A Randomized Comparison of Self-Expandable and Balloon-Expandable Prostheses in Patients Undergoing Transfemoral Transcatheter Aortic Valve Replacement

The CHOICE Trial

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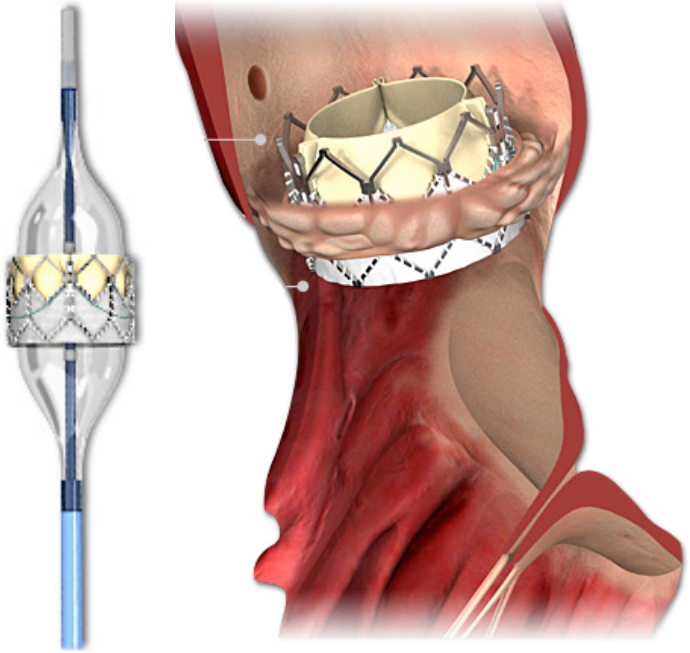
on behalf of the CHOICE investigators

Background (I)

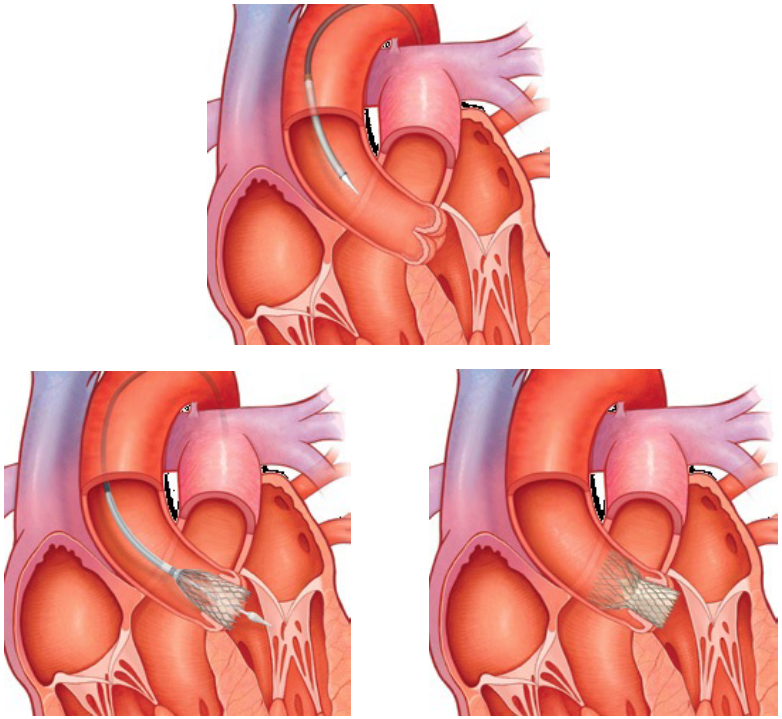
- Transcatheter aortic valve replacement is an effective treatment option for high-risk patients with severe aortic stenosis.
- Different from surgery, TAVR requires either a balloon-expandable or self-expandable system.
- Two device types are in widespread use:
  - the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences)
  - the self-expandable Medtronic CoreValve (Medtronic Inc.)

Background (II)

Balloon-expandable THV
Edwards Sapien XT
(Cobalt chromium stent frame, bovine pericardium)



Self-expandable THV
Medtronic CoreValve
(Nitinol stent frame, porcine pericardium)



Background (III)

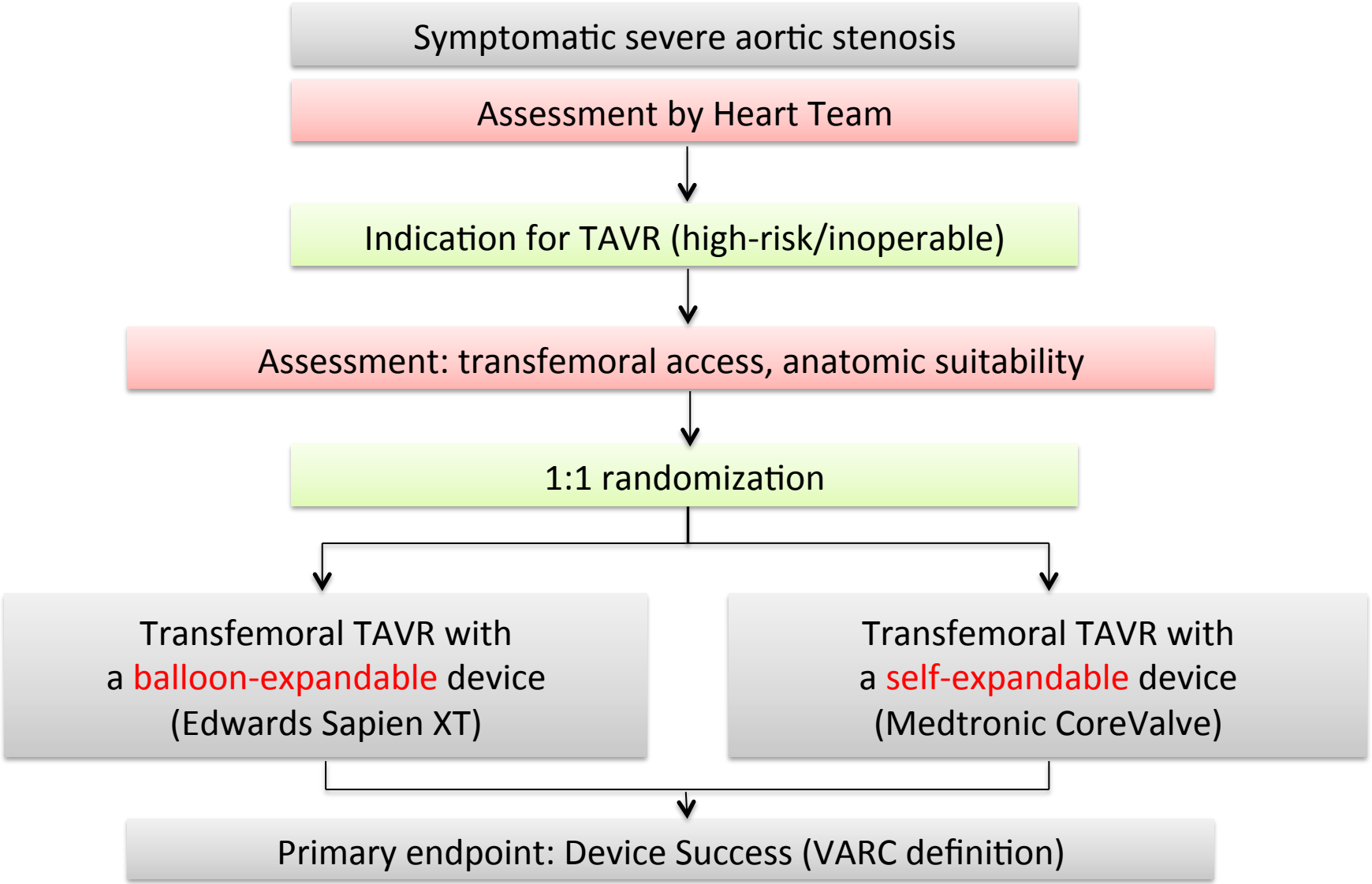
- Some observational registries have reported a lower frequency of post-procedural paravalvular aortic regurgitation with the balloon-expandable device*.
- However, recent improvements in pre-procedural imaging and device size selection, refinements in implantation technique, and the recognition of paravalvular leaks as a relevant clinical complication, might affect the functional outcome of both valves.
- A randomized comparison of both devices is lacking.

*Moat et al, J Am Coll Cardiol 2011 - Gilard et al, N Engl J Med 2012 - Nombela-Franco et al, Am J Cardiol 2013 - Abdel-Wahab et al, JACC Cardiovasc Interv 2014.

Purpose of CHOICE

to compare the performance of balloon expandable and self-expandable transcatheter aortic valves regarding overall device success in a randomized clinical trial for patients with symptomatic severe aortic stenosis at high-risk for surgery.

CHOICE: Study Design



Inclusion and Exclusion Criteria

- Main inclusion criteria
  - Severe symptomatic aortic stenosis (aortic valve area ≤ 1cm^2 or 0.6 cm^2/m^2)
  - High risk for surgery (age > 75 years and/or Logistic EuroSCORE ≥ 20% and/or STS risk score ≥ 10% and/or contraindication to conventional surgical replacement)
  - Native aortic valve annulus measuring 20-27 mm
  - Suitable transfemoral vascular access
- Main exclusion criteria
  - Native aortic valve annulus < 20 mm and > 27 mm
  - Pre-existing aortic bioprosthesis
  - Cardiogenic shock or hemodynamic instability

Primary Endpoint

- 'Device success' (first VARC definition), which is a 'technical' composite endpoint including:
  - successful vascular access, delivery and deployment of the device and retrieval of the delivery system
  - correct position of the device in the proper anatomical location
  - intended performance of the prosthetic heart valve (aortic valve area > 1.2 cm^2 and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR)
  - only one valve implanted in the proper anatomical location
- Power calculation:
  - The assumed incidence of device success was 70% with the self-expandable valve and 85% with the balloon-expandable valve*
  - Power of 80%, alpha level of 0.05
  - The calculated sample size was a total of 240 patients, 120 patients per group

*Moat et al, J Am Coll Cardiol 2011 - Gilard et al, N Engl J Med 2012 - Nombela-Franco et al, Am J Cardiol 2013 - Abdel-Wahab et al, JACC Cardiovasc Interv 2014.

Thirty-Day Secondary Endpoints*

- Cardiovascular mortality
- Major and minor vascular complications
- Major and minor bleeding
- Post-procedural pacemaker implantation
- NYHA class improvement (by at least one functional class)
- Combined safety endpoint (a composite of all cause mortality, major stroke, life threatening or disabling bleeding, acute kidney injury stage 3 including renal replacement therapy, peri-procedural myocardial infarction, major vascular complications and repeat procedure for valve-related dysfunction)
- Major adverse cardiovascular and cerebrovascular events (a composite of myocardial infarction, cardiac or vascular surgery and stroke)

* Endpoints defined according to VARC 1
Further follow-up is planned at 6 months, 1 year, 2 and 5 years

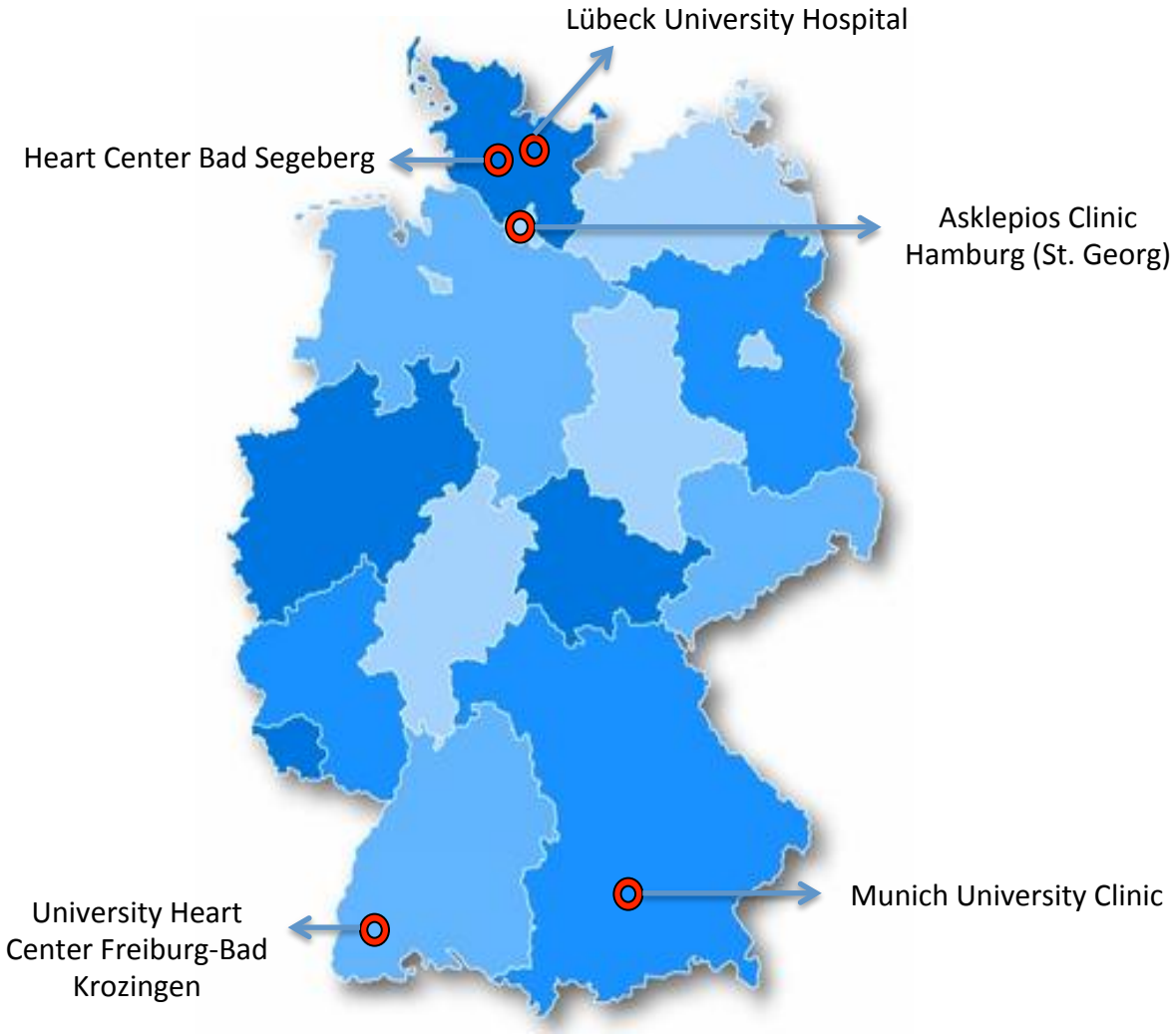
Study Methodology

- Device size selection was based on manufacturer's sizing charts, but the steering committee strongly recommended sizing to be based on three-dimensional imaging:
  - MDCT-based annular area for the balloon-expandable valve
  - MDCT-based annular perimeter for the self-expandable valve
- All procedures were performed by experienced operators in centers with an established multidisciplinary TAVR program.
- The procedure was mainly performed under analgo-sedation using fluoroscopic guidance (TEE only in selected cases).

Assessment of Aortic Regurgitation

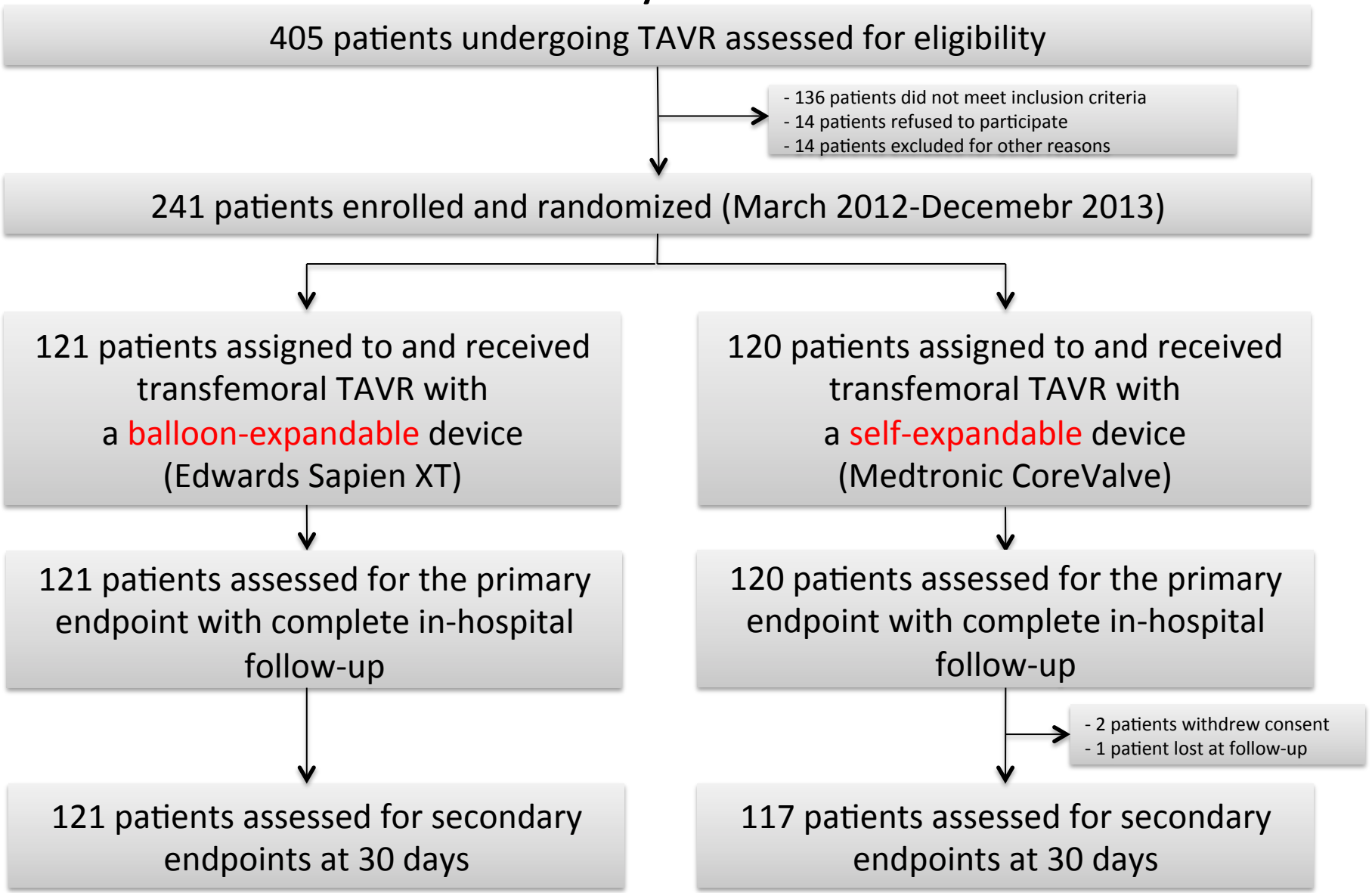
- Assessment of AR after implantation was performed using:
  1) Angiography (standardized acquisition, core-lab adjudicated)
  2) Transthoracic echocardiography (VARC 1 criteria)
  3) Invasive hemodynamic measurements (AR Index)
- Assessment of valve function at follow-up was performed using:
  1) Transthoracic echocardiography (48 hours, 30 days, and will be further assessed at intermediate and long-term follow-up)
  2) Cardiac MRI in a subgroup of patients (7-14 days and 6 months after TAVR)
- Assessment of post-procedural AR as a criterion of the primary endpoint was performed using core-lab angiography.

Study Sites and Organisation



Steering Committee:
G. Richardt, M. Abdel-Wahab
Clinical Endpoints Committee:
H.-W. Beurich, M. Abdel-Wahab
Data Management:
Zentrum für Klinische Studien, Bad Segeberg, Germany
Data Safety and Monitoring Board:
E.-G. Kraatz (chair)
Angiographic core lab:
A. Kastrati, ISAR center, Munich, Germany
Statistical core lab:
D. R. Robinson, University of Sussex, Brighton, England
Funding:
Heart Center, Segeberger Kliniken GmbH, Bad Segeberg, Germany

Study Flow


405 patients undergoing TAVR assessed for eligibility
- 136 patients did not meet inclusion criteria
- 14 patients refused to participate
- 14 patients excluded for other reasons
241 patients enrolled and randomized (March 2012-Decemebr 2013)
121 patients assigned to and received transfemoral TAVR with a balloon-expandable device (Edwards Sapien XT)
120 patients assigned to and received transfemoral TAVR with a self-expandable device (Medtronic CoreValve)
121 patients assessed for the primary endpoint with complete in-hospital follow-up
120 patients assessed for the primary endpoint with complete in-hospital follow-up
- 2 patients withdrew consent
- 1 patient lost at follow-up
121 patients assessed for secondary endpoints at 30 days
117 patients assessed for secondary endpoints at 30 days

Baseline Patient Characteristics

Demographics

	Balloon-expandable (n=121)	Self-expandable (n=120)	p-value
Age (years)	81.9±6.7	79.6±15.8	0.14
Females	69/121 (57.0%)	86/120 (71.7%)	0.02
BMI (kg/m^2)	26.4±4.2	26.6±5.2	0.77
Logistic EuroSCORE	21.5±12.9	22.1±14.7	0.72
EuroSCORE II	6.4±6.7	6.2±5.8	0.76
STS score	5.6±2.9	6.2±3.9	0.17
NYHA class III or IV	97/121 (80.2%)	98/120 (81.7%)	0.76

Baseline Patient Characteristics

Comorbidities

	Balloon-expandable (n=121)	Self-expandable (n=120)	p-value
Diabetes mellitus	38/121 (31.4%)	32/120 (26.7%)	0.42
Coronary artery disease	73/121 (60.3%)	79/120 (65.8%)	0.38
Previous CABG	19/121 (15.7%)	15/120 (12.5%)	0.48
Previous PCI	44/121 (36.4%)	51/120 (42.5%)	0.33
Peripheral vasc. disease	20/121 (16.5%)	22/120 (18.3%)	0.88
Pulmonary disease	27/121 (22.3%)	24/120 (20.0%)	0.66
Creatinine level (mg/dl)	1.1±0.4	1.2±0.5	0.18
Atrial fibrillation	39/117 (33.3%)	29/117 (24.8%)	0.15
Permanent pacemaker	7/117 (5.9%)	9/117 (7.7%)	0.60

Baseline Transthoracic Echocardiography

	Balloon-expandable (n=120)	Self-expandable (n=116)	p-value
AVA (cm^2)	0.7±0.2	0.7±0.2	0.71
Indexed AVA (cm^2/m^2)	0.4±0.1	0.4±0.1	0.34
Mean gradient (mmHg)	43.3±15.4	43.0±13.9	0.90
LVEF (%)	52.5±13.8	54.9±11.9	0.15
LVEF ≤35%	18/120 (15.0%)	11/115 (9.6%)	0.21
Moderate or severe AR	17/118 (14.4%)	24/115 (20.9%)	0.19
Moderate or severe MR	44/119 (36.9%)	38/116 (32.7%)	0.49
sPAP (mmHg)	37.3±13.1	39.2±13.6	0.34

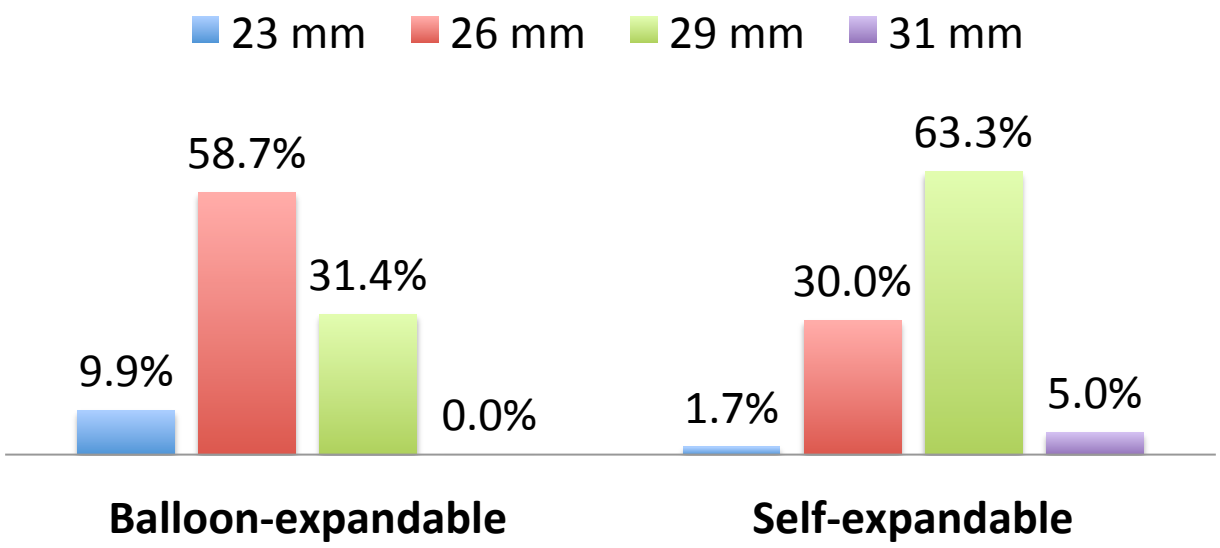
Baseline Transesophageal Echocardiography

	Balloon-expandable (n=107)	Self-expandable (n=102)	p-value
Annulus diameter (mm)	23.3±2.2	23.1±1.9	0.46
Leaflet calcification			0.60
moderate	31/106 (29.2%)	33/101 (32.7%)	
severe	75/106 (70.8%)	68/101 (67.3%)	
Asymmetric calcification	26/94 (27.7%)	26/101 (25.7%)	0.76
Eccentric valve orifice	9/97 (9.3%)	12/100 (12.0%)	0.54
Bicuspid aortic valve	0/107 (0.0%)	0/102 (0.0%)	--

Baseline Multislice CT

	Balloon-expandable (n=97)	Self-expandable (n=94)	p-value
Aortic annulus			
Mean diameter (mm)	24.1±1.7	23.6±2.0	0.09
Eccentricity index	0.17±0.06	0.18±0.07	0.75
Leaflet calcification			0.99
Mild	9/94 (9.6%)	20/93 (21.5%)	
Moderate	52/94 (55.3%)	33/93 (35.5%)	
Severe	33/94 (35.1%)	40/93 (43.0%)	
LVOT calcification			0.15
None	45/94 (47.9%)	56/93 (60.2%)	
Mild	21/94 (22.3%%)	15/93 (16.1%)	
Moderate	23/94 (24.5%%)	16/93 (17.2%)	
Severe	5/94 (5.3%)	6/93 (6.5%)	

Procedural Factors: Valve Sizes

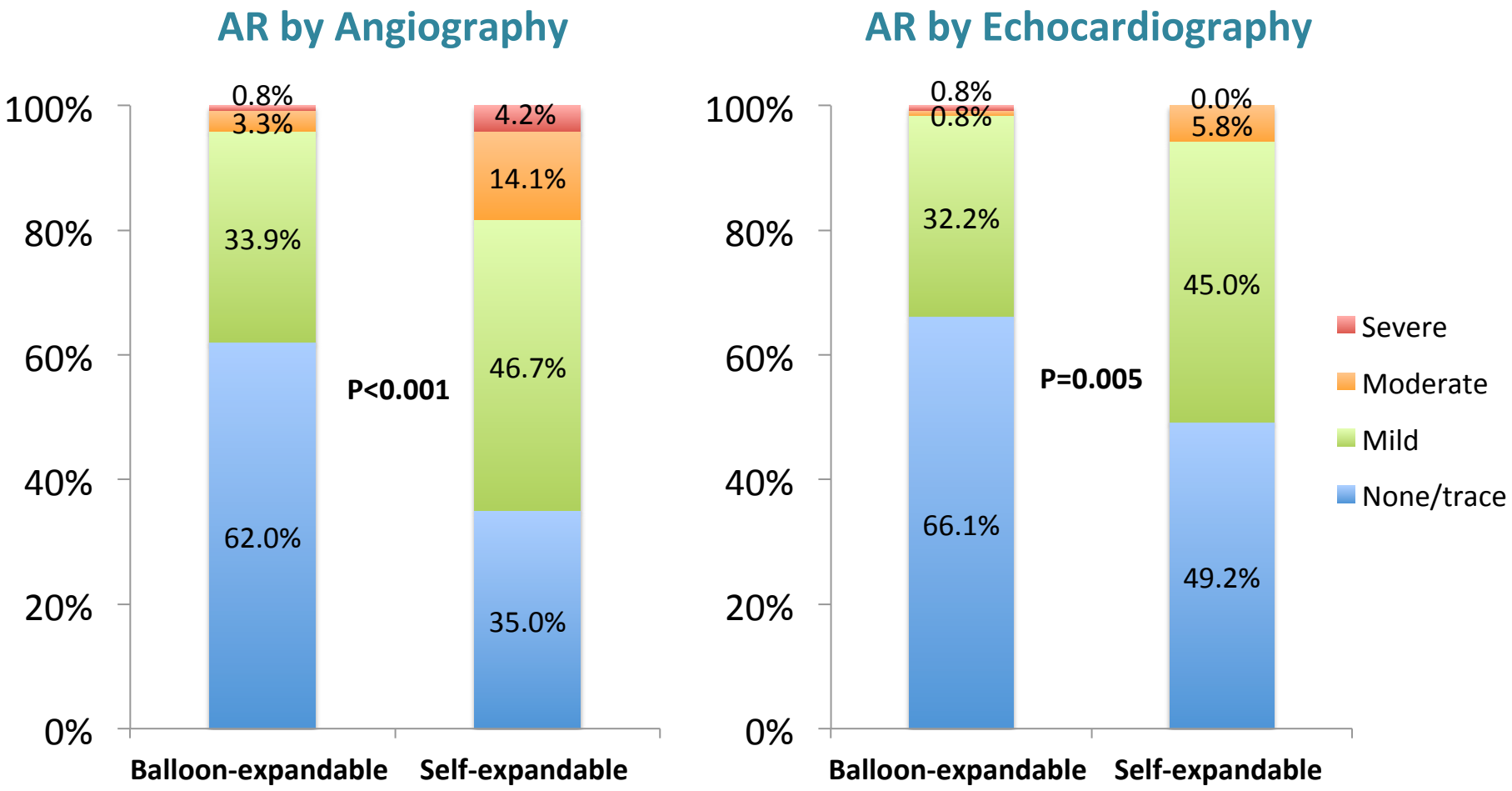


	Balloon-expandable	Self-expandable	p-value
Percent oversizing			
TEE diameter	12.8±5.4	17.7±5.9	<0.001
Mean MDCT diameter	9.6±5.6	15.8±4.5	<0.001
MDCT area	19.5±8.0	30.8±8.2	<0.001
MDCT perimeter	7.2±4.9	14.8±4.9	<0.001

Procedural Details

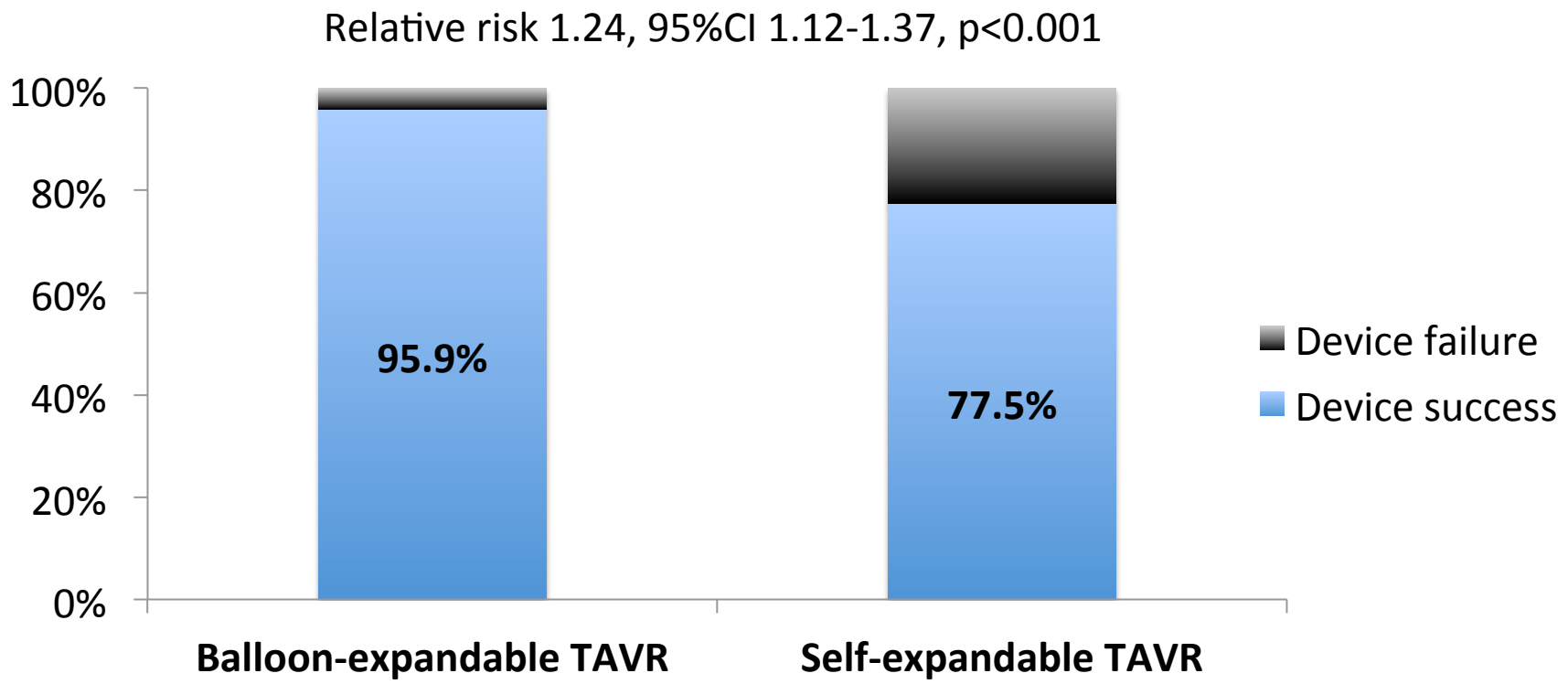
	Balloon-expandable (n=121)	Self-expandable (n=120)	p-value
Balloon pre-dilatation	121/121 (100%)	106/120 (88.3%)	<0.001
AR after initial implantation			<0.001
none/trace	72/121 (59.5%)	31/120 (25.8%)	
mild	34/121 (28.1%)	38/120 (31.7%)	
moderate	10/121 (8.3%)	33/120 (27.5%)	
severe	5/121 (4.1%)	18/120 (15.0%)	
Maneuvres to improve AR			
balloon post-dilatation	24/121 (19.8%)	59/120 (49.2%)	<0.001
valve snaring	0/121 (0.0%)	2/120 (1.7%)	0.24
implantation of ≥ 2 valves	1/121 (0.8%)	7/120 (5.8%)	0.03
Coronary obstruction	2/121 (1.6%)	0/120 (0.0%)	0.49
Annular rupture	0/121 (0%)	0/120 (0%)	--
Left-to-right shunt	2/121 (1.6%)	2/120 (1.7%)	0.99
Depth of implantation (mm)	--	5.2±3.2	--
Procedural duration (min)	74.5±29.5	80.5±40.5	0.20
Contrast amount (ml)	208.6±71.4	223.1±98.2	0.19

Post-Procedural Aortic Regurgitation



	Balloon-expandable (n=116)	Self-expandable (n=114)	p-value
Dimensionless AR Index	29.0±7.1	27.3±7.2	0.08

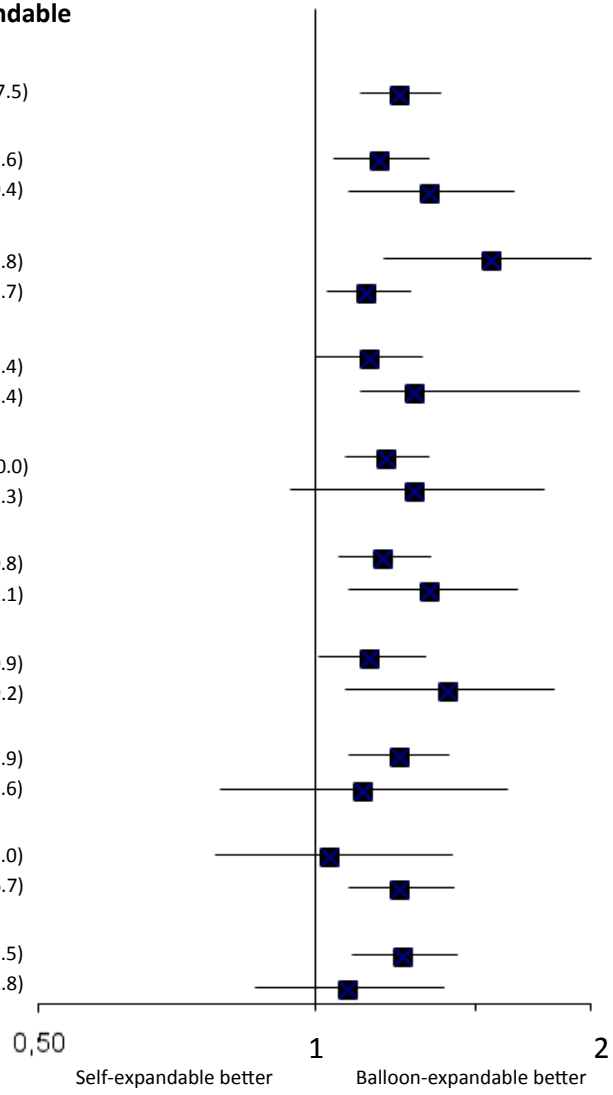
Primary Endpoint – Device Success



Causes of device failure	Balloon-expandable (n=121)	Self-expandable (n=120)
Unsuccessful vascular access, delivery and deployment	0/121 (0)	0/120 (0)
Incorrect position with implantation of more than one valve	1/121 (0.8)	7/120 (5.8)
Inadequate performance of the prosthetic heart valve - Aortic valve area < 1.2 cm^2 or mean aortic valve gradient > 20 mmHg	0/121 (0)	0/120 (0)
- Moderate or severe prosthetic valve regurgitation	5/121 (4.1)	22/120 (18.3)
Total (hierarchical)	5/121 (4.1)	27/120 (22.5)

Subgroup analysis
Relative risk of the primary endpoint

	No. of events/total (%)		Risk ratio (95%CI)	p for interaction
	Balloon-expandable	**Self-expandable**		
All patients	116/121 (95.9)	93/120 (77.5)	1.24 (1.12-1.37)	
Age				0.89
≥80 years	82/85 (96.5)	62/76 (81.6)	1.18 (1.05-1.33)	
<80 years	34/36 (94.4)	31/44 (70.4)	1.34 (1.09-1.65)	
Gender				0.22
Male	50/52 (96.1)	21/34 (61.8)	1.56 (1.19-2.04)	
Female	66/69 (95.6)	72/86 (83.7)	1.14 (1.03-1.27)	
Coronary artery disease				0.84
No	47/48 (97.9)	35/41 (85.4)	1.15 (1.00-1.31)	
Yes	69/73 (94.5)	58/79 (73.4)	1.29 (1.12-1.49)	
LV ejection fraction				0.95
>35%	97/101 (96.0)	80/100 (80.0)	1.20 (1.08-1.33)	
≤35%	18/19 (94.7)	11/15 (73.3)	1.29 (0.94-1.78)	
Mitral regurgitation				0.70
No/mild	72/75 (96.0)	63/78 (80.8)	1.19 (1.06-1.34)	
Moderate/severe	42/44 (95.5)	27/38 (71.1)	1.34 (1.09-1.66)	
CT annulus diameter				0.23
<25 mm	56/60 (93.3)	55/68 (80.9)	1.15 (1.01-1.32)	
≥25 mm	34/35 (97.1)	18/26 (69.2)	1.40 (1.08-1.82)	
Annular eccentricity				0.37
≤ 0.25	81/84 (96.4)	60/77 (77.9)	1.24 (1.09-1.40)	
> 0.25	8/9 (88.9)	11/14 (78.6)	1.13 (0.79-1.62)	
Leaflet calcification				0.28
No/mild	8/9 (88.9)	17/20 (85.0)	1.04 (0.78-1.41)	
Moderate/severe	81/85 (95.3)	56/73 (76.7)	1.24 (1.09-1.42)	
LVOT calcification				0.15
No/mild	64/66 (97.0)	55/71 (77.5)	1.25 (1.10-1.43)	
Moderate/severe	25/28 (89.3)	18/22 (81.8)	1.09 (0.86-1.38)	



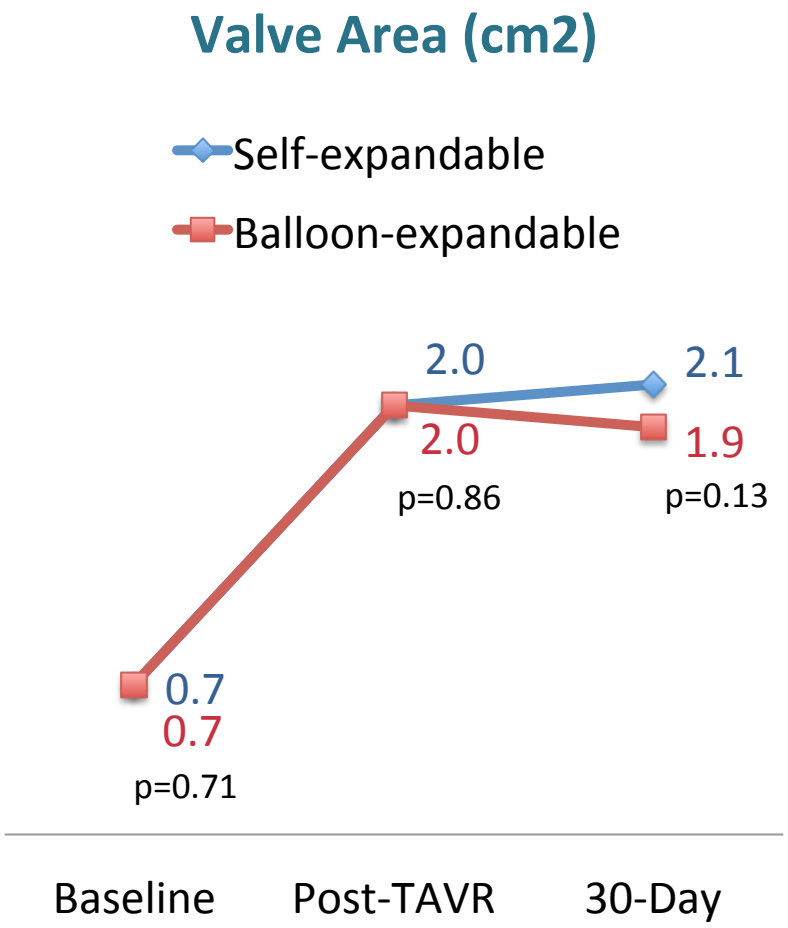
Clinical Outcome at 30 Days (I)

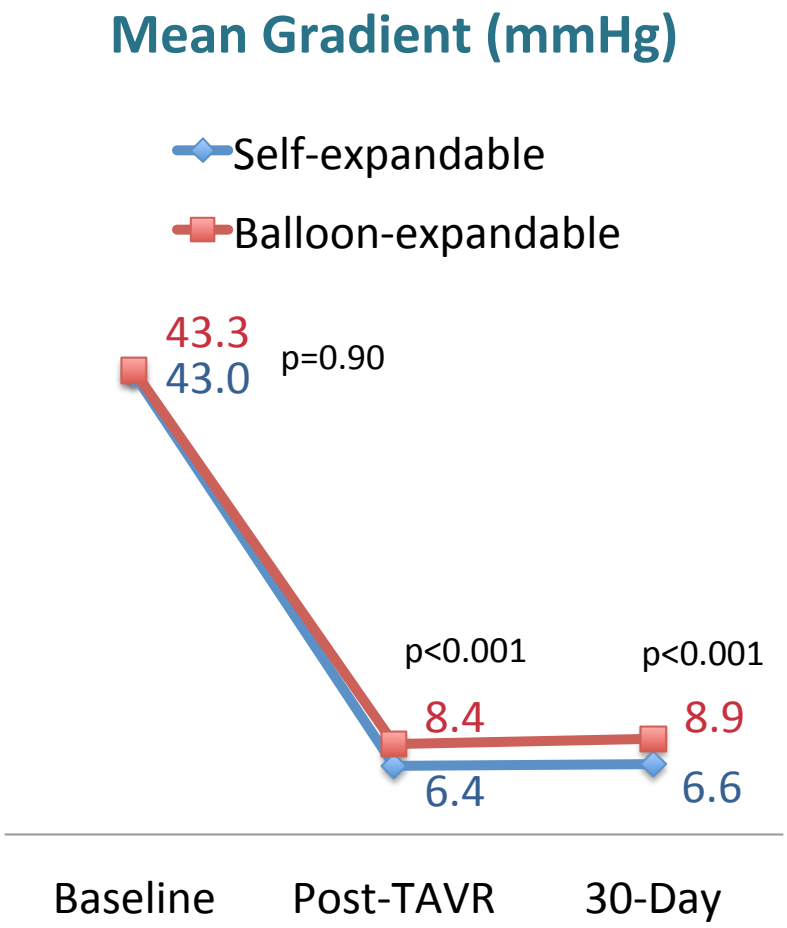
	Balloon-expandable (n=121)	Self-expandable (n=117)	p-value
Death			
From any cause	5/121 (4.1%)	6/117 (5.1%)	0.77
From CV causes	5/121 (4.1%)	5/117 (4.3%)	0.99
Stroke	7/121 (5.8%)	3/117 (2.6%)	0.33
Major	3/121 (2.5%)	3/117 (2.6%)	0.99
Minor	4/121 (3.3%)	0/117 (0.0%)	0.12
Myocardial infarction	1/121 (0.8%)	0/117 (0.0%)	0.99
Bleeding			
Life threatening	10/121 (8.3%)	14/117 (12.0%)	0.35
Major	23/121 (19.0%)	17/117 (14.5%)	0.36
Minor	11/121 (9.1%)	9/117 (7.7%)	0.70
Major or minor	34/121 (28.1%)	26/117 (22.2%)	0.30
Vascular complications			
All	17/121 (14.0%)	15/117 (12.8%)	0.78
Major	12/121 (9.9%)	13/117 (11.1%)	0.76
Minor	5/121 (4.1%)	2/117 (1.7%)	0.28

Clinical Outcome at 30 Days (II)

	Balloon-expandable (n=121)	Self-expandable (n=117)	p-value
Acute kidney injury	5/121 (4.1)	11/117 (9.4)	0.13
Repeat proc. for valve-related dysfunction	1/121 (0.8)	2/117 (1.7)	0.62
Combined safety endpoint	22/121 (18.2)	27/117 (23.1)	0.42
MACCE	8/121 (6.6)	4/117 (3.4)	0.38
Rehospitalization for heart failure	0/119 (0.0)	5/117 (4.3)	0.02
NYHA class improvement	100/106 (94.3)	91/105 (86.7)	0.06
Quality of life score	71.0±14.9	65.9±18.2	0.02
New permanent pacemaker	19/110 (17.3)	38/101 (37.6)	0.001

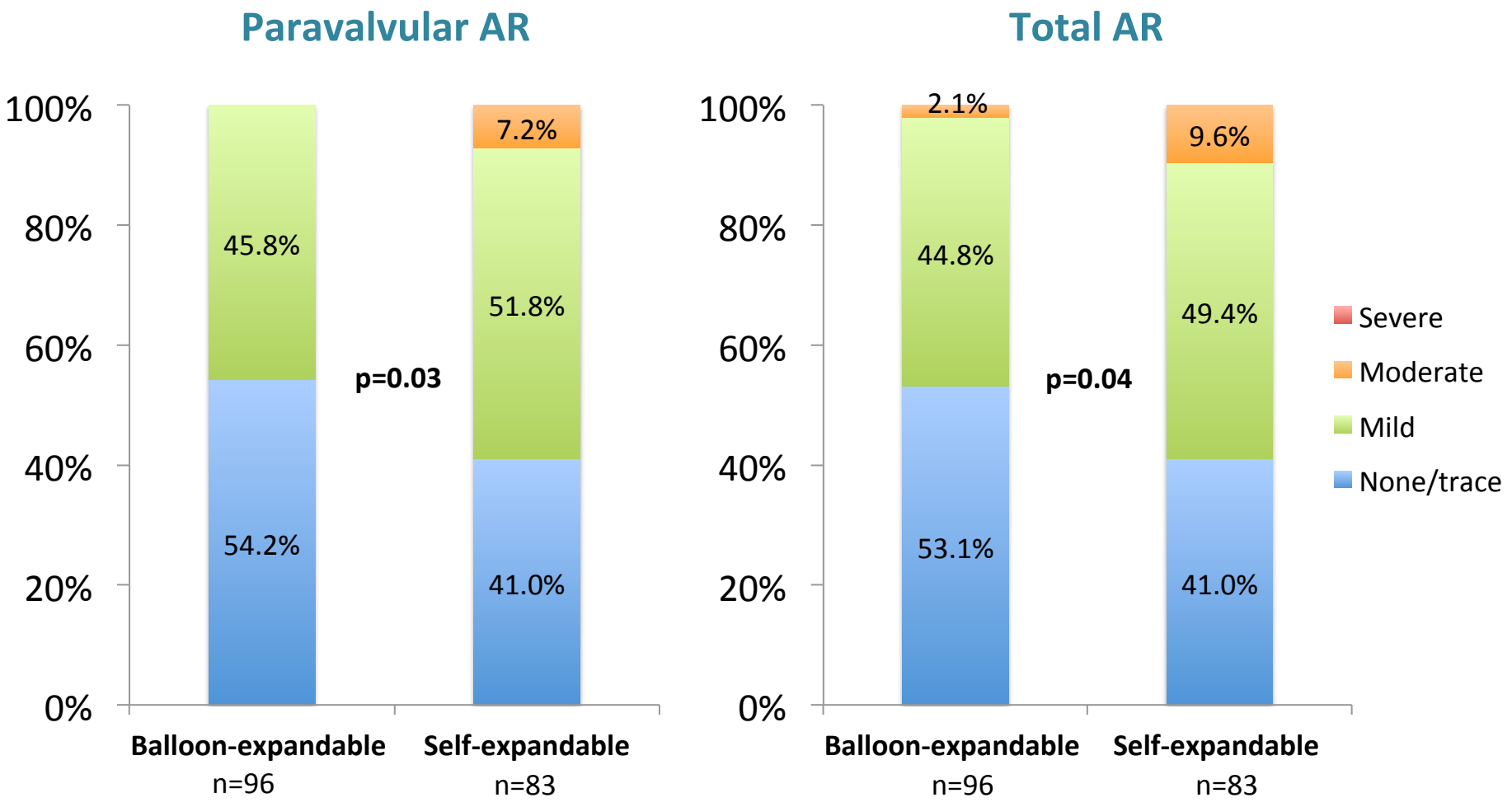
Echocardiographic Findings (I)





Echocardiographic Findings (II)

Aortic Regurgitation at 30 Days



Cardiac MRI Subgroup

	Balloon-expandable (n=56)	Self-expandable (n=34)	p-value
LV ejection fraction (%)	55.6±12.8	56.5±9.8	0.72
Antegrade volume (ml)	70.8±15.0	70.1±17.1	0.84
Retrograde volume (ml)	2.9±2.9	4.5±6.0	0.21
Regurgitant fraction (%)	4.2±3.9	7.1±8.2	0.06
More-than-mild AR (RF≥15%)	1/55 (1.8%)	6/33 (18.2%)	0.01

Study Limitations

- Assessment of AR as a criterion of the primary end point using core lab angiography and the lack of an echocardiographic core lab.

However, the following points need to be considered:

1) lack of validation of the VARC echocardiographic grading criteria
2) possible underestimation of AR severity by echo*
3) prognostic relevance of angiographic AR at least as strong as echocardiographic AR**
4) the timing, angiographic views, and amount and flow-rate of contrast were standardized
5) the angiographic findings were confirmed by a wide range of assessment tools, including echo, hemodynamic measurements and cardiac MRI

- Sherif et al, EuroIntervention 2011

** Abdel-Wahab et al, JACC Cardiovasc Interv 2014

Conclusions

- Among patients with high-risk aortic stenosis undergoing transfemoral TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve.
- At 30 days, improvement of heart failure symptoms was more frequently observed with the balloon-expandable valve, while minor stroke rates were numerically higher.
- Long-term follow-up of the CHOICE population should be awaited, to determine whether the observed differences will translate into a clinically relevant overall benefit for the balloon-expandable valve.