We should not move quickly

Jian Ye, MD, FRCSC
Clinical Professor of Surgery
St. Paul's Hospital and Vancouver General Hospital
University of British Columbia, Vancouver, Canada

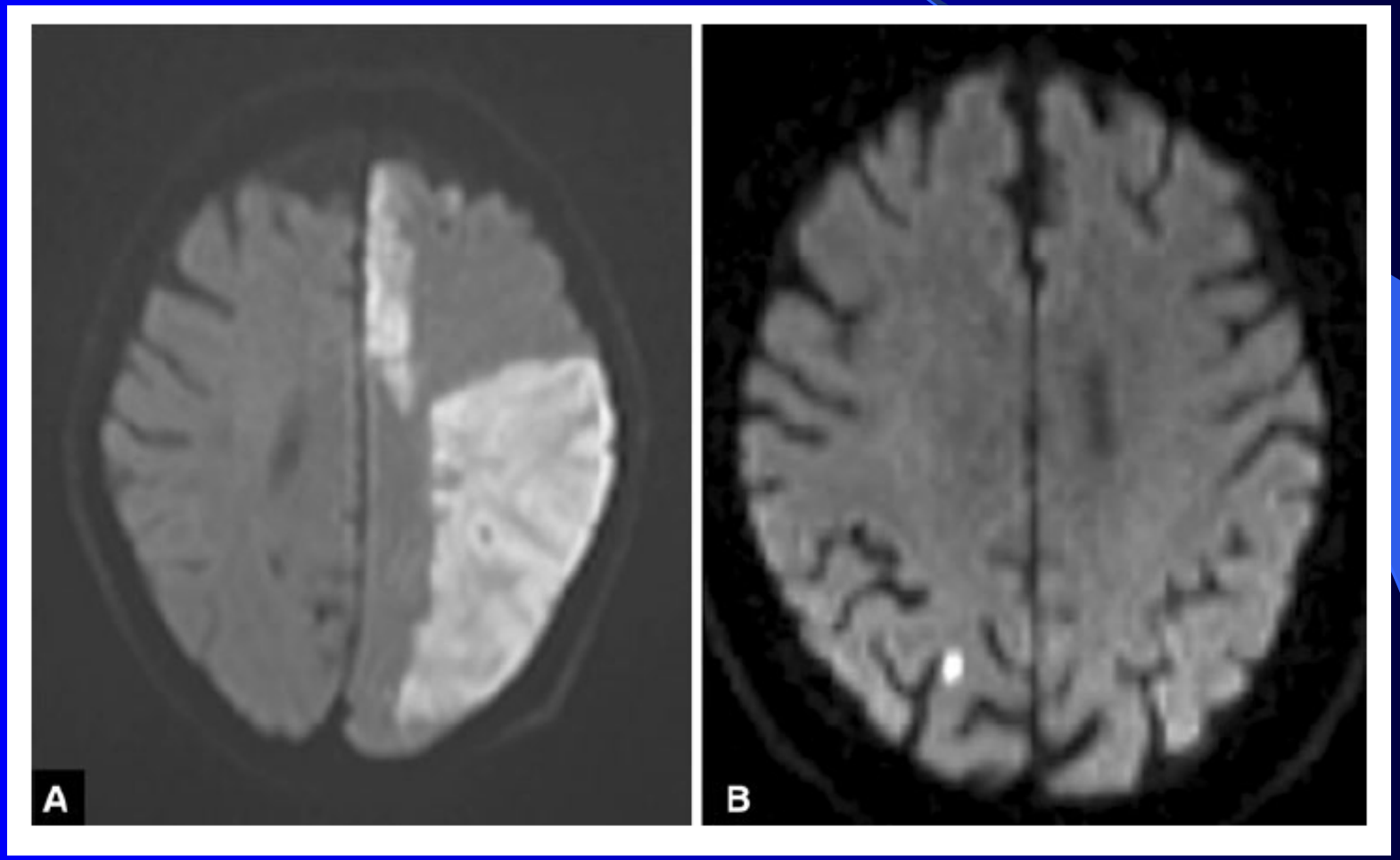
TAVI Summit, Korea 2013

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Consulting Fees/Honoraria	• Edwards Lifesciences

Higher Incidence of Cerebral Embolic Events



Incidences of Stroke

Table 1 Overview of selected, referenced studies

	n	TF/TA (%)	ES/MCV (%)	Procedural major stroke (%)	30-Day major stroke (%)	1-Year major stroke (%)
Randomized controlled clinical trials						
Leon [3]/Makkar [14]	179	100/0	100/0	1.7	5.0	7.8
Smith [4]/Kodali [13]/Miller [23]	348	70/30	100/0	n.g.	3.8	5.1
Multicenter registries						
Gilard [17]	3,195	74.6/17.8	66.9/33.1	n.g.	1.9	2.2
Nombela-Franco [27]	1,061	68.4/30.3	64/36	1.6 (within 24 h)	2.8	4.9 %
Tamburino [29]	663	90.3/0	0/100	n.g.	n.g.	n.g.
				stroke: 1.2	stroke: n.g.	stroke: 2.5 %
Single-center registries						
Tay [24]	253	66/34	98/2	n.g.	n.g.	n.g.
				CeV: 4.3 (within 24 h)	CeV rate: 6.7	CeV rate: 8.7
Stortecky [25]	389	79/20	42/58	2.1 (within 24 h)	3.1	n.g.
Nuis [26]	214	97/0	0/100	1.9 (within 24 h)	2.8	n.g.
Amat-Santos [40]	138	27.5/72.5	100/0	n.g.	3.6	no additional major stroke
Meta-analyses						
Eggebrecht [15]*	10,037	66.5 ± 29.9	57.2 ± 42.4	1.4 ± 1.5	2.9 ± 1.8	5.2 ± 3.4
		30.8 ± 40.0	41.6 ± 42.8			

n number, *TF* transfemoral, *TA* transapical, *ES* Edwards SAPIEN, *MVC* Medtronic CoreValve, *n.g.* not given, *CeV* cerebrovascular events

* A table overviewing all 53 studies included in this meta-analysis can be found in the original publication

J Thromb Thrombolysis (2013) 35:436–449

Positive Imaging Findings

Table 2 Overview of current neuroimaging studies with TAVI

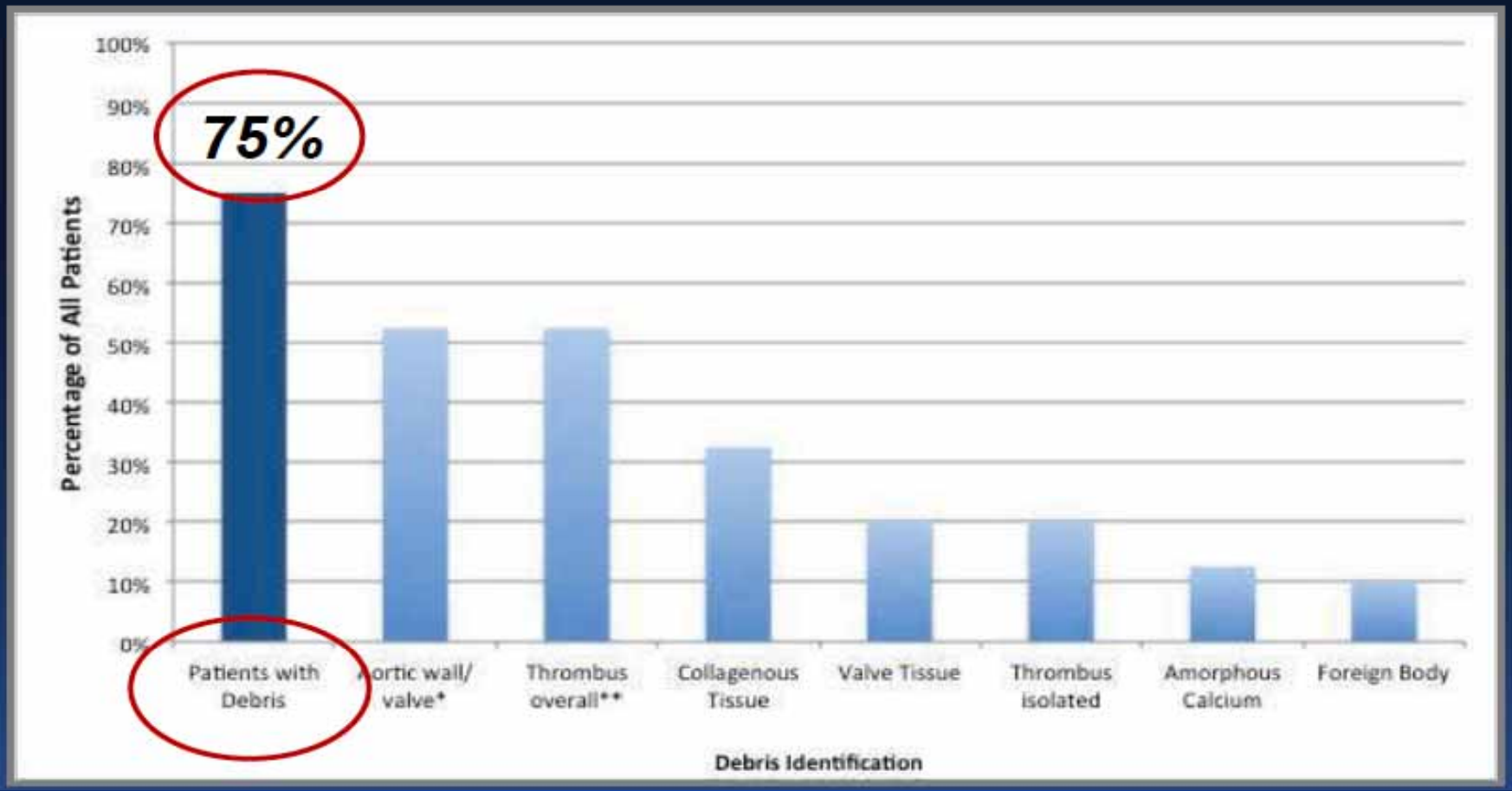
	n	Access	Valve type	Number of new lesions on DW-MRI	Incidence of new DW-MRI lesions	Stroke rate	Neurological impairment (including stroke)	Neurological assessment and stroke definition
Kahlert et al. [5]	32	TF	ES	ES: 89 lesions in 22 pts.	ES: 86 %	ES: 0 %	none	NIHSS, MMSE, mRS
			($n = 22$)	MCV: 26 lesions in 10 pts.	MCV: 80 %	MCV: 0 %		stroke: a neurological deficit lasting >24 h
			MCV	Overall: 115 lesions in 32 pts	Overall: 84 %	Overall: 0 %		
			($n = 10$)					
Ghanem et al. [6]	22	TF	MCV	75 lesions in 16 pts.	73 %	NA	Transient: 2 pts.	NIHSS
							persistent: 1 pt.	stroke: not defined
Fairbairn et al. [10]	31	TF	MCV	131 lesions in 24 pts.	77 %	6.0 %	Transient: 0 pts.	NIHSS
							persistent: 2 pts.	stroke: a neurological deficit lasting >24 h
Arnold et al. [7]	25	TA	ES	Number of new lesions not given	68 %	4.0 %	Transient: 4 pts.	Clinical assessment
							persistent: 1 pt.	stroke: not defined
Rodés-Cabau et al. [8]	60	TF	ES	TF: 83 lesions in 19 pts.	TF: 66 %	TF: 3.4 %	TF/TA transient: 0/0	NIHSS, MMSE
		($n = 29$)		TA: 168 lesions in 22 pts.	TA: 71 %	TA: 3.2 %	pts.	stroke: not defined
		TA		Overall: 251 lesions in 41 pts	Overall: 68 %	Overall:	persistent: 1/1 pt.	
		($n = 31$)				3.3 %		
Astarci et al. [9]	35	TF	ES	TF: 114 lesions in 19 pts.	TF: 90 %	TF: 0 %	None	NIHSS
		($n = 21$)		TA: 86 lesions in 13 pts.	TA: 93 %	TA: 0 %		stroke: not defined
		TA		Overall: 200 lesions in 32 pts	Overall: 91 %	Overall: 0 %		
		($n = 14$)						

n number, *DW-MRI* diffusion-weighted magnetic resonance imaging, *TF* transfemoral, *TA* transapical, *ES* Edwards SAPIEN, *MVC* Medtronic CoreValve, *NIHSS* National Institute of Health Stroke Scale, *MMSE* mini-mental state examination, *mRS* modified Rankin scale, *NA* not applicable

J Thromb Thrombolysis (2013) 35:436–449

Recent Publications

Embolic Debris Evidence



Van Mieghem, Circulation May 2013 ISSN 1524-4539

Adapted from Eberhard Grube, TVT 2013

Recent Publications

DW-MRI Data

	Treatment TAVI + Embrella (N=33)
Time from TAVI procedure, days, median (min, max)	3 (1-7)
Patients with new Lesions	33 (100%)
Total No. of lesions, patients	
Anterior cerebral artery	7 (21%)
Medial cerebral artery	29 (88%)
Posterior cerebral artery	22 (67%)
Cerebellum	23 (70%)
Border zone	2 (6%)
Patients with single lesions	4 (12%)
Patients with multiple lesions	29 (88%)
Lesions per patient, median (min, max)	8 (1, 70)
Lesion volume (mm^3), median (IQR)	42.3 (27.5, 85.0)

PROTAVI-C

Adapted from John Webb, TVT 2013

Early stroke is 3.5-5 fold increased mortality

Higher Incidence of PPM

Incidence PPM post TAVR

- **Khatri et al: Meta-analysis of 33 studies with 12,116 patients: 4602 MCV, 6074 ESV**
  - Overall PPM 13.1%
  - MCV 25.4% vs ESV 6.4%, p<0.001.
  - No significant difference transarterial or transapical

- **Genereux: Weighted meta-analysis, VARC defs 2914 patients – 496 MCV, 1453 ESV**
  - Overall PPM 13.9%
  - MCV 28.9% vs ESV 4.9%, p<0.0001

Katri et al. Ann Intern Med 2013;158:35-46.
Genereux et al. JACC 2012;59:2317-26.

Adapted from Tamim Nazif, TVT 2013

Matched TAVI and AVR Patients

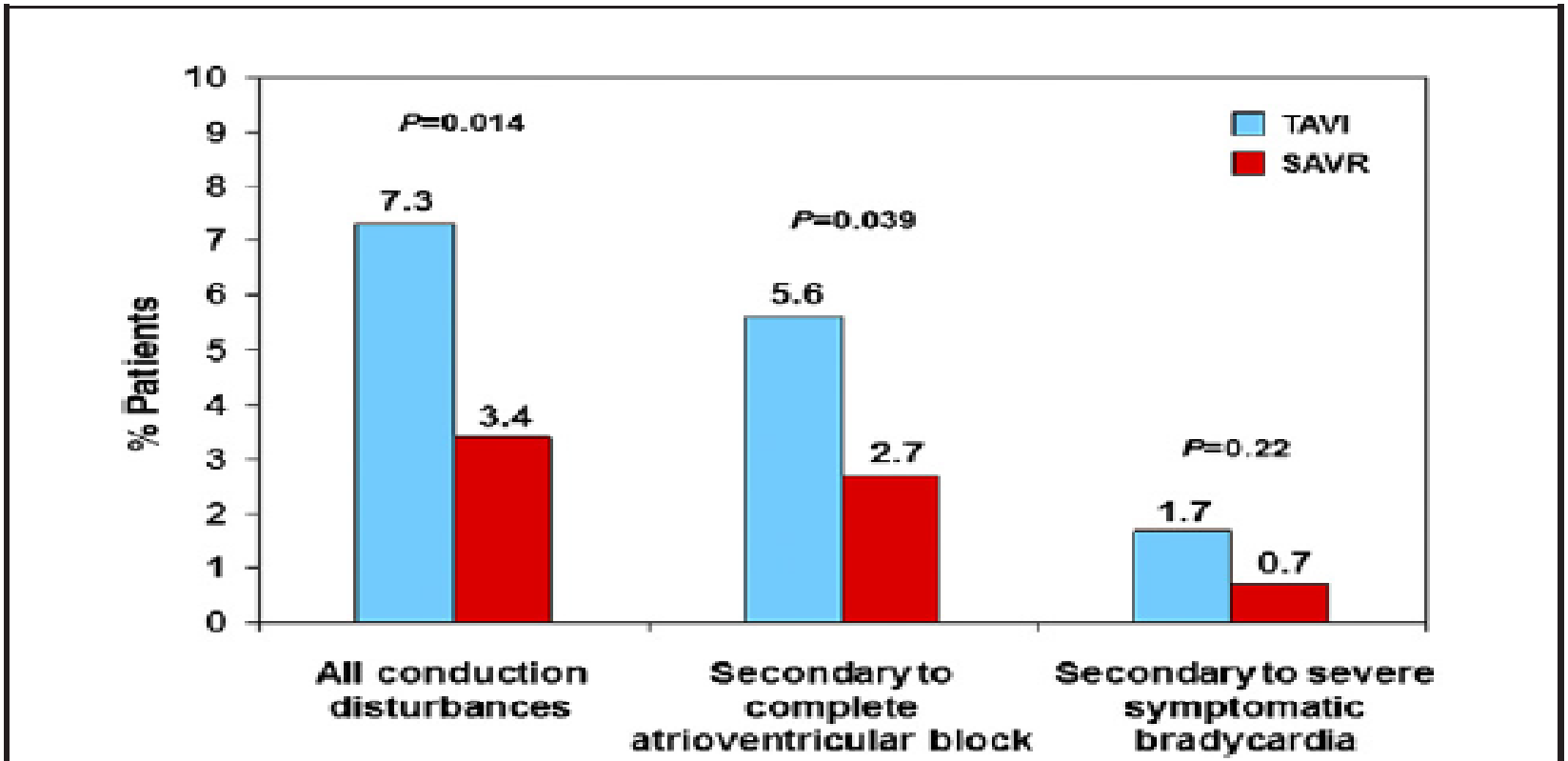


Figure 2. Permanent Pacemaker Implantation After TAVI and SAVR

Percentage of patients who needed a permanent pacemaker within 30 days after transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) procedures for the treatment of severe aortic stenosis.

Bagur et al. JACC Intv 2012:5:540-51

Higher Incidence of PVL

Reported Incidences of PVL

Publications (Edwards valve) (>100pts)	Incidence of PVL	
	Mild	>mild
Rodes-Cabau, 2010	78%	6%
Walther, Source 2010		1.9%
Leon, PARTNER2010	68%	12%
Nombela-Franco, 2012	30.8%	49.2%
Gripari, 2012	48.1%	20.7%
Unbehaun, 2012	47%	0.6%
Walther 2012	30.7%	29.8%
Webb, 2009	58%	42%

Reported Incidences of PVL

Publications (CoreValve) (>100pts)	Incidence of PVL	
	Mild	>Mild
Ussia, 2012	52.8%	15.2%
Buellesfeld , 2011	32%	9%
Sinning, 2012	48.2%	15%

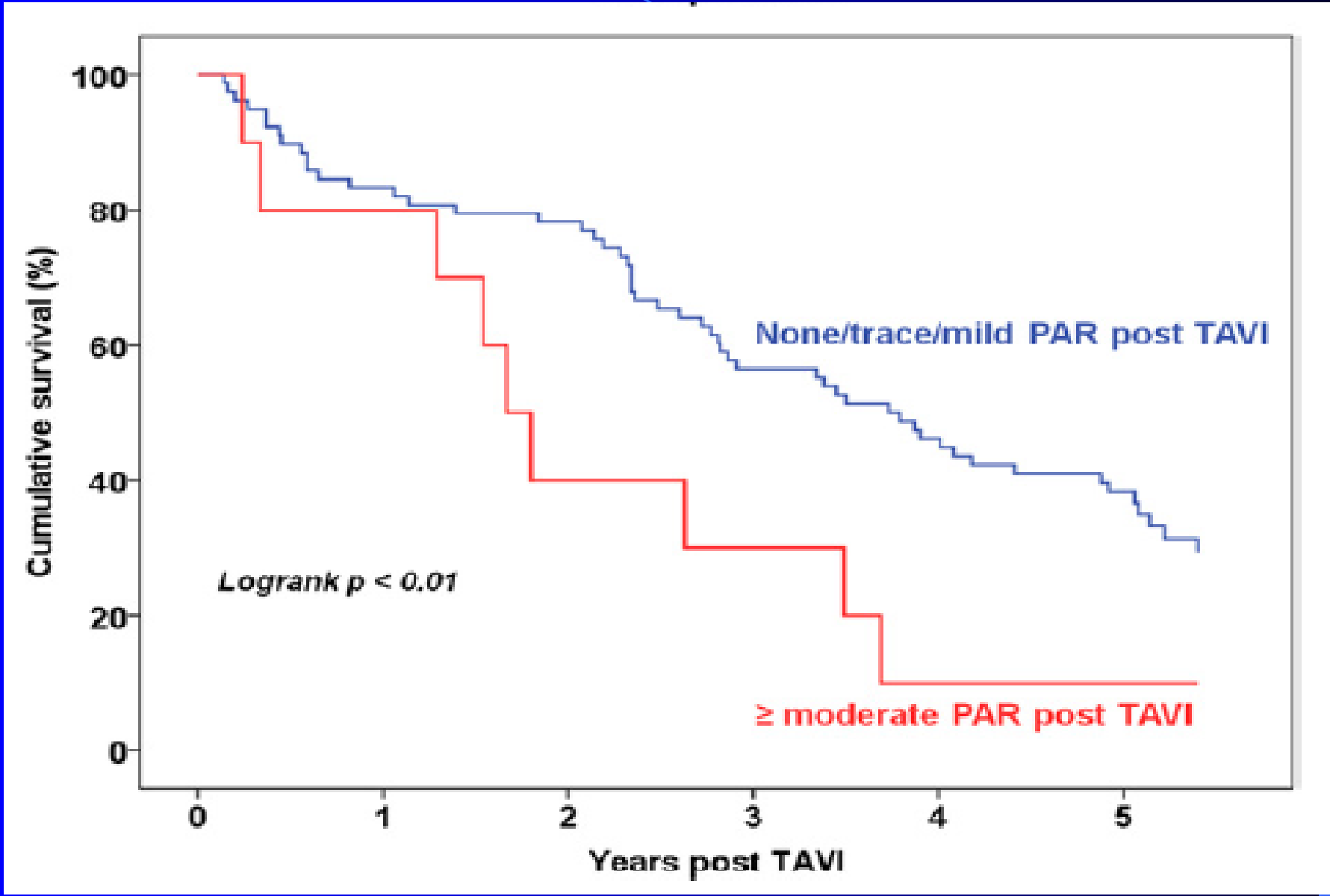
Publications (Mixed) (>100pts)	Incidence of PVL	
	Mild	>Mild
Eltchaninoff, 2011		9.5%
Gilard, 2012	47.4%	17.1%
Abdel-Wahab, 2011	54.9%	17.5%
Moat, 2011	47.4%	13.6%

Much lower incidence of PVL after AVR

Moderate-severe PVL in PARTNER:

	1-year	2-year
TAVI	7.0%	6.9%
AVR	1.9%	0.9%

Reduced Survival



Toggweiler et al. JACC 2013;61:613-9 (Vancouver experience)

Reduced Survival

In the PARTNER trial, even mild PVL was found to be significantly associated with increased mortality (hazard ratio of 2.11 for ≥ mild PAR compared to none or trace PAR).

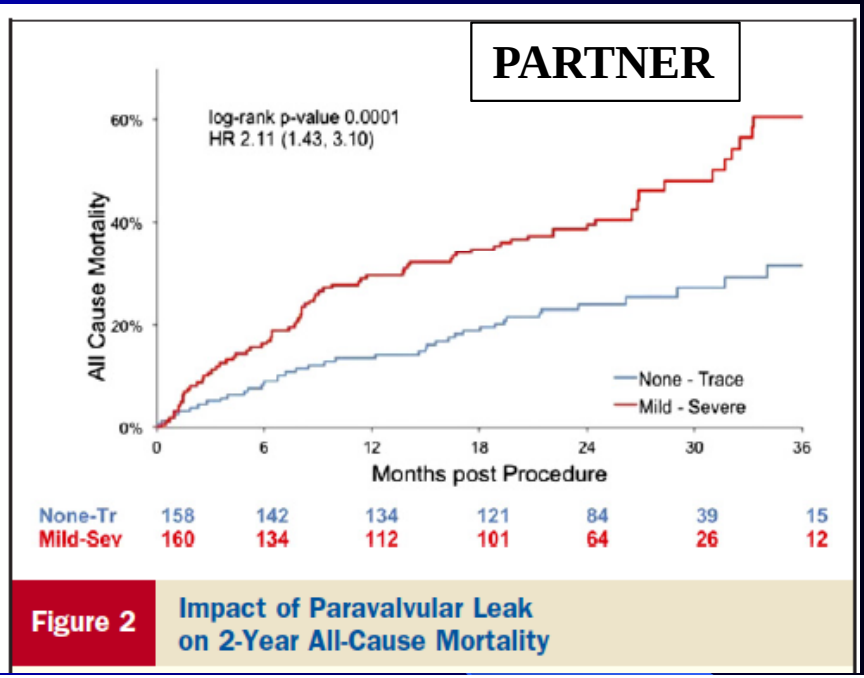


Figure 2 Impact of Paravalvular Leak on 2-Year All-Cause Mortality

Table 3 Outcomes Associated With Aortic and/or Paravalvular Regurgitation

First Author, Year (Ref. #)	n	Variable	Outcome	Univariate Analysis	Multivariate Analysis
Abdel-Wahab, 2011 (3)	690	AR ≥2	In-hospital mortality	OR = 2.50 (95% CI 1.37–4.55)	OR = 2.43 (95% CI 1.22–4.85)
Gotzmann, 2011 (4)	122	AR ≥2	6-month mortality No clinical improvement	—	OR = 4.26 (95% CI 1.59–11.45) OR = 10.1 (95% CI 3.20–31.94)
Takagi, 2011 (15)	41	AR ≥2	6-month mortality	12.2% vs. 25.0% (p = 0.25)	—
Hayashida, 2012 (89)	260	AR ≥2	Median 217 days (IQR: 54–401)	HR = 1.97 (95% CI 1.19–3.28)	—
Leber, 2011 (90)	69	AR >2	1-year mortality	9% vs. 37.5% (95% CI p = 0.07)	—
Moat, 2011 (5)	870	AR ≥2	1-year mortality	HR = 1.49 (95% CI 1.00–2.21)	HR = 1.66 (95% CI 1.10–2.51)
Sinning, 2012 (91)	152	PVL ≥2	1-year mortality	HR = 4.0 (95% CI 2.1–7.5)	HR = 4.9 (95% CI 2.5–9.6)
Tamburino, 2011 (6)	663	PVL ≥2	Late mortality	—	HR = 3.79 (95% CI 1.57–9.10)
Sinning, 2012 (41)	146	Moderate/severe PVL	1-year survival	HR = 3.9 (95% CI 2.0–7.5)	HR = 2.4 (95% CI 1.0–5.4)
Unbehaun, 2012 (26)	358	No vs. trace vs. mild AR	2-year survival	66% vs. 72% vs. 67% (p = 0.77)	—
Kodali, 2012 (8)	158	Mild to severe AR	2-year survival	HR = 1.75 (95% CI 1.17–2.61)	Not significant
		Mild to severe PVL	2-year survival	HR = 2.11 (95% CI 1.43–3.10)	Not significant

Genereux, et al. J Am Coll Cardiol 2013;61:1125-36

Transcatheter Heart Valves

No Long-term Durability Data

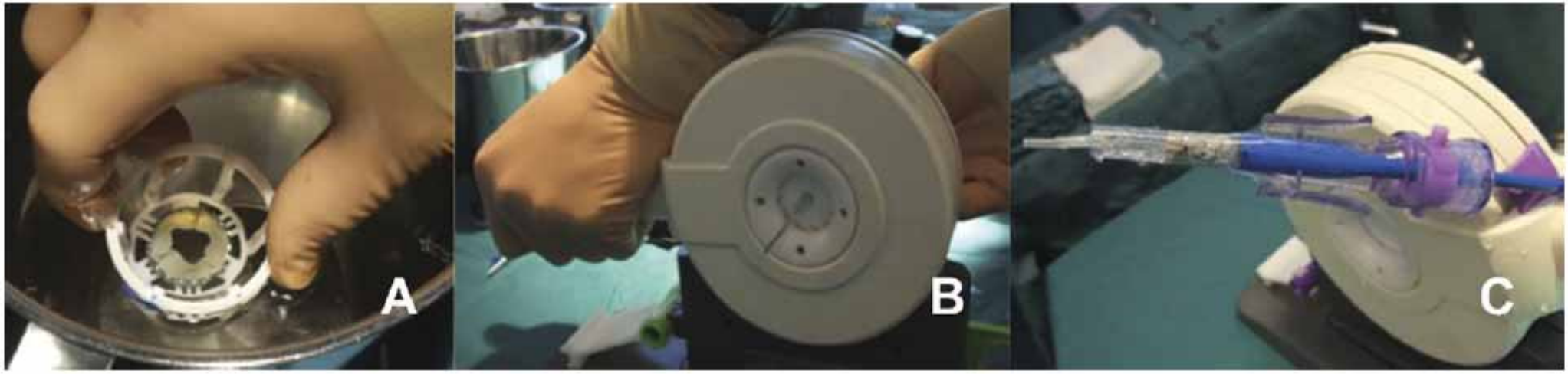
No RCT data in intermediate risk patients

No data in young patients (<65-70 y/o)

Probably more leaflet stress in THVs

Crimping May Affect the Durability of Transcatheter Valves: An Experimental Analysis

Philipp Kiefer, MD, Felix Gruenwald, Joerg Kempfert, MD, Heike Aupperle, PhD, Joerg Seeburger, MD, Friedrich Wilhelm Mohr, MD, PhD, and Thomas Walther, MD, PhD



Influence of time-depending Crimping on valvular leaflets

Edwards Sapien
(n=20, 60 leaflets)

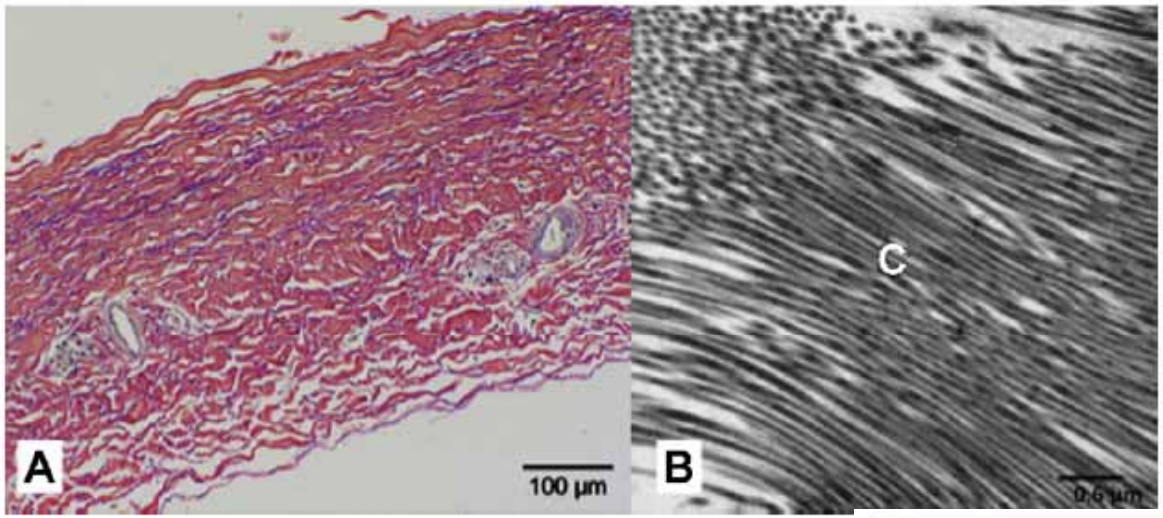
Perimount Magna
(n=5, 15 leaflets)

- Uncrimped (n=5)
- One hour (n=5)
- One day (n=5)
- One month (n=5)
- Control (uncrimped, n=5)

Resection of the valve leaflets (overall n = 75)

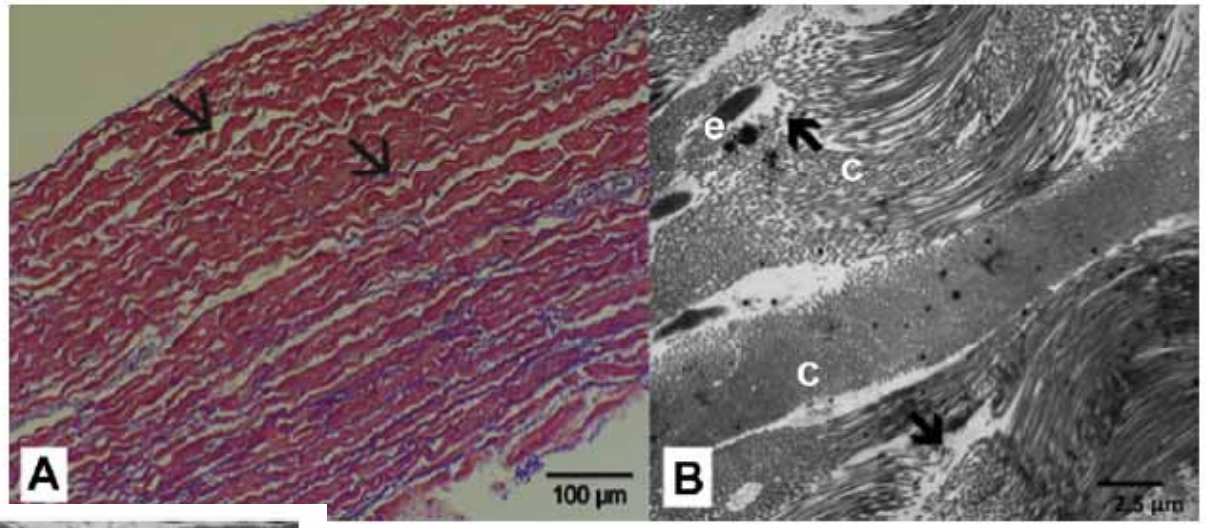
Subcutaneous rat model (n = 15)

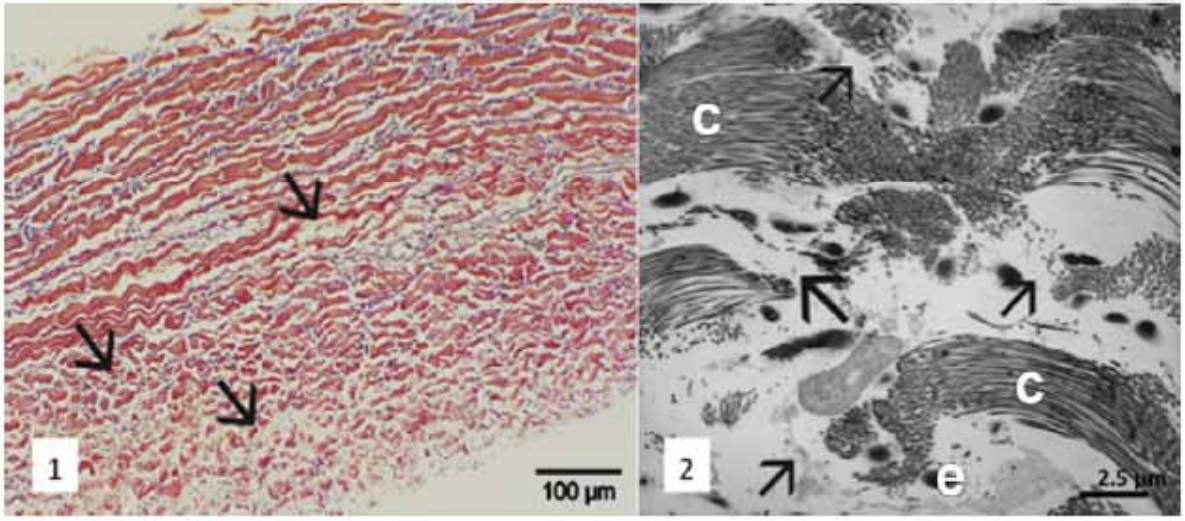
1 leaflet from each group (n=5) was individually implated in dorsal subcutaneous pouches



Uncrimped Sapien Valve
Normal structure

1hr crimped Sapien Valve
abnormal structure





1 day crimped Sapien Valve
abnormal structure

Degree of Fragmentation

Table 2. Degrees of Fragmentation and Irregularity of the Leaflet Collagen Fibers [a]

Group	Crimp Time	Regular No.	Irregular, No.		
			Mildly	Moderately	Markedly
Magna	(uncrimped)	13	2		
Sapien	(uncrimped)	2	11	2	
	1 hour		5	7	3
	1 day		2	8	4
	1 mon		2	5	8

[a] Data are for 15 leaflets.

Prolonged or tight crimping likely causes structural changes of leaflets and may affect durability.

TAVI – longest follow-up

5-Year Outcome After Transcatheter Aortic Valve Implantation

Stefan Toggweiler, MD, Karin H. Humphries, DSc, May Lee, MSc, Ronald K. Binder, MD, Robert R. Moss, MD, Melanie Freeman, MBBS, Jian Ye, MD, Anson Cheung, MD, David A. Wood, MD, John G. Webb, MD

Vancouver, British Columbia, Canada

Objectives The purpose of this study was to investigate the 5-year outcome following transcatheter aortic valve implantation (TAVI).

Background Little is known about long-term outcomes following TAVI.

Methods The 5-year outcomes following successful TAVI with a balloon-expandable valve were evaluated in 88 patients. Patients who died within 30 days after TAVI were excluded.

Results Mean aortic valve gradient decreased from 46 ± 18 mm Hg to 10 ± 4.5 mm Hg after TAVI and 11.8 ± 5.7 mm Hg at 5 years (p for post-TAVI trend = 0.06). Mean aortic valve area increased from 0.62 ± 0.17 cm^2 to 1.67 ± 0.41 cm^2 after TAVI and 1.40 ± 0.25 cm^2 at 5 years (p for post-TAVI trend <0.01). At 5 years, 3 patients (3.4%) had moderate prosthetic valve dysfunction (moderate transvalvular regurgitation in 1, moderate stenosis in 1, and moderate mixed disease in 1). Survival rates at 1 to 5 years were 83%, 74%, 53%, 42%, and 35%, respectively. Median survival time after TAVI was 3.4 years (95% confidence interval [CI]: 2.6 to 4.3), and the risk of death was significantly increased in patients with chronic obstructive pulmonary disease (adjusted hazard ratio [HR]: 2.17; 95% CI: 1.28 to 3.70) and at least moderate paravalvular regurgitation (adjusted HR: 2.98; 95% CI: 1.44 to 6.17).

Conclusions Our study demonstrated favorable long-term outcomes after TAVI. Signs of moderate prosthetic valve failure were observed in 3.4% of patients. No patients developed severe prosthetic regurgitation or stenosis. Comorbidities, notably chronic lung disease and at least moderate paravalvular regurgitation, were associated with reduced long-term survival. (J Am Coll Cardiol 2013;61:413–9)

5-year Durability of Transcatheter Heart Valve

At 5 years (only 31 survivors), 3 out of 88 patients (83±7 y/o) (3.4%) developed moderate prosthetic valve dysfunction:

One had moderate transvalvular regurgitation
One had moderate stenosis
One had mixed disease

Surgical Bioprostheses

Good Long-term durability of surgical valves has been well documented

Freedom from SVD
Surgical porcine valve

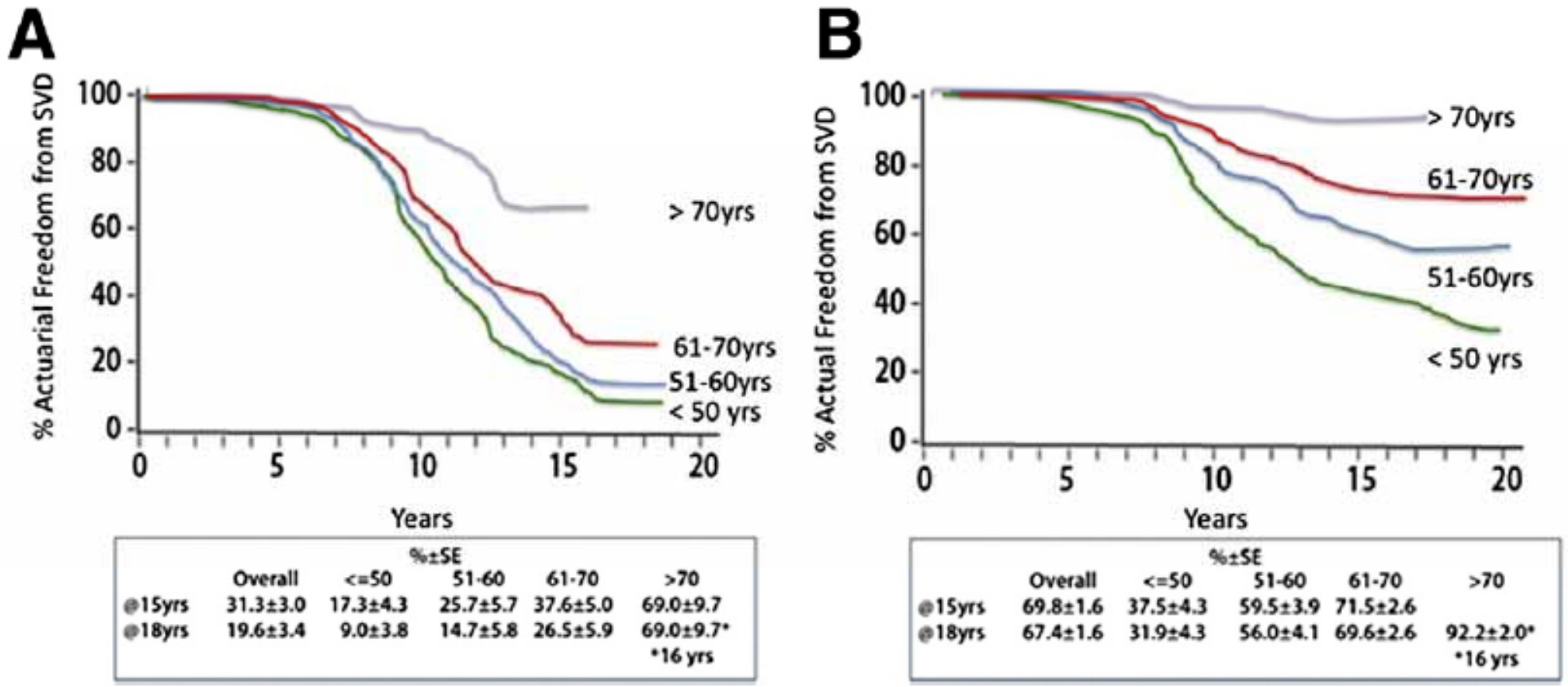


Figure 2. (A) Actuarial and (B) actual freedom from structural valve deterioration according to age group for mitral valve replacement with the Carpentier-Edwards porcine bioprosthesis (data from 1175 patients operated on between 1982 and 2000). (Adapted with permission from Jamieson et al.[31]) (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)

Freedom from SVD
Surgical pericardial valve

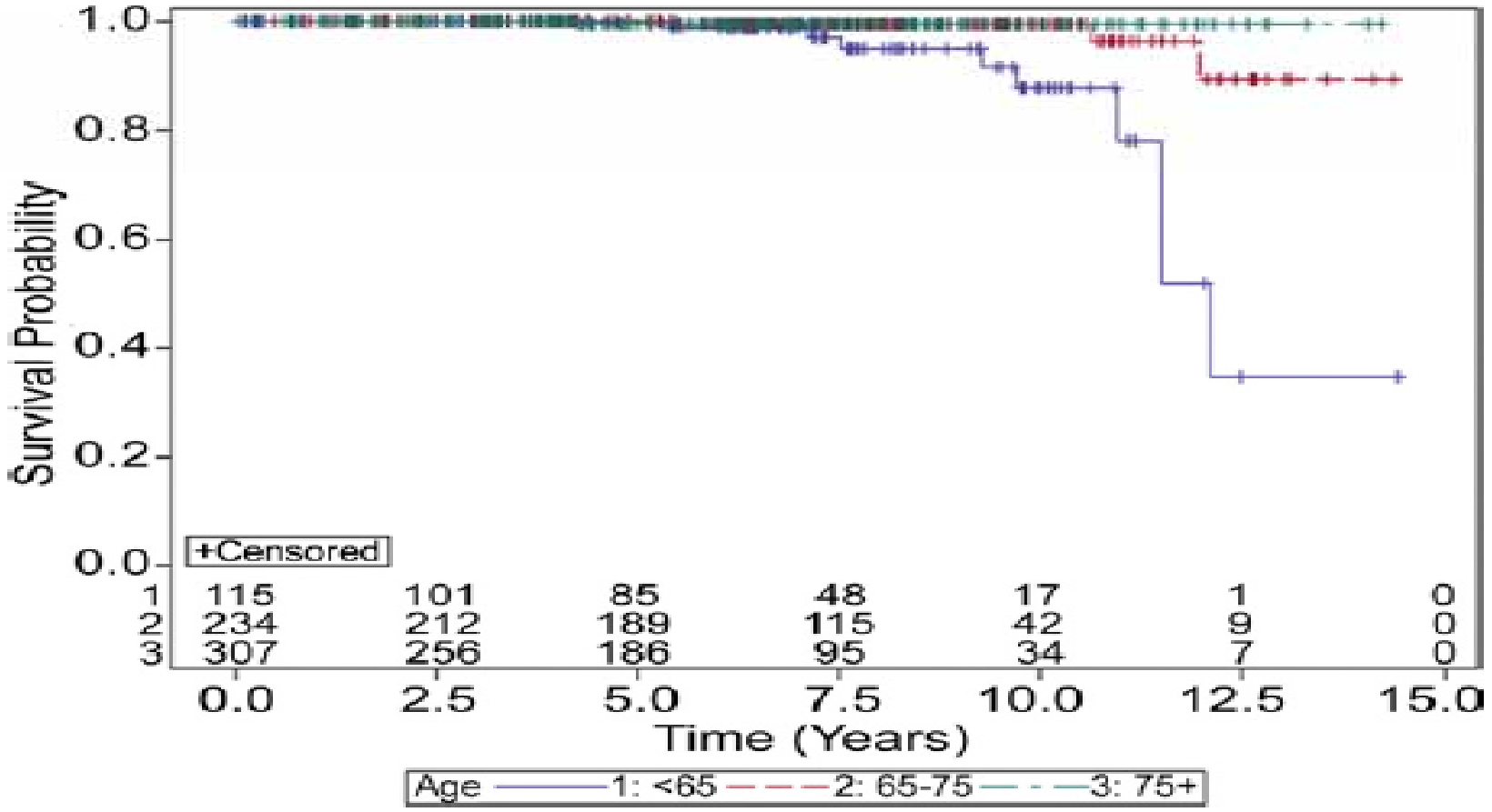


Fig 2. Age-stratified freedom from structural valve deterioration necessitating reoperation using the Carpentier-Edwards pericardial aortic bioprosthesis. (Blue line = age less than 65 years; red line = age 65 to 75 years; green line = age 75 years or more.)

McClure, Ann Thorac Surg 2010;89:1410-16

Freedom from Any Complications
Surgical pericardial valve

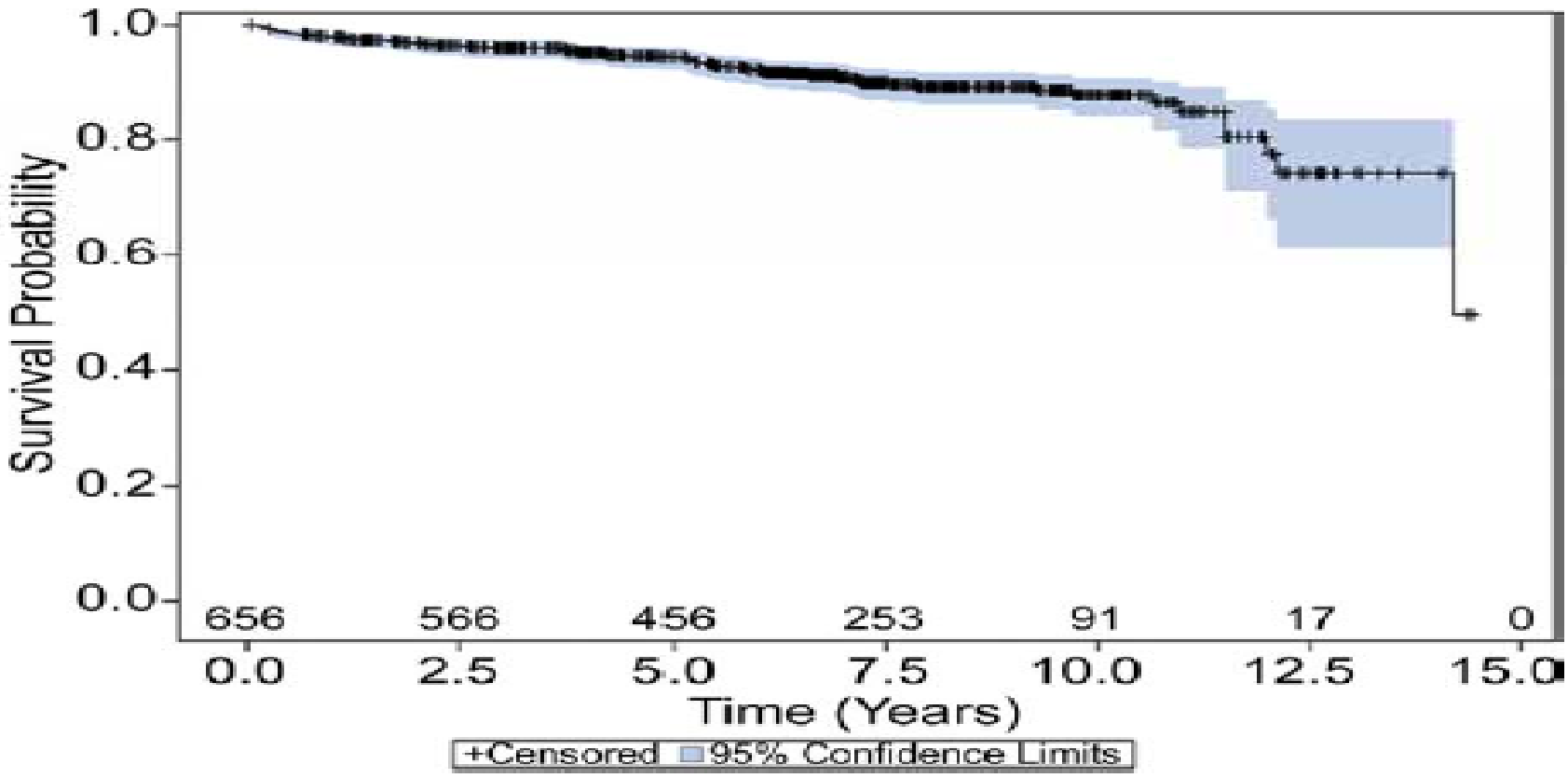


Fig 3. Overall freedom from any complication using the Carpentier-Edwards bioprosthesis. Blue-shaded area indicates 95% confidence interval.

McClure, Ann Thorac Surg 2010;89:1410-16

Freedom from SVD

Table 3. Long-Term Outcomes Assessment for Structural Valve Deterioration With Various Aortic Valve Replacement Options

Valve Type	Model	Author [Ref], Year	Follow-Up Maximum, Mean (Years)	Time of SVD Estimate (Years)	Age (Years)	Freedom From SVD (%)
Stented bioprostheses						
Bovine pericardium	Carpentier-Edwards	Biglioli [3], 2004	18, 6.0	18	67 (mean)	52.9 ± 9.9
					<65	35.8 ± 10.7
					≥65	83.7 ± 8.9
					65 (mean)	77 (CI: 74–82)
	Carpentier-Edwards	Banbury [4], 2001	17, 12	15	<50	48
					50–70	80
					≥70	90
	Carpentier-Edwards	McClure, current study	17, 6.0	15	74 (mean)	82.3 (CI: 67–91)
					<65	34.7 (CI: 6–67)
					65–75	89.4 (CI: 63–97)
					≥75	99.5 (CI: 97–99.9)
	Carpentier-Edwards	Poirier [6], 1998	15, 4.8	14	NR (mean)	79.9 ± 5.0
					<60	84.7
				10	60–69	87.9
					≥70	100
	Carpentier-Edwards	Dellgren [5], 2002	14, 5	12	71 (mean)	86 ± 9.0
					>65	100
	Carpentier-Edwards	Neville [7], 1998	12, 4.7	12	68 (mean)	94 (CI: 90–98)
					<60	89 (CI: 80–98)
					≥60	98 (CI: 96–100)
	Sorin Mitroflow	Yankah [11], 2008	21, 4.1	20	73 (mean)	62.3 ± 5.0
					≥65	71.8 ± 6.0
					≥70	84.8 ± 0.7
Porcine	St. Jude Biocor	Myken [12], 2009	20, 6.0	20	71 (mean)	61.1 ± 8.5
					≤50	37.7 ± 8.6
					51–60	60.7 ± 10.3
					61–70	81.0 ± 5.1
					71–80	97.8 ± 1.2
					>80	100

McClure, Ann Thorac Surg 2010;89:1410-16

Explant for SVD

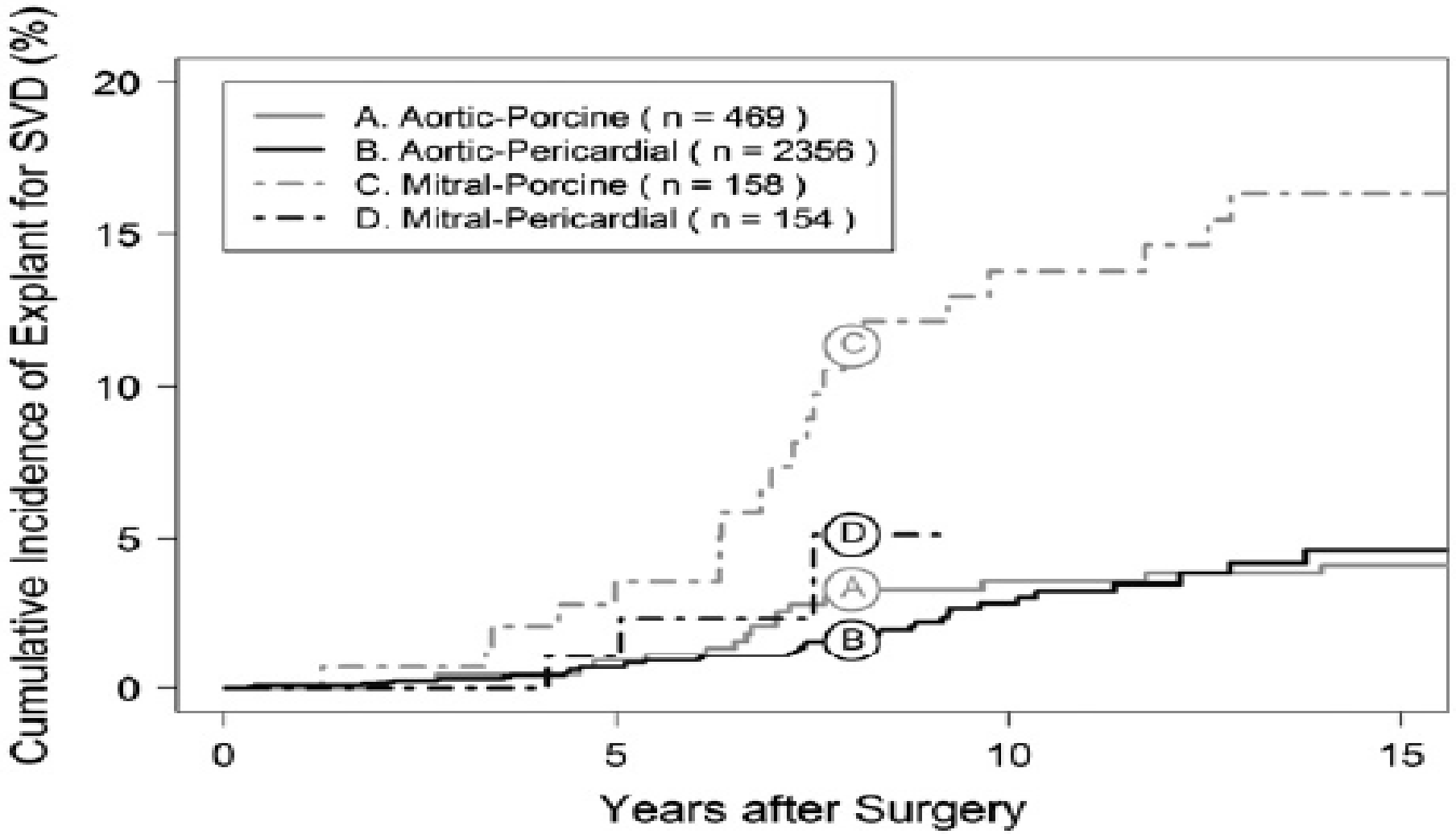
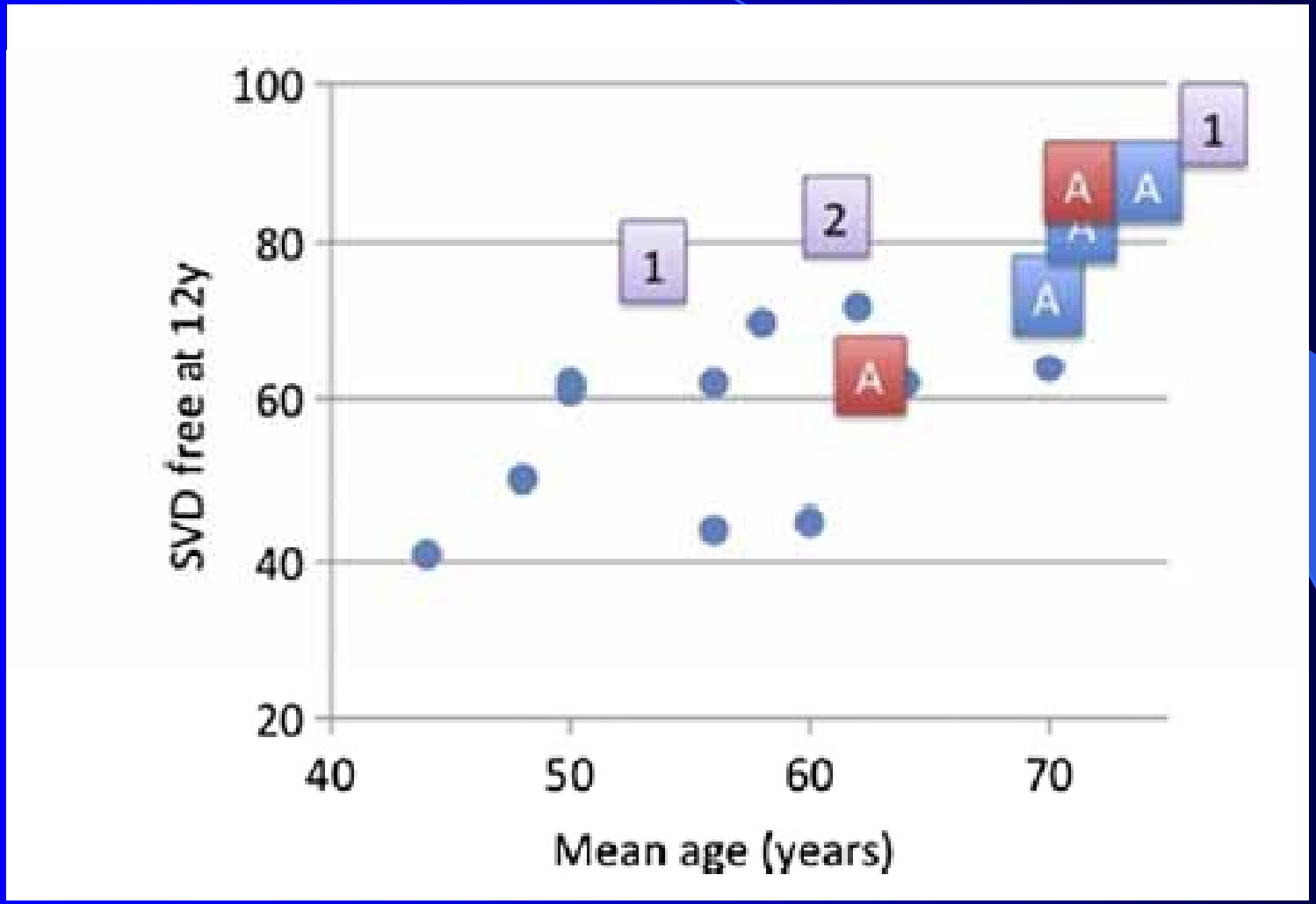


FIGURE 3. Cumulative incidence function estimates of explant for structural valve deterioration *(SVD)* in operative survivors.

Grunkemeier et al. J Thorac Cardiovasc Surg 2012;144:1381-6

Freedom from SVD

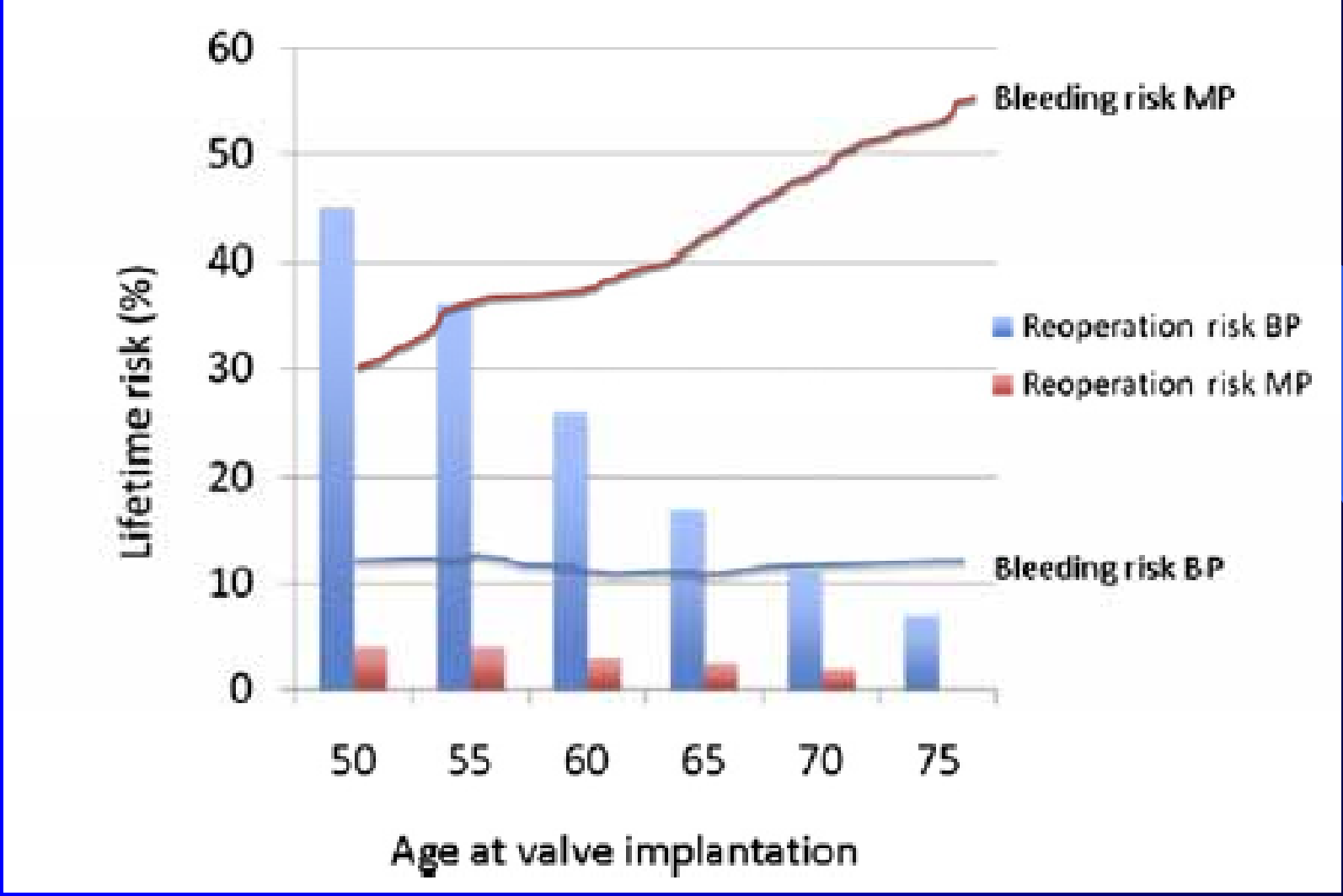
New generation of surgical valves



Blue square = pericardial valve; Red square = 2nd generation bioprostheses; Dot = 1st generation bioprostheses; numbered square = 3rd generation bioprostheses

http://www.semthorcardiovascsurg.com

Higher Chance of Reoperation in Young Patients



http://www.semthorcardiovascsurg.com

We should not move quickly

- High incidences of major complications with TAVI
  - Cerebrovascular events
  - Paravalvular leak
  - AV block/PPM
- Unknown long-term durability of THVs even in elderly patients
- No RCT data available in intermediate risk patients
- No data in young patients
- Known limited durability of surgical bioprosthesis in young patients