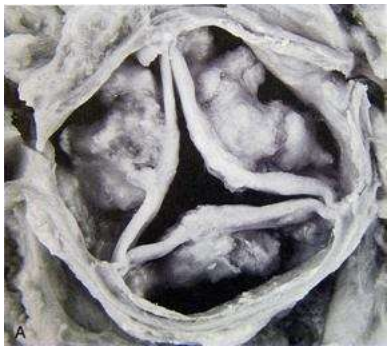
TAVR – Lessons on the Natural History of Aortic Stenosis



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April 29, 2018

Disclosures

Research:

PARTNER 3 trial
EARLY TAVR trial
REFLECT trial

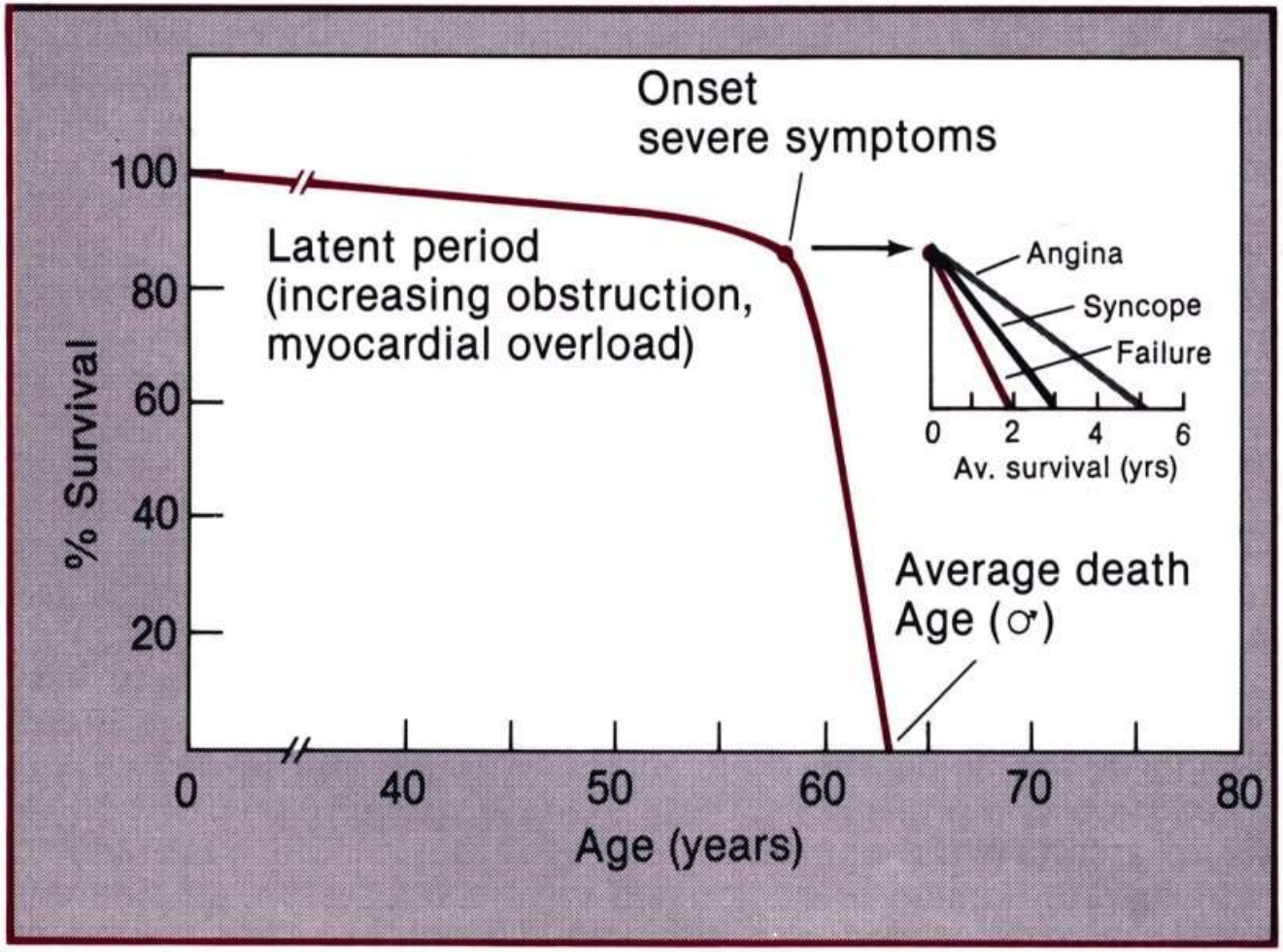
Overview

- Life Expectancy and Quality of Life
- Cardiac Function Before and After
- Biomarkers and TAVR
- TAVR and Other Organ Systems

Life Expectancy and Quality of Life

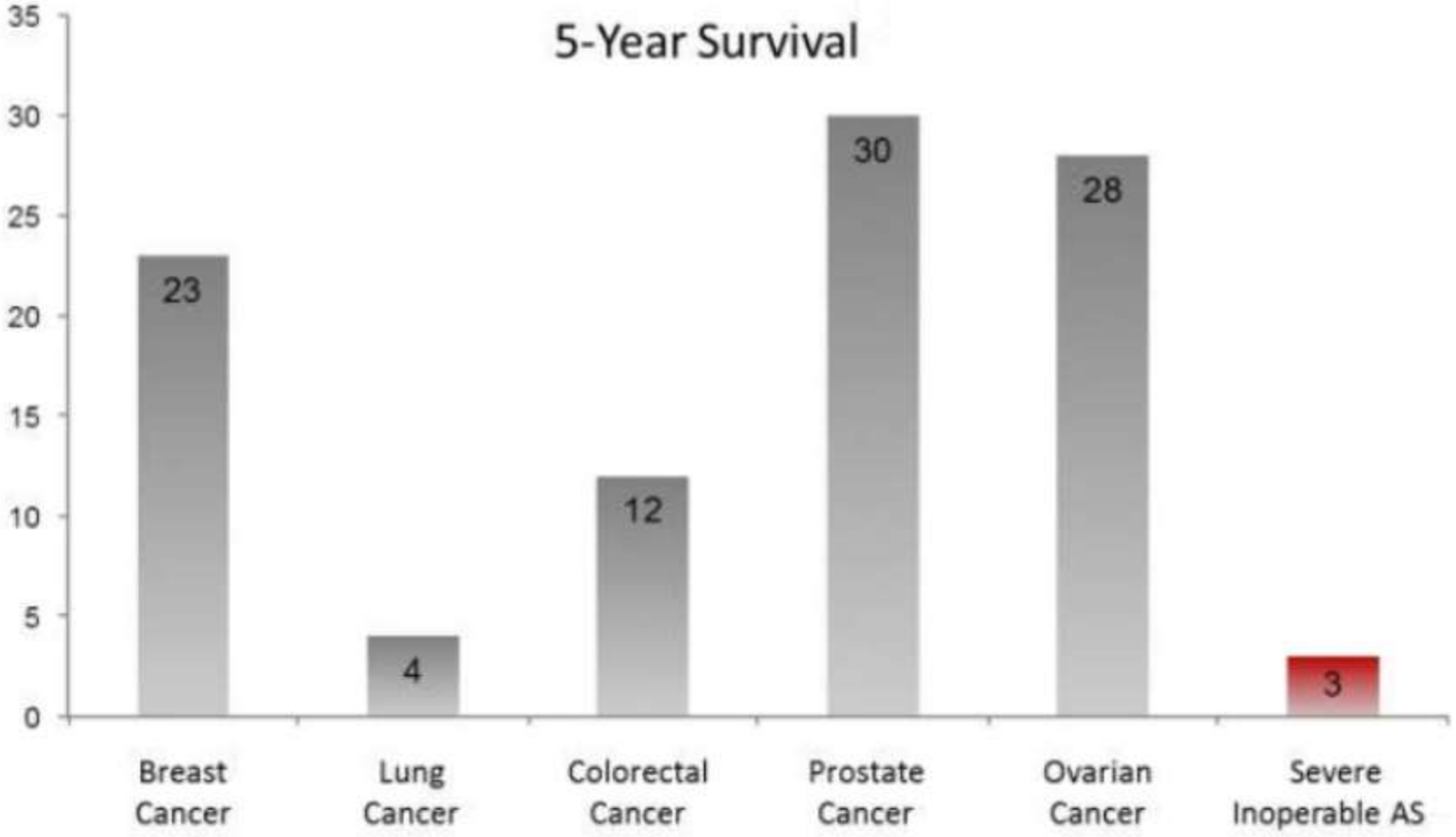
TAVR has confirmed that severe AS is a terminal diagnosis and treatment can extend both length and quality of life.

Natural History of Aortic Stenosis



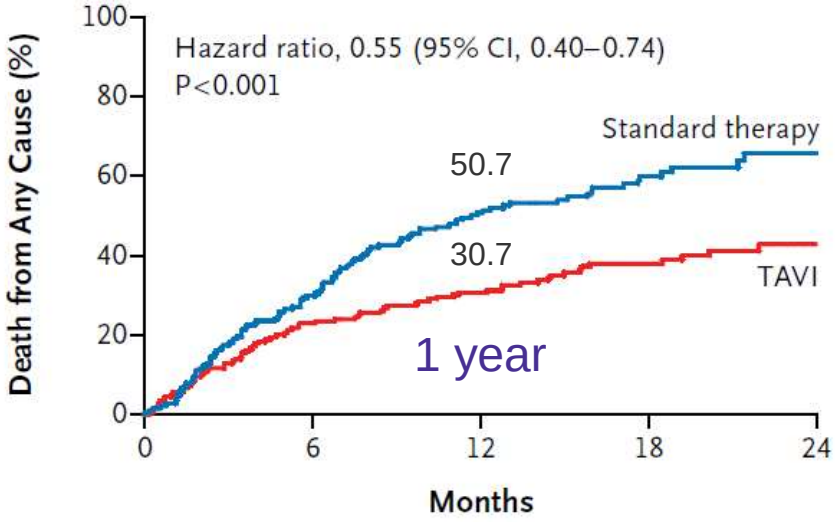
Ross & Braunwald *Circulation* 1968;38S

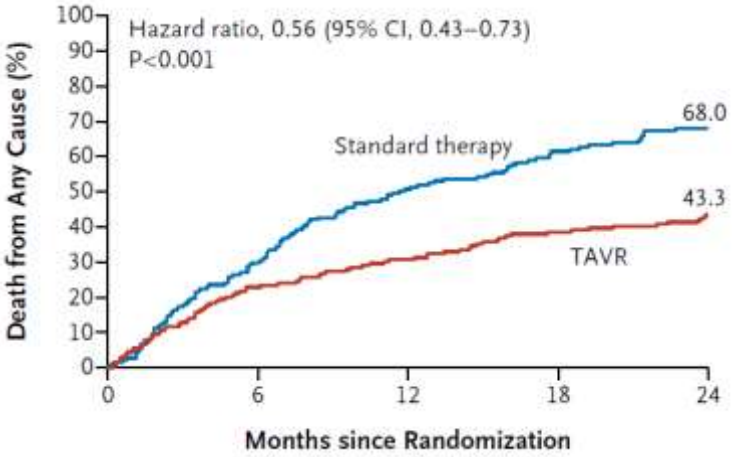
Severe Aortic Stenosis is a Terrible Diagnosis

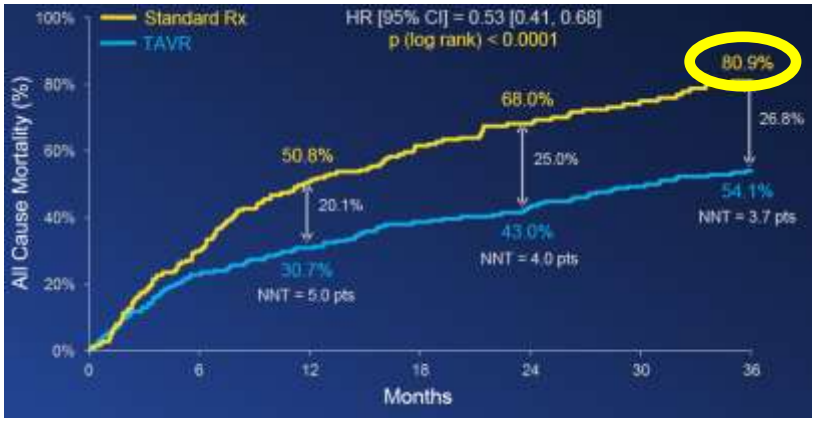


Courtesy of Murat Tuczu, MD

PARTNER Cohort B - Inoperable



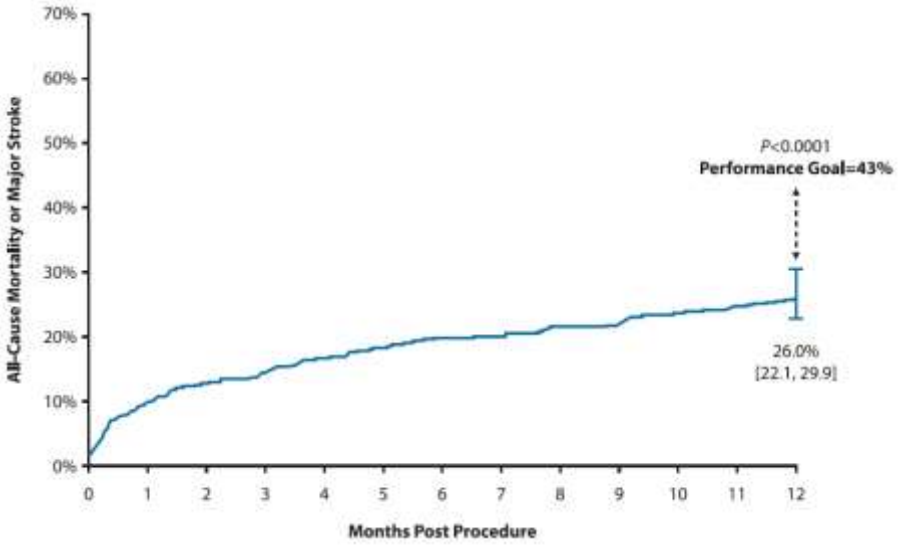


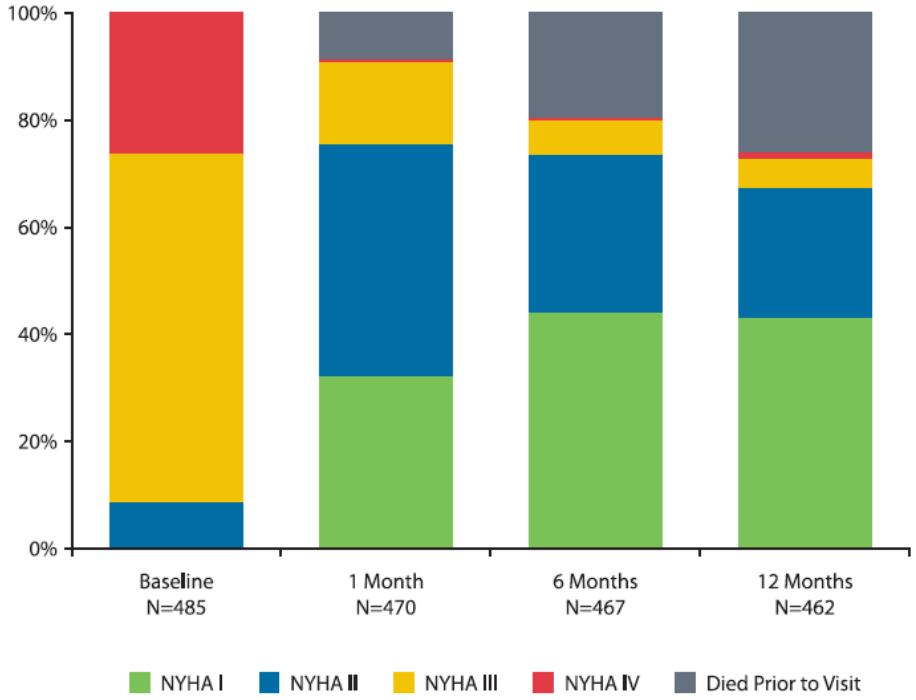


2 years

3 years

US CoreValve Extreme Risk – 1 year Outcomes





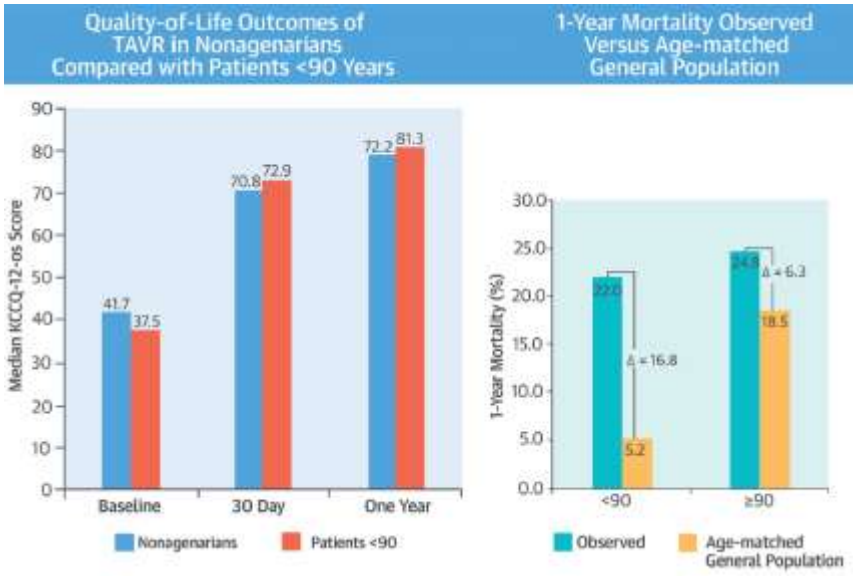
J Am Coll Cardiol 2014;63:1972–81

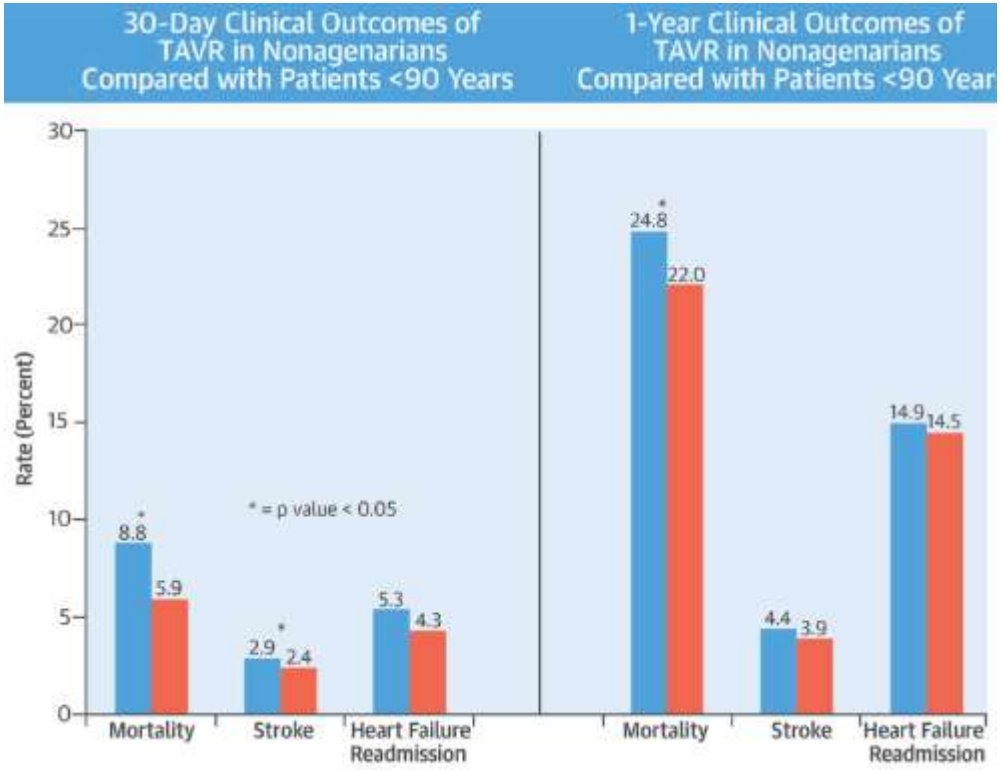
Should Transcatheter Aortic Valve Replacement Be Performed in Nonagenarians?

Insights From the STS/ACC TVT Registry

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

- 24,025 TAVR pts 11/11-9/14
- 15.7% ≥ 90 yrs
- 2.8% absolute higher 1 year mortality
- STS higher (10.9% vs. 8.1%), (same O/E)
- ↓ QOL at 30 d (vs. <90 yr)





Arsalan et al 2016;67:1387-95

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Cardiac Function Before and After

Aortic Stenosis contributes to structural and functional cardiac dysfunction – likely before symptoms become manifest.

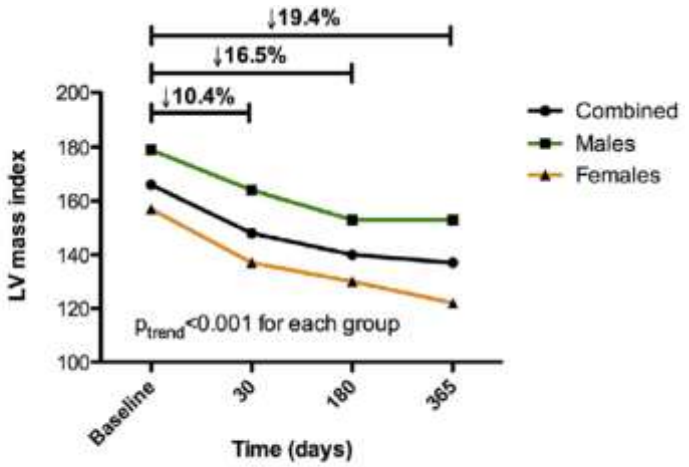
Cardiac Function Before and After

- LV Structure and Function
- Myocardial Fibrosis
- RV Function
- Pulmonary Hypertension
- Mitral Regurgitation
- The Conduction System

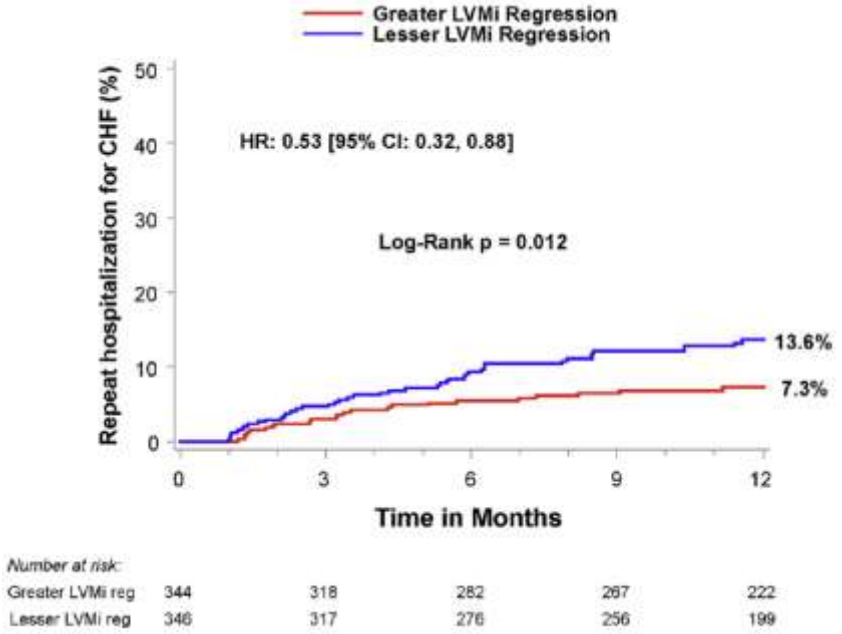
Early Regression of Severe Left Ventricular Hypertrophy After Transcatheter Aortic Valve Replacement Is Associated With Decreased Hospitalizations

JACC Cardiovascular Interventions

- 690 PARTNER Cohort A pts with severe LVH
- LVH regression after TAVR measured at 30 days
- Early regression – no effect on mortality but ↓ hospitalization (for HF), lower BNP and ↑QOL



# with LVMi measured				
Males	247	247	176	122
Females	347	347	225	131



Number at risk:					
Greater LVMi reg	344	318	282	267	222
Lesser LVMi reg	346	317	276	256	199

Lindman et al 2014;7:662-73

Diastolic Function and Transcatheter Aortic Valve Replacement

- 120 TAVR pts 1/12-6/14
- Baseline DD grade associated with ↓ survival
- Post-TAVR improvement in parameters of DD (lateral e' velocity, E/lateral e', LA volume index)

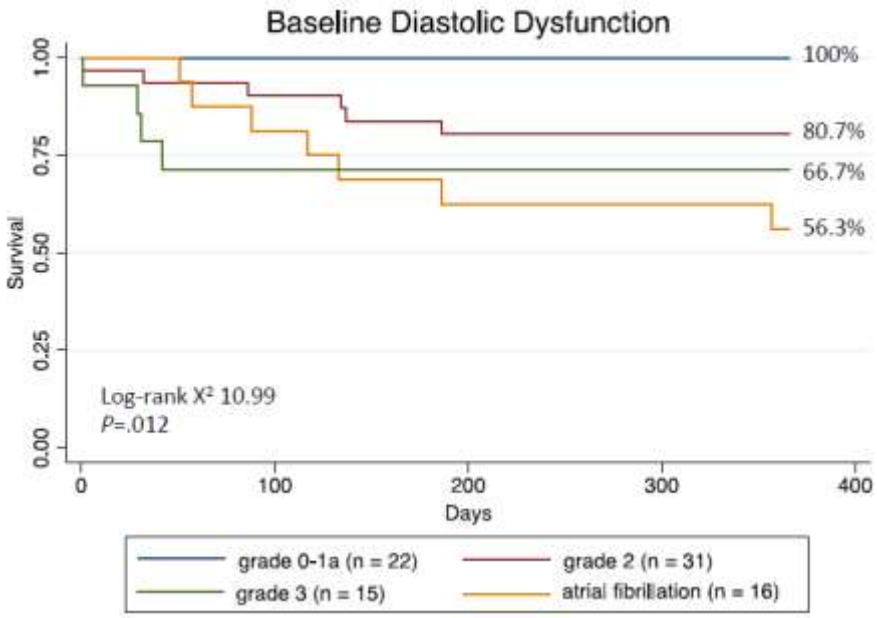


Table 4 Multivariate factors associated with adverse outcomes after TAVR

Variable	HR	*P* value
One-year death		
Inotrope	1.219 (1.020–1.417)	.032
Baseline diastolic dysfunction (per grade)	1.163 (1.049–1.277)	.0050
Trough systolic blood pressure (per 1 mmHg)	0.993 (0.987–1.000)	.051
One-year death or cardiovascular hospitalization		
Inotrope	1.340 (1.116–1.564)	.0030
Baseline diastolic dysfunction (per grade)	1.174 (1.032–1.318)	.018

Blair … Flaherty 2017;30:541-51

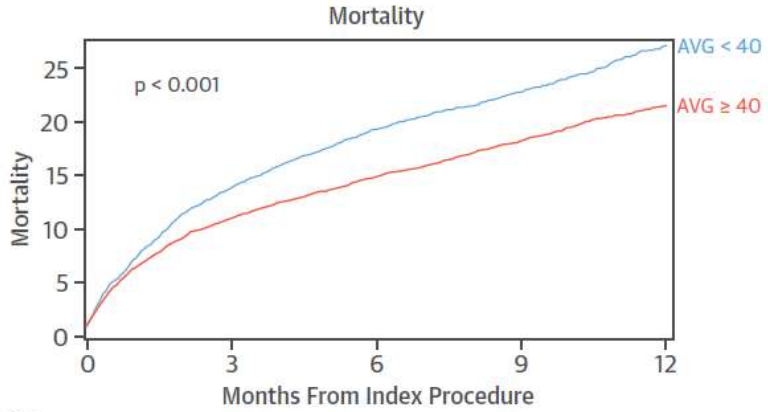
Impact of Ejection Fraction and Aortic Valve Gradient on Outcomes of Transcatheter Aortic Valve Replacement

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

- 11,292 TAVR pts TVT registry
- Lower LVEF associated with ↓ survival and ↑ recurrent HF
- After adjustment, only low gradient (<40 mmHg) remained associated with ↓ survival (HR 1.21, p<0.001) and ↑ recurrent HF (HR 1.52, p<0.001)

Number at Risk

LVEF <30%	803	622	481	379	283
LVEF 30-50%	2,902	2,254	1,812	1,452	1,128
LVEF >50%	7,587	6,117	4,880	3,908	3,010



Number at Risk

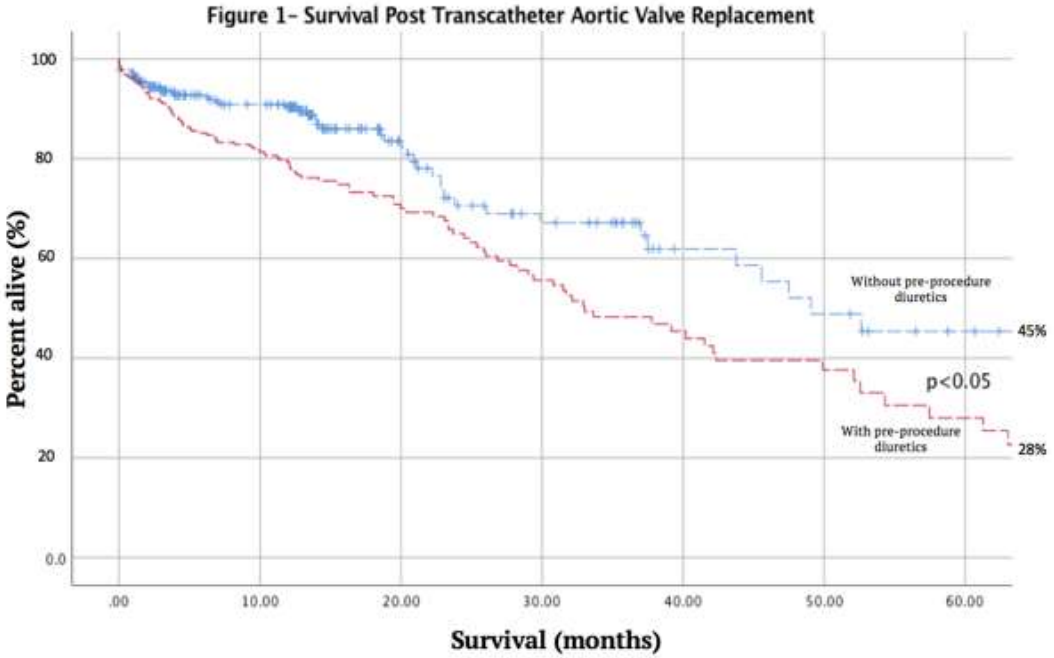
AVG < 40mmHg	3880	3024	2337	1868	1428
AVG ≤ 40mmHg	7412	5959	4834	3867	2999

Baron et al 2016;67:2349-58

Loop Diuretic Use Prior to TAVR is Associated with Increased Mortality

ACC.18

- 572 TAVR patients
- 52.1% on loop diuretics pre-TAVR
- ↓ survival at 1 year on loop diuretics (79.4% vs. 90.4%, p=0.003)
- For every 10 mg of furosemide daily equivalent, there was 5.1% increase risk of death



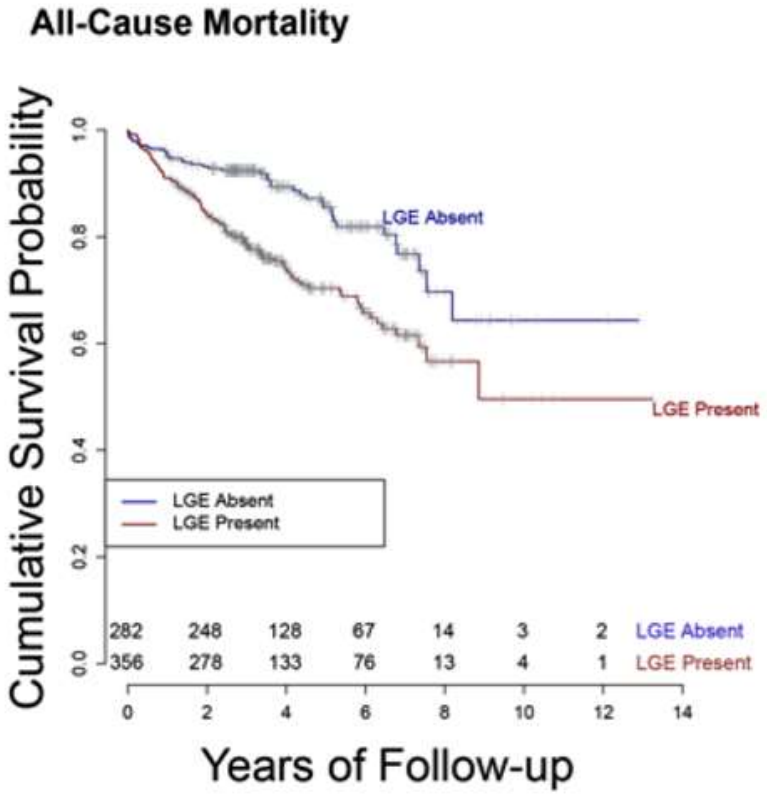
Canty … Flaherty ACC '18 Orlando

Myocardial Scar Predicts Mortality in Severe Aortic Stenosis:

Data from the BSCMR Valve Consortium

ESC CONGRESS BARCELONA 2017

- 703 pts with severe AS underwent TAVR or SAVR 1/03-5/15 and had CMR
- 51% with myocardial scar
- Scar associated with double long-term mortality (28.7% vs. 14.5%, p<0.001)
- For every 1% ↑ scar burden then was a 10% ↑ all-cause mortality

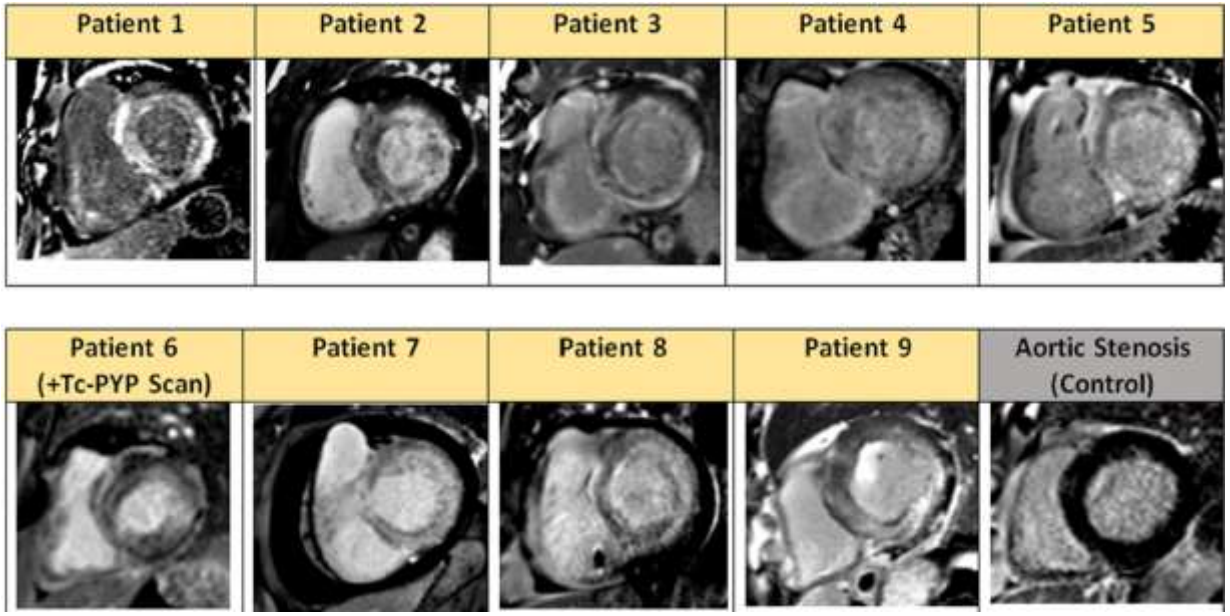


Thomas Treibel et al

Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis

Journal of Cardiovascular Magnetic Resonance

- 113 pts with AS & underwent CMR
- Suspected CA in 9 (8%)
- All > 80 yrs, 89% male
- Low-flow low gradient AS in 7/9 (78%)
- AS + CA higher mortality at 1 year than AS alone (56% vs. 20%, p<0.0001) including those treated

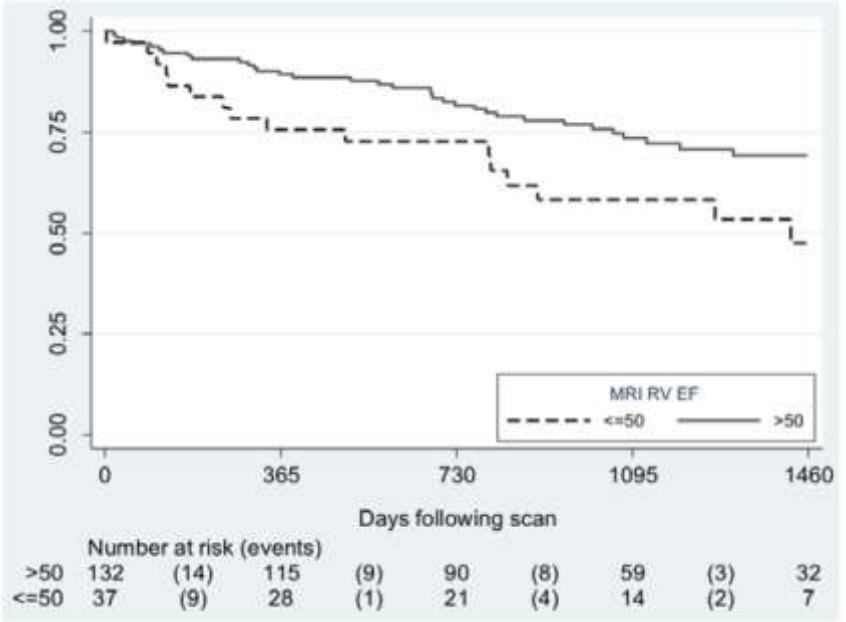


Cavalcante et al 2017;19:98

Prevalence and Prognostic Significance of Right Ventricular Systolic Dysfunction in Patients Undergoing Transcatheter Aortic Valve Implantation

Circulation
Cardiovascular Interventions

- 190 TAVR pts who underwent CMR
- Impaired RV function in 23.7%
- RV dysfxn associated with lower LVEF (42% vs. 69%)
- RV dysfxn (RVEF ≤ 50%) associated with worse long-term survival after TAVR (HR 2.12, p=0.017)

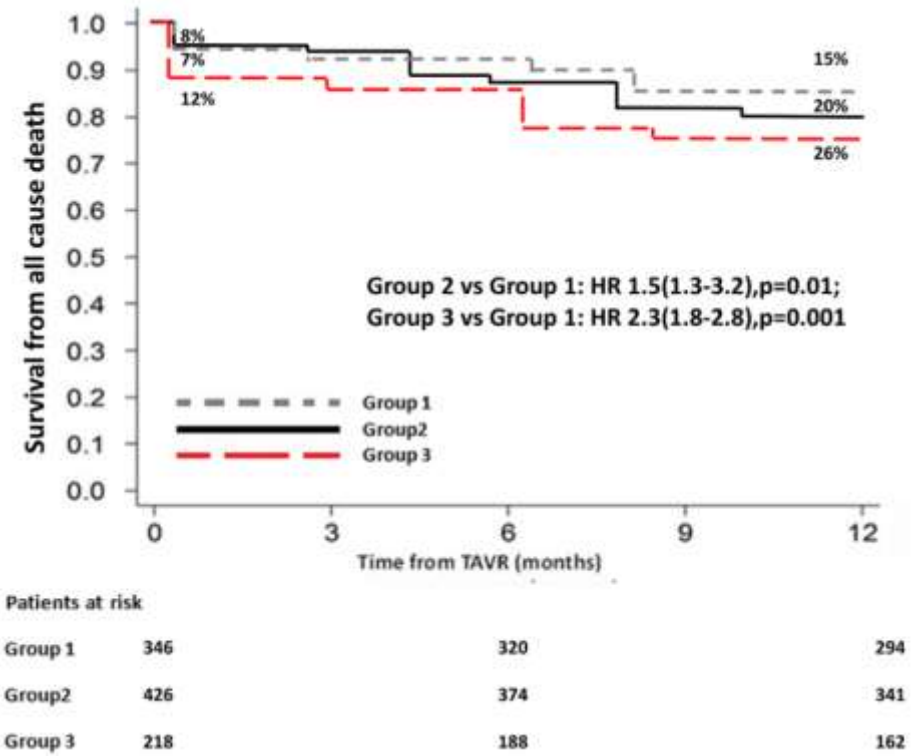


Lindsay et al 2016;9:e003486

Persistence of Severe Pulmonary Hypertension After Transcatheter Aortic Valve Replacement

Circulation
Cardiovascular Interventions

- 990 TAVR pts:
  - Group 1 PASP <40 mmHg (35%)
  - Group 2 PASP 40-60 mmHg (43%)
  - Group 3 PASP >60 mmHg (22%)
- Similar 30 day survival, but worse HF outcomes in Group 3
- PASP dropped ≥15 mmHg in 32% of Group 2 and 35% of Group 3 at 30 days
- Worse 1 year survival in Groups 2 and 3
- Worst survival at 1 year (HF 2.4, p=0.04) when PASP remained >60 mmHg at 30 days

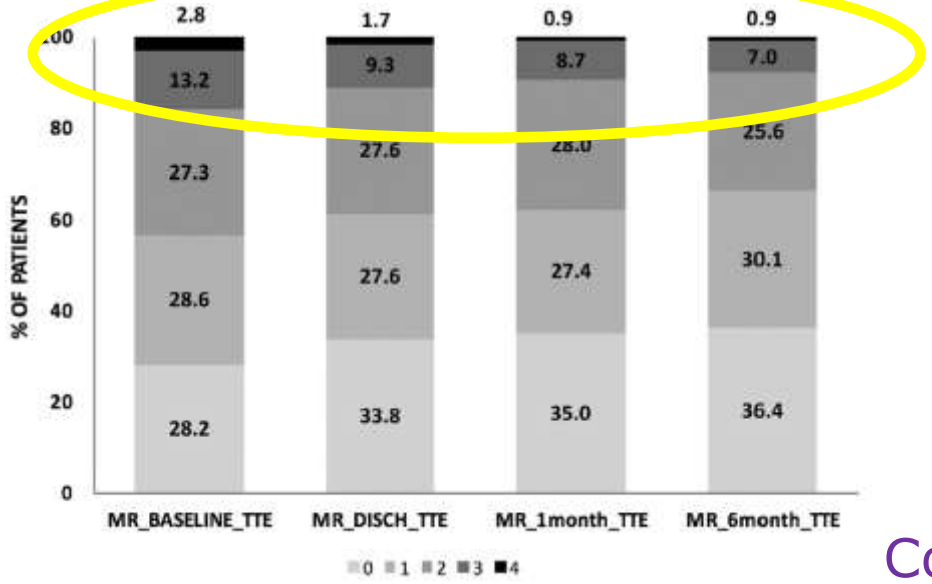


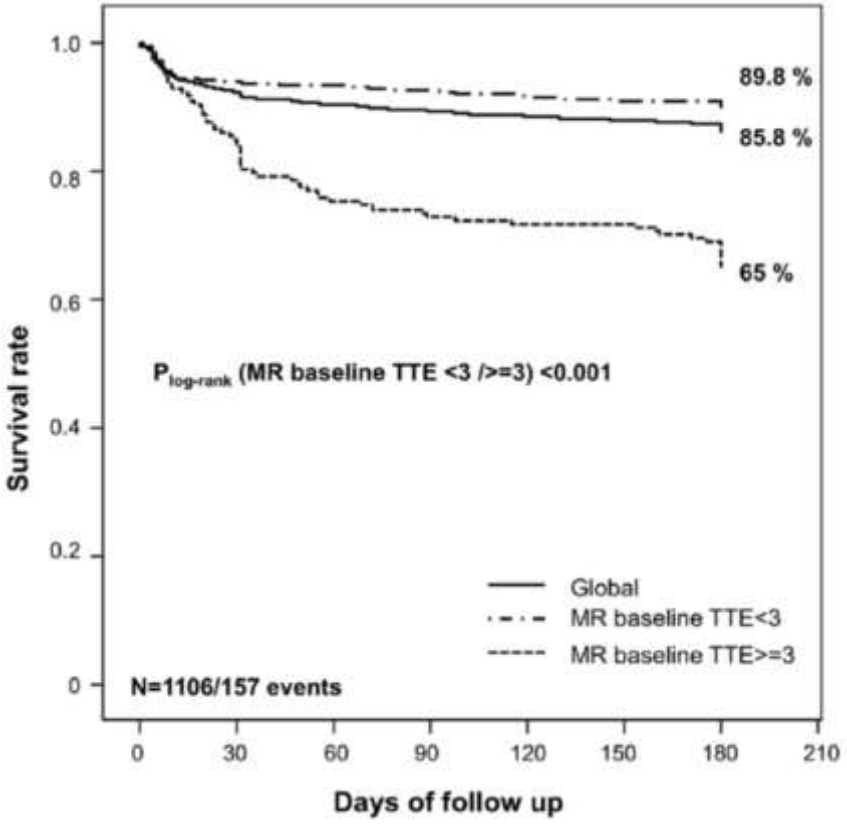
Testa et al 2016;9:e003563

Mitral Regurgitation After Transcatheter Aortic Valve Replacement

JACC Cardiovascular Interventions

- 1,110 TAVR pts, 16% with MR pre-TAVR
- Degree of MR improved in 60%
- ↑Mitral annular diameter and mitral apparatus calcification predictive of persistent MR
- 13.1% with persistent MR could be eligible for percutaneous mitral valve therapies





Cortes et al 2016;9:2189-99

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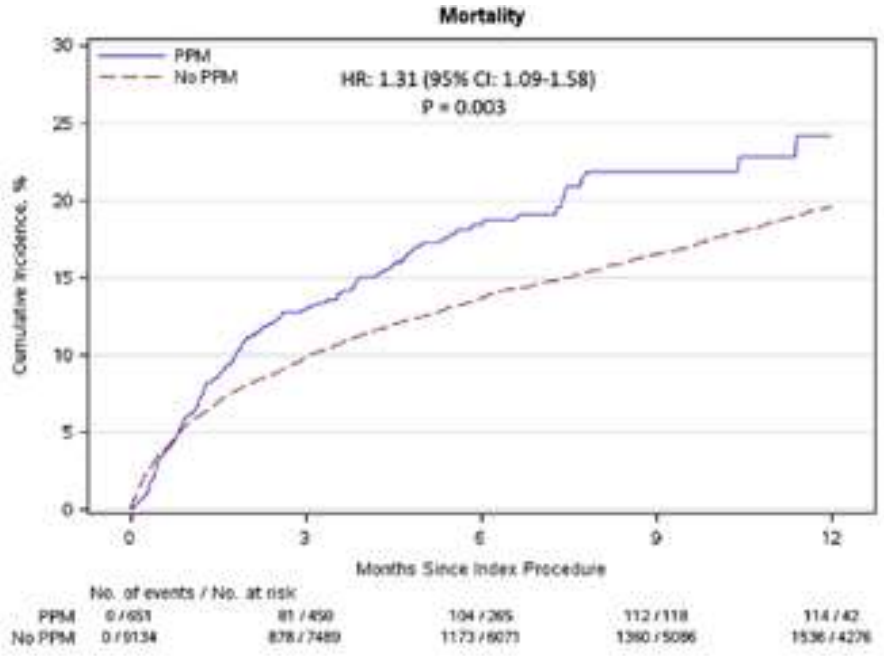
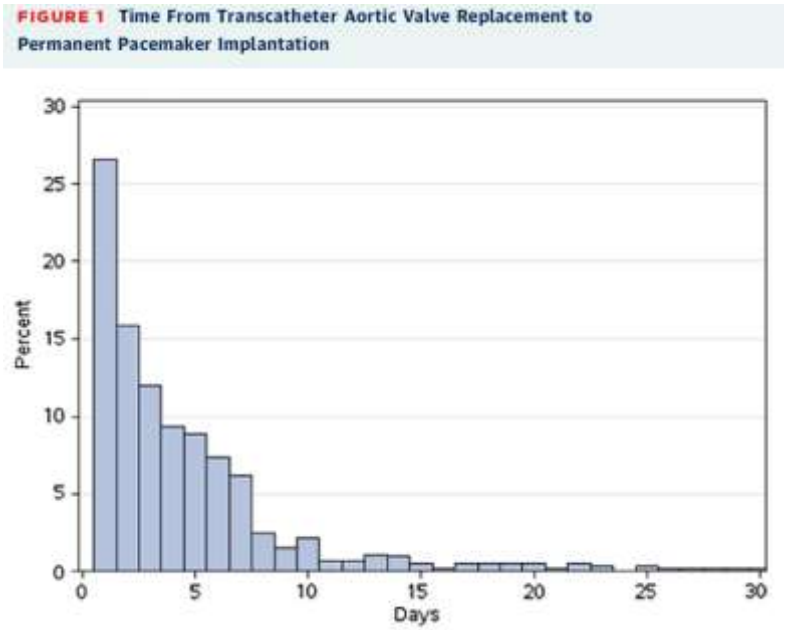
Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement

JACC Cardiovascular Interventions

- 9,785 TAVR pts TVT registry 11/11-9/14
- 25.1% of self-expanding, 4.3% of balloon-expandable
- PPM associated with ↑ mortality at 1 year (HR 1.31) (p=0.003)





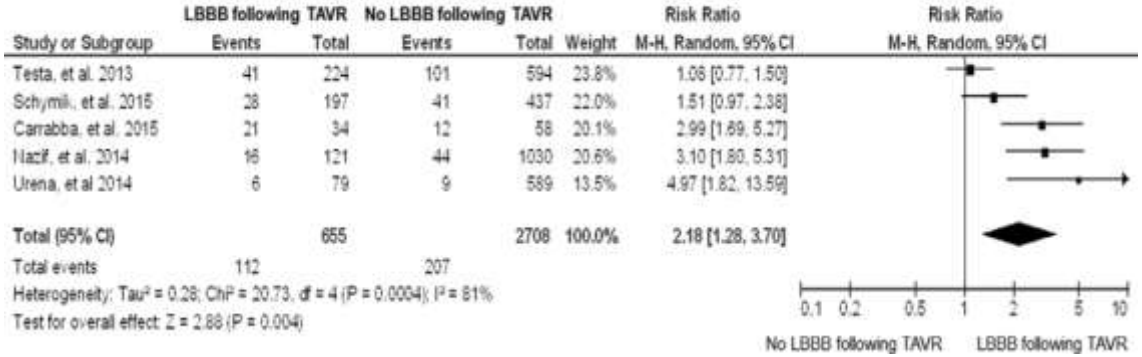
Fadahunsi et al 2016;9:2189-99

Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement

Circulation
Cardiovascular Interventions

- 17 studies, ~ 12,000 pts
- New LBBB 13.3 – 37.0%
- New LBBB associated with new PPM (RR 2.18) and cardiac death (RR 1.39)

1-year RR of permanent pacemaker implantation

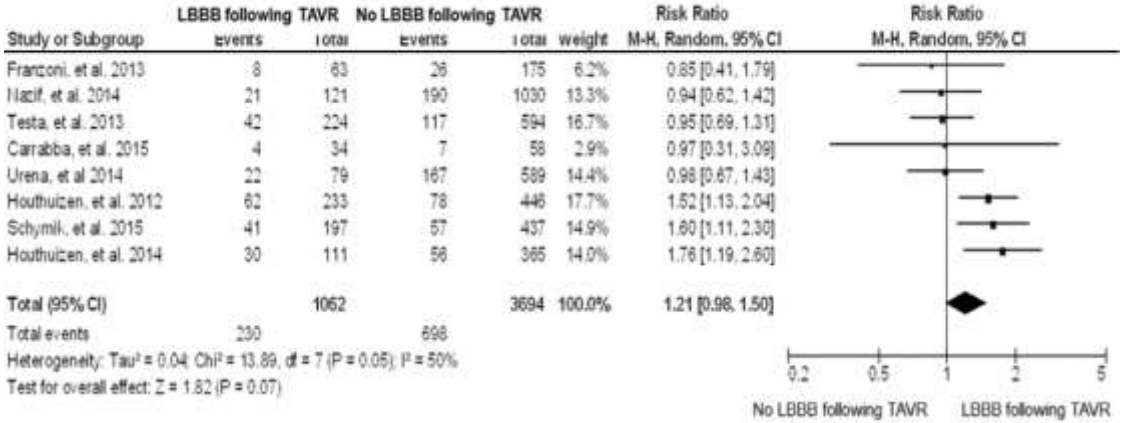


Study or Subgroup	LBBB following TAVR Events	Total	No LBBB following TAVR Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Testa, et al. 2013	41	224	101	594	23.8%	1.08 [0.77, 1.50]
Schymik, et al. 2015	28	197	41	437	22.0%	1.51 [0.97, 2.36]
Carrabba, et al. 2015	21	34	12	58	20.1%	2.99 [1.69, 5.27]
Nazif, et al. 2014	16	121	44	1030	20.6%	3.10 [1.80, 5.31]
Urena, et al 2014	6	79	9	589	13.5%	4.97 [1.82, 13.59]
Total (95% CI)		655		2708	100.0%	2.18 [1.28, 3.70]
Total events	112		207			

Heterogeneity: Tau² = 0.28; Chi² = 20.73, df = 4 (P = 0.0004); I² = 81%
Test for overall effect: Z = 2.88 (P = 0.004)

Risk Ratio M-H, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
No LBBB following TAVR LBBB following TAVR

1-year RR of all-cause death



Study or Subgroup	LBBB following TAVR Events	Total	No LBBB following TAVR Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Franzoni, et al. 2013	8	63	26	175	6.2%	0.85 [0.41, 1.79]
Nazif, et al. 2014	21	121	190	1030	13.3%	0.94 [0.62, 1.42]
Testa, et al. 2013	42	224	117	594	16.7%	0.95 [0.69, 1.31]
Carrabba, et al. 2015	4	34	7	58	2.9%	0.97 [0.31, 3.09]
Urena, et al 2014	22	79	167	589	14.4%	0.98 [0.67, 1.43]
Houthuizen, et al. 2012	62	233	78	446	17.7%	1.52 [1.13, 2.04]
Schymik, et al. 2015	41	197	57	437	14.9%	1.60 [1.11, 2.30]
Houthuizen, et al. 2014	30	111	56	365	14.0%	1.76 [1.19, 2.60]
Total (95% CI)		1062		3694	100.0%	1.21 [0.98, 1.50]
Total events	230		698			

Heterogeneity: Tau² = 0.04; Chi² = 13.89, df = 7 (P = 0.05); I² = 50%
Test for overall effect: Z = 1.82 (P = 0.07)

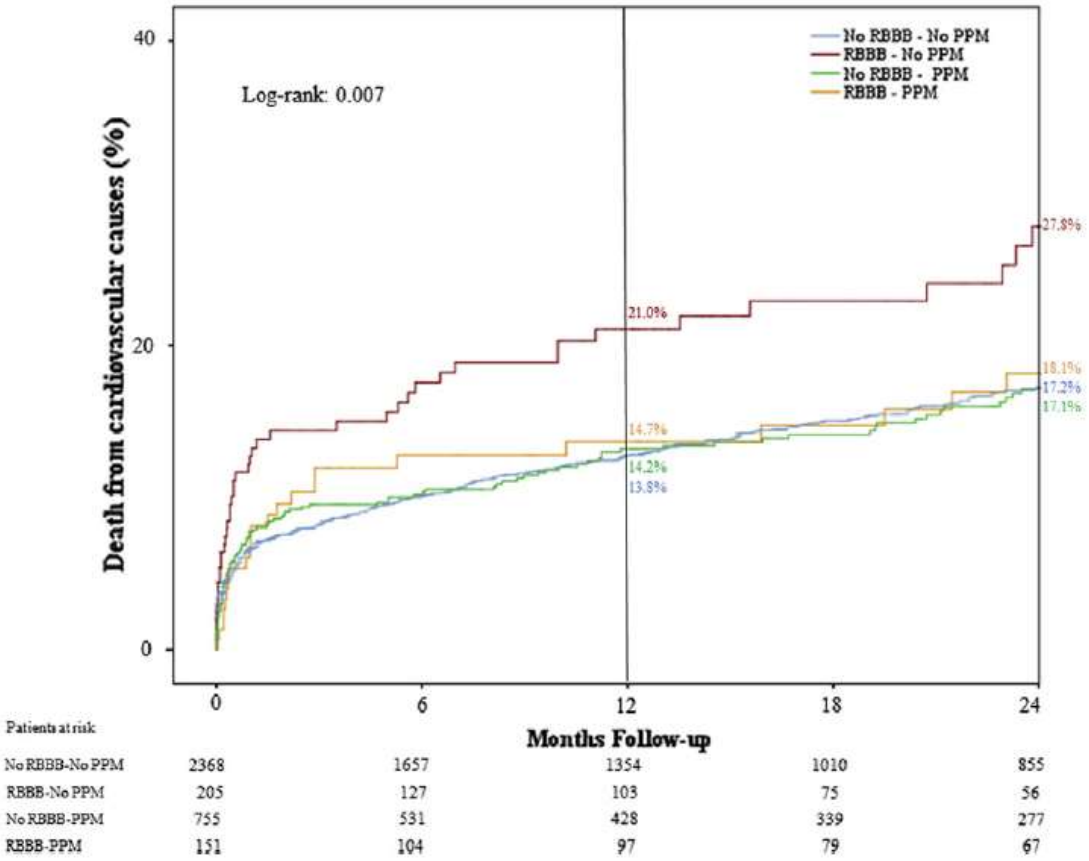
Risk Ratio M-H, Random, 95% CI
0.2 0.5 1 2 5
No LBBB following TAVR LBBB following TAVR

Regueiro et al 2016;9:e003635

Clinical Impact of Baseline Right Bundle Branch Block in Patients Undergoing Transcatheter Aortic Valve Replacement

JACC Cardiovascular Interventions

- 3,527 TAVR pts
- 10.3% with RBBB
- ↑ PPM (40.1% vs. 13.5%, p<0.001)
- ↑30 day death (10.2% vs. 6.9%, p=0.024)
- RBBB and no new PPM had highest risk of CV death at 2 years



Auffret et al 2017;10:1564-74

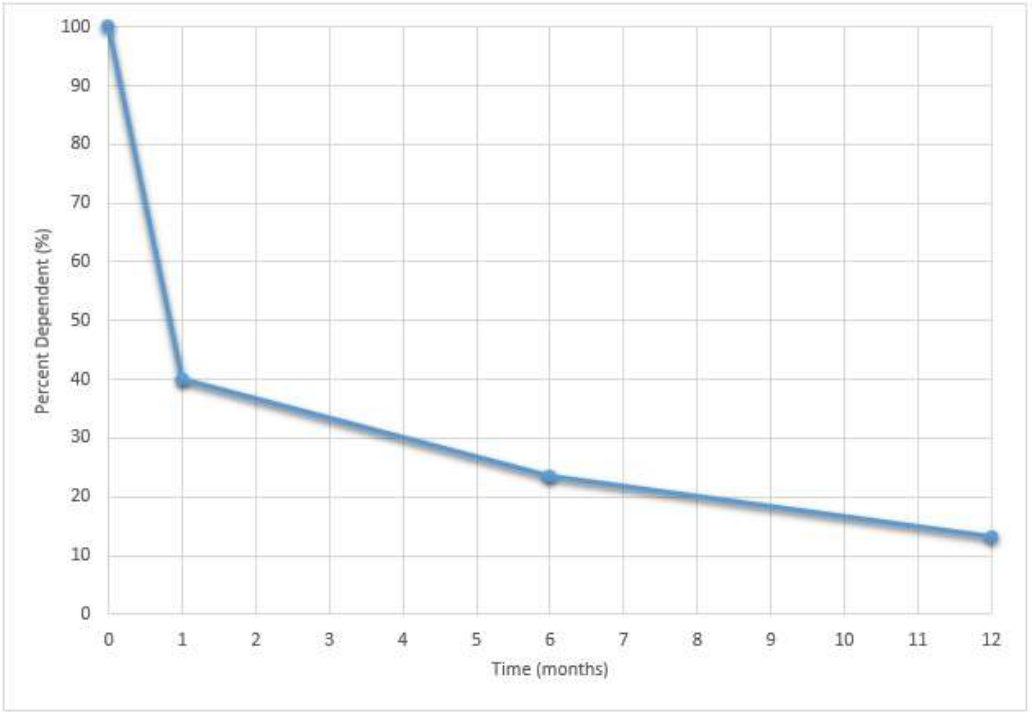
Post-Balloon Dilation Following TAVR Implantation Increases Pacemaker Dependency

tct2017

- 474 TAVR pts w/o PPM,14.1% new PPM
- 40% pacer dependent at 30 days, 10.9% dependent at 1 year
- PPM dependency more common after self-expanding valve (75.0% vs. 30.2%, p<0.01)
- Post-balloon dilation associated with ↑ PPM (17.5% vs. 9.8%, p=0.04) and ↑ dependency (66.7% vs. 19.32%, p<0.01)

Conduction Recovery After TAVR

Figure 1. Percent of patients who remain pacemaker dependent over 1 year follow-up



Kaplan … Flaherty *JACC* 70:B230

TAVR and Other Organ Systems

The deleterious effects of aortic stenosis and the benefits from it's treatment are not limited to the cardiovascular system.

TAVR and Other Organ Systems

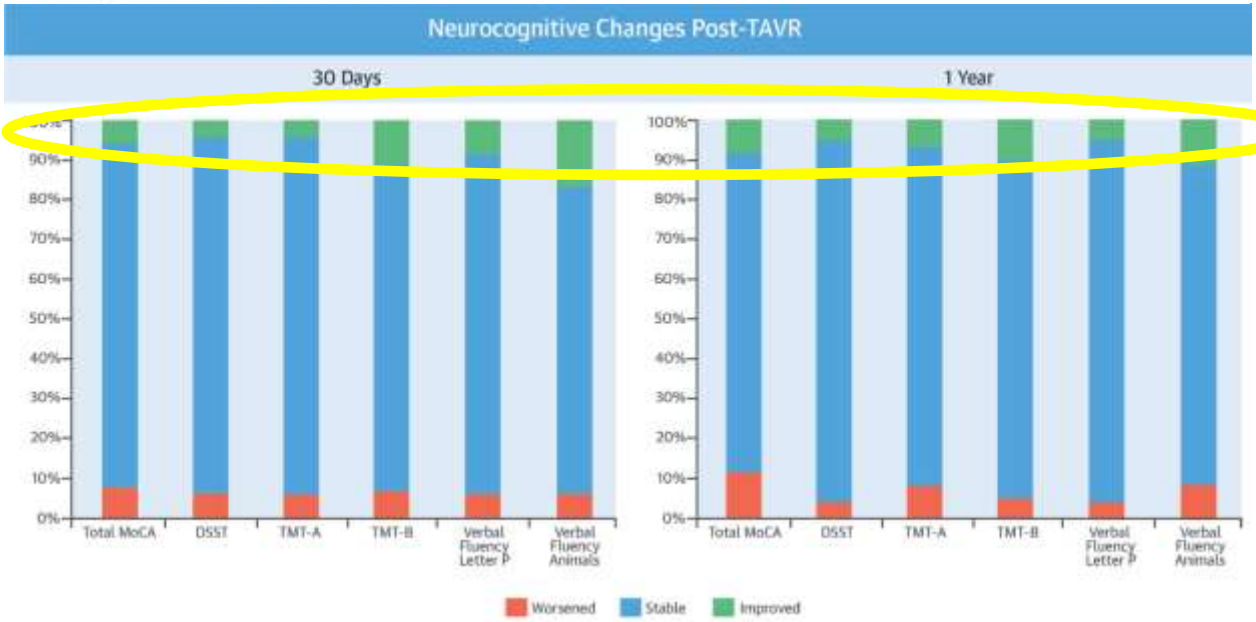
- The Brain
- The GI Tract
- The Kidneys

Neurocognitive Changes, Silent Emboli and TAVR

Serial Changes in Cognitive Function Following Transcatheter Aortic Valve Replacement

Auffret *et al.*
2016;68:2129-41

JACC



51 TAVR patients

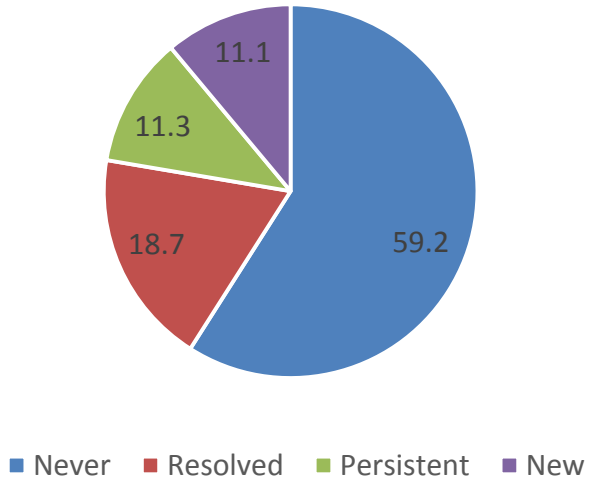
- "Silent" cerebral embolic common after TAVR (68-98%)
- Associated with cognitive decline and dementia
- Consequences can be hard to detect and quantify

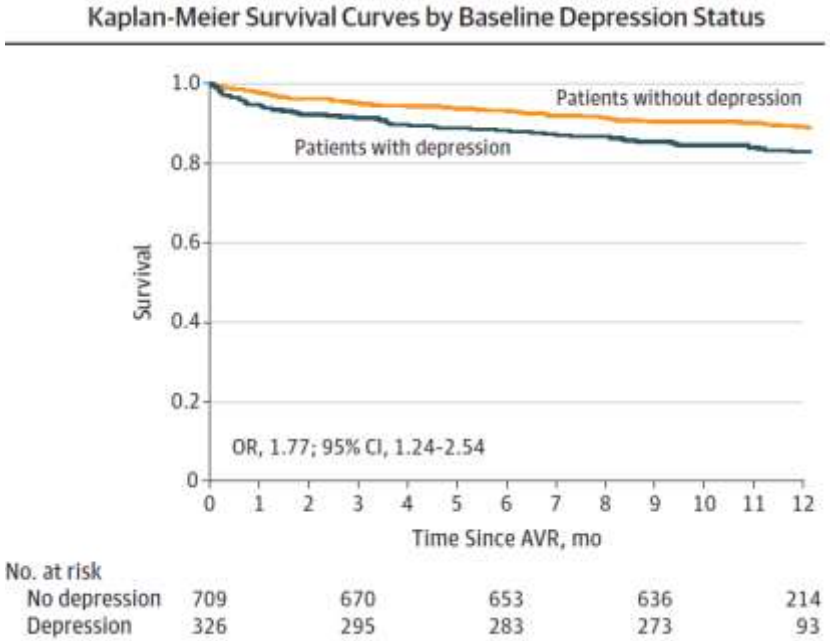
Association of Depression With Mortality in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement

JAMA Cardiology

- 1035 TAVR patients ≥ 70 yrs
- 31.5% + screening for depression (but only 8.6% documented)
- Baseline depression associated with increased mortality at 30 d (OR 2.20) and 1 year (OR 1.53)
- Persistent depression (at 6 mo) even worse 1 year mortality (OR 2.98)

Depression at 6 months





Drudi et al 2018;3:191-7

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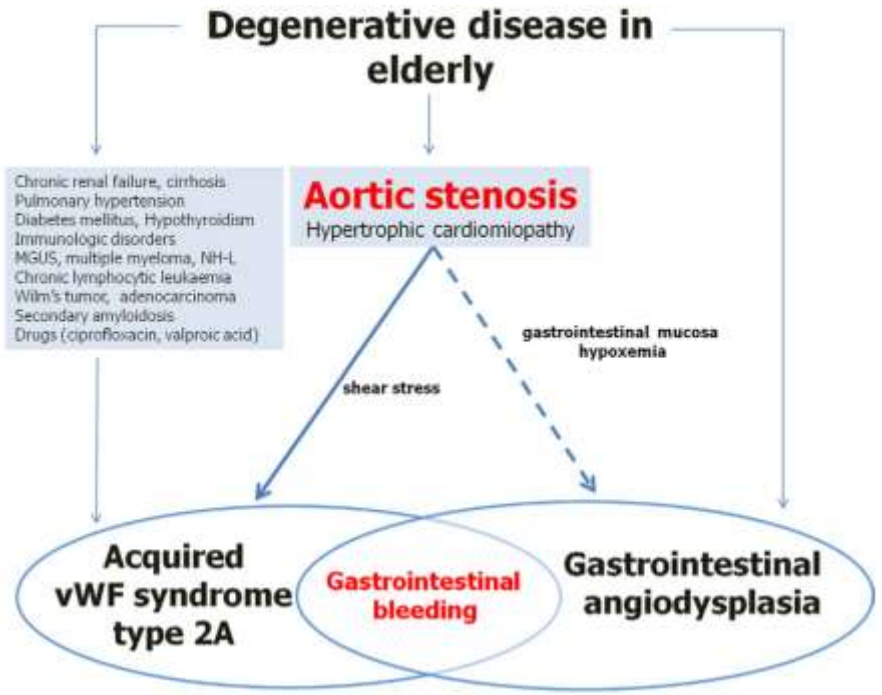
Heyde's Syndrome and TAVR

- AS and GI Bleeding (Edward J. Heyde 1958)
- Acquired wWF deficiency
- About 2% of AS pts
- TAVR usually curative

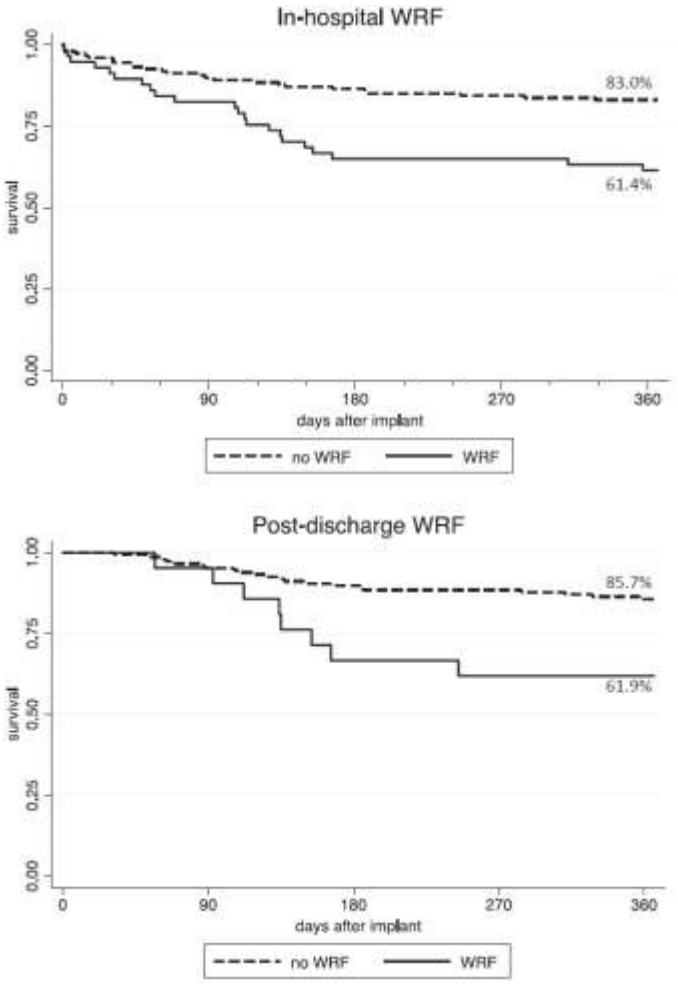


Godino et al *JACC* 2013;61:687-9

Inhospital and Post-discharge Changes in Renal Function After Transcatheter Aortic Valve Replacement

The American Journal of Cardiology

- 208 TAVR pts 6/08-6/14
- Worsening renal function (WRF) = ↑ creatinine ≥ 0.3 mg/dl)
- WRF 28% in-hospital, 12% 30 day
- IRF 37% in-hospital, 15% 30 day
- WRF at 30 days associated with ↑ 1 year mortality (HF 1.18 for every 1 mg/dl ↑ creatinine)



Blair … Flaherty 2016;117:633-9

Biomarkers and TAVR

There is an emerging abundance of bloodstream information related to aortic stenosis that has prognostic implications before and after TAVR.

Biomarkers and TAVR

- BNP
- Troponin
- Others

BNP and Troponin

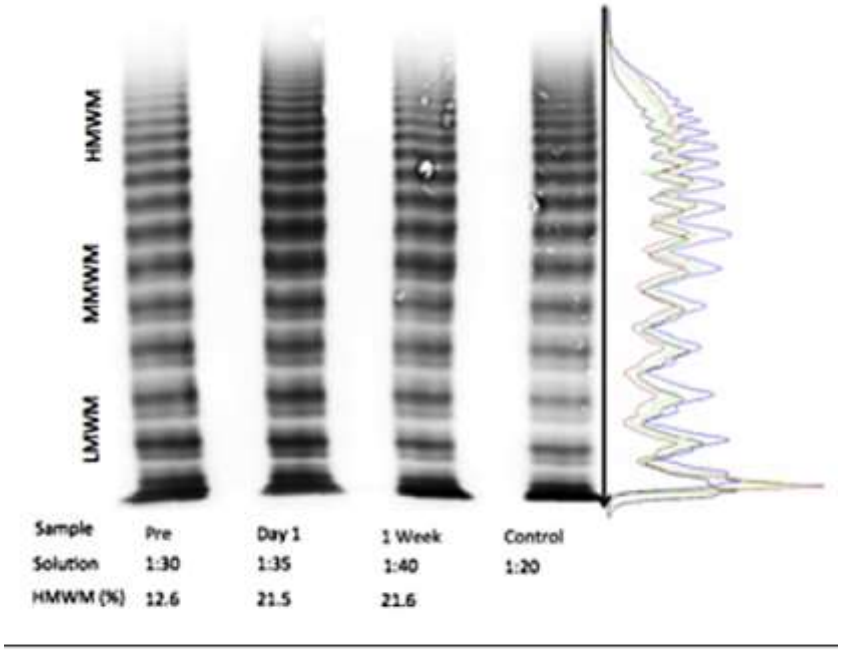
- BNP elevation *before* and *after* TAVR correlates with worse long-term outcomes
- Troponin elevation *before* TAVR correlates with worse long-term outcomes
- Troponin elevation is common *after* TAVR but does not correlate with worse long-term outcomes (in predominant transfemoral cohort using latest generation TAVR systems)

Thanassoulis et al *NEJM* 2013;368:503-12
Kamstrup et al *JACC* 2014;63:470-7
Elmariah et al *JACC Intv* 2017;10:2345-6
Stundl et al *JACC Intv* 2017;10:1550-60

Treatment of Acquired von Willebrand Syndrome in Aortic Stenosis With Transcatheter Aortic Valve Replacement

JACC Cardiovascular Interventions

- 95 TAVR patients
- 42% with abnl vWF multimers
- Abnormal vWF multimers proportion to AV gradient
- vWF corrected in most pts after TAVR
- Residual AI was associated with less vWF recovery



Exemplary illustration of the multimer analysis by gel electrophoresis and quantitative densitometry. HMWM = high-molecular-weight multimer; LMWM = low-molecular-weight multimer; MMWM = medium-molecular-weight multimer.

Spagenberg et al 2015;8:692-700

Novel Biomarkers with AS & TAVR

- Lipoprotein(a)
  - Genetic variations in LPA locus (mediated by Lpa levels) correlates with aortic valve calcifications
  - Elevated Lp(a) levels correlate with AS
- Acylcarnitines
  - Pre-TAVR elevations correlate with maladaptive LV remodeling and metabolic derangements
- Soluble ST2, Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR)
  - Pre-TAVR elevations correlate with worse outcomes

Abramowitz et al *AJC* 2015;116:1904-9
Mizutani et al *JAHA* 2017;6:e006 1 12
Koflet et al *JAMA Card* In Press

Stundl et al *AJC* 2017;120:986-93
Condado et al *Int J Card* 2016;223:444-9

Conclusions

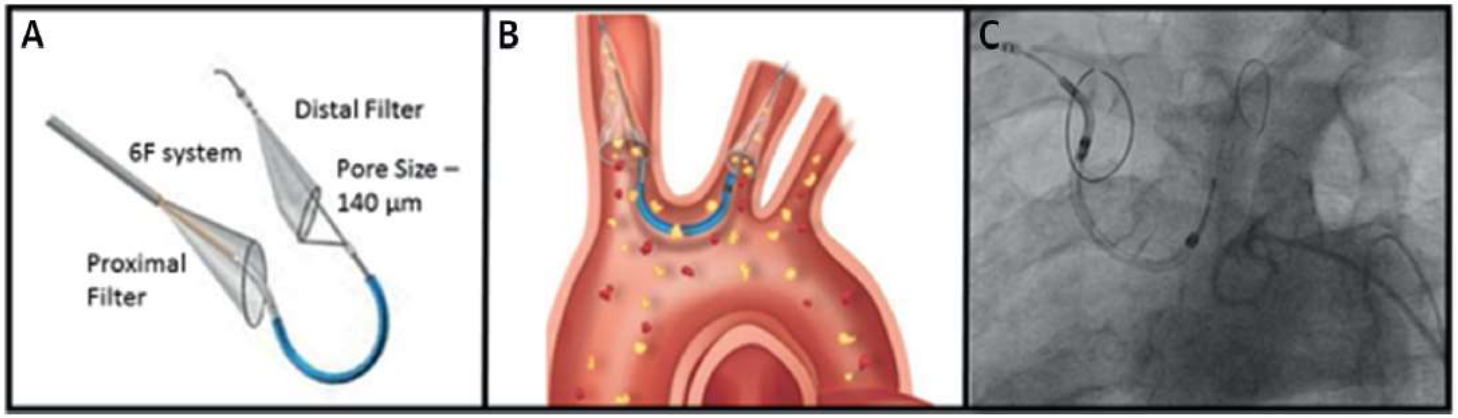
- Severe symptomatic aortic stenosis is a terminal diagnosis.
- AS confers structural and functional changes on the heart – some of which may reverse with TAVR.
- TAVR has reinforced and revealed the impact of aortic stenosis on the rest of the body and on biomarkers.
- The totality of the evidence thus far argues strongly in favor of early intervention in the treatment of AS.
- Through large RCT's and registries, TAVR has created a massive research platform to better understand the natural history of aortic stenosis.

SENTINEL Trial

Kapadia *et al.*
2017;69:367-77

JACC

Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement

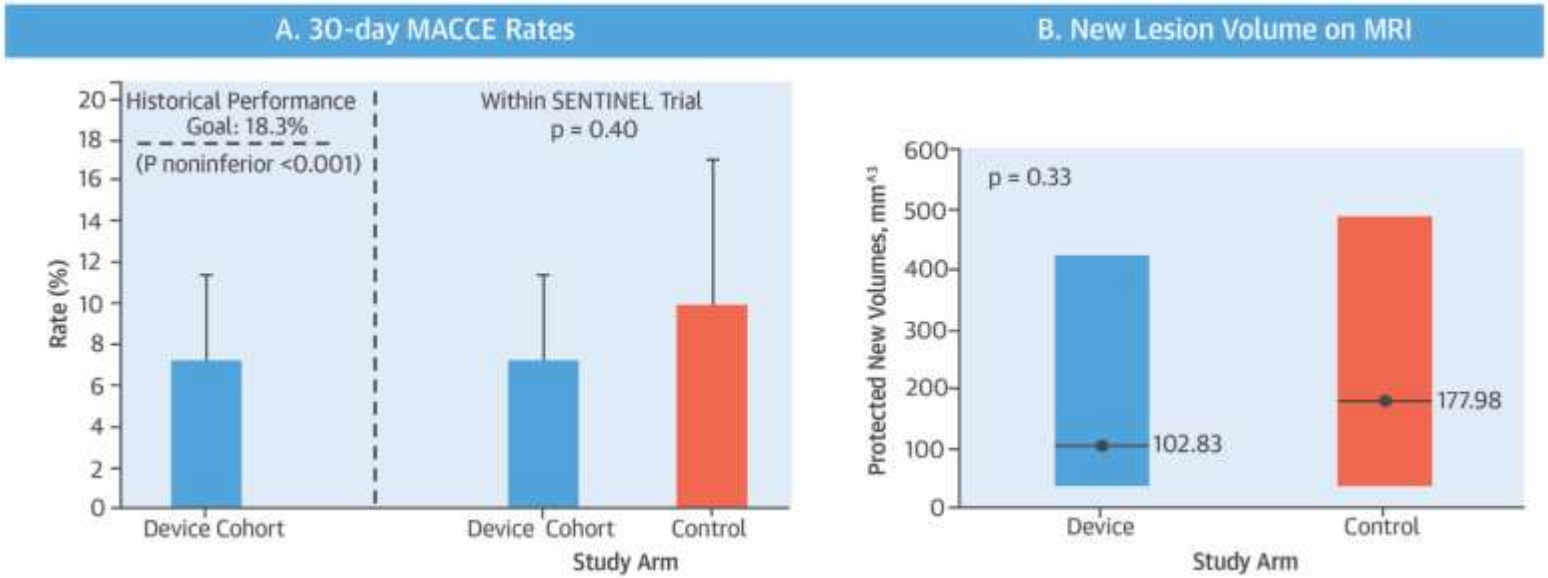


Right Transradial 91.2% (6Fr)
↑ time 15 ½ minutes

Both filters 92.0%
At least 1 filter 99.1%

SENTINEL Trial

- 363 patients (device/control/safety)
- Safety endpoint – MACCE at 30 d
- Efficacy endpoint –↓ new lesion volume by MRI



- stroke at 30 days: 5.6% vs. 9.1% (p=0.25)
- neurocognitive function similar (decline α lesion volume)
- debris found in 99% of baskets