SUPPLEMENTAL MATERIAL

Three-Year Outcomes Following TAVR in Younger (<75 Years) Low Surgical Risk Severe Aortic Stenosis Patients

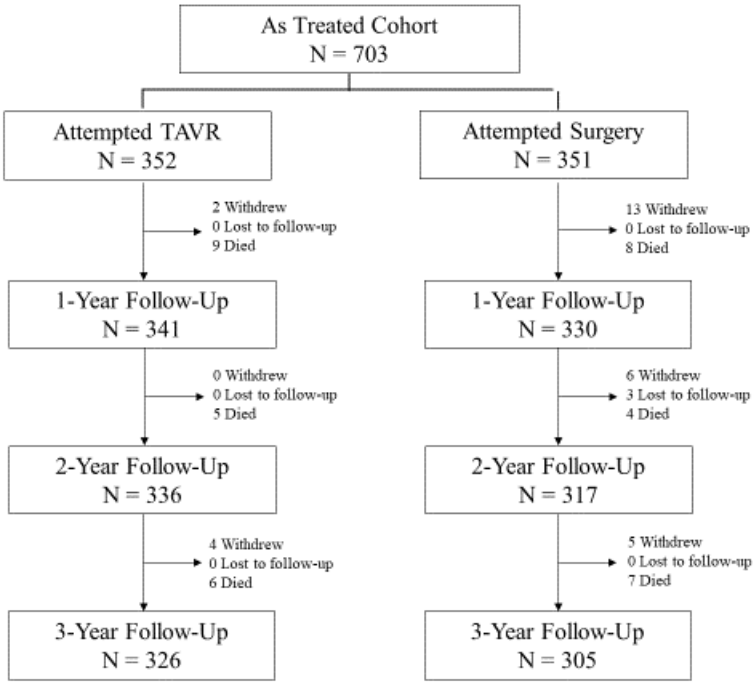
Thomas Modine, MD, PhD, MBA; Didier Tchétché, MD, PhD; Nicolas M. Van Mieghem, MD, PhD; G. Michael Deeb, MD; Stanley J. Chetcuti, MD; Steven J. Yakubov, MD; Paul Sorajja, MD; Hemal Gada, MD,MBA; Mubashir Mumtaz, MD; Basel Ramlawi, MD; Tanvir Bajwa, MD; John Crouch, MD; Paul S. Teirstein, MD; Neal S. Kleiman, MD; Ayman Iskander, MD; Rodrigo Bagur, MD; Michael W. A. Chu, MD; Pierre Berthoumieu, MD; Arnaud Sudre, MD; Rik Adrichem, MD; Saki Ito, MD; Jian Huang, MD, MSc; Jeffrey J. Popma, MD; John K. Forrest, MD; Michael J. Reardon, MD

Table of Contents

Contents

Supplemental Figures and Figure Legends

Supplemental Figure S1. Patient Flow Through 3 Years

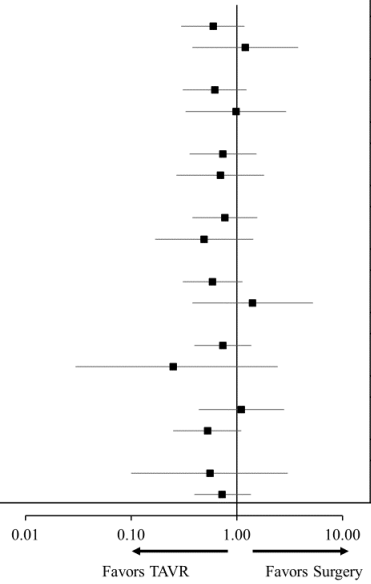


Follow-up includes those with known status.

TAVR=transcatheter aortic valve replacement

Supplemental Figure S2. Three-Year Death or Disabling Stroke Subgroup Analysis.

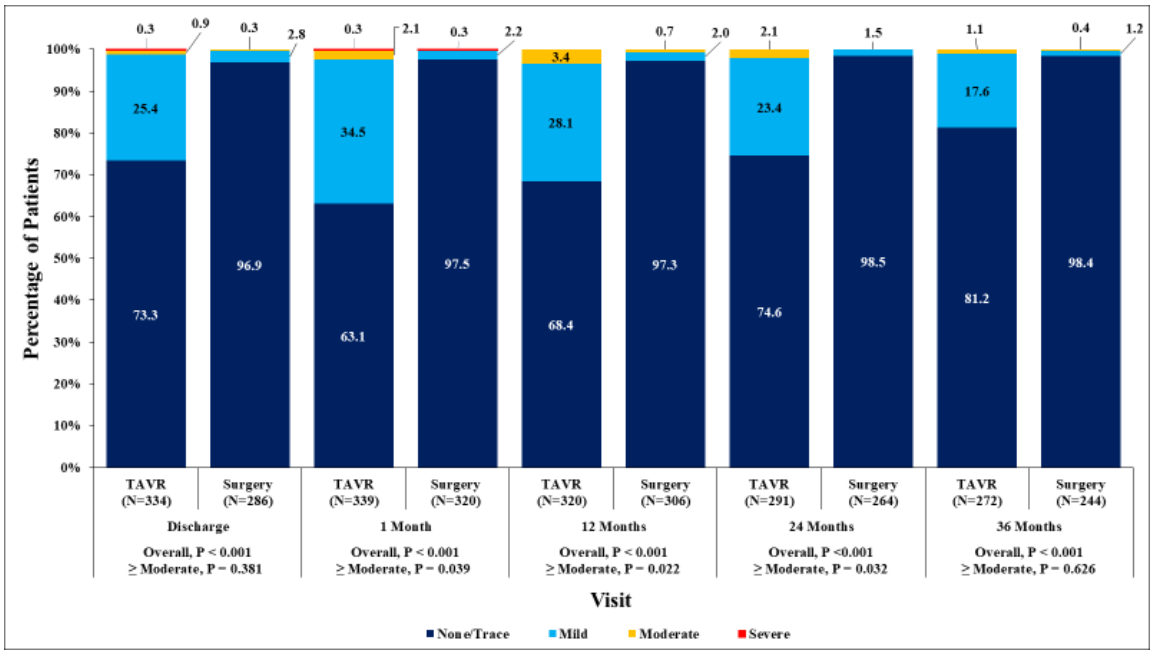
Variable		TAVR n/N (KM rate at 3 years)	Surgery n/N (KM rate at 3 years)	Hazard Ratio	P-Value for Interaction
Sex					0.31
	Male	13/222 (5.9%)	22/236 (9.6%)	0.60 (0.30-1.19)	
	Female	7/130 (5.4%)	5/115 (4.6%)	1.21 (0.38-3.80)	
STS Score (%)					0.49
	< 2.0	13/249 (5.3%)	21/262 (8.3%)	0.62 (0.31-1.24)	
	≥ 2.0	7/103 (6.8%)	6/89 (6.9%)	0.99 (0.33-2.94)	
NYHA					0.94
	I/II	13/268 (4.9%)	16/253 (6.6%)	0.74 (0.36-1.54)	
	III/IV	7/84 (8.4%)	11/98 (11.5%)	0.70 (0.27-1.81)	
Baseline KCCQ Overall Score					0.49
	≤ 72	14/186 (7.6%)	17/182 (9.7%)	0.77 (0.38-1.57)	
	> 72	5/163 (3.1%)	10/167 (6.2%)	0.49 (0.17-1.44)	
COPD					0.24
	No	15/278 (5.4%)	23/266 (9.0%)	0.59 (0.31-1.13)	
	Yes	5/64 (7.9%)	4/71 (5.7%)	1.41 (0.38-5.26)	
Baseline AF/ Atrial Flutter					0.37
	No	18/302 (6.0%)	24/312 (8.0%)	0.74 (0.40-1.37)	
	Yes	1/47 (2.1%)	3/38 (8.0%)	0.25 (0.03-2.44)	
BMI (kg/m^2)					0.22
	≤ 30	9/135 (6.7%)	9/154 (6.0%)	1.11 (0.44-2.80)	
	> 30	11/217 (5.1%)	18/197 (9.5%)	0.53 (0.25-1.11)	
Age (years)					0.77
	< 65	2/42 (4.8%)	4/48 (8.4%)	0.56 (0.10-3.05)	
	≥ 65 and < 75	18/310 (5.8%)	23/303 (7.9%)	0.73 (0.40-1.36)	



Black squares indicate the hazard ratio for TAVR vs surgery with horizontal lines indicating the 95% confidence intervals. No adjustments were made for multiplicity. P values for interaction are based on the Cox proportional hazards model.

AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA=New York Heart Association (functional classification); STS=Society of Thoracic Surgeons; TAVR=transcatheter aortic valve replacement

Supplemental Figure S3: Three-Year Paravalvular Regurgitation in All Treated Patients (Unpaired Data).



The rates of residual moderate or greater paravalvular regurgitation (PVR) were not different in those assigned to TAVR or surgery. Similar rates (no statistically significant differences) were observed in the rates of residual moderate or greater PVR (TAVR 1.1%, surgery 0.4%, *P*=0.626) between the two treatment groups at three years.

PVR=paravalvular regurgitation; TAVR=transcatheter aortic valve replacement

Supplemental Tables

Supplemental Table S1. Clinical Endpoint Definitions

Endpoint	Definition
Clinical Valve Thrombosis	Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment and is associated with any of the following clinical sequelae: any ischemic stroke, any peripheral embolic event, ST segment elevation or non-ST elevation myocardial infarction, or hemodynamic impairment associated with a worsening heart failure
Subclinical Valve Thrombosis	Thromboses without evident clinical sequelae causing a hemodynamic impediment meeting the following criteria: increase in aortic regurgitation resulting in moderate or severe paravalvular regurgitation (PVR), a post-discharge mean gradient of ⩾ 20 mm Hg that increased by > 50%, or a decrease in the Doppler Velocity Index (DVI) by > 50%.
Prosthesis Patient Mismatch[16]	Defined per VARC-3 definition.
BMI < 30 m^2	No PPM was defined as an EOAi > 0.85 cm^2/m^2, moderate PPM was defined as 0.65 cm^2/m^2 < EOAi ⩽ 0.85 cm^2/m^2; and severe PPM was defined as an EOAi ⩽ 0.65 cm^2/m^2.
BMI ≥30 m^2	No PPM was defined as an EOAi > 0.70 cm^2/m^2, moderate PPM was defined as 0.55 cm^2/m^2 < EOAi ⩽ 0.70 cm^2/m^2, and severe PPM was defined as an EOAi⩽ 0.55 cm^2/m^2.

BMI=body mass index; EOAi=effective orifice area index; PPM=prosthesis patient mismatch

Supplemental Table S2. Thirty Day Clinical Outcomes

Outcome	TAVR	Surgery	p-value*	HR 95% CI
All-cause mortality or disabling stroke	0.9% (3)	2.6% (9)	0.081	0.33 (0.09, 1.22)
All-cause mortality	0.6% (2)	0.9% (3)	0.652	0.67 (0.11, 3.98)
Cardiovascular death	0.6% (2)	0.9% (3)	0.652	0.67 (0.11, 3.98)
All stroke	3.1% (11)	3.1% (11)	0.994	1.00 (0.44, 2.31)
Disabling stroke	0.3% (1)	1.7% (6)	0.057	0.17 (0.02, 1.37)
Non-Disabling Stroke	2.8% (10)	1.4% (5)	0.193	2.01 (0.69, 5.88)
Life threatening or disabling bleeding	2.3% (8)	5.7% (20)	0.020	0.39 (0.17, 0.90)
Major vascular complication	3.7% (13)	1.7% (6)	0.105	2.17 (0.83, 5.72)
Acute kidney injury	2.8% (10)	9.7% (34)	0.0002	0.29 (0.14, 0.58)
Myocardial infarction	0.9% (3)	1.7% (6)	0.315	0.50 (0.13, 2.00)
Atrial fibrillation	7.4% (26)	32.3% (116)	<0.001	0.21 (0.14, 0.32)
Permanent pacemaker implant†	17.3% (59)	5.3% (18)	<0.001	3.57 (2.10, 6.04)
Permanent pacemaker implant‡	16.8% (59)	5.1% (18)	<0.001	3.51 (2.07, 5.95)

Clinical outcomes are presented as Kaplan-Meier estimate % (N).

*P values based on the log-rank test.

†Patients with pacemaker or ICD at baseline are not included.

‡Patients with pacemaker or ICD at baseline are included.

CI=confidence interval; HR=hazard ratio; ICD=implantable cardioverter-defibrillator;

TAVR=transcatheter aortic valve replacement

Supplemental Table S3. Procedural Information for TAVR patients

Assessment	TAVR (N=352)
Number of index implant procedures	351
Type of anesthesia	
General, %	55.8 (196/351)
Local, %	44.2 (155/351)
Implanted valve size	
Evolut R, %	74.2 (260/350)
23 mm, %	1.4 (5/350)
26 mm, %	12.3 (43/350)
29 mm, %	27.1 (95/350)
34 mm, %	33.4 (117/350)
Evolut PRO, %	23.1 (81/350)
23 mm, %	0 (0/350)
26 mm, %	6.3 (22/350)
29 mm, %	16.9 (59/350)
CoreValve 31mm, %	2.6 (9/350)
Pre-balloon valvuloplasty, %	32.2 (113/351)
Post-implant dilatation, %	31.6 (111/351)
Access route, %	
Left/Right femoral	99.4 (349/351)
Left/Right subclavian axillary	0.6 (2/351)
InLine sheath used, %	79.2 (271/342)
Vascular closure device used, %	87.2 (306/351)
Embolic protection device used, %	2.0 (7/350)

NCC Implant depth by aortography, mm	3.9 ± 2.1
LCC Implant depth by aortography, mm	5.0 ± 2.3
PCI performed during or after TAVR, %	7.1 (25/351)
Multiple (≥ 2) valve implanted, %	1.4 (5/351)
Resheath or recapture, %	40.5 (138/341)
Time delivery catheter in the body, min	12.0 (7.0, 20.0) (N = 331)
Time in Interventional Suite, min	138.0 (112.0, 173.0) (N = 350)

Values reported as % (n/N) or mean ± standard deviation. Time reported as median (Q1, Q3). For patients with two implant procedures only the index procedure was used. Index procedure is defined as the first procedure that the Medtronic TAV system delivery catheter was introduced. LCC=left coronary cusp; NCC=non coronary cusp; PCI=percutaneous coronary intervention; TAVR=transcatheter aortic valve replacement

Supplemental Table S4. Procedural Information for Surgery Patients

Assessment	Surgery (N=351)
Number of index implant procedures	351
Total bypass time, min	88.0 (67.0, 113.0) (347)
Total cross-clamp time, min	64.0 (50.0, 82.0) (345)
Incision type	
Full sternotomy, %	67.0 (235/351)
Mini sternotomy, %	14.2 (50/351)
Right anterior thoracotomy, %	18.5 (65/351)
Other*, %	0.3 (1/351)
Valve size (mm)	
19, %	3.4 (12/351)
21, %	19.4 (68/351)
23, %	29.9 (105/351)
25, %	26.5 (93/351)
27, %	7.4 (26/351)
29, %	0.0 (0/351)
Other†, %	13.4 (47/351)
Surgical Valve Type	
Edwards Intuity Valve	16.5 (58/351)
Edwards Magna Ease	4.8 (17/351)
Edwards Perimount‡	36.5 (128/351)
Edwards Inspiris Resilia	0.6 (2/351)
Edwards RSR	0.9 (3/351)
Medtronic Avalus	0.3 (1/351)

Medtronic Freestyle	0.6 (2/351)
Medtronic Hancock II	1.4 (5/351)
Medtronic Mosaic	6.3 (22/351)
St. Jude Medical Biocor	0.3 (1/351)
St. Jude Medical Epic	0.9 (3/351)
St. Jude Medical Trifecta	16.5 (58)
Sorin Mitroflow	1.1 (4/351)
Sorin Perceval[†]	13.4 (47/351)
Time in Operating room, min	260.5 (218.0, 320.5) (344)

Values reported as % (n/N) or mean ± standard deviation with (N). Time reported as median (Q1, Q3).

[*]Others for incision type: right mini-thoracotomy converted to full sternotomy and median sternotomy.

[†]Others included sutureless valves categorized as “S”, “M”, or “L” for valve size.

[‡]Includes Perimount Magna and Perimount Magna Ease.

Supplemental Table S5. One Year Clinical Outcomes

Outcome	TAVR	Surgery	p-value*	HR (95% CI)
All-cause mortality or disabling stroke	2.8% (10)	4.3% (15)	0.293	0.65 (0.29, 1.45)
All-cause mortality	2.6% (9)	2.3% (8)	0.828	1.11 (0.43, 2.88)
Cardiovascular death	2.3% (8)	2.0% (7)	0.813	1.13 (0.41, 3.12)
All stroke	3.1% (11)	4.3% (15)	0.431	0.73 (0.34, 1.60)
Disabling stroke	0.3% (1)	2.3% (8)	0.019	0.12 (0.02, 0.99)
Non-Disabling Stroke	2.8% (10)	2.0% (7)	0.462	1.43 (0.55, 3.77)
Aortic valve hospitalization	3.7% (13)	6.1% (21)	0.146	0.60 (0.30, 1.20)
All-cause mortality, disabling stroke, or aortic valve rehospitalization	6.3% (22)	9.5% (33)	0.106	0.64 (0.38, 1.10)
Life threatening or disabling bleeding	2.9% (10)	6.0% (21)	0.041	0.47 (0.22, 0.99)
Major vascular complication	3.7% (13)	2.3% (8)	0.270	1.63 (0.68, 3.93)
Acute kidney injury	2.8% (10)	9.7% (34)	<0.001	0.29 (0.14, 0.58)
Myocardial infarction	2.3% (8)	2.3% (8)	0.988	0.99 (0.37, 2.65)
Valve endocarditis	0.0% (0)	0.6% (2)	0.156	NA
Permanent pacemaker implant†	18.2% (62)	5.9% (20)	<0.001	3.38 (2.04, 5.59)

Permanent pacemaker implant‡	17.7% (62)	5.7% (20)	<0.001	3.33 (2.01, 5.51)
Atrial fibrillation	8.8% (31)	35.8% (125)	<0.001	0.22 (0.15, 0.32)
Valve thrombosis (clinical or sub-clinical)	0.9% (3)	0.6% (2)	0.665	1.48 (0.25, 8.86)
Valve thrombosis (clinical)	0.3% (1)	0.3% (1)	0.989	0.98 (0.06, 15.68)
Valve thrombosis (sub-clinical)	0.6% (2)	0.3% (1)	0.570	1.98 (0.18, 21.82)
Reintervention	0.6% (2)	0.6% (2)	0.994	0.99 (0.14, 7.04)

Clinical outcomes are presented as Kaplan-Meier estimate % (N).

*P values based on the log-rank test.

†Patients with pacemaker or ICD at baseline are not included.

‡Patients with pacemaker or ICD at baseline are included.

CI=confidence interval; HR=hazard ratio; ICD=implantable cardioverter-defibrillator; TAVR=transcatheter aortic valve replacement

Supplemental Table S6. Thirty Day, One Year, and Two Year Bioprosthetic Valve Performance

	Thirty Days			One Year			Two Years		
	TAVR	**Surgery**	**p-value**	**TAVR**	**Surgery**	**p-value**	**TAVR**	**Surgery**	**p-value**
Mean aortic gradient, mm Hg	9.0±3.6	11.1±4.2	<0.001	9.1±3.5	11.7±4.9	<0.001	9.5±4.3	12.6±5.8	<0.001
Maximal aortic valve velocity, m/sec	2.0±0.4	2.2±0.4	<0.001	2.0±0.4	2.3±0.4	<0.001	2.1±0.4	2.3±0.5	<0.001
Aortic valve area, cm^2	2.1±0.5	2.0±0.6	0.002	2.2±0.6	1.9±0.6	<0.001	2.3±0.6	1.9±0.6	<0.001
Paravalvular aortic regurgitation			<0.001			<0.001			<0.001
None/trace	63.1% (214/339)	97.5% (312/320)		68.4% (219/320)	97.4% (298/306)		74.6% (217/291)	98.5% (260/264)	
Mild	34.5% (117/339)	2.2% (7/320)		28.1% (90/320)	2.0% (6/306)		23.4% (68/291)	1.5% (4/264)	
Moderate	2.1% (7/339)	0.0% (0/320)		3.4% (11/320)	0.7% (2/306)		2.1% (6/291)	0.0% (0/264)	
Severe	0.3% (1/339)	0.3% (1/320)		0.0% (0/320)	0.0% (0/306)		0.0% (0/291)	0.0% (0/264)	
≥ Moderate	2.4% (8/339)	0.3% (1/320)	0.039	3.4% (11/320)	0.7% (2/306)	0.022	2.1% (6/291)	0.0% (0/264)	0.032
Total aortic regurgitation			<0.001			<0.001			<0.001

None/trace	63.2% (216/342)	95.5% (315/330)		67.6% (219/324)	93.0% (292/314)		73.3% (220/300)	94.9% (259/273)	
Mild	34.5% (118/342)	4.2% (14/330)		28.7% (93/324)	6.1% (19/314)		24.3% (73/300)	4.8% (13/273)	
Moderate	2.0% (7/342)	0.0% (0/330)		3.7% (12/324)	1.0% (3/314)		2.3% (7/300)	0.4% (1/273)	
Severe	0.3% (1/342)	0.3% (1/330)		0.0% (0/324)	0.0% (0/314)		0.0% (0/300)	0.0% (0/273)	
≥ Moderate	2.3% (8/342)	0.3% (1/330)	0.038	3.7% (12/324)	1.0% (3/314)	0.033	2.3% (7/300)	0.4% (1/273)	0.071
Prosthesis-patient mismatch									
None, %	88.9% (256/288)	77.9% (219/281)	<0.001	94.4% (255/270)	72.0% (193/268)	<0.001	91.8% (234/255)	70.0% (156/223)	<0.001
Moderate, %	10.4% (30/288)	18.1% (51/281)		4.4% (12/270)	20.9% (56/268)		5.9% (15/255)	23.3% (52/223)	
Severe, %	0.7% (2/288)	3.9% (11/281)		1.1% (3/270)	7.1% (19/268)		2.4% (6/255)	6.7% (15/223)	
Bioprosthetic valve dysfunction									
Structural valve deterioration*									

Mean gradient ≥ 20 mm Hg	1.2% (4/339)	4.2% (14/334)	0.017	0.6% (2/320)	6.4% (20/314)	<0.001	3.4% (10/298)	9.9% (27/272)	0.002
≥ 10 mm Hg increase from 1 month/discharge†	NA	NA	NA	1.3% (4/320)	2.9% (9/310)	0.169	1.7% (5/298)	6.7% (18/268)	0.002
Non-structural valve dysfunction*									
Severe PVR	0.3% (1/339)	0.3% (1/320)	>0.999	0.0% (0/320)	0.0% (0/306)	NA	0.0% (0/291)	0.0% (0/264)	NA
Severe PPM	0.7% (2/288)	3.9% (11/281)	0.011	1.1% (3/270)	7.1% (19/268)	<0.001	2.4% (6/255)	6.7% (15/223)	0.020
Valve thrombosis (clinical)	0.0% (0)	0.0% (0)	NA	0.3% (1)	0.3% (1)	0.989	0.3% (1)	0.3% (1)	0.989
Valve endocarditis*	0.0% (0)	0.3% (1)	0.315	0.0% (0)	0.6% (2)	0.156	0.3% (1)	1.2% (4)	0.168

Continuous data reported as mean±standard deviation; categorical data reported as percentage (number of patients / total). P values are based on the chi-square test for PVR and PPM. Valve endocarditis is reported as Kaplan-Meier estimate % (N).

*****Non-cumulative data, reported as simple proportion rate. Numerators were "Structural valve deterioration at specific visit post procedure. Denominators were based on available post procedural echocardiographic data at the specific visit.

†If 1 month echocardiogram was not available the discharge echocardiogram was used.

BMI=body mass index; EOAi=effective orifice area index; PPM=prosthesis patient mismatch; PVR=paravalvular regurgitation; TAVR=transcatheter aortic valve replacement; VARC=Valve Academic Research Consortium