Supplemental Material of the accepted author's manuscript. Published in final edited form as: Catheterization and Cardiovascular Interventions 2021 (in press). Publisher DOI: 10.1002/ccd.29700

SUPPLEMENTAL INFORMATION

HEART VALVE SIZING AND CLINICAL OUTCOMES IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

Okuno et al.

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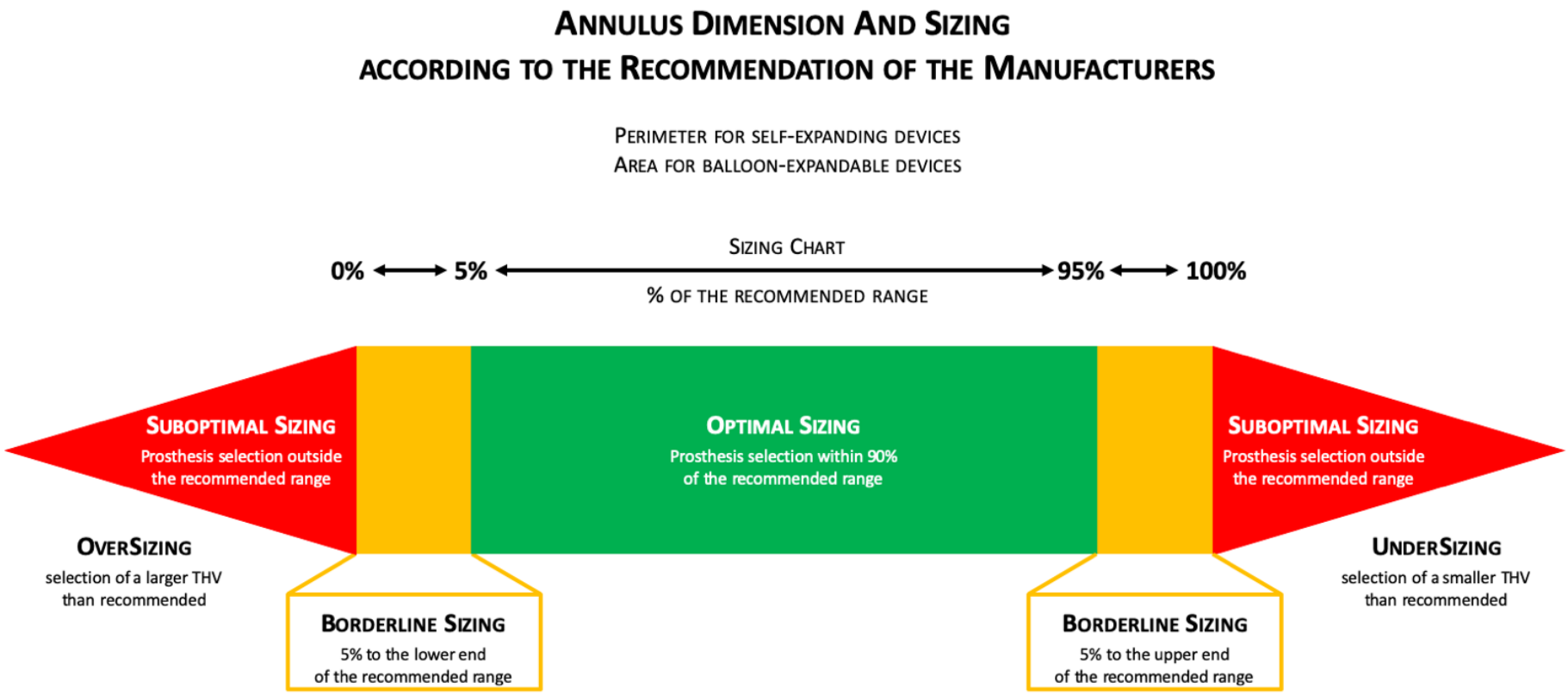
ADDITIONAL METHODS. Data collection and clinical endpoints.

Baseline clinical, procedural, and follow-up data were entered into a dedicated web-based database, held and maintained at the Clinical Trials Unit at the University of Bern, Bern, Switzerland. Follow-up data was obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries at 30 days and 1 year. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee according to the Valve Academic Research Consortium (VARC-2) criteria.(1) VARC-2 device success was defined as the absence of procedural mortality and correct positioning of a single prosthetic heart valve into the proper anatomical location and intended performance. Given the high prevalence of prosthesis-patient mismatch,(2) modified device success defined as VARC-2 device success excluding prosthesis-patient mismatch was also assessed in the present analysis. VARC-2 early safety endpoint included a combination of all-cause mortality, stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure at 30 days. The VARC-2 time-related valve safety endpoint included valve dysfunction, endocarditis, thrombotic complications of the prosthesis, and bleeding events up to 1 year. Unplanned repeat intervention was defined as a composite endpoint including repeat TAVI, repeat balloon valvuloplasty in another setting, surgical revision, or paravalvular leak closure for the implanted THV. The primary endpoint of the present analysis was a composite of all-cause death or unplanned repeat intervention at 1 year after TAVI.

SUPPLEMENTAL FIGURE. Annulus dimension and sizing according to the recommendation of the manufacturers.



SUPPLEMENTAL TABLE 1. Sizing algorithm for each transcatheter heart valves (THV).

Patients treated with SAPIEN THV/XT				
Implanted size	~~**20mm**~~	**23mm**	**26mm**	**29mm**
Annulus size recommendation		Area 314-415 (101) mm^3	Area 415-530 (115) mm^3	Area 530-660 (130) mm^3
Optimal sizing		$319mm^3$<Area<$410mm^3$	$421mm^3$<Area<$524mm^3$	$537mm^3$<Area<$653mm^3$
Borderline sizing		Area 314-$319mm^3$ Area 410-$415mm^3$	Area 415-$421mm^3$ Area 524-$530mm^3$	Area 530-$537mm^3$ Area 653-$660mm^3$
Suboptimal sizing		Area <$314mm^3$ Area >$415mm^3$	Area <$415mm^3$ Area >$530mm^3$	Area <$530mm^3$ Area >$660mm^3$
Oversizing		Area <$319mm^3$	Area <$421mm^3$	Area <$537mm^3$
Undersizing		Area >$410mm^3$	Area >$524mm^3$	Area >$653mm^3$
Patients treated with SAPIEN 3				
Implanted size	~~**20mm**~~	**23mm**	**26mm**	**29mm**

Annulus size recommendation		Area 338-430 (93) mm^3	Area 430-546 (116) mm^3	Area 540-683 (143) mm^3
Optimal sizing		343mm^3<Area<425mm^3	436mm^3<Area<540mm^3	547mm^3<Area<676mm^3
Borderline sizing		Area 338-343mm^3 Area 425-430mm^3	Area 430-436mm^3 Area 540-546mm^3	Area 540-547mm^3 Area 676-683mm^3
Suboptimal sizing		Area <338mm^3 Area >430mm^3	Area <430mm^3 Area >546mm^3	Area <540mm^3 Area >683mm^3
Oversizing		Area <343mm^3	Area <436mm^3	Area <547mm^3
Undersizing		Area >425mm^3	Area >540mm^3	Area >676mm^3
Patients treated with CoreValve*				
Implanted size	**23mm**	**26mm**	**29mm**	**31mm**
Annulus size recommendation	Perimeter 56.5-62.8 (6.3) mm	Perimeter 62.8-72.3 (9.5) mm	Perimeter 72.3-84.8 (12.5) mm	Perimeter 81.6-91.1 (9.5) mm
Optimal sizing	56.8mm<Perimeter<62.5mm	63.3mm<Perimeter<71.8mm	72.9mm<Perimeter<84.2mm	82.1mm<Perimeter<90.6mm
Borderline sizing	Perimeter 56.5-56.8mm Perimeter 62.5-62.8mm	Perimeter 62.8-63.3mm Perimeter 71.8-72.3mm	Perimeter 72.3-72.9mm Perimeter 84.2-84.8mm	Perimeter 81.6-82.1mm Perimeter 90.6-91.1mm
Suboptimal sizing	Perimeter <56.5mm Perimeter >62.8mm	Perimeter <62.8mm Perimeter >72.3mm	Perimeter <72.3mm Perimeter >84.8mm	Perimeter <81.6mm Perimeter >91.1mm

Oversizing	Perimeter <56.8mm	Perimeter <63.3mm	Perimeter <72.9mm	Perimeter <82.1mm
Undersizing	Perimeter >62.5mm	Perimeter >71.8mm	Perimeter >84.2mm	Perimeter >90.6mm
Evolut R/PRO				
Implanted size	**23mm**	**26mm**	**29mm**	**34mm**
Annulus size recommendation	Perimeter 56.5-62.8 (6.3) mm	Perimeter 62.8-72.3 (9.5) mm	Perimeter 72.3-81.7 (9.4) mm	Perimeter 81.7-94.2 (12.5) mm
Optimal sizing	56.8mm<Perimeter<62.5mm	63.3mm<Perimeter<71.8mm	72.8mm<Perimeter<81.2mm	82.3mm<Perimeter<93.6mm
Borderline sizing	Perimeter 56.5-56.8mm Perimeter 62.5-62.8mm	Perimeter 62.8-63.3mm Perimeter 71.8-72.3mm	Perimeter 72.3-72.8mm Perimeter 81.2-81.7mm	Perimeter 81.7-82.3mm Perimeter 93.6-94.2mm
Suboptimal sizing	Perimeter <56.5 Perimeter >62.8mm	Perimeter <62.8 Perimeter >72.3mm	Perimeter <72.3mm Perimeter >81.7mm	Perimeter <81.7mm Perimeter >94.2mm
Oversizing	Perimeter <56.8mm	Perimeter <63.3mm	Perimeter <72.8mm	Perimeter <82.3mm
Undersizing	Perimeter >62.5mm	Perimeter >71.8mm	Perimeter >81.2mm	Perimeter >93.6mm
SJM Portico				
Implanted size	**23mm**	**25mm**	**27mm**	**29mm**

Annulus size recommendation	Perimeter 60-66 (6) mm	Perimeter 66-73 (7) mm	Perimeter 72-79 (7) mm	Perimeter 79-85 (6) mm
Optimal sizing	60.3mm<Perimeter<65.7mm	66.4mm<Perimeter<72.6mm	72.4mm<Perimeter<78.6mm	79.3mm<Perimeter<84.7mm
Borderline sizing	Perimeter 60-60.3mm Perimeter 65.7-66mm	Perimeter 66-66.4mm Perimeter 72.6-73mm	Perimeter 72-72.4mm Perimeter 78.6-79mm	Perimeter 79-79.3mm Perimeter 84.7-85mm
Suboptimal sizing	Perimeter <60mm Perimeter >66mm	Perimeter <66mm Perimeter >73mm	Perimeter <72mm Perimeter >79mm	Perimeter <79mm Perimeter >85mm
Oversizing	Perimeter <60.3mm	Perimeter <66.4mm	Perimeter <72.4mm	Perimeter <79.3mm
Undersizing	Perimeter >65.7mm	Perimeter >72.6mm	Perimeter >78.6mm	Perimeter >84.7mm

Symetis Acurate/Acurate neo			
Implanted size	**S**	**M**	**L**
Annulus size recommendation	Perimeter 66-72 (6) mm	Perimeter 72-79 (7) mm	Perimeter 79-85 (6) mm
Optimal sizing	66.3mm<Perimeter<71.7mm	72.4mm<Perimeter<78.6mm	79.3mm<Perimeter<84.7mm
Borderline sizing	Perimeter 66-66.3mm Perimeter 71.7-72mm	Perimeter 72-72.4mm Perimeter 78.6-79mm	Perimeter 79-79.3mm Perimeter 84.7-85mm
Suboptimal sizing	Perimeter <66mm Perimeter >72mm	Perimeter <72mm Perimeter >79mm	Perimeter <79mm Perimeter >85mm

Oversizing	Perimeter <66.3mm	Perimeter <72.4mm	Perimeter <79.3mm
Undersizing	Perimeter >71.7mm	Perimeter >78.6mm	Perimeter >84.7mm
Lotus/Lotus edge			
Implanted size	**23mm**	**25mm**	**27mm**
Annulus size recommendation	Perimeter 62.8-72.3 (9.5) mm	Perimeter 72.3-78.5 (6.2) mm	Perimeter 78.5-84.8 (6.3) mm
Optimal sizing	63.3mm<Perimeter<71.8mm	72.6mm<Perimeter<78.2mm	78.8mm<Perimeter<84.5mm
Borderline sizing	Perimeter 62.8-63.3mm Perimeter 71.8-72.3mm	Perimeter 72.3-72.6mm Perimeter 78.2-78.5mm	Perimeter 78.5-78.8mm Perimeter 84.5-84.8mm
Suboptimal sizing	Perimeter <62.8mm Perimeter >72.3mm	Perimeter <72.3mm Perimeter >78.5mm	Perimeter <78.5mm Perimeter >84.8mm
Oversizing	Perimeter <63.3mm	Perimeter <72.6mm	Perimeter <78.8mm
Undersizing	Perimeter >71.8mm	Perimeter >78.2mm	Perimeter >84.5mm
*Manufacturer only provided annulus diameter for the recommendation. The recommended perimeter is derived from Eur Heat J 2014:35:2627-2638.			

SUPPLEMENTAL TABLE 2. MDCT and Procedural characteristics according to Over-/Under-sized THV

	OVERSIZING (N=212)	**UNDERSIZING** (N=198)	**P-VALUE**
COMPUTED TOMOGRAPHY DATA			
Bicuspid valve (n, %)	12 (5.7%)	19 (9.6%)	0.14
Annulus area (mm^2)	425.9±68.2	500.8±108.5	<0.001
Annulus perimeter (mm)	74.5±6.0	80.6±8.5	<0.001
SOV diameter (mm)	31.7±3.7	34.1±4.3	<0.001
AVC calcium (mm^3)	283.0±322.1	453.5±514.5	<0.001
LVOT calcium (mm^3)	15.2±49.8	25.5±60.2	0.058
Eccentricity of annulus (0 to 1)	0.76±0.06	0.76±0.06	0.89
PROCEDURAL CHARACTERISTICS			
Fluoroscopy time (min)	15.1±7.8	20.5±18.1	<0.001
General anesthesia (n, %)	47 (22.2%)	44 (22.2%)	1.00
Conversion from Local to General anesthesia (n, %)	6 (3.8%)	1 (0.8%)	0.14
Femoral main access site (n, %)	188 (88.7%)	178 (89.9%)	0.75
Type of valve (n, %)			<0.001
Balloon-expandable*	155 (73.1%)	44 (22.2%)	
Self-expanding**	52 (24.5%)	128 (64.6%)	
Mechanical-expanding***	5 (2.4%)	26 (13.1%)	
Valve size (n, %)			0.345
≤26mm	137 (64.6%)	119 (60.1%)	
>26mm	75 (35.4%)	79 (39.9%)	
Pre dilation (n, %)	143 (67.5%)	160 (80.8%)	0.002
Post dilation (n, %)	39 (18.4%)	92 (46.5%)	<0.001

Depicted are means with standard deviations (±SD) or counts with percentages (%).
* SAPIEN THV/XT, SAPIEN; ** CoreValve, Evolut R/ PRO, Portico, Symetis ACURATE/ACURATE neo; *** Lotus/ Lotus Edge
STS PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; NYHA = New York Heart Association; CKD = Chronic kidney disease; GFR = Glomerular filtration rate; COPD = Chronic obstructive pulmonary disease; LVEF = Left ventricular ejection fraction; AR = Aortic regurgitation; MR = Mitral regurgitation; TR = Tricuspid regurgitation; AVC = Aortic valvular complex; LVOT = Left ventricular outflow tract.

SUPPLEMENTAL TABLE 3. Procedural complications and outcomes according to Over-/Under-sized THV

	OPTIMAL SIZING (N=1228)	OVERSIZING (N=212)	UNDERSIZING (N=198)	CRUDE RISK RATIO			
	A	B	C	B vs A		C vs A	
				RR (95% CI)	P-VALUE	RR (95% CI)	P-VALUE
PROCEDURAL COMPLICATIONS							
Valve in series (n, %)	17 (1.4)	3 (1.4)	7 (3.5)	1.02 (0.30-3.46)	0.97	2.55 (1.07-6.08)	0.034
Valve migration/embolization (n, %)	21 (1.7)	3 (1.4)	8 (4.0)	0.83 (0.25-2.75)	0.76	2.36 (1.06-5.26)	0.035
Annulus rupture/aortic dissection (n, %)	6 (0.5)	3 (1.4)	1 (0.5)	2.90 (0.73-11.50)	0.13	1.03 (0.13-8.55)	0.98
Cardiac tamponade/rupture (n, %)	10 (0.8)	4 (1.9)	0 (0.0)	2.32 (0.73-7.32)	0.15	0.29 (0.02-4.93)	0.37
Coronary artery occlusion (n, %)	5 (0.4)	1 (0.5)	0 (0.0)	1.16 (0.14-9.87)	0.89	0.56 (0.03-10.09)	1.0
Conversion to Surgery (n, %)	10 (0.8)	1 (0.5)	0 (0.0)	0.58 (0.07-4.50)	0.60	0.29 (0.02-4.93)	0.37
PROCEDURAL OUTCOMES							
VARC-2 device success (n, %)	555 (57.8%)	89 (54.3%)	77 (47.8%)	0.94 (0.81-1.09)	0.41	0.83 (0.70-0.98)	0.029
Modified device Success (n, %)*	1035 (87.4)	191 (91.8)	154 (79.0)	1.05 (1.00-1.10)	0.036	0.90 (0.84-0.97)	0.008
Mean prosthetic gradient > 20mmHg (n, %)	25 (2.0)	6 (2.8)	2 (1.0)	1.38 (0.57-3.33)	0.47	0.50 (0.12-2.08)	0.34
Prosthesis-patient mismatch (n, %)	309 (33.5)	61 (38.6)	50 (34.7)	1.15 (0.93-1.43)	0.20	1.04 (0.81-1.32)	0.77
Moderate or severe AR (n, %)**	77 (7.2)	5 (2.4)	28 (14.2)	0.33 (0.14-0.80)	0.014	1.98 (1.33-2.95)	0.001

Procedural, discharge and post-procedure outcomes analyzed with robustified binomial generalized linear models using a log-link and risk ratios RR (95% confidence interval CI) are reported.
*Device success is defined as VARC-2 device success excluding prosthesis patient mismatch.
VARC = Valve Academic Research Consortium; AR = Aortic regurgitation.

SUPPLEMENTAL TABLE 4. 30-days and 1-year clinical outcomes according Over-/Under-sized THV

	OPTIMAL SIZING (N=1228)	OVER-SIZING (N=212)	UNDER-SIZING (N=198)	CRUDE HAZARD RATIO				ADJUSTED HAZARD RATIO			
	A	B	C	B vs A		C vs A		B vs A		C vs A	
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR_{adj} (95% CI)	p-value	HR_{adj} (95% CI)	p-value
At 30 days											
VARC-2 Early safety (n, %)	223 (18.2)	42 (19.8)	45 (22.7)	1.10 (0.79-1.53)	0.58	1.27 (0.92-1.74)	0.15	1.17 (0.84-1.63)	0.35	1.26 (0.92-1.74)	0.15
All-cause mortality (n, %)	29 (2.4)	9 (4.3)	11 (5.6)	1.82 (0.86-3.84)	0.12	2.37 (1.18-4.75)	0.015	2.05 (0.96-4.36)	0.063	2.25 (1.12-4.51)	0.023
All stroke (disabling and nondisabling) (n, %)	37 (3.0)	6 (2.9)	11 (5.6)	0.94 (0.40-2.23)	0.89	1.88 (0.96-3.69)	0.065	0.95 (0.40-2.25)	0.90	1.90 (0.96-3.74)	0.064
Life-threatening bleeding (n, %)	80 (6.5)	15 (7.1)	16 (8.1)	1.09 (0.63-1.89)	0.76	1.24 (0.73-2.13)	0.43	1.20 (0.69-2.10)	0.51	1.29 (0.75-2.21)	0.36
Major vascular complication (n, %)	131 (10.7)	28 (13.2)	15 (7.6)	1.24 (0.83-1.87)	0.30	0.71 (0.41-1.20)	0.20	1.31 (0.87-1.97)	0.20	0.70 (0.41-1.19)	0.19
Acute kidney injury stage 2 or 3 (n, %)	246 (20.2)	34 (16.3)	45 (23.1)	0.54 (0.17-1.78)	0.31	1.37 (0.60-3.10)	0.45	0.67 (0.20-2.22)	0.52	1.52 (0.67-3.48)	0.32
Permanent pacemaker implantation (n, %)	223 (18.2)	42 (19.8)	45 (22.7)	0.78 (0.54-1.12)	0.17	1.15 (0.84-1.58)	0.39	0.78 (0.55-1.12)	0.19	1.09 (0.79-1.50)	0.60
1 year											
Composite of all-cause death or unplanned repeat intervention (n, %)	149 (12.3)	23 (10.9)	44 (22.2)	0.90 (0.58-1.39)	0.622	1.92 (1.37-2.69)	<0.001	0.94 (0.61-1.46)	0.79	1.86 (1.32-2.60)	<0.001
VARC-2 Time-related valve safety (n, %)	488 (40.5)	65 (31.7)	90 (46.3)	0.72 (0.55-0.93)	0.012	1.25 (1.00-1.57)	0.051	0.73 (0.56-0.94)	0.017	1.23 (0.99-1.55)	0.067
All-cause mortality (n, %)	142 (11.7)	22 (10.5)	41 (20.7)	0.90 (0.57-1.41)	0.644	1.87 (1.32-2.65)	<0.001	0.95 (0.61-1.50)	0.834	1.80 (1.27-2.55)	0.001
Cardiovascular mortality (n, %)	94 (7.9)	14 (6.8)	29 (15.1)	0.86 (0.49-1.52)	0.612	1.99 (1.31-3.02)	0.001	0.93 (0.53-1.64)	0.811	1.94 (1.28-2.95)	0.002
Unplanned repeat intervention (n, %)	10 (0.8)	1 (0.5)	5 (2.7)	0.58 (0.07-4.56)	0.607	3.17 (1.08-9.27)	0.035	0.54 (0.07-4.24)	0.559	3.35 (1.13-9.91)	0.029

Outcomes analyzed with Cox's regressions with hazard ratios (HR 95% CI) reported, censoring patients at last valid contact or death; adjusting for age, gender, BMI >30 kg/m^2, LVEF <40%, STS PROM, access site.

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