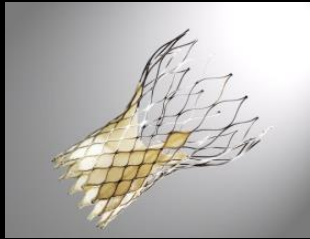
PVR at 30 day	PVR at 1 Year						Total
	None	Trace	Mild	Mild-to-Moderate	Moderate	Severe	
None	267	57	26	2	0	0	352
Trace	112	150	56	5	0	0	323
Mild	55	96	207	45	4	0	407
Mild-to-Moderate	1	7	34	49	7	0	98
Moderate	0	3	6	14	7	1	31
Moderate-to-Severe	0	0	0	1	1	0	2
Total	435	313	329	116	19	1	1213

- **73%** (24/33) of the patients with $\geq$ moderate PVR at 30 days showed a reduction in PVR severity at 1 year
- **0.9%** (11/1180) of the patients with $<$ moderate PVR at 30 days had a worsening to moderate PVR at 1 year

Paired comparison of PVR at 30 days vs.1 year



Paired comparison of PVR grade at 30 days vs. 1 year in the CoreValve Pivotal Trial



	<i>One Year</i>				
<i>Discharge</i>	None (N=123)	Trivial (N=143)	Mild (N=102)	Moderate (N=14)	Severe (N=1)
None	49	18	7	1	0
Trivial	50	48	34	2	0
Mild	23	66	42	6	0
Moderate	1	11	18	5	1
Severe	0	0	1	0	0

Improvement in PVAR by at least 1 grade
 Worsening in PVAR by at least 1 grade

9.7 % $\geq$ Moderate PVR at discharge

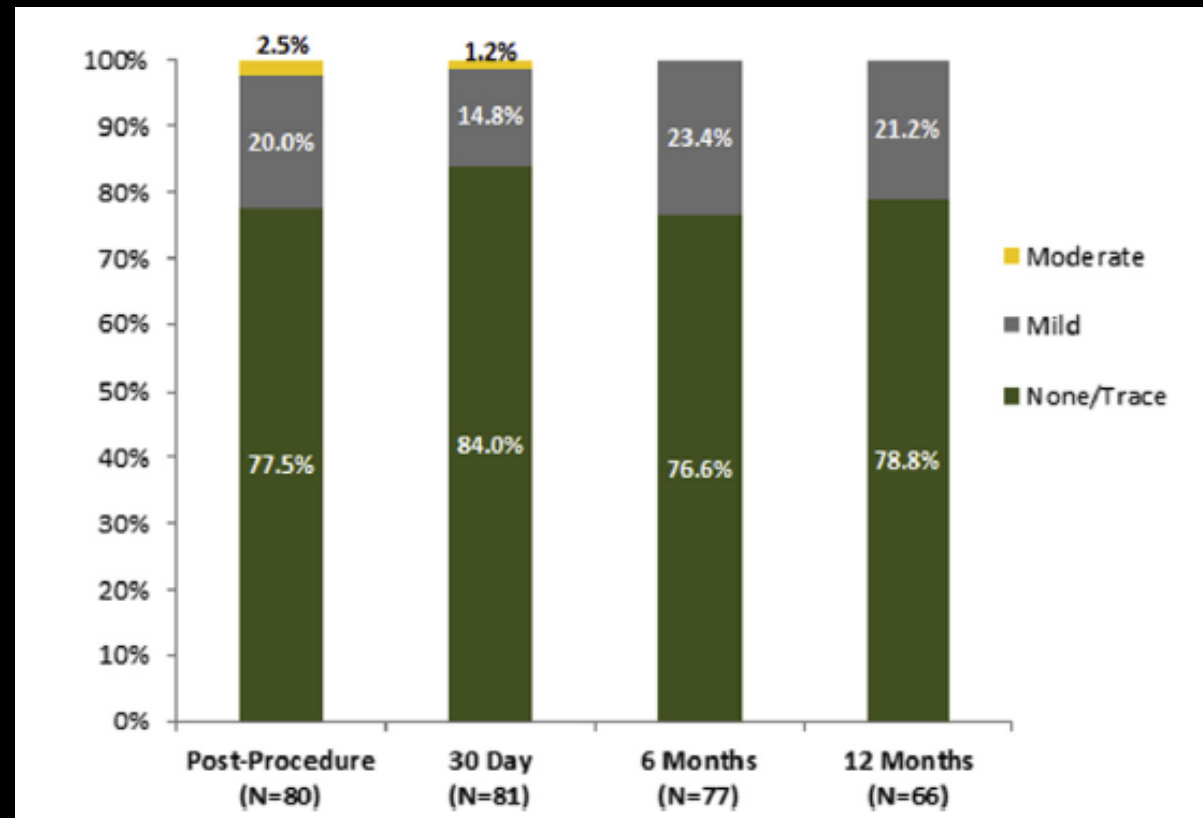
4.0% $\geq$ Moderate PVR at 1-year



Evolut R: 3.8% $\geq$ Moderate PVR at discharge

Oh et al. JACCImg.
2015; 8:1364-75

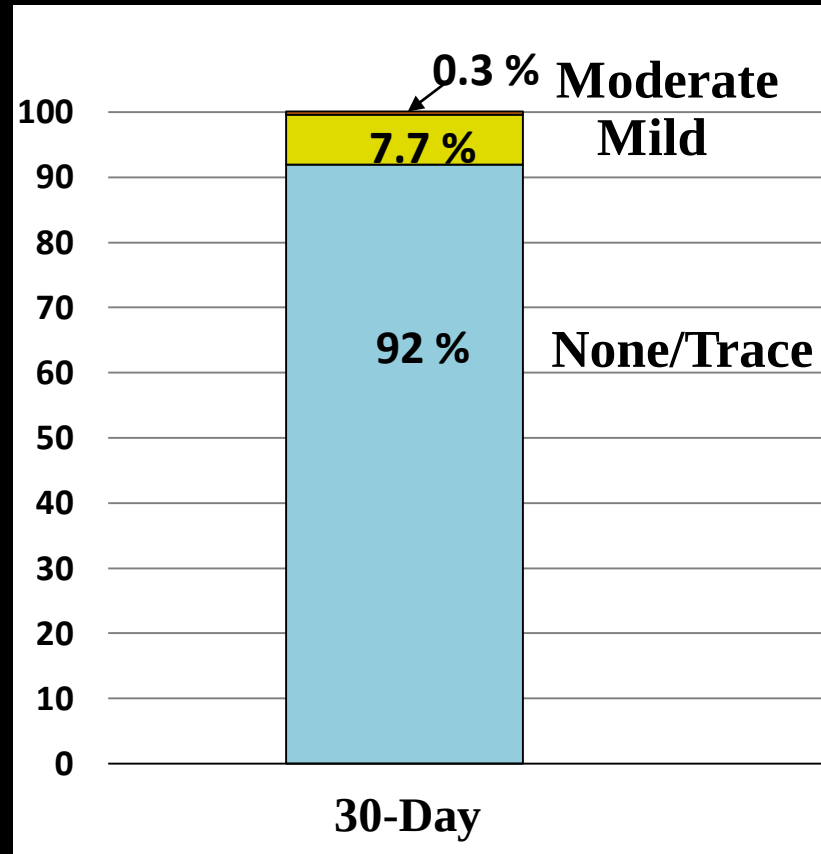
Prevalence of PVR after TAVR with the Direct Flow THV



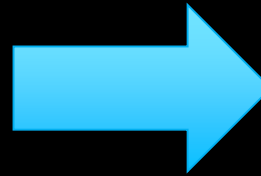
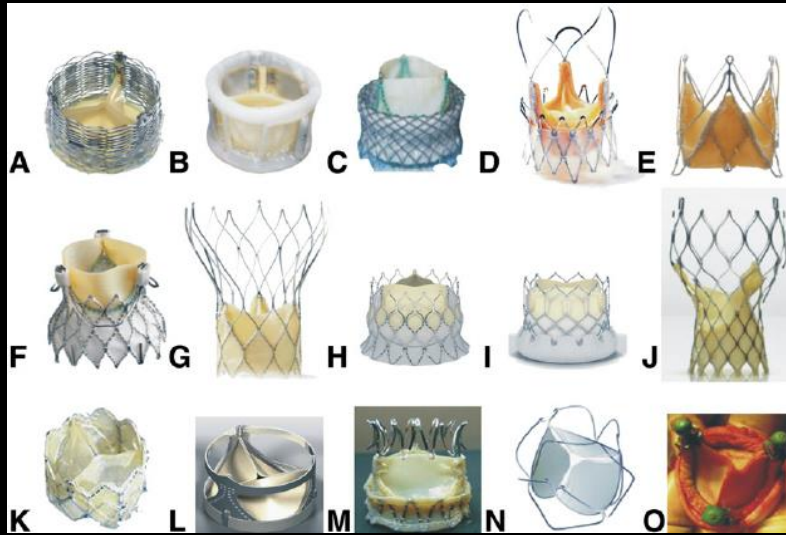
Incidence of PVR at 30 days with LOTUS Valve RESPOND Registry (n=1000 patients)



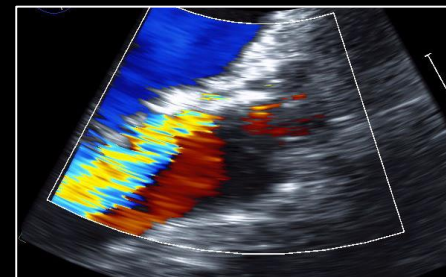
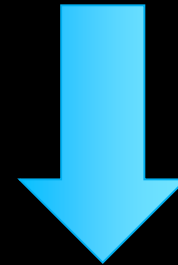
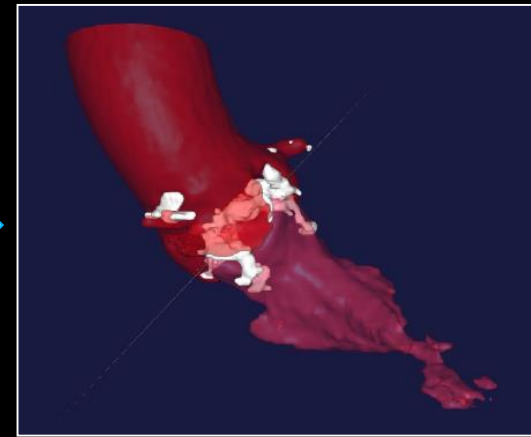
Percentage of Patients (%)



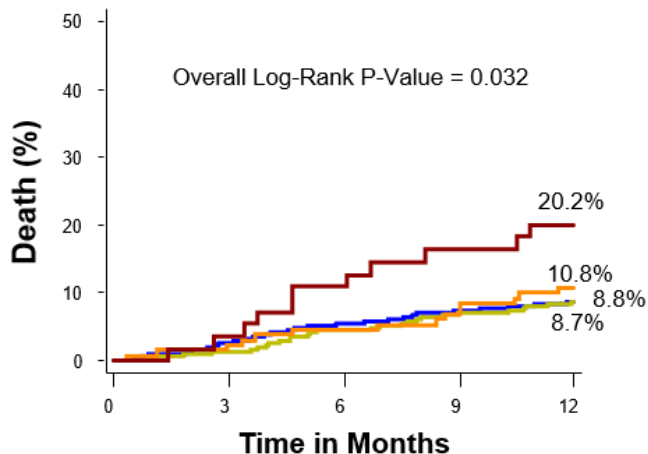
New Generations of THV



Hostile Anatomy

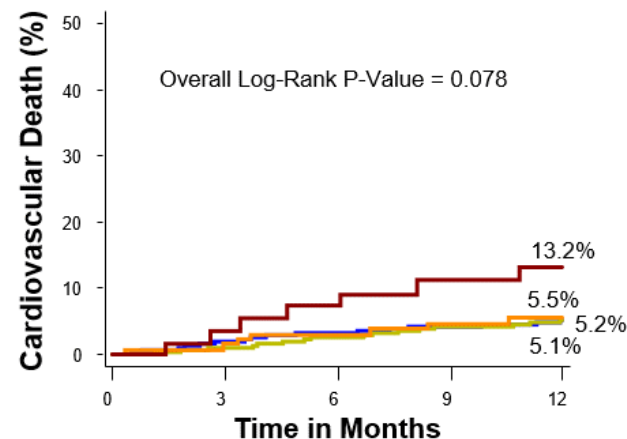


Impact of PVR on 1-year Outcomes – SAPIEN 3



Number at risk:

None/Trace	887	860	831	811	788
Mild	519	508	491	475	459
Mild-to-Moderate	131	127	124	121	115
≥Moderate	55	53	49	45	42

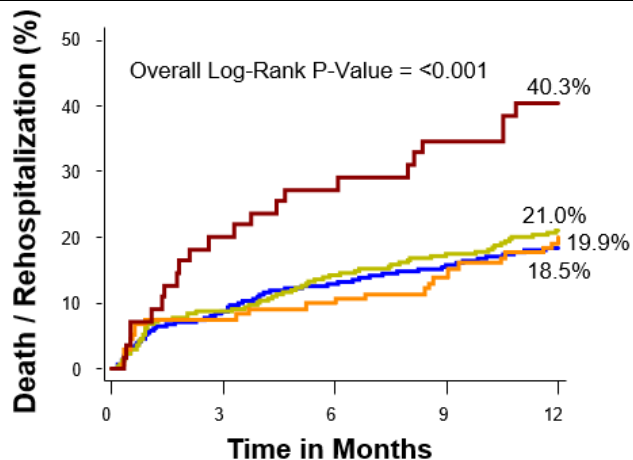


Number at risk:

None/Trace	887	860	831	811	788
Mild	519	508	491	475	459
Mild-to-Moderate	131	127	124	121	115
≥Moderate	55	53	49	45	42

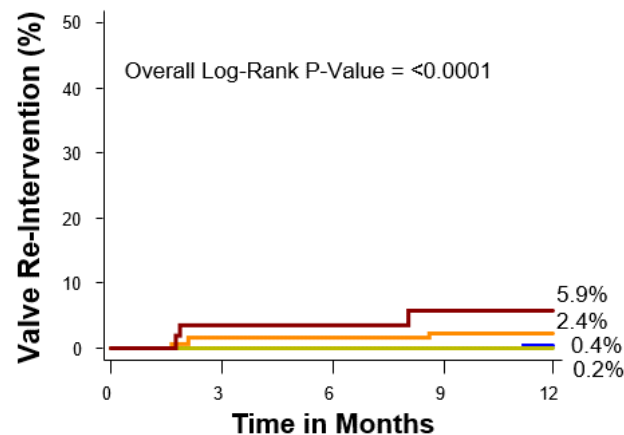


— None/Trace
— Mild
— Mild-Moderate
— ≥Moderate



Number at risk:

None/Trace	887	806	766	739	704
Mild	519	469	440	421	396
Mild-to-Moderate	131	120	117	112	105
≥Moderate	55	44	40	35	31

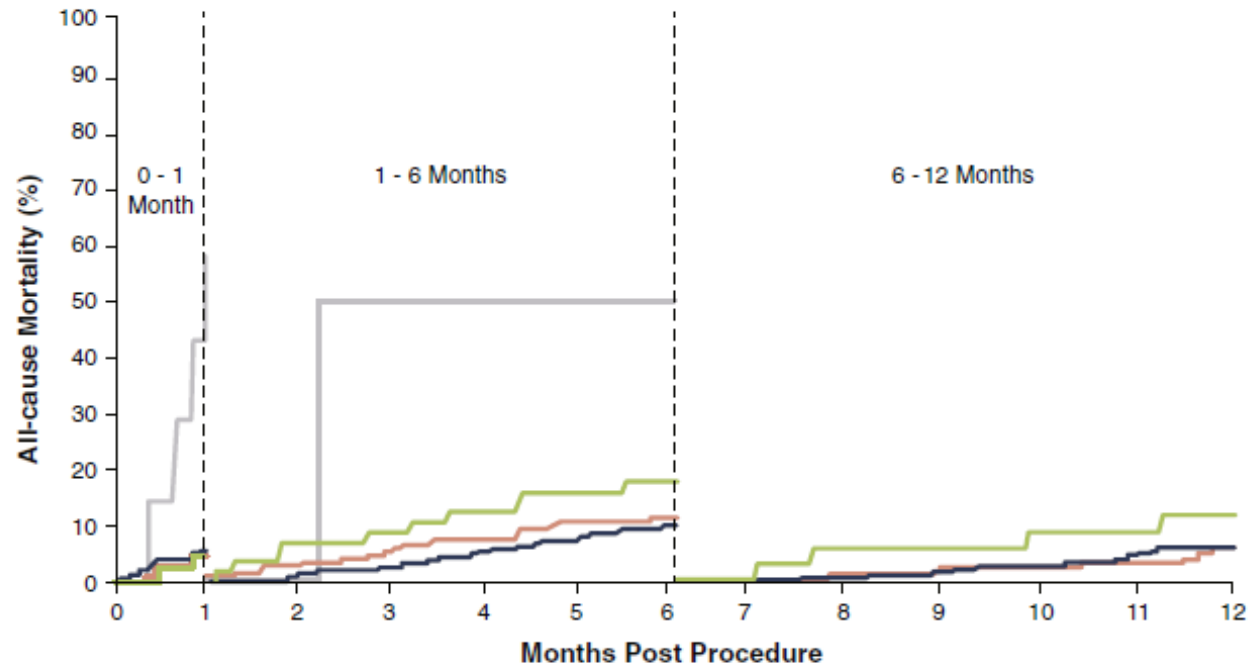
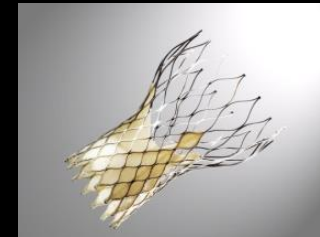


Number at risk:

None/Trace	887	859	830	810	786
Mild	519	508	490	474	458
Mild-to-Moderate	131	126	124	120	114
≥Moderate	55	51	47	42	39

Pibarot et al.
TCT 2016

Impact of PVR on 1 year Outcomes - CoreValve

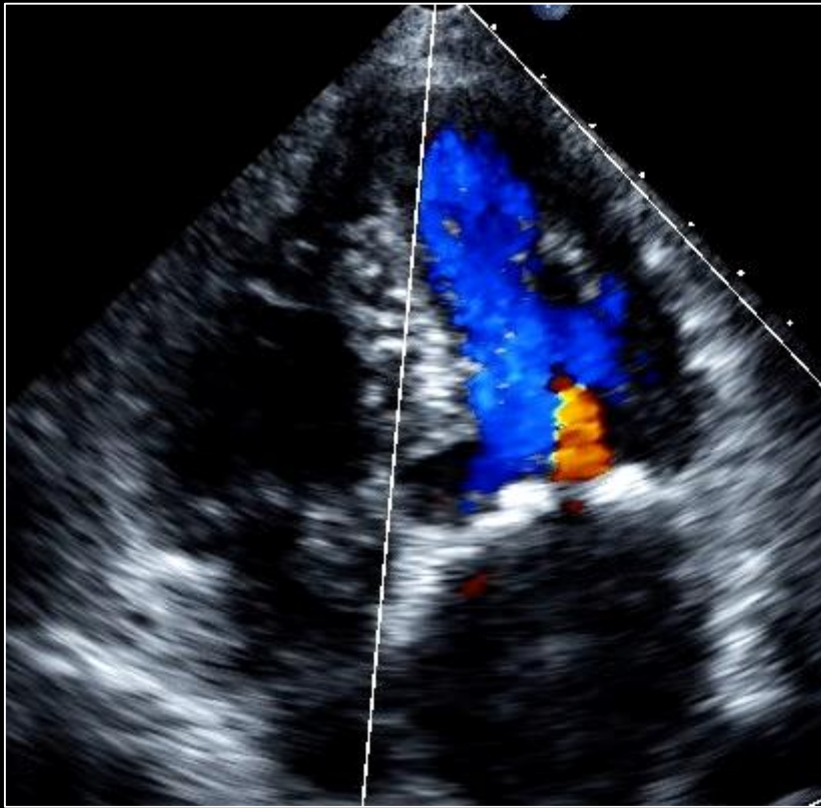


Numbers at Risk

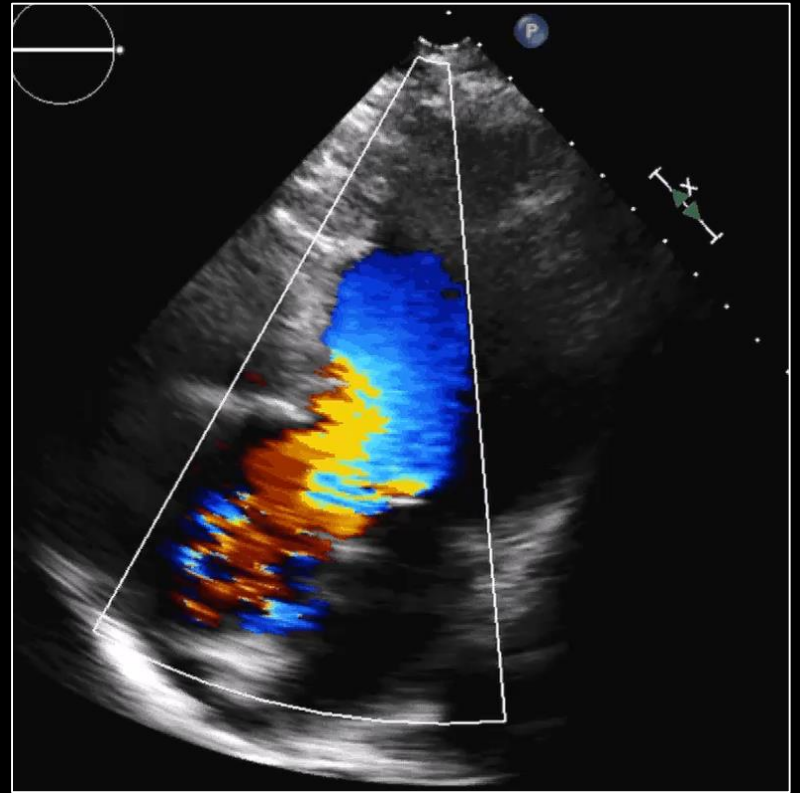
None/Trivial	296	262	276	259
Mild	216	206	150	141
Moderate	49	57	34	29
Severe	7	2	0	0



*A mild PVR may be harmful
in patients with pure AS*

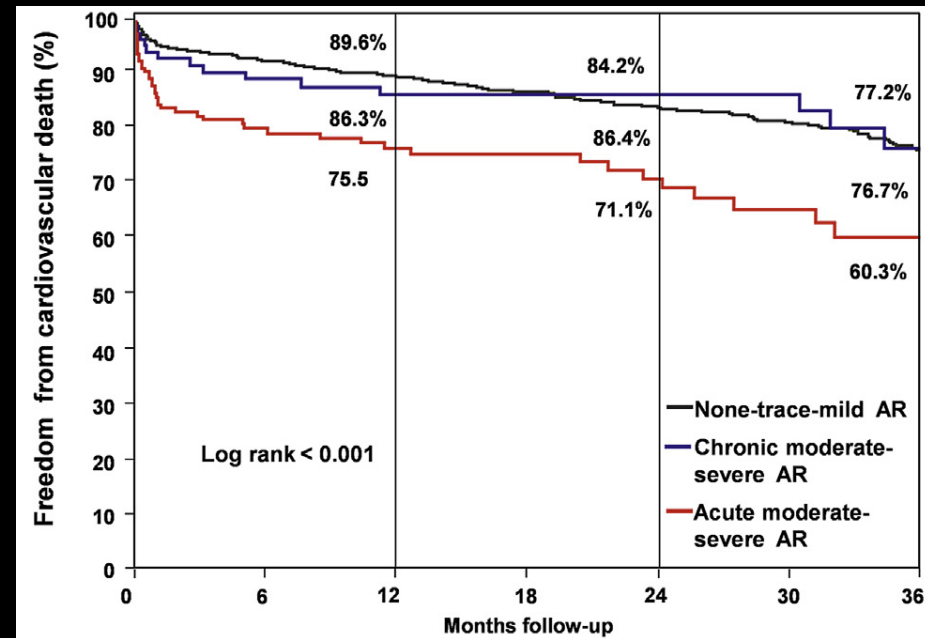
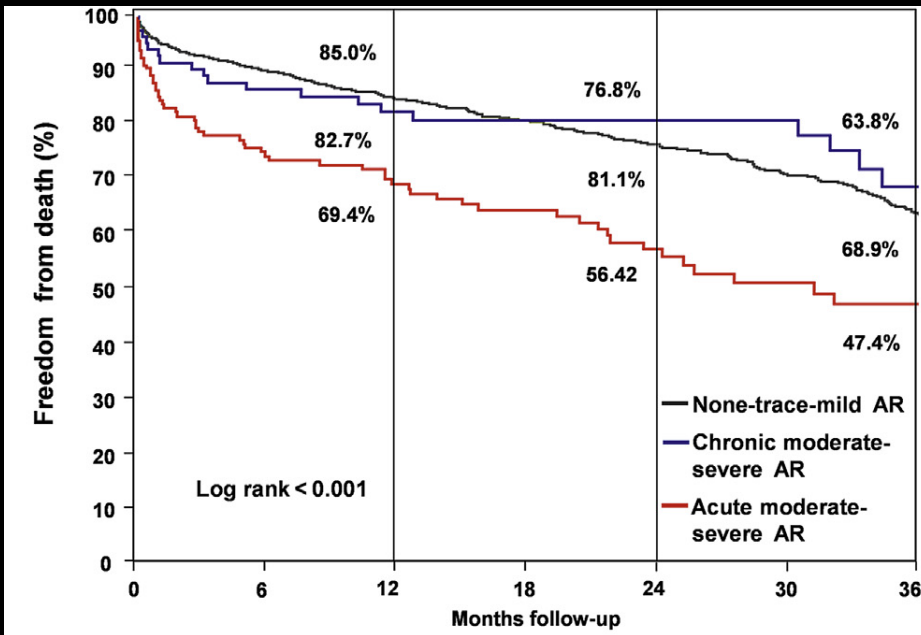


*A moderate PVR may be well tolerated
by patients with pre-existing AR*



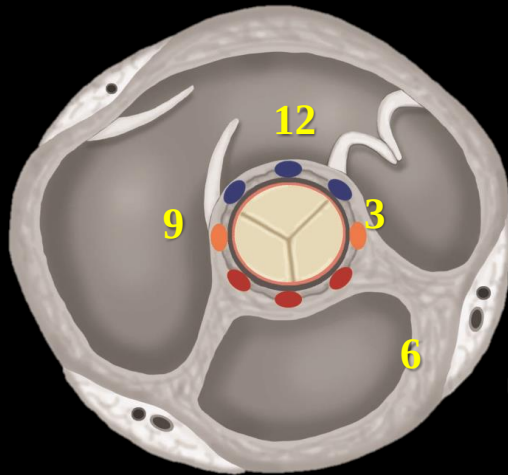
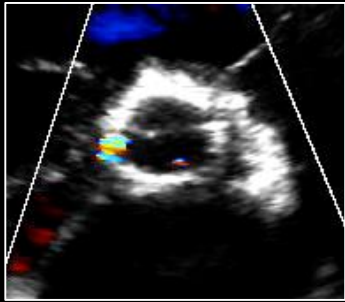
Effect of Acuteness of AR on Mortality After TAVR

Multicenter Study (1735 Patients)

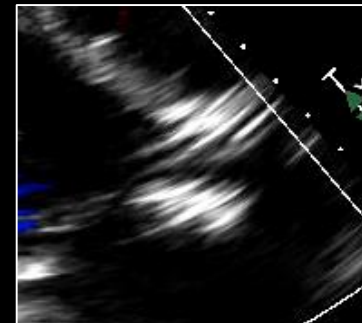
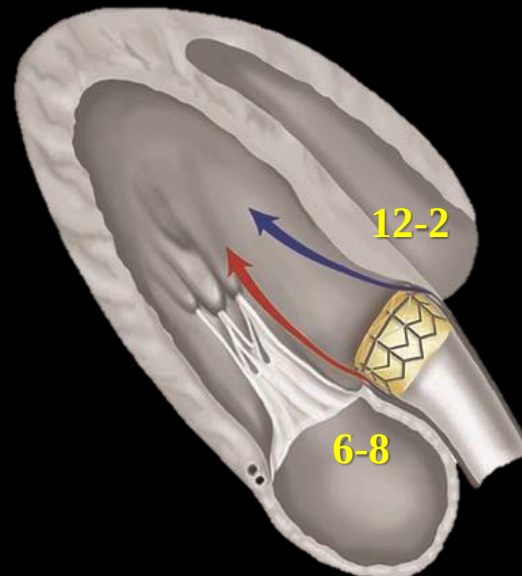
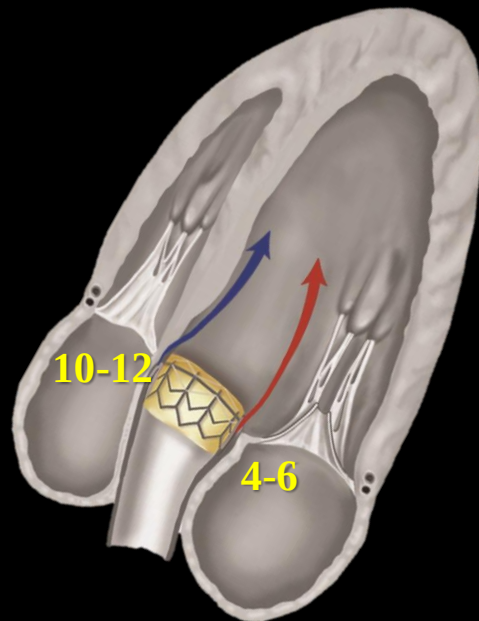
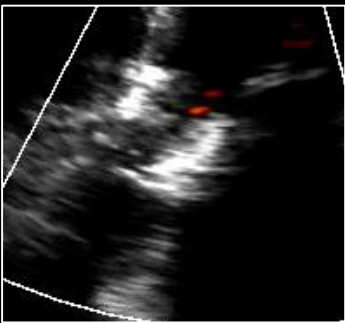
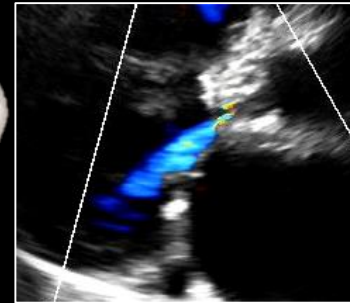
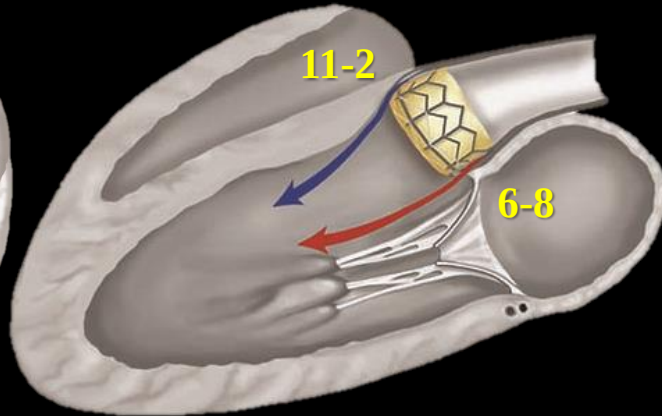


Assessment of PVR by Echo: Multi-window Imaging is Key!

PSAX



PLAX



Ap-5Ch

Ap-3Ch

Assessment of PVR by Echo: Multi-Parameter Integrative Approach is Key!

JACC: CARDIOVASCULAR IMAGING

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PUBLISHED BY ELSEVIER INC.

VOL. 8, NO. 3, 2015

ISSN 1936-878X/\$36.00

<http://dx.doi.org/10.1016/j.jcmg.2015.01.008>

Assessment of Paravalvular Regurgitation Following TAVR

A Proposal of Unifying Grading Scheme

Philippe Pibarot, DVM, PhD,* Rebecca T. Hahn, MD,† Neil J. Weissman, MD,‡ Mark J. Monaghan, PhD§



CrossMark



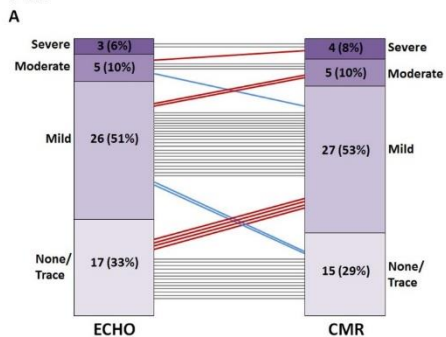
JACC: CARDIOVASCULAR IMAGING CME

Pibarot et al. JACC CV Imaging; 8:340-360, 2015

3-CLASS GRADING SCHEME	TRACE	MILD		MODERATE		SEVERE
4-CLASS GRADING SCHEME	1	1	2	2	3	4
UNIFYING 5-CLASS GRADING SCHEME	TRACE	MILD	MILD-TO-MODERATE	MODERATE	MODERATE-TO-SEVERE	SEVERE
Structural Parameters						
• Valve stent	Usually normal	Usually normal	Normal/ abnormal	Normal/ abnormal	Usually abnormal	Usually abnormal†
Doppler parameters (qualitative or semi-quantitative)						
• Jet features						
Extensive/wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Jet path visible along the stent	Absent	Absent	Possible	Often present	Usually present	Present
Proximal Flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
• Jet width at its origin (%LVOT diameter): color Doppler	Narrow (<5)	Narrow (5-15)	Intermediate (15-30)	Intermediate (30-45)	Large (45-60)	Large (>60)
○ Jet deceleration rate (PHT, ms): CW Doppler	Slow (>500)	Slow (>500)	Slow (>500)	Variable (200-500)	Variable (200-500)	Steep (<200)
○ Diastolic flow reversal in the descending aorta: PW Doppler	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (end-diast. vel.>20 cm/s)	Holodiastolic (end-diast. vel.>25 cm/s)
• Circumferential extent of PVR (%) color Doppler	<10	<10	10-20	20-30	>30	>30
Doppler parameters (quantitative)						
○ Regurgitant fraction (%)	<15	<15	15-30	30-40	40-50	>50

Assessment of PVR by CMR

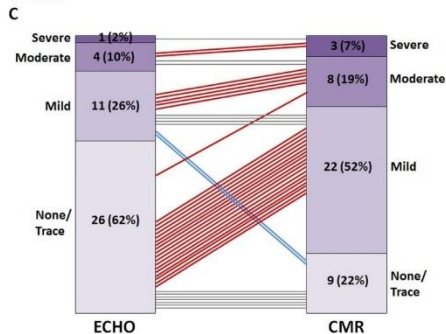
PRE



B

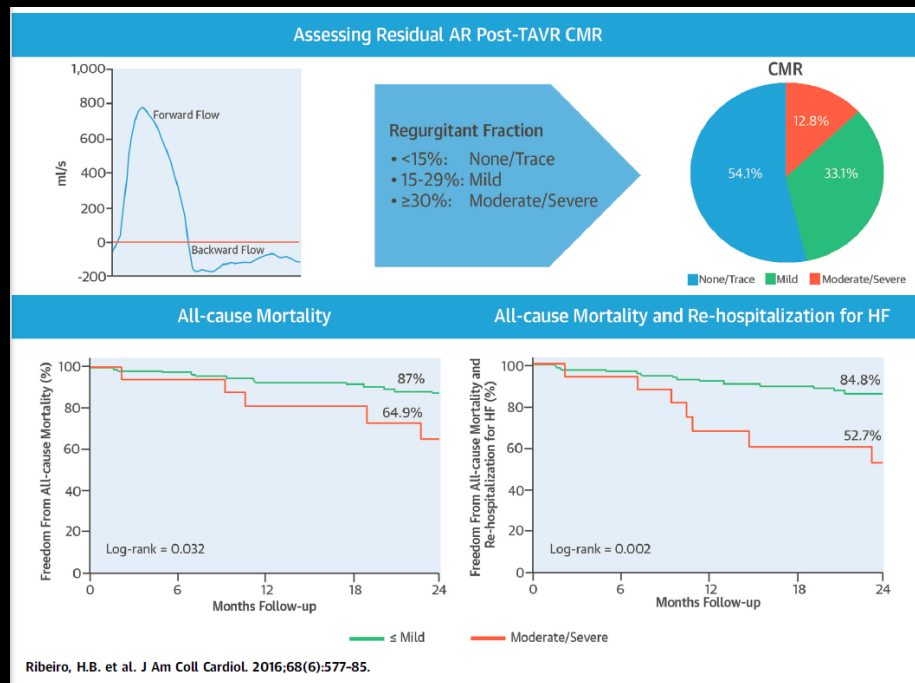
ECHO \ CMR	None/Trace	Mild	Moderate	Severe	Total
None/Trace	13 (76)	2 (8)	-	-	15
Mild	4 (24)	22 (84)	1 (20)	-	27
Moderate	-	2 (8)	3 (60)	-	5
Severe	-	-	1 (20)	2 (100)	3
Total	17	26	5	2	40/50 (80)

POST



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 et al. Heart 2016

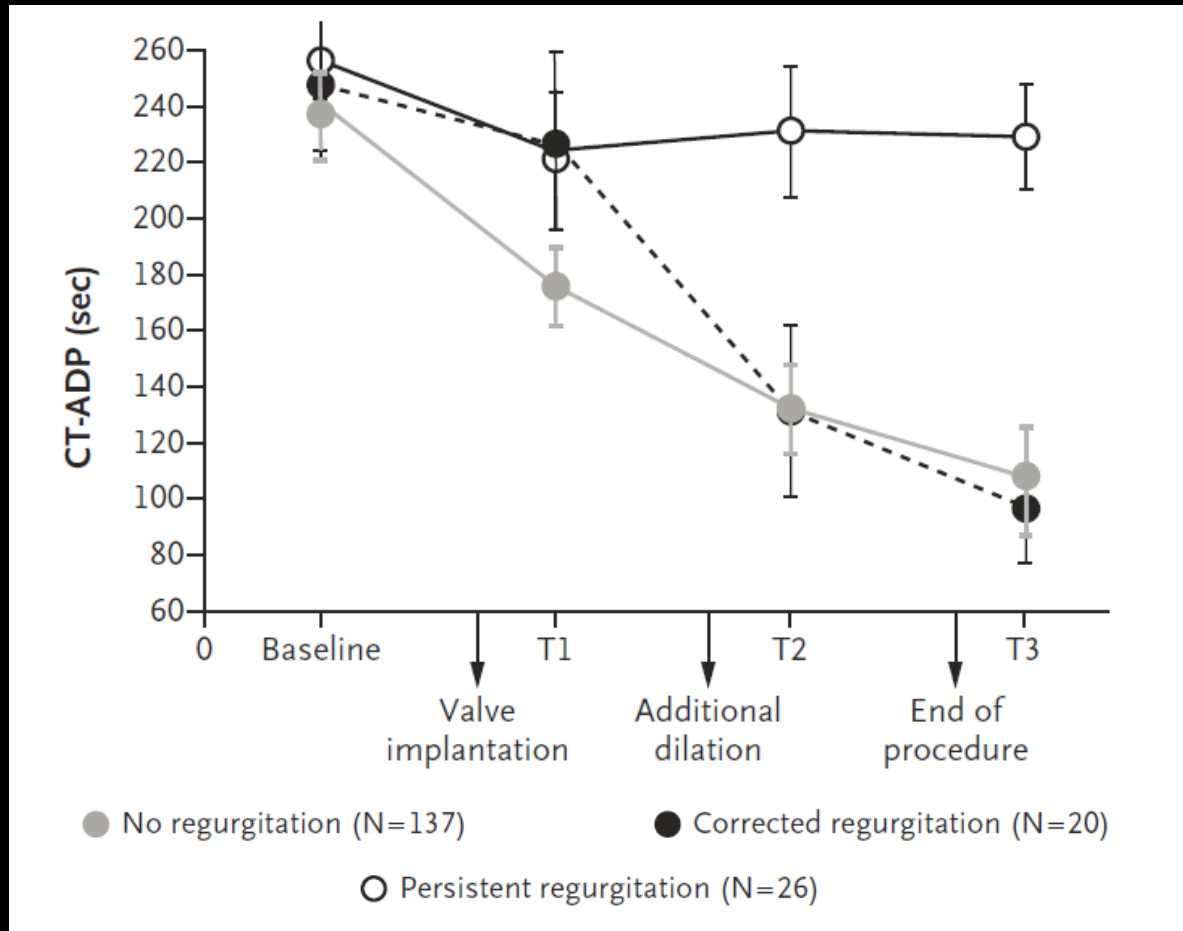
Evolution of TAVR in 2017

- **Less and less invasive TAVR:** majority of cases performed under conscious sedation ($\geq 70\%$) with transfemoral approach ($\geq 90\%$)
- **Consequences of this evolution:**
 - Less and less comprehensive imaging:
 - No TEE
 - Ventriculography only
 - Suboptimal TTE
 - **Risk of underdetection of PVR** at the time of procedure

Usefulness of Von Willebrand Factor (or CT-ADP) for Detection of Significant PVR at the time of Procedure

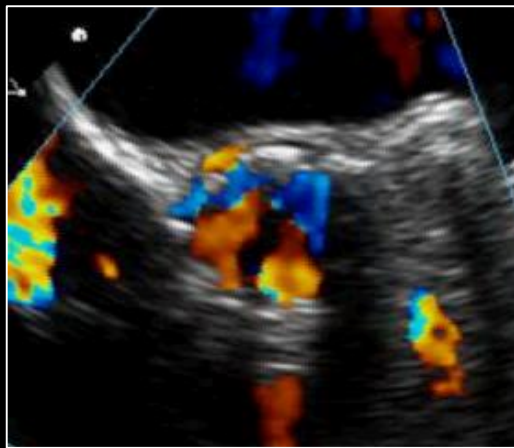


PFA Analyzer

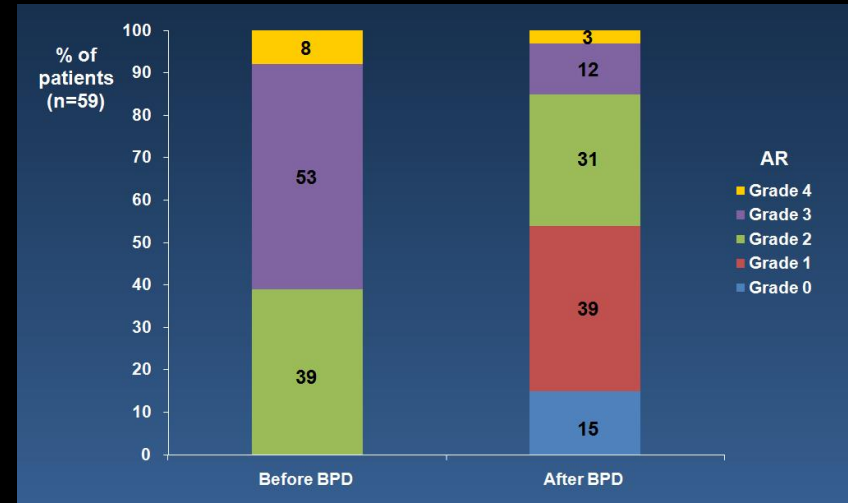
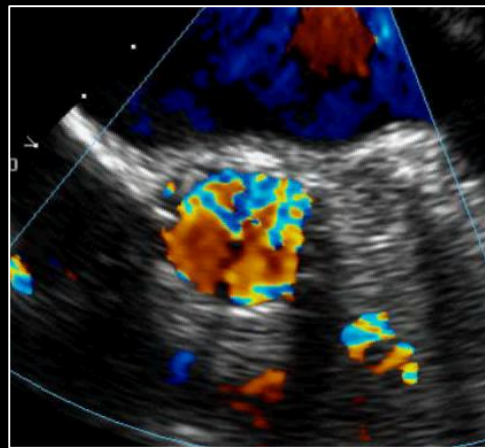


Impact of Balloon Post-dilation on PVR And Outcomes

Pre-BPD



Post-BPD



BPD: 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

**Any Degree of AR at Ventriculography and / or blood CT-ADP > 180 s
post THV Deployment**

No AR

**TEE / TTE for quantitation of AR severity and identification
of AR location (paravalvular vs. central) and etiology**

Trace

Mild

Moderate

Severe

**Presence of vulnerability factors to AR
and/or
Absence of risk factors for complications
with corrective procedures**

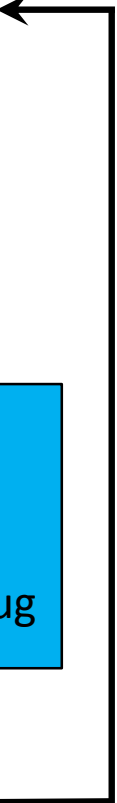
Yes

Corrective Procedures
Balloon post-dilation
Valve-in-valve
Closure of the leak with a plug

No

No More Procedures

Reassess



Conclusions

- **PVR is less and less an issue over time...
but it is still an issue in 2017**
- **Moderate/severe PVR:**
 - 2-4% of patients with new generations of THVs
 - 2-2.5 fold increase in the risk of mortality
 - Better tolerated in patients with pre-existing native AR
- **Mild PVR:**
 - 10-40% of patients with new generations of THVs
 - Impact on mortality if underestimated or if it occurs in a patient with no pre-existing AR and/or restrictive LV physiology

Take Home Message

- **Continue efforts for prevention of PVR**
 - **Optimize valve sizing and positioning**
 - **Optimize detection of PVR at the time of procedure:
imaging / hemodynamic / blood biomarkers**
 - **Rationale utilization of corrective procedures in light of:
severity of PVR vs. vulnerability factors to AR vs. risk for procedure
complications**



***By failing to prepare,
you are preparing to fail”***

Benjamin Franklin