SMART Trial

SMall **A**nnuli **R**andomized **t**o Evolut or SAPIEN

SMART

Self-Expanding Versus Balloon-Expandable TAVR in Patients with Aortic Stenosis and Small Aortic Annuli

Primary Outcomes from the Randomized SMART Trial

Howard C. Herrmann, MD | Roxana Mehran, MD | Didier Tchétché, MD
on behalf of the SMART Trial Investigators

Disclosure of relevant financial relationships

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

Financial Relationship	Company
Institutional grants/research support	Abbott Vascular, Boston Scientific, Edwards LifeSciences, Medtronic, Highlife Med, Innovalve, Shockwave
Consulting fees/honoraria	Edwards Lifesciences, Johnson & Johnson, Medtronic, Prolifagen, Truffle Capital, Wells Fargo
Shareholder/equity	Microinterventional Devices, Holistick
Editorial	Mass Medical Society

Background

In multiple studies, the supra-annular self-expanding Evolut™ valve has been shown to have superior hemodynamic properties compared with the intra-annular balloon-expandable SAPIEN™* platform.[1]

- Hemodynamic valve performance is linked to long-term outcomes.[2]
- These hemodynamic differences may be particularly important in patients with a small aortic annulus who comprise up to 40% of patients, typically women who are under-represented in clinical trials.[3]
- Compared with men, women with aortic stenosis present differently[4] and are at greater risk of complications following surgery and TAVR.

The SMART Trial

was designed to compare the performance and safety of the supra-annular, self-expanding Evolut valve (SEV) to the intra-annular, balloon-expandable SAPIEN valve (BEV) in TAVR patients with severe symptomatic aortic stenosis and a small aortic valve annulus.

1. Abdel-Wahab M, et al. JACC Cardiovasc Interv 2020;13(9):1071-1082.
2. Playford D, et al. J Am Soc Echocardiogr 2020;33(9):1077-1086.
3. Freitas-Ferraz AB, et al. Circulation 2019;139(23):2685-2702.
4. DesJardin JT, et al. Circulation Research. 2022;130:455–473.

Trial organization

Executive committee

- Howard Herrmann
- Roxana Mehran
- Didier Tchétché

Independent steering committee

- Sabine Bleiziffer
- Joshua Rovin
- Linda Gillam
- Mohammed Abdel-Wahab
- Guilherme Attizzani
- Wayne Batchelor
- Hemal Gada
- Mayra Guerrero
- Howard Herrmann
- Paul Mahoney
- Roxana Mehran
- Anna Sonia Petronio
- Toby Rogers
- Molly Szerlip
- Didier Tchétché
- Brian Whisenant

Independent physician case planning committee

- Michael Deeb
- Kendra Grubb
- Joshua Rovin
- Guilherme Attizzani
- Philipe Genereux
- Howard Herrmann
- Paul Mahoney
- Roxana Mehran
- Toby Rogers
- Didier Tchétché
- Brian Whisenant

Independent CEC and DSMB

Core laboratories
(blinded to clinical outcomes)

- Echocardiography: Mayo Clinic
- Angiography: Baim Institute for Clinical Research

Statistical analysis

- Performed by the sponsor
- Medtronic (Minneapolis, MN)

Global site participation
83 sites in 13 countries

Trial design

Prospective, randomized controlled, post-market trial conducted at 83 international sites
All-comer trial with all surgical risk categories including bicuspid patients

Key eligibility
- Symptomatic severe AS†
- Small aortic annulus (< 430 mm^2 by MDCT)

Randomization
1:1 stratified by site & sex

Medtronic (N=355)
Evolut PRO/PRO+/FX

716
patients treated

Edwards (N=361)
SAPIEN 3/SAPIEN 3 Ultra

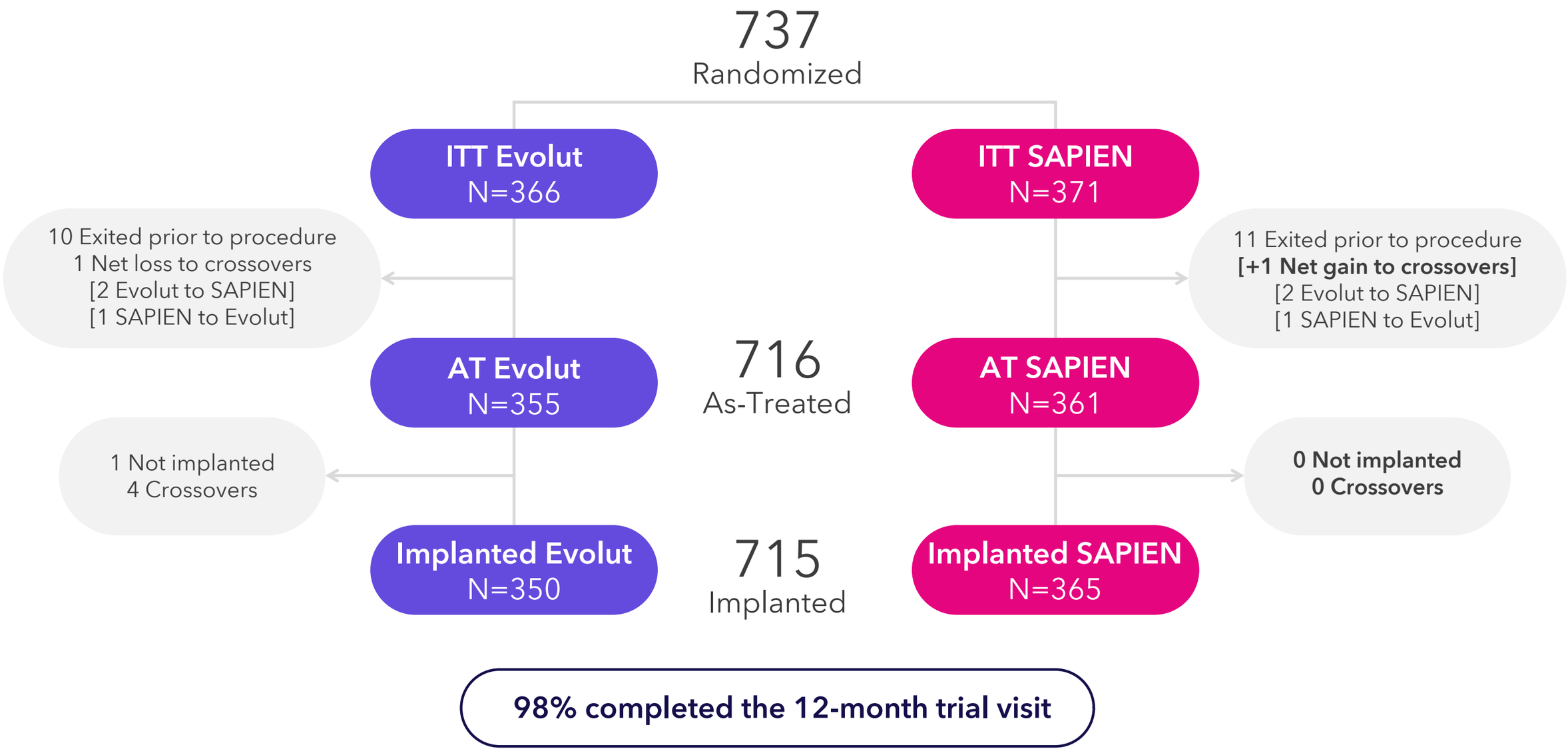
Co-Primary Endpoints at 1 year with planned 5-year follow-up

Co-Primary Endpoint 1:
Composite of mortality, disabling stroke, or heart failure rehospitalization through 12 months

Co-Primary Endpoint 2:
Bioprosthetic valve dysfunction through 12 months

†AVA ≤1.0 cm^2 (AVAi ≤0.6 cm^2/m^2) or mean gradient ≥40 mmHg or max velocity ≥4.0 m/s; 30-day predicted risk of surgical mortality <15% by heart team assessment.

Patient flow



98% completed the 12-month trial visit

Statistical methods

Co-primary endpoint #1

Clinical outcome composite through 12 months

- Mortality
- Disabling stroke
- Heart failure rehospitalization

- Powered for **noninferiority,** margin of 8%
- As-treated population (1st attempted device)
- K-M estimate with risk difference (90% CI) through 12 months
- 85% power with 700 patients

Co-primary endpoint #2

Bioprosthetic valve dysfunction through 12 months

- Hemodynamic structural valve dysfunction:
  Mean gradient ≥20 mmHg
- Nonstructural valve dysfunction:
  Severe PPM (VARC-3), ≥moderate total AR
- Clinical valve thrombosis (VARC-2)
- Endocarditis (Duke criteria)
- Aortic valve reintervention

- Powered for **superiority**
- Implanted population (final valve received)
- K-M estimate with risk difference (95% CI) through 12 months
- >99% power with 700 patients

Statistical methods

If both primary endpoints were met, hierarchical testing of secondary endpoints occurred in a prespecified order.

Powered for superiority

Hypothesis-tested secondary endpoints

1. Hemodynamic mean gradient at 12 months
2. Effective orifice area at 12 months
3. Hemodynamic SVD (mean gradient ≥20 mmHg) through 12 months
4. BVD in women through 12 months
5. Moderate/severe prosthesis-patient mismatch at 30 days

Baseline characteristics

Characteristic	**Evolut** (N=355)	**SAPIEN** (N=361)
Age – yr	**80.1 ± 6.3**	**80.3 ± 6.1**
Female sex	**87.9%**	**85.6%**
STS-PROM score – %	**3.3 ± 1.9**	**3.2 ± 1.7**
NYHA functional class III/IV	43.3%	39.9%
Diabetes	29.3%	34.1%
Hypertension	82.5%	86.7%
COPD or chronic lung disease	18.0%	17.6%
Cerebrovascular disease	12.0%	11.4%
Previous CABG	3.4%	5.0%
Previous PCI	17.0%	23.3%
Previous myocardial infarction	5.4%	8.0%
History of RBBB	5.9%	6.9%
Coronary artery disease	35.2%	41.0%
Pre-existing permanent pacemaker/ICD	8.5%	6.9%
Bicuspid aortic valve morphology	3.9%	4.2%

Data presented as mean ± SD or %

Valve and procedural data

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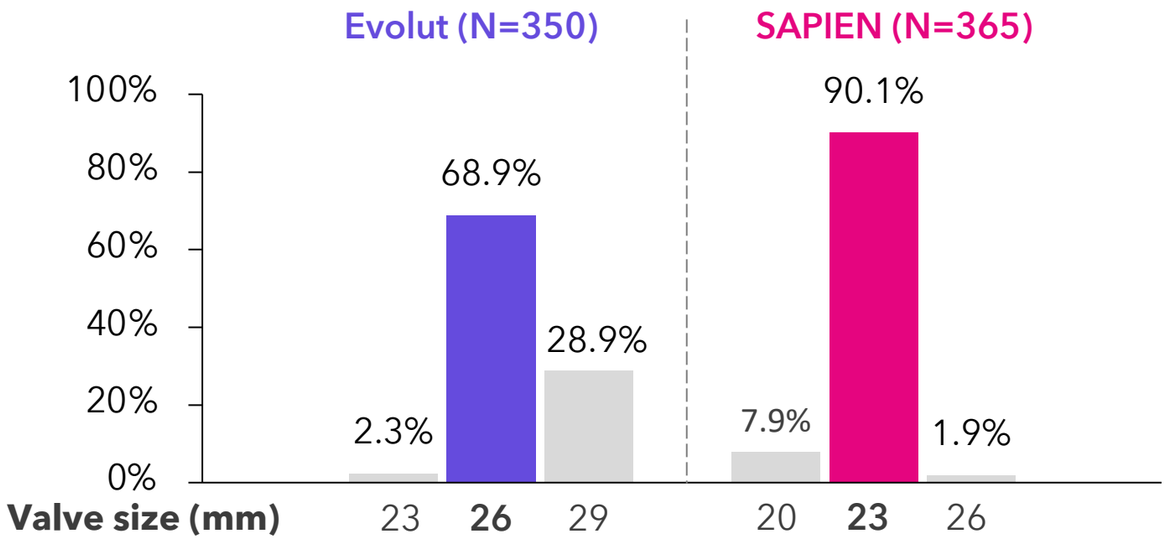
Valve size

Aortic annulus size	Evolut (N=355)	SAPIEN (N=361)
Mean area (mm^2)	380.9 ± 34.2	382.8 ± 33.9
Mean perimeter (mm)	70.3 ± 3.2	70.4 ± 3.2



Procedural characteristics and outcomes

Characteristic	Evolut (N=355)	SAPIEN (N=361)	P Value[a]
Total time in the procedure room[b] (min)	116 ± 44	106 ± 43	0.002
Catheter (device) time in the body (min)	18 ± 15	14 ± 12	<0.001
Contrast volume[c] (ml)	121 ± 59	95 ± 43	<0.001
Valve embolization	1.1	0.0	0.06
Device success at 30 days (VARC-2)[d]	85.2%	59.2%	<0.001
Device success at 30 days (VARC-3)[e]	94.5%	86.6%	<0.001

[a]Continuous variables compared using t-tests; categorical variables compared using chi-squared tests.
[b]Data available for 354 Evolut and 361 SAPIEN patients.
[c]Data available for 347 Evolut and 357 SAPIEN patients.
[d]Evaluated according to VARC-2 criteria in 291 Evolut and 319 SAPIEN patients.
[e]Evaluated according to VARC-3 criteria in 327 Evolut and 328 SAPIEN patients.

Co-primary endpoint 1:

Clinical outcome composite through 12 months powered for noninferiority

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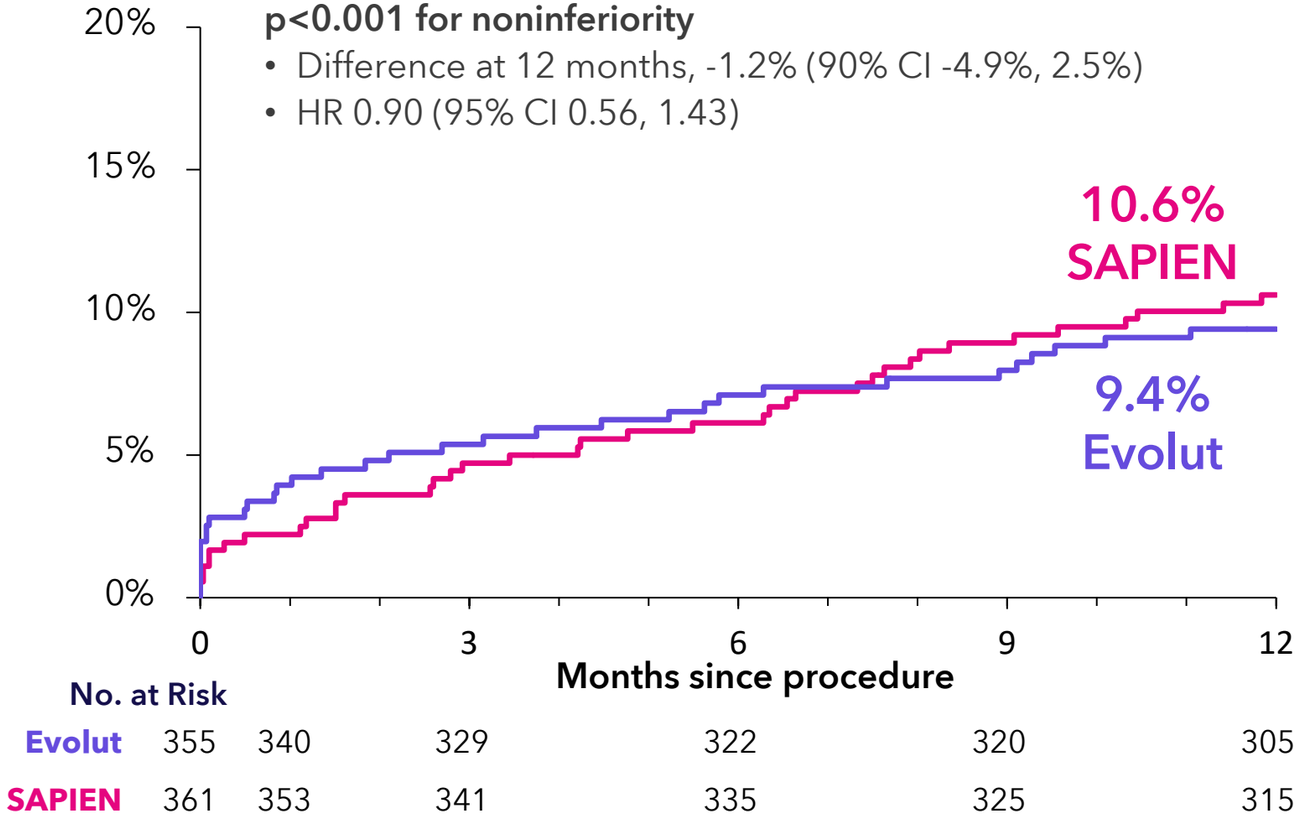
Mortality, Disabling Stroke, or HF Rehospitalization



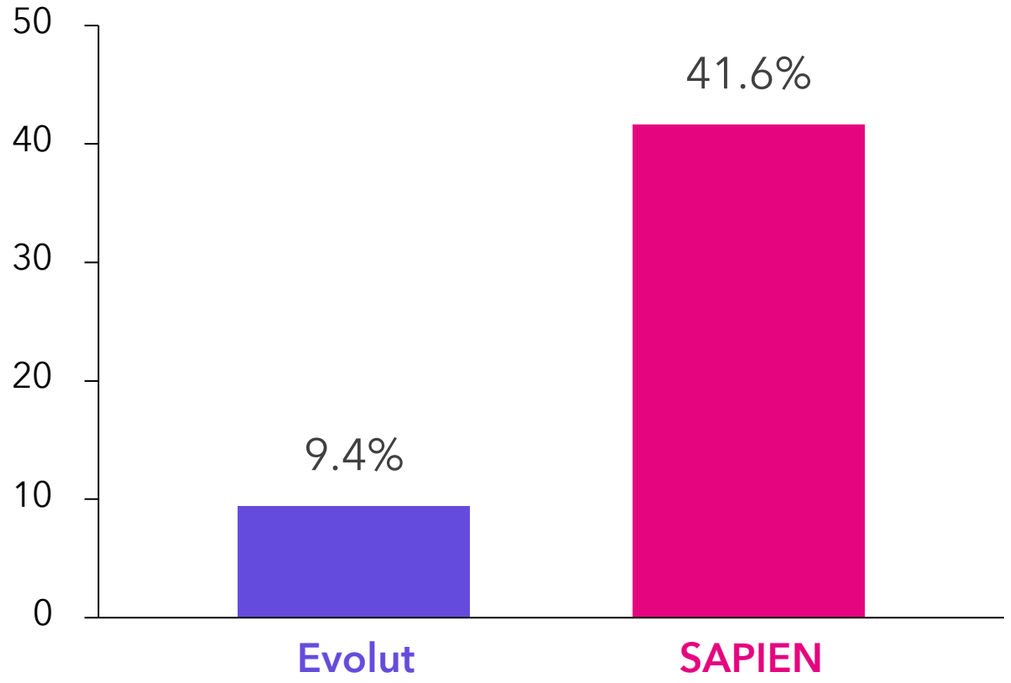
12 Months	Evolut (N=355)	SAPIEN (N=361)	HR (95% CI)
All-cause mortality	5.1%	5.9%	0.88 (0.47, 1.65)
Disabling stroke	3.1%	2.6%	1.26 (0.52, 3.03)
HF rehosp	3.8%	3.5%	1.11 (0.51, 2.44)

Co-primary endpoint 2:

BVD through 12 months powered for superiority

Bioprosthetic Valve Dysfunction through 12 months

Difference, -32.2% (95% CI -38.7%, -25.6%)
p<0.001 for superiority



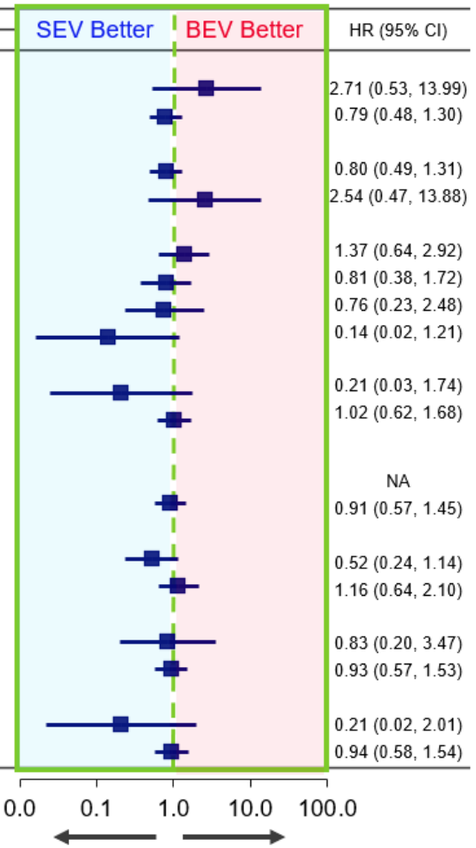
	Evolut (N=350)	SAPIEN (N=365)	P Value
BVD composite	**9.4%**	**41.6%**	**<0.001**
HSVD	3.2%	32.2%	
NSVD	5.9%	18.2%	
Thrombosis (clinical)	0.3%	0.3%	
Endocarditis	0.6%	2.3%	
AV Reintervention	0.9%	0.6%	

HSVD = Mean gradient ≥ 20 mmHg
NSVD = Severe PPM per VARC-3 or ≥moderate total AR

Prespecified subgroup analyses for the co-primary endpoints

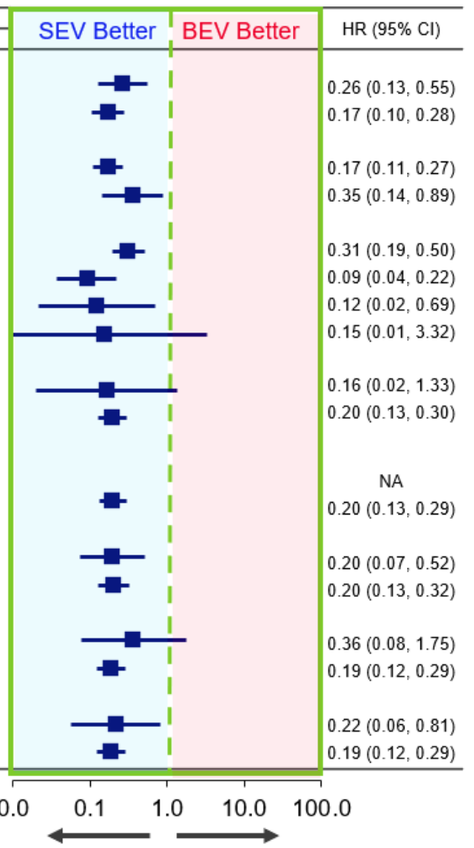
Clinical Outcome Composite Through 12 Months

Variable	SEV KM rate through 12 months	BEV KM rate through 12 months	HR (95% CI)
Age, years			
<75	8.1%	3.1%	2.71 (0.53, 13.99)
≥75	9.7%	12.2%	0.79 (0.48, 1.30)
Sex			
Female	9.4%	11.8%	0.80 (0.49, 1.31)
Male	9.3%	3.8%	2.54 (0.47, 13.88)
STS-PROM, %			
<3	8.3%	6.3%	1.37 (0.64, 2.92)
≥3 - <5	9.9%	12.2%	0.81 (0.38, 1.72)
≥5 - <8	13.7%	17.8%	0.76 (0.23, 2.48)
≥8	7.7%	41.7%	0.14 (0.02, 1.21)
LVEF, %			
<50	6.7%	27.3%	0.21 (0.03, 1.74)
≥50	9.3%	9.3%	1.02 (0.62, 1.68)
Renal dysfunction (on dialysis)			
Yes	0.0%	0.0%	NA
No	9.6%	10.7%	0.91 (0.57, 1.45)
Atrial fibrillation/flutter			
Yes	14.7%	26.2%	0.52 (0.24, 1.14)
No	8.3%	7.4%	1.16 (0.64, 2.10)
Prior cerebrovascular accident			
Yes	13.3%	16.7%	0.83 (0.20, 3.47)
No	9.3%	10.1%	0.93 (0.57, 1.53)
Pre-existing LBBB/CHB			
Yes	3.7%	16.1%	0.21 (0.02, 2.01)
No	9.6%	10.2%	0.94 (0.58, 1.54)



BVD Through 12 Months

Variable	SEV KM rate through 12 months	BEV KM rate through 12 months	HR (95% CI)
Age, years			
<75	19.2%	52.8%	0.26 (0.13, 0.55)
≥75	7.5%	39.0%	0.17 (0.10, 0.28)
Sex			
Female	8.4%	41.8%	0.17 (0.11, 0.27)
Male	16.5%	40.3%	0.35 (0.14, 0.89)
STS-PROM, %			
<3	14.1%	39.8%	0.31 (0.19, 0.50)
≥3 - <5	5.0%	47.4%	0.09 (0.04, 0.22)
≥5 - <8	3.4%	34.5%	0.12 (0.02, 0.69)
≥8	0.0%	33.3%	0.15 (0.01, 3.32)
LVEF, %			
<50	10.0%	46.3%	0.16 (0.02, 1.33)
≥50	9.4%	41.2%	0.20 (0.13, 0.30)
Renal dysfunction (on dialysis)			
Yes	0.0%	0.0%	NA
No	9.6%	42.0%	0.20 (0.13, 0.29)
Atrial fibrillation/flutter			
Yes	8.5%	41.9%	0.20 (0.07, 0.52)
No	9.8%	40.6%	0.20 (0.13, 0.32)
Prior cerebrovascular accident			
Yes	10.5%	33.7%	0.36 (0.08, 1.75)
No	9.5%	42.2%	0.19 (0.12, 0.29)
Pre-existing LBBB/CHB			
Yes	13.1%	49.0%	0.22 (0.06, 0.81)
No	9.3%	42.0%	0.19 (0.12, 0.29)

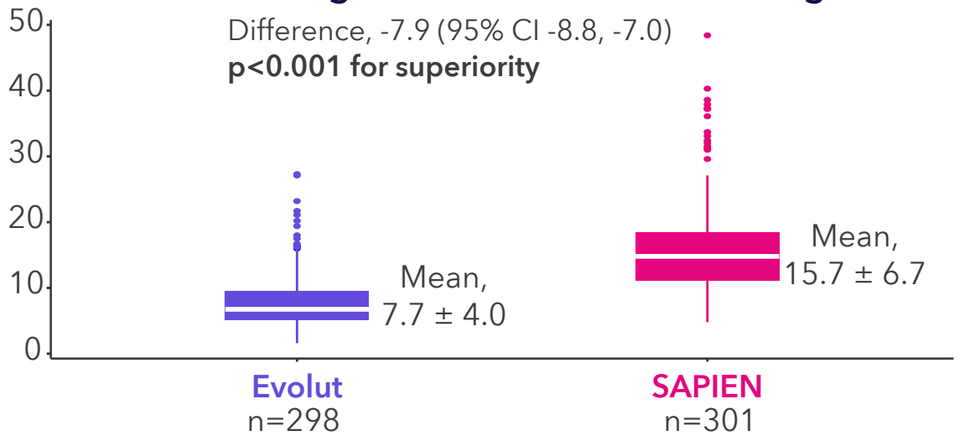


No significant interactions were observed between treatment and any of the prespecified baseline subgroups with respect to either of the co-primary endpoints.

Hypothesis-tested secondary endpoints

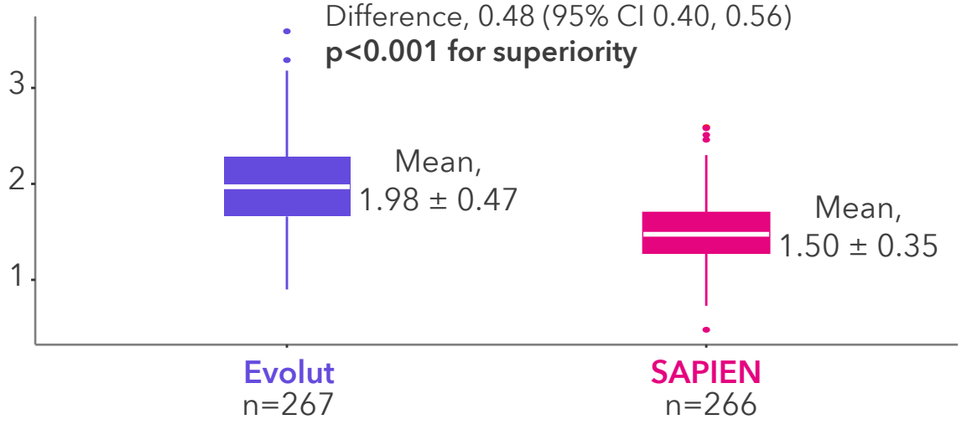
Mean gradient at 12 months, mmHg

Difference, -7.9 (95% CI -8.8, -7.0)
p<0.001 for superiority



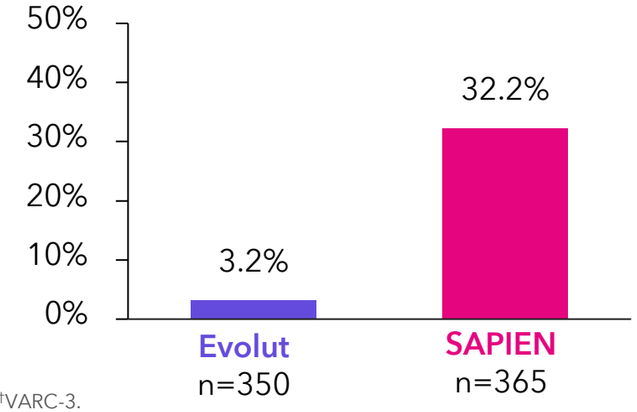
EOA at 12 months, cm²

Difference, 0.48 (95% CI 0.40, 0.56)
p<0.001 for superiority



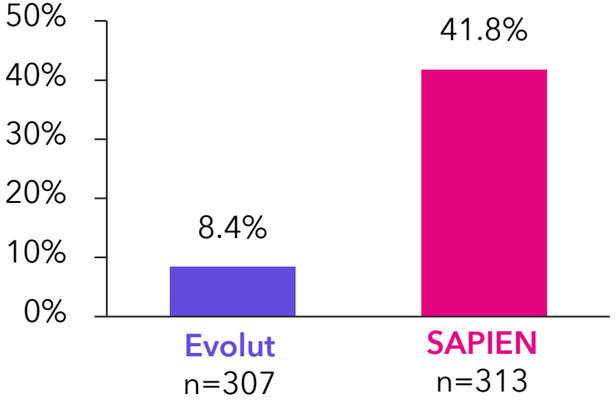
HSVD through 12 months, %

Difference, -29.1% (95% CI -34.6%, -23.5%)
p<0.001 for superiority



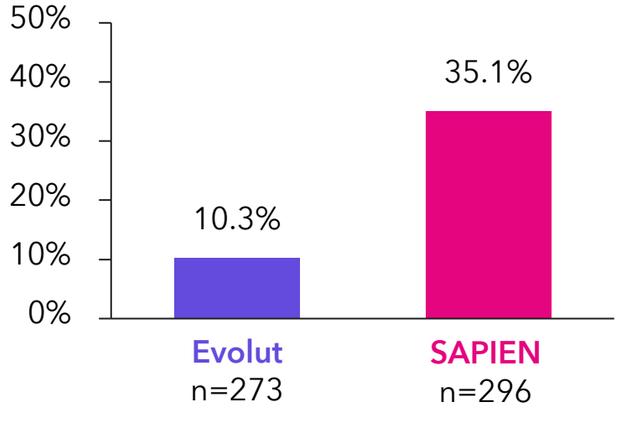
BVD in women through 12 months, %

Difference, -33.4% (95% CI -40.4%, -26.4%)
p<0.001 for superiority



Moderate/severe PPM† at 30 days, %

Difference, -24.9% (95% CI -31.4%, -18.4%)
p<0.001 for superiority



†VARC-3.

Additional safety outcomes

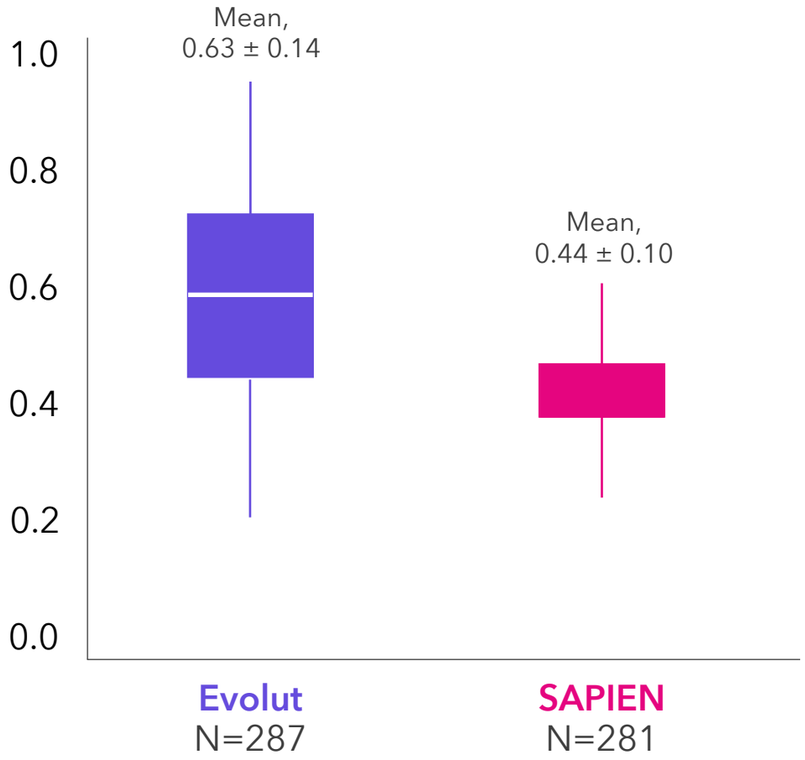
	30 Days			12 Months		
KM%	Evolut (N=355)	SAPIEN (N=361)	Log-Rank P Value	Evolut (N=355)	SAPIEN (N=361)	Log-Rank P Value
Pacemaker implant[a]	12.1%	7.8%	0.055	14.0%	9.3%	0.051
Pacemaker implant	11.1%	7.2%	0.067	12.8%	8.7%	0.063
Prosthetic valve endocarditis	0.0%	0.0%	N/A	0.6%	2.3%	0.063
Coronary artery obstruction	0.6%	0.3%	0.55	0.6%	0.3%	0.55
Acute kidney injury stage 2/3	0.3%	0.3%	0.99	0.3%	0.3%	0.99
Cardiovascular hospitalizations	4.9%	5.3%	0.77	15.7%	16.6%	0.79
Hospital readmission	8.6%	11.2%	0.25	29.7%	32.1%	0.50
Clinical valve thrombosis	0.0%	0.0%	N/A	0.3%	0.3%	0.99
Sub-clinical valve thrombosis	0.0%	0.6%	N/A	0.0%	1.1%	N/A

[a]Patients with pacemaker/ICD at baseline are excluded

Other hemodynamic outcomes at 12 months

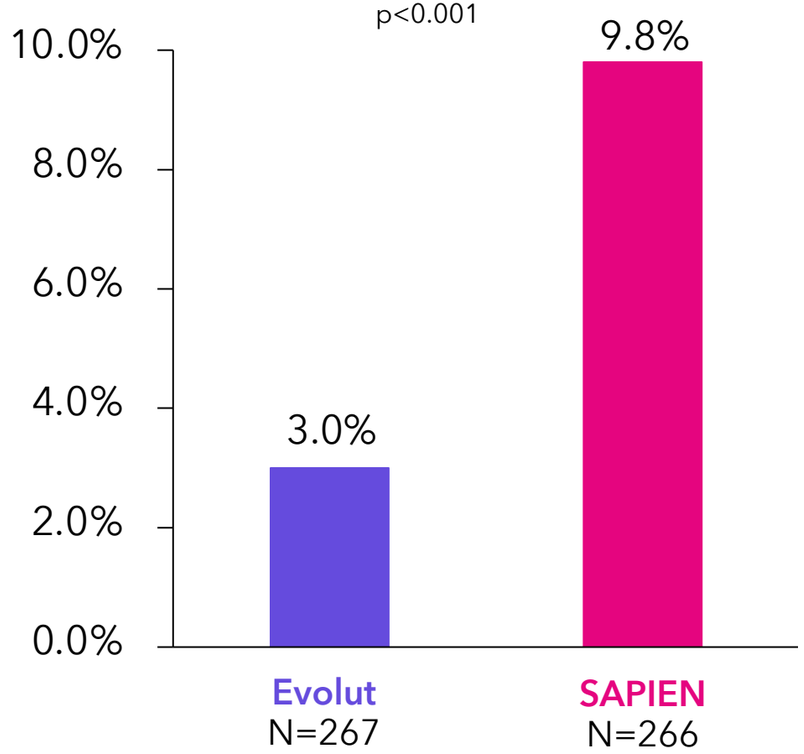
Doppler velocity index

Difference, 0.19 (95% CI 0.17, 0.21)
p<0.001



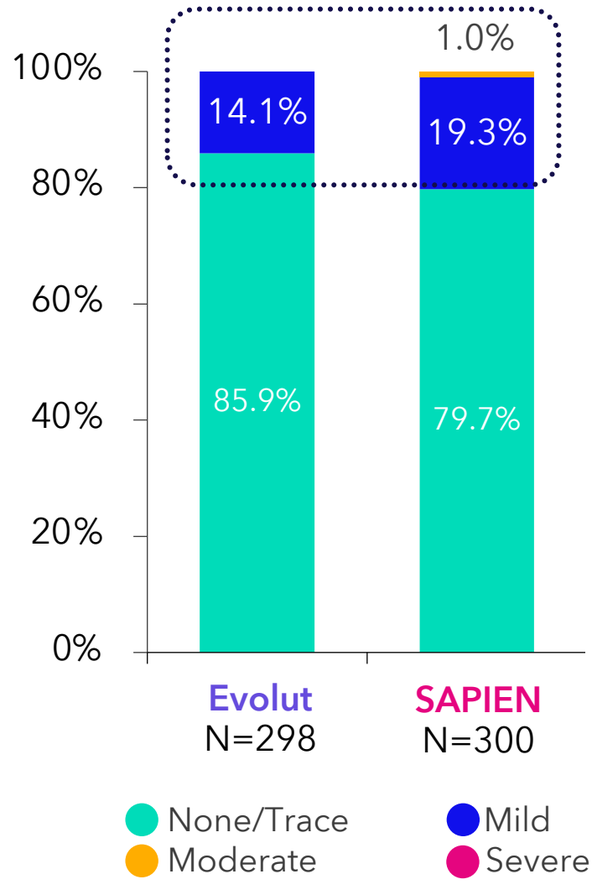
Severe Prosthesis-Patient Mismatch (VARC-3)

Difference, -6.8% (95% CI -10.9, -2.7)
p<0.001



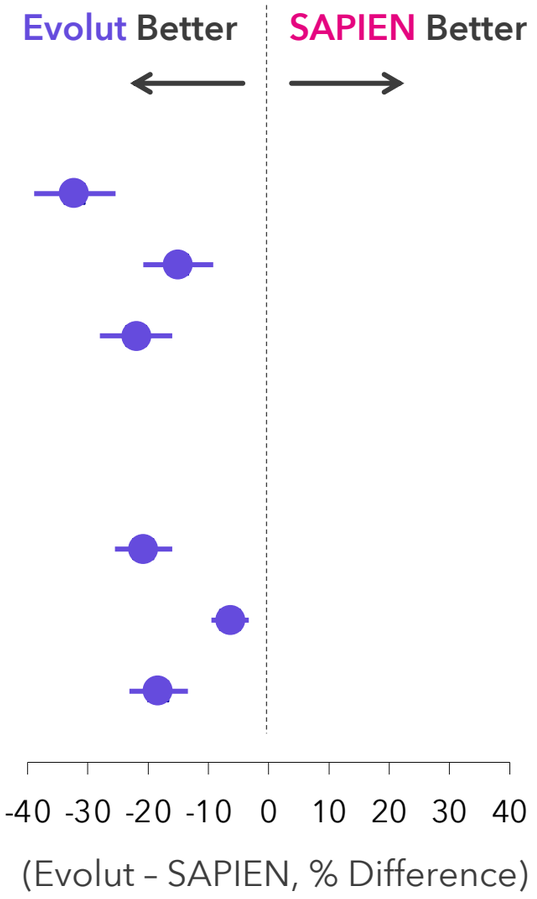
Total Aortic Regurgitation

≥Mild total AR at 12 months:
14.1% Evolut vs 20.3% SAPIEN, p=0.043



Alternative bioprosthetic valve dysfunction definitions

Alternative definition	Evolut (N=350)	SAPIEN (N=365)	Difference	P Value (Superiority)
BVD composite				
ESC (Capodanno)[1]	11.5%	43.7%	-32.2%	<0.001
VARC-3[2]	7.4%	22.4%	-15.0%	<0.001
SMART (primary endpoint with 12 mo echo only)[3]	6.3%	28.3%	-22.0%	<0.001
HSVD				
Playford (NEDA)[4]	1.3%	22.0%	-20.8%	<0.001
O'Hair[5]	0.4%	6.7%	-6.4%	<0.001
SMART (HSVD w 12 mo echo only)[6]	2.0%	20.3%	-18.3%	<0.001



Evolut was superior to SAPIEN for the BVD endpoint for all definitions tested

[1]Capodanno D, et al. Eur Heart J 2017;38(45):3382-3390. [2]Genereux P, et al. J Am Coll Cardiol 2021;77(21):2717-2746. [3]12-month echocardiograms were available in 270 Evolut and 279 SAPIEN patients.
[4]Playford D, et al. J Am Soc Echocardiogr 2020;33(9):1077-1086.e1. [5]O'Hair D, et al. JAMA Cardiol 2023;8(2):111-119. 612-month echocardiograms were available in 298 Evolut and 301 SAPIEN patients.

Quality of life

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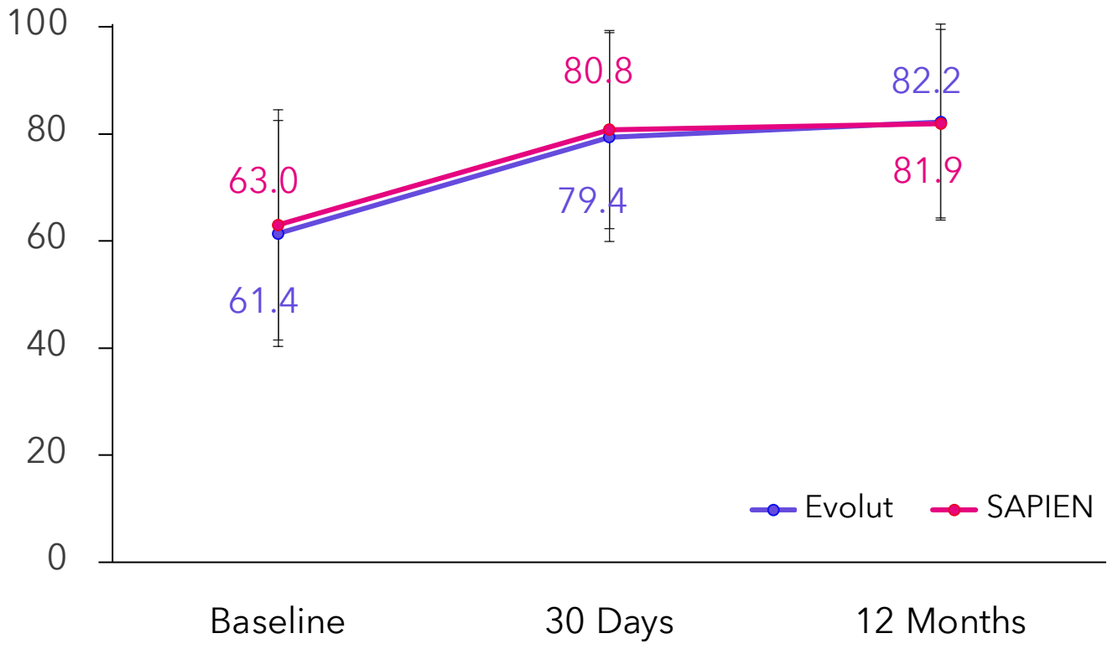
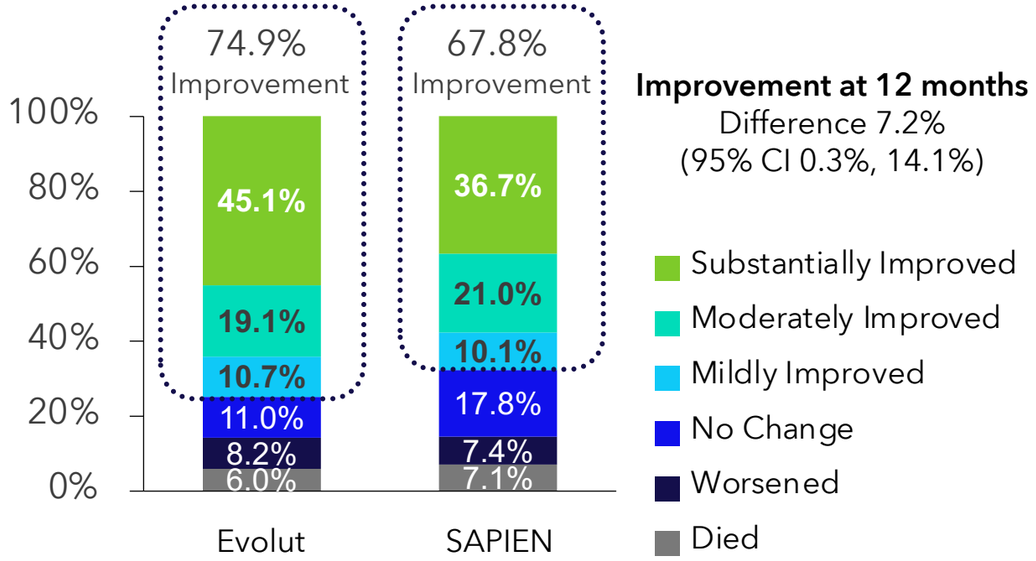
Evolut demonstrated significantly better VARC-3 Ordinal Outcome for quality of life at 12 months

KCCQ Overall Summary Score, Mean ± SD



VARC-3 KCCQ ordinal outcome at 12 months
Evolut vs SAPIEN, p=0.034



VARC-3 ordinal outcome:
(i) death; (ii) worsened: decrease from baseline >5 points; (iii) no change: change between -5 and <5 points; (iv) mildly improved: increase between 5 and <10 points; (v) moderately improved: increase between 10 and <20 points; (vi) substantially improved: increase ≥20 points

Summary

SMART Trial

The SMART trial is the largest, most rigorous trial to date, to randomize patients to the 2 most widely used TAVR devices, and the largest TAVR trial to enroll mostly women.

The SMART trial met both primary and all 5 prespecified secondary endpoints.

Compared with SAPIEN, the supra-annular Evolut demonstrated:

- Noninferior clinical outcomes at 1 year
- Superior valve performance at 1 year:
  - 32.2% lower incidence of BVD
  - 8 mmHg lower mean gradient
  - 0.5 cm^2 greater effective orifice area
  - 0.19 larger Doppler velocity index
  - 6.8% lower incidence of severe PPM
- Improvements in other secondary outcomes at 1 year:
  - Less total AR and better QOL per the KCCQ ordinal outcome

Based on the large differences observed in valve performance, **Dr. Herrmann expects that Evolut will demonstrate improved valve durability and outcomes during longer follow-up**

Thank You to All of Our Trial Investigators, Research Coordinators, and Top Enrolling Sites!

- Kath Saint Johannes-Gesellschaft, Dortmund, Germany
- The Leeds Teaching Hospitals NHS Trust, Leeds, UK
- Allegheny General Hospital, Pittsburgh, PA
- Helios Health Institute Standort Leipzig, Germany
- Montreal Heart Institute, Montreal, Canada
- Sentara Norfolk General Hospital, Norfolk, VA
- Deutsches Herzzentrum München, Germany
- Herz- und Diabeteszentrum NRW, Bad Oeynhausen, Germany
- Hospital of the University of Pennsylvania, Philadelphia, PA
- Saint Paul's Hospital, Vancouver, Canada
- Lankenau Medical Center, Wynnewood, PA
- UPMC Pinnacle Harrisburg Campus, Mechanicsburg, PA
- Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
- Tufts Medical Center, Boston, MA
- Spectrum Health Hospitals, Grand Rapids, MI
- Azienda Ospedaliera Universitaria Integrata Verona, Italy
- Clinique Pasteur, Toulouse, France
- Hospital Vall D'Hebron, Barcelona, Spain

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ORIGINAL ARTICLE

Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus

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Backup

Definitions

Severe prosthesis-patient mismatch per VARC-3[1]: indexed effective orifice area of ≤0.65 cm^2/m^2 for body-mass index (BMI) <30 kg/m^2 or ≤0.55 cm^2/m^2 for BMI ≥30 kg/m^2.

Bioprosthetic valve dysfunction per VARC-3[1]: Based on a composite of (1) structural valve dysfunction, defined as mean gradient ≥20 mmHg with a change from the reference echo of ≥10 mmHg, AND an effective orifice area decrease of ≥0.3 OR percent effective orifice area decrease of ≥25% OR Doppler Velocity Index decrease of ≥0.1 OR percent Doppler Velocity Index decrease of ≥20%, OR moderate/severe transvalvular AR with an increase from the reference echo; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch or moderate/severe paravalvular regurgitation at any follow-up echo from discharge through the 12-month study visit; (3) thrombosis (time to first event, ≤365 days); and (4) endocarditis (time to first event, ≤365 days). The reference echo was at 30 days or at discharge if the 30-day echo was unavailable.

Bioprosthetic valve dysfunction per the European Society of Cardiology (Capodanno)[2]: Based on a composite of (1) structural valve dysfunction, defined as mean gradient ≥20 mmHg at any follow-up echo from discharge through the 12-month study visit; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch using the VARC-2 definition without the obesity correction or moderate/severe total AR at any follow-up echo from discharge through the 12-month study visit; (3) thrombosis (time to first event, ≤365 days); and (4) endocarditis (time to first event, ≤365 days).

Bioprosthetic valve dysfunction per the SMART primary endpoint with 12-month echo only: Based on a composite of (1) structural valve dysfunction, defined as mean gradient ≥20 mmHg on the 12-month visit echo; (2) nonstructural valve dysfunction, defined as severe prosthesis-patient mismatch or moderate/severe total AR on the 12-month visit echo; (3) thrombosis (time to first event, ≤365 days); (4) endocarditis (time to first event, ≤365 days); and (5) reintervention (time to first event, ≤365 days).

Hemodynamic structural valve dysfunction per Playford[3]: Based on structural valve dysfunction, defined as mean gradient ≥22.5 mmHg at any follow-up echo from discharge through the 12-month study visit.

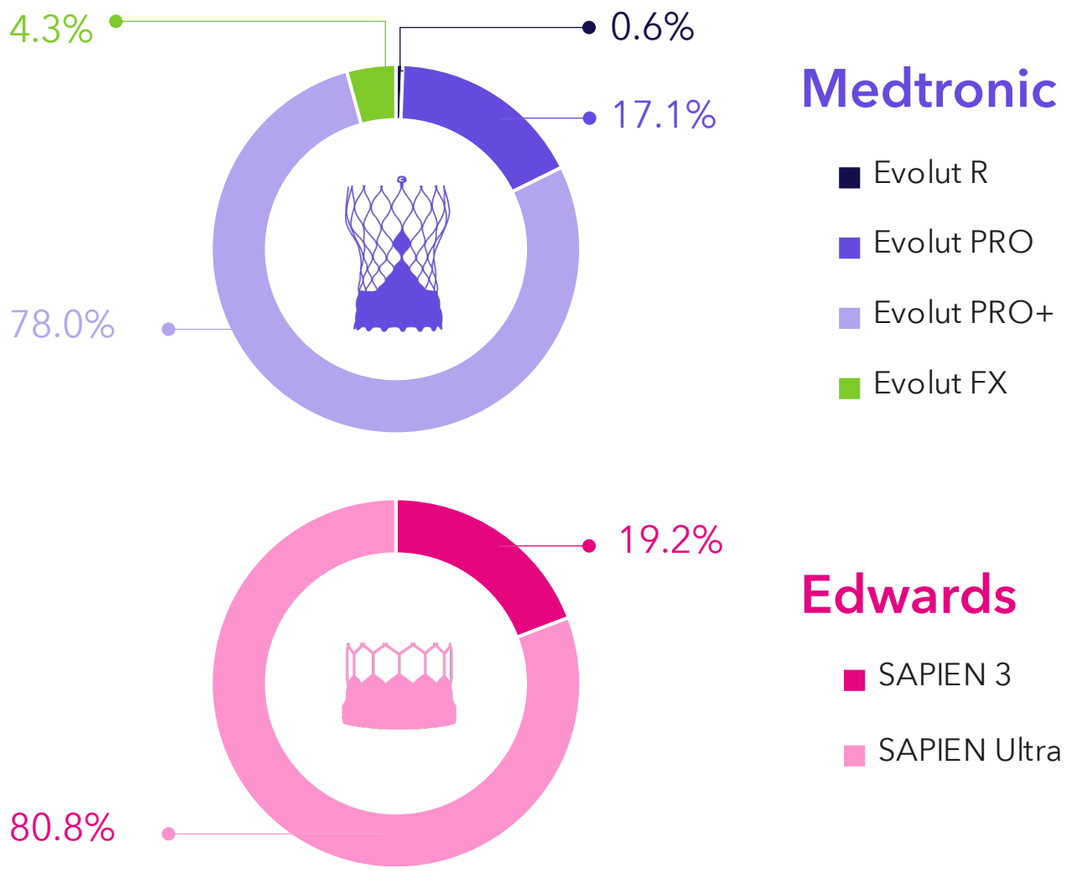
Hemodynamic structural valve dysfunction per O'Hair[4]: Based on structural valve dysfunction, defined as mean gradient ≥20 mmHg with a change from the reference echo of ≥10 mmHg OR moderate/severe transvalvular AR with increase from the reference echo. The reference echo was at 30 days or at discharge if the 30-day echo was unavailable.

Hemodynamic structural valve dysfunction per the SMART primary endpoint with 12-month echo only: Based on structural valve dysfunction, defined as mean gradient ≥20 mmHg on the 12-month visit echo

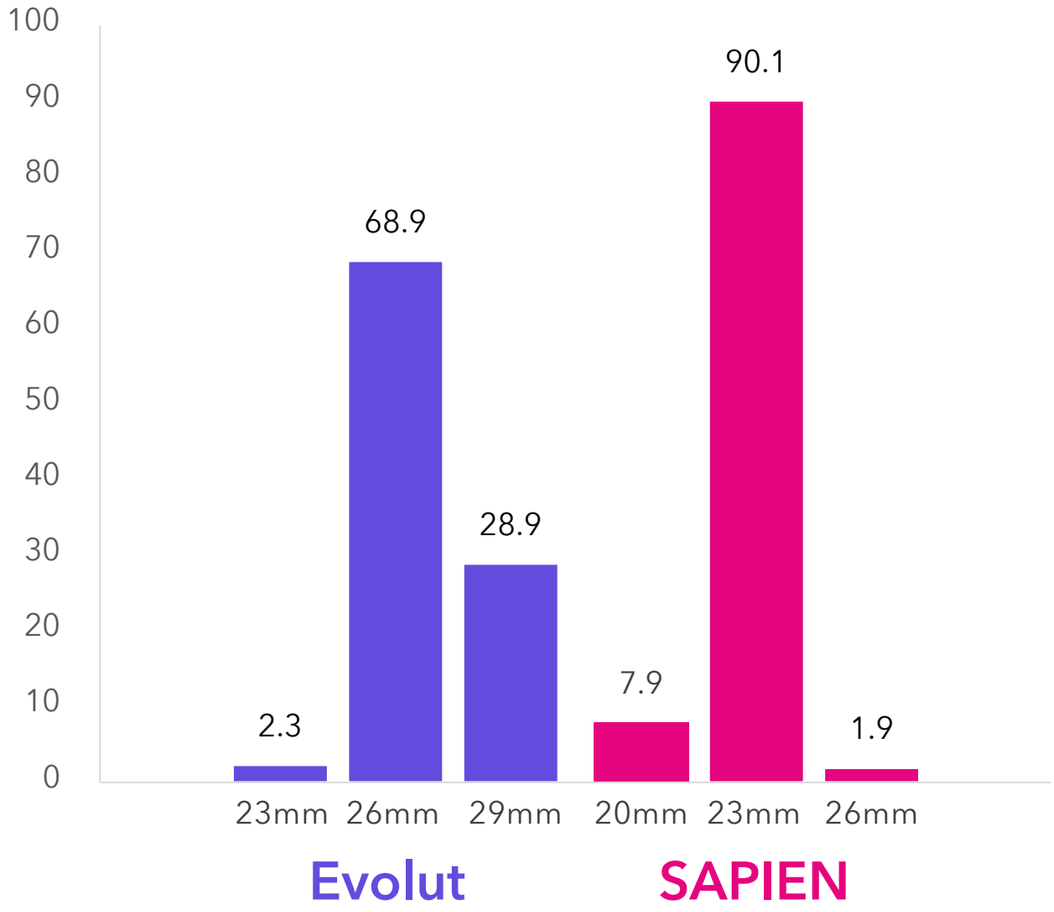
[1]Genereux P, et al. *J Am Coll Cardiol* 2021;77(21):2717-2746.
[2]Capodanno D, et al. *Eur Heart J* 2017;38(45):3382-3390.
[3]Playford D, et al. *J Am Soc Echocardiogr* 2020;33(9):1077-1086.e1.
[4]O'Hair D, et al. *JAMA Cardiol* 2023;8(2):111-119.

Summary of valve sizes and valves implanted

Last implanted valve model

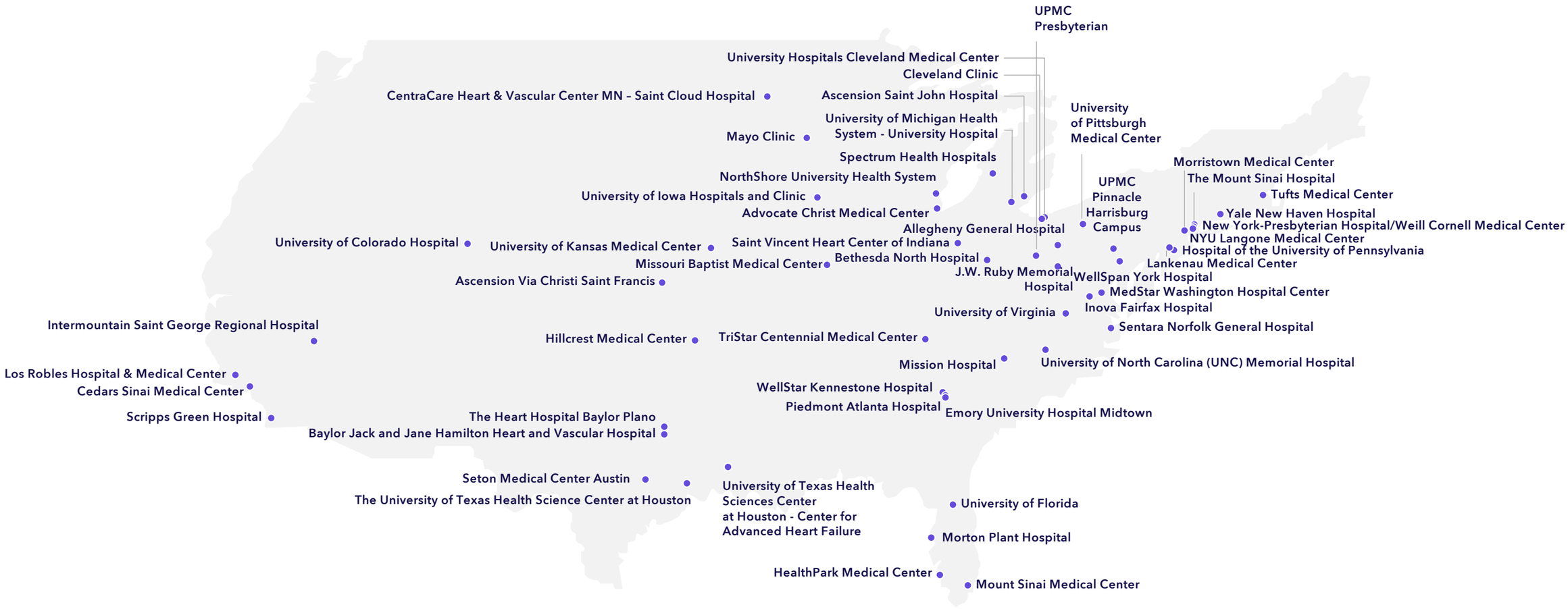


Last implanted valve size



Global site participation

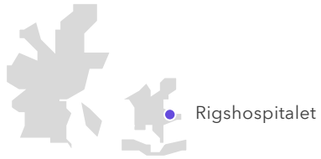
United States



Global site participation

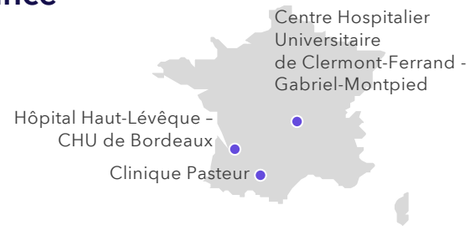
Canada

Denmark



Finland

France



Germany

Israel

Italy

Netherlands

Portugal

Spain

Switzerland

United Kingdom