Two-Year Outcomes of the Five-Year SMART Trial

SMART

Small Annuli Randomized to Evolut or SAPIEN

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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:

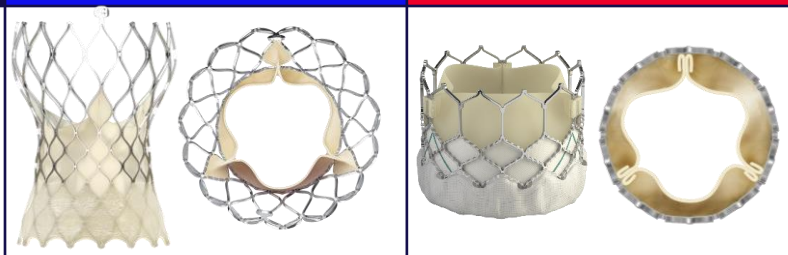
Financial Relationship	Company
Institutional grants/research support	Abbott Vascular, Edwards LifeSciences, Medtronic, Shockwave, Vivasure
Consulting fees/honoraria	Affluent Medical, Caranx, Edwards Lifesciences, Johnson & Johnson, Medtronic, Microinterventional Devices, Wells Fargo
Editorial	Mass Medical Society

- ***Discussion may include unapproved and off-label devices, procedures, and indications***

Background

The SMART Trial:

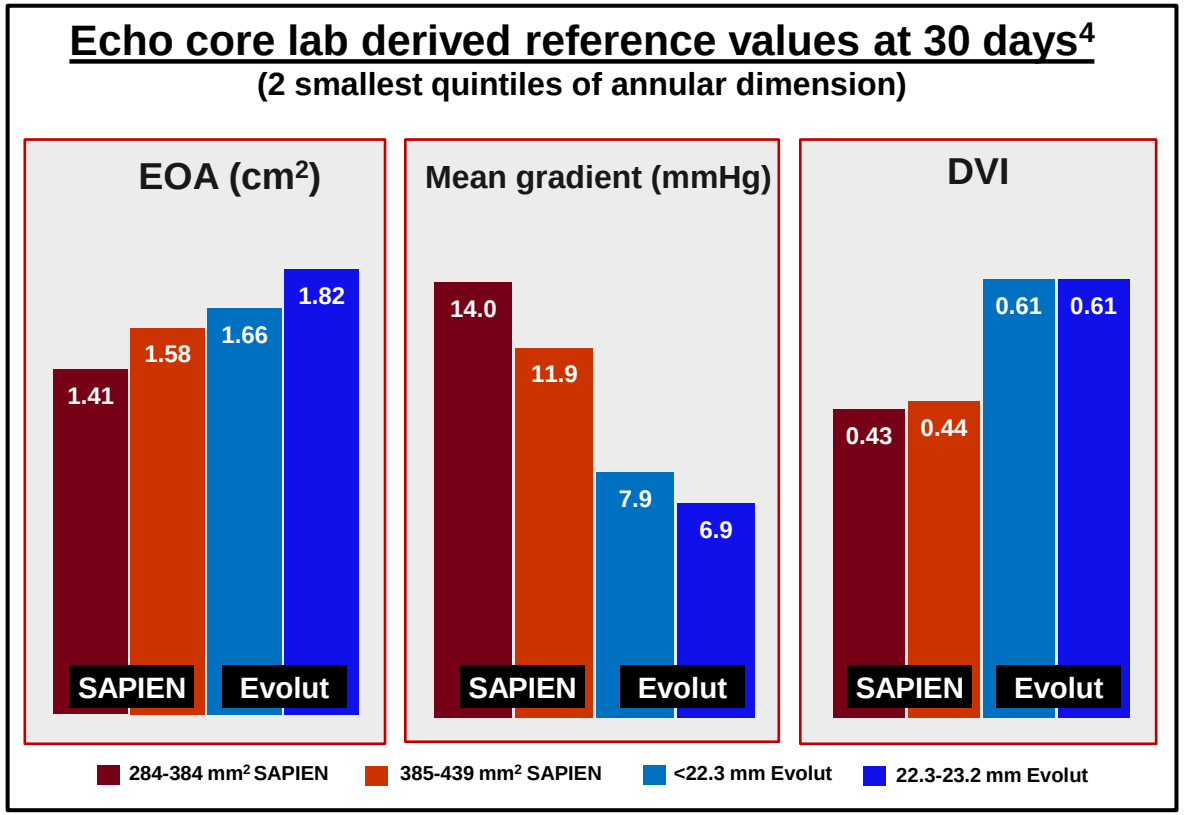
- Designed to compare performance for 2 most widely available commercial transcatheter aortic valve replacement (TAVR) devices in patients with severe aortic stenosis and a small aortic valve annulus.[1]

Valve Characteristic	Evolut PRO/PRO+/FX	SAPIEN 3/SAPIEN 3 Ultra
Front and top view		
Annular Position	Supra-annular	Intra-annular
Platform in SMART	78.0% Evolut PRO+	80.8% SAPIEN 3 Ultra
Annulus Range	17/18-30 mm	16-28 mm
Available Valve Sizes	23, 26, 29, 34 mm	20, 23, 26, 29 mm
Frame Material	Nitinol (SE)	Cobalt-chromium (BE)
Tissue Material	Porcine	Bovine
Recapturable	Yes	No
Other Features	Designed to retain frame circularity[2]	Risk for asymmetrical expansion[3]

[1]Herrmann et al, Am Heart J 2022; 243:92-102. [2]Puri et al, JSCAI 2025; 4:102488 (Bench testing may not be indicative of clinical performance). [3]Maznyczka et al, JACC CV Interv 2024; 17;2011-2022

Prior Evidence:

- Hemodynamics of Evolut valve are superior to those of SAPIEN valve.



[4]Derived from Hahn et al, JACC Imaging 2019; 12:25-34

SMART Trial Design

Prospective, randomized controlled, post-market trial conducted at 83 international sites

All-comer trial with all surgical risk categories including bicuspid patients

716 Patients Treated

Randomization

1:1 stratified by site & sex

(N=355)

Medtronic Evolut PRO/PRO+/FX

(N=361)

Edwards SAPIEN 3/SAPIEN 3 Ultra

Key eligibility

- Symptomatic severe AS*
- Small aortic annulus (≤430 mm^2 by MDCT)

Co-primary endpoints powered at 1 year

- **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.

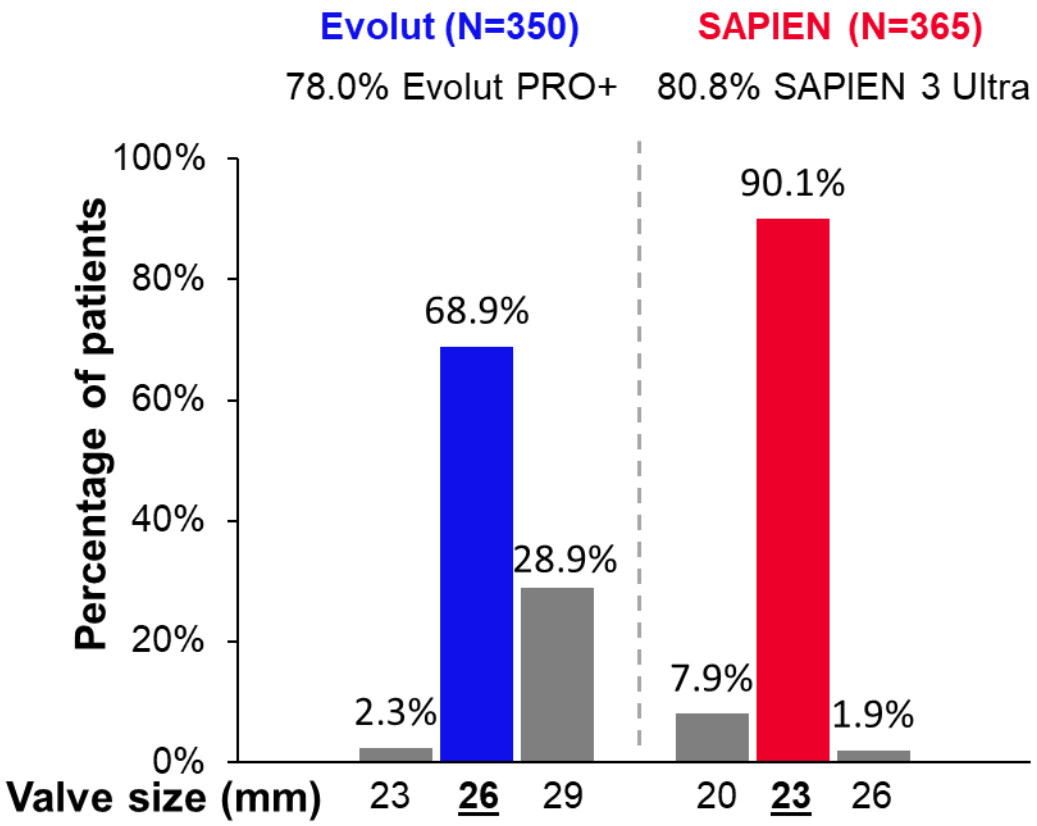
Baseline characteristics

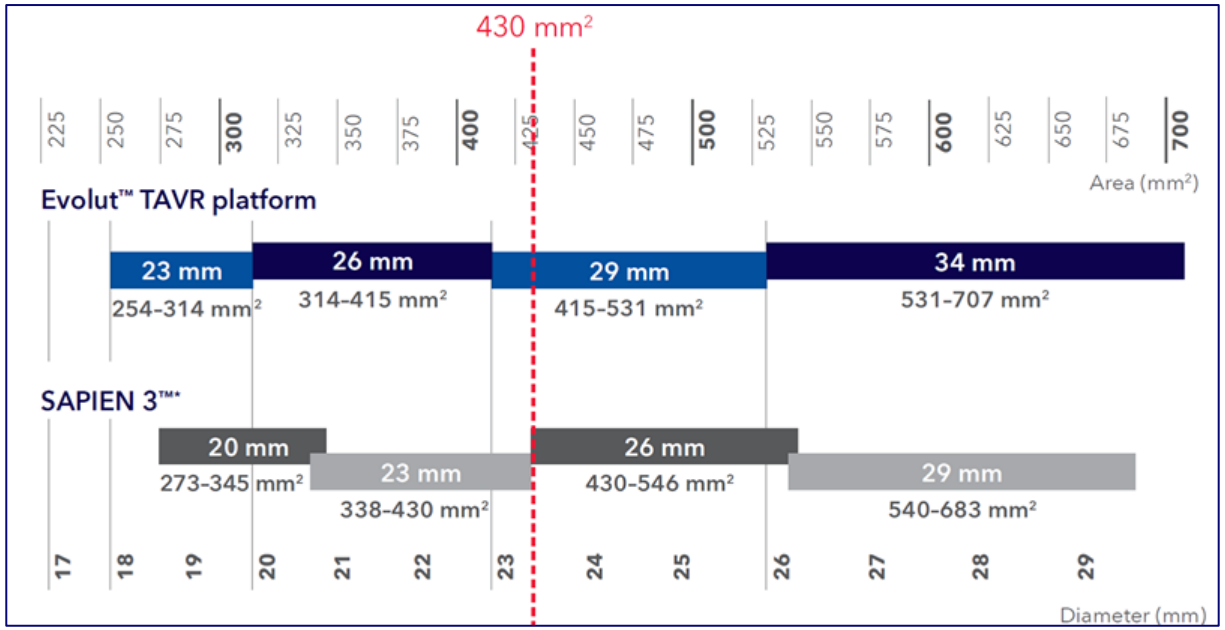
Characteristic	**Evolut** (N=355)	**SAPIEN** (N=361)
Age – yr	**80.1 ± 6.3**	**80.3 ± 6.1**
Female sex	**87.9%**	**85.6%**
STS-PROM score – %	**3.3 ± 1.9**	**3.2 ± 1.7**
NYHA functional class III/IV	43.4%	39.9%
Diabetes	29.3%	34.3%
Hypertension	82.5%	86.7%
COPD or chronic lung disease	18.0%	17.6%
Cerebrovascular 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%
Atrial fibrillation / atrial flutter	19.8%	18.4%
Bicuspid aortic valve morphology	3.9%	4.2%

Data presented as mean ± SD or %

Valve sizing

Aortic annulus size	Evolut (N=355)	SAPIEN (N=361)
Mean area (mm²)	380.9 ± 34.2	382.8 ± 33.9
Mean perimeter (mm)	70.3 ± 3.2	70.4 ± 3.2





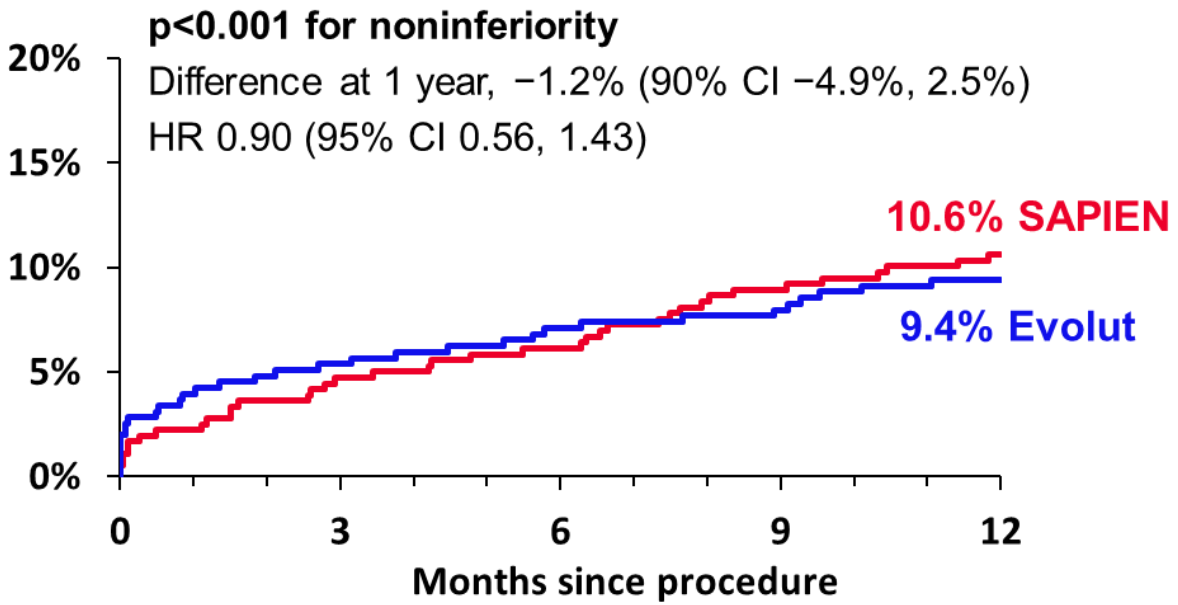
Chosen size based on IFU

Device Sizing	Evolut (N=350)	SAPIEN (N=365)
Smaller than recommended	14 (4.0%)	6 (1.6%)
Recommended	309 (88.3%)	336 (92.1%)
Larger than recommended	27 (7.7%)	23 (6.3%)

p=0.11 (Chi-square)

SMART Trial results at 1 year: Co-primary outcomes

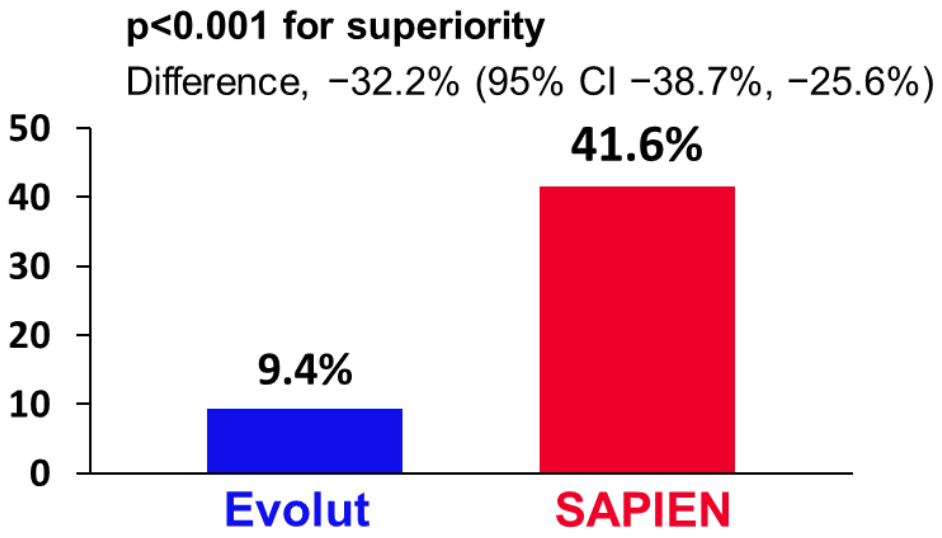
Mortality, Disabling Stroke, or HF Rehospitalization



Events Through 1 Year	Evolut (N=355)	SAPIEN (N=361)	HR (95% CI)
All-cause mortality	5.1%	5.9%	0.88 (0.47, 1.64)
Disabling stroke	3.1%	2.6%	1.26 (0.52, 3.03)
HF rehosp	3.8%	3.5%	1.11 (0.51, 2.44)

Herrmann et al. N Engl J Med. 2024; 390:1959-1971.

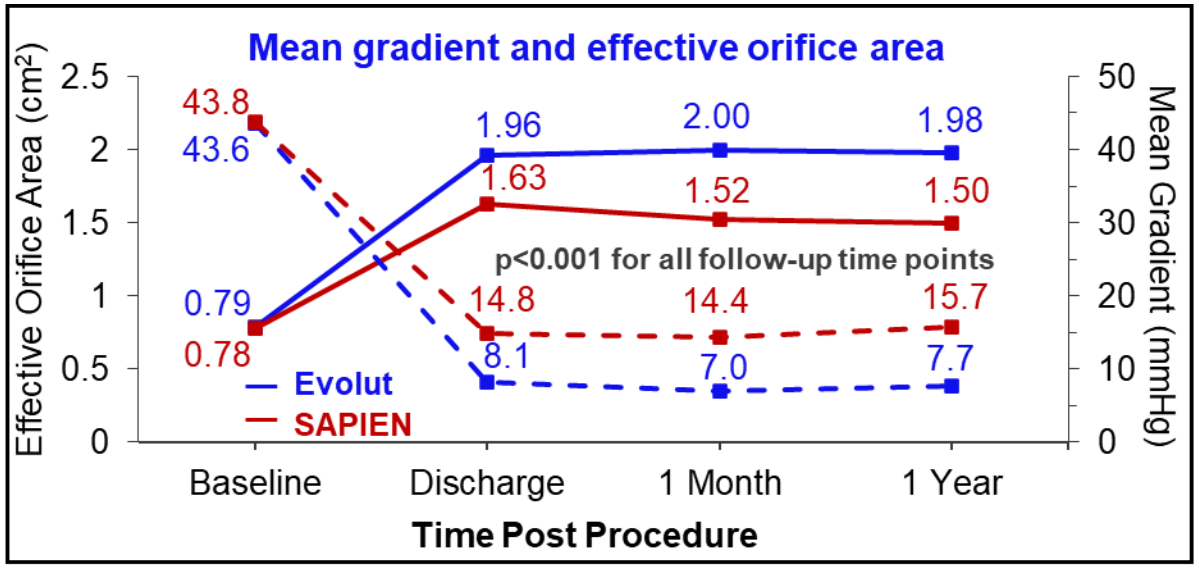
Bioprosthetic Valve Dysfunction

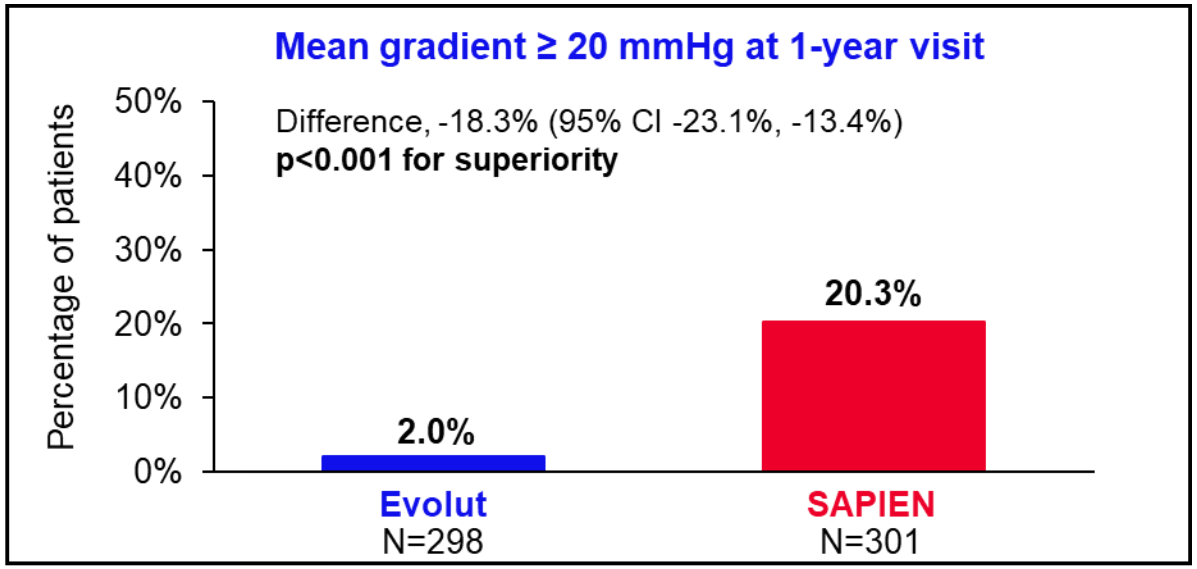


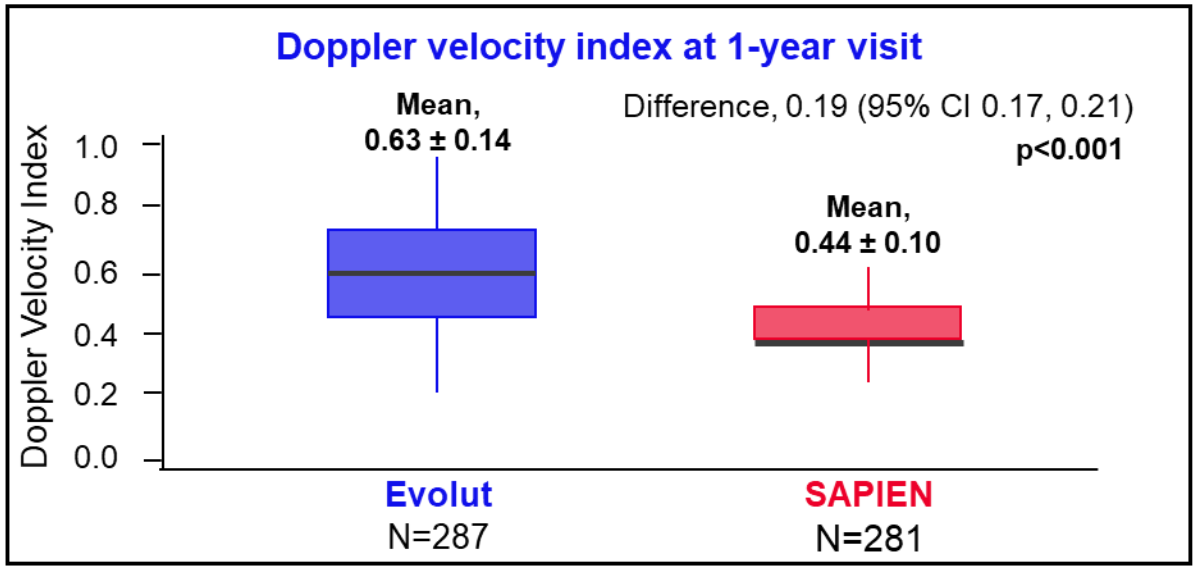
Events Through 1 Year	Evolut (N=350)	SAPIEN (N=365)	P Value
BVD composite	**9.4%**	**41.6%**	**<0.001**
HSVD	3.2%	32.2%	<0.001
NSVD	5.9%	18.2%	<0.001
Thrombosis (clinical)	0.3%	0.3%	0.96
Endocarditis	0.6%	2.3%	0.06
AV Reintervention	0.9%	0.6%	0.63

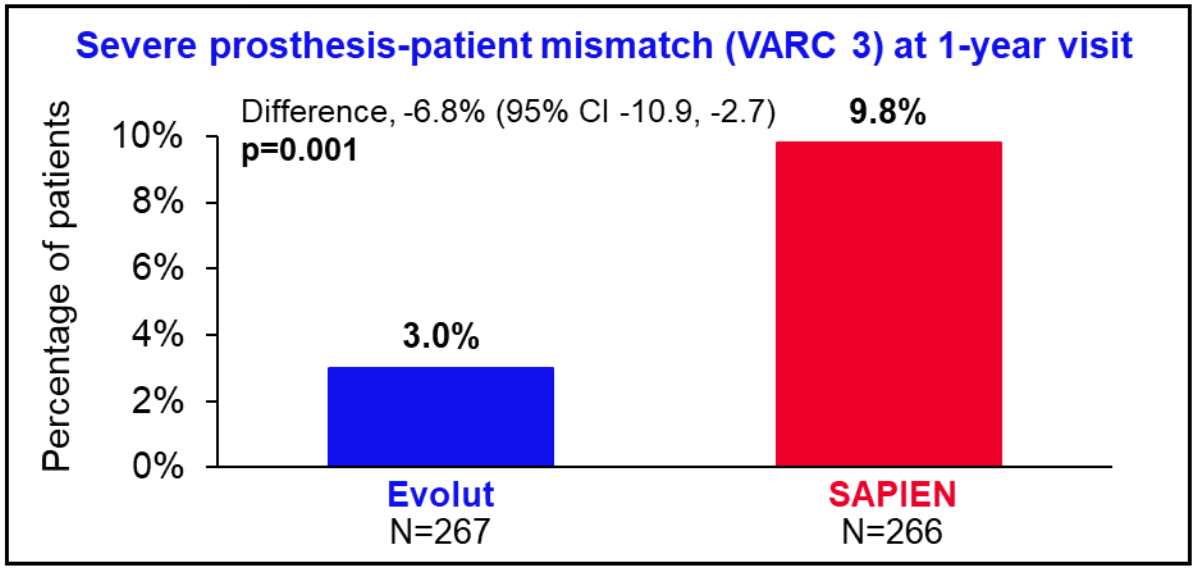
HSVD = Mean gradient ≥ 20 mmHg; NSVD = Severe PPM through 1 year per VARC-3 or ≥mod total AR

SMART Trial results at 1 year: Hemodynamics









SMART Trial

Values based on independent Echocardiography Core Laboratory (Mayo) assessment.

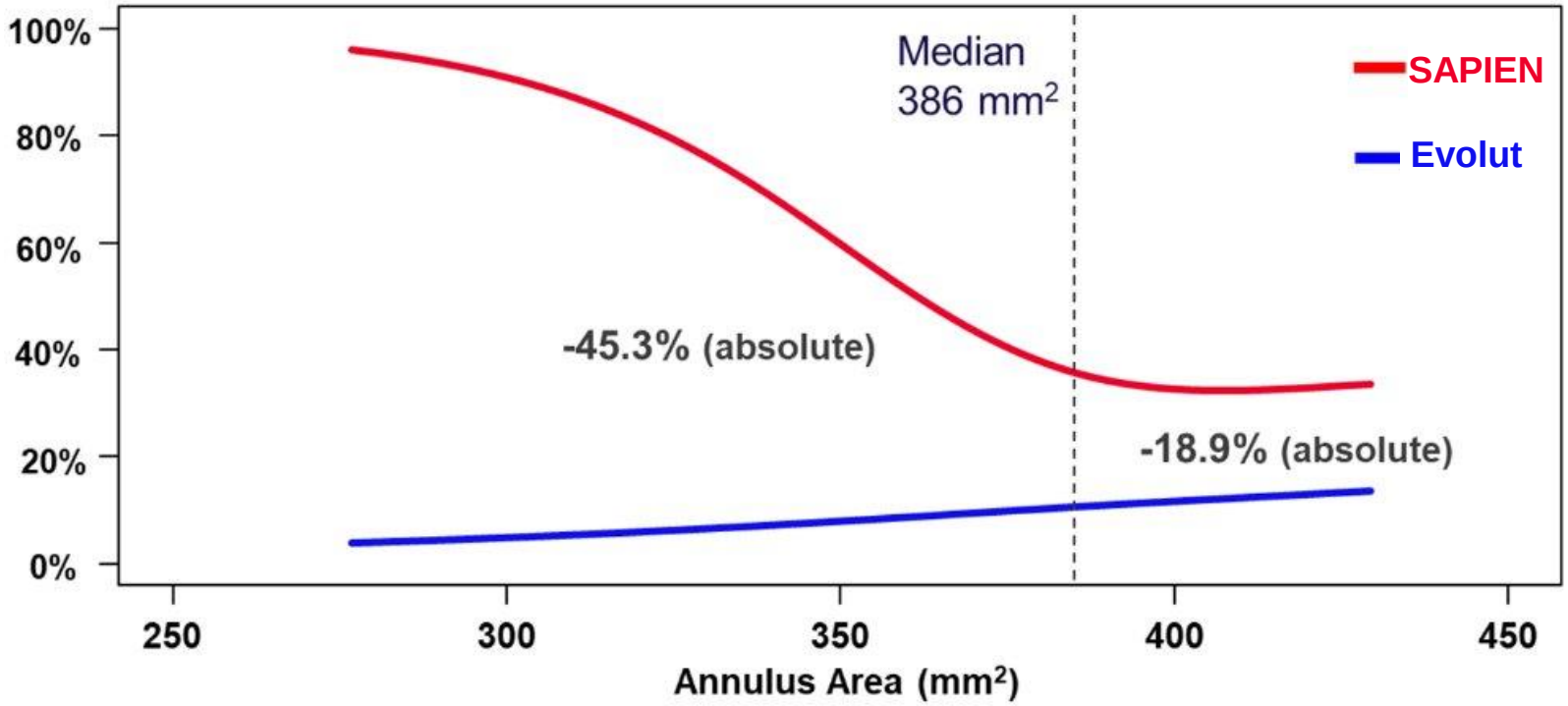
Use of SAPIEN valve was a predictor of BVD

Finding consistent throughout entire range of annulus area in the trial

Multivariable predictors of BVD through 1 Year

Overall Cohort (Evolut + SAPIEN)	Odds Ratio (95% CI)	P Value
SAPIEN (vs Evolut)	**8.21 (5.10-13.23)**	**<0.001**
BSA (per 0.1 m^2)	1.27 (1.13-1.43)	<0.001
Aortic annulus area (per 1 mm^2)	0.99 (0.98-0.99)	<0.001

Incidence of BVD

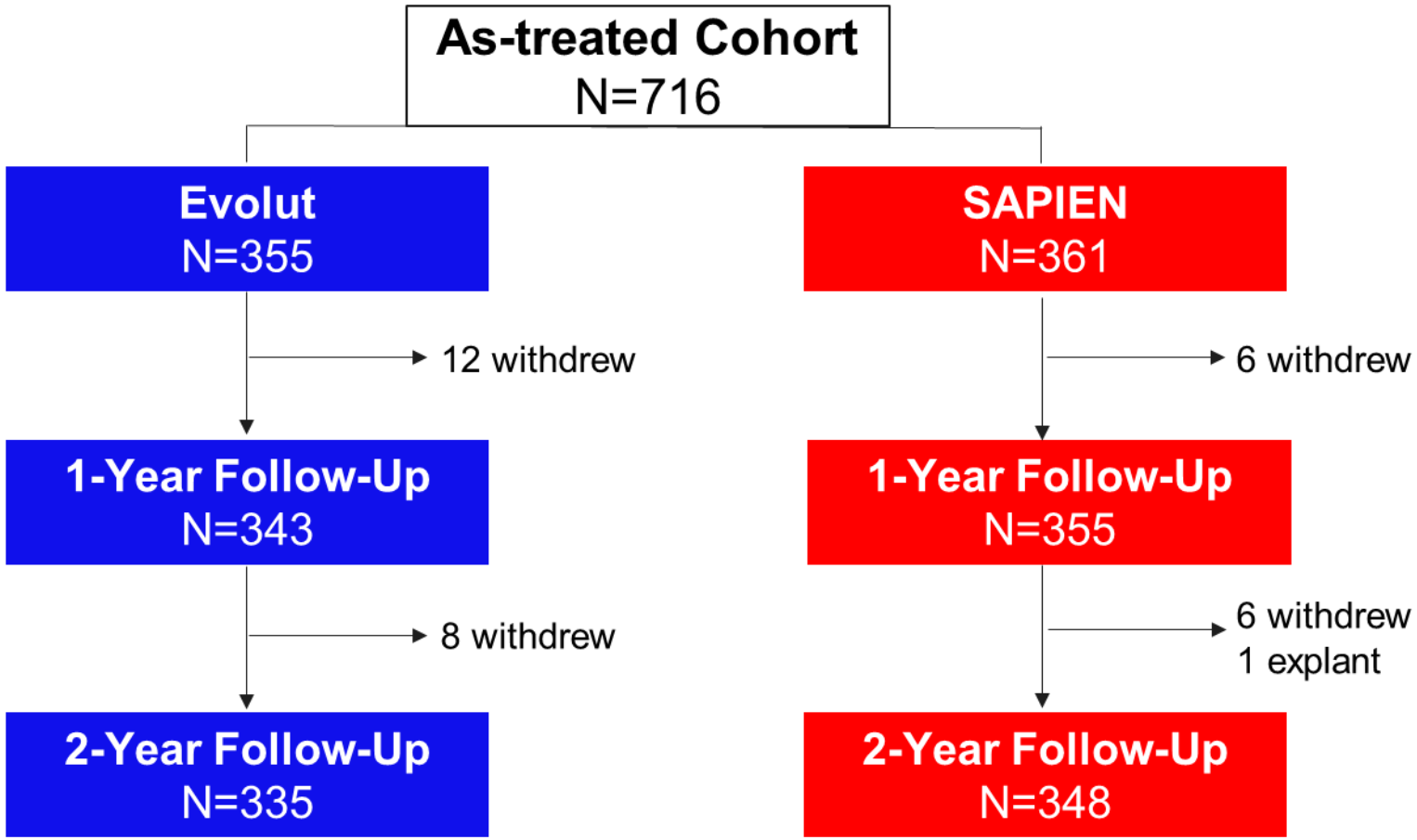


BVD	Evolut		SAPIEN		Difference (95% CI)	P Value
Annulus Area <386 mm^2	N=171	9 (6.1%)	N=187	82 (51.4%)	−45.3% (−54.2% , −36.4%)	<0.001
Annulus Area ≥386 mm^2	N=179	19 (12.7%)	N=178	49 (31.6%)	−18.9% (−28.2% , −9.7%)	<0.001

Herrmann et al. Presented at NY Valves 2024, June 5-7, New York, NY

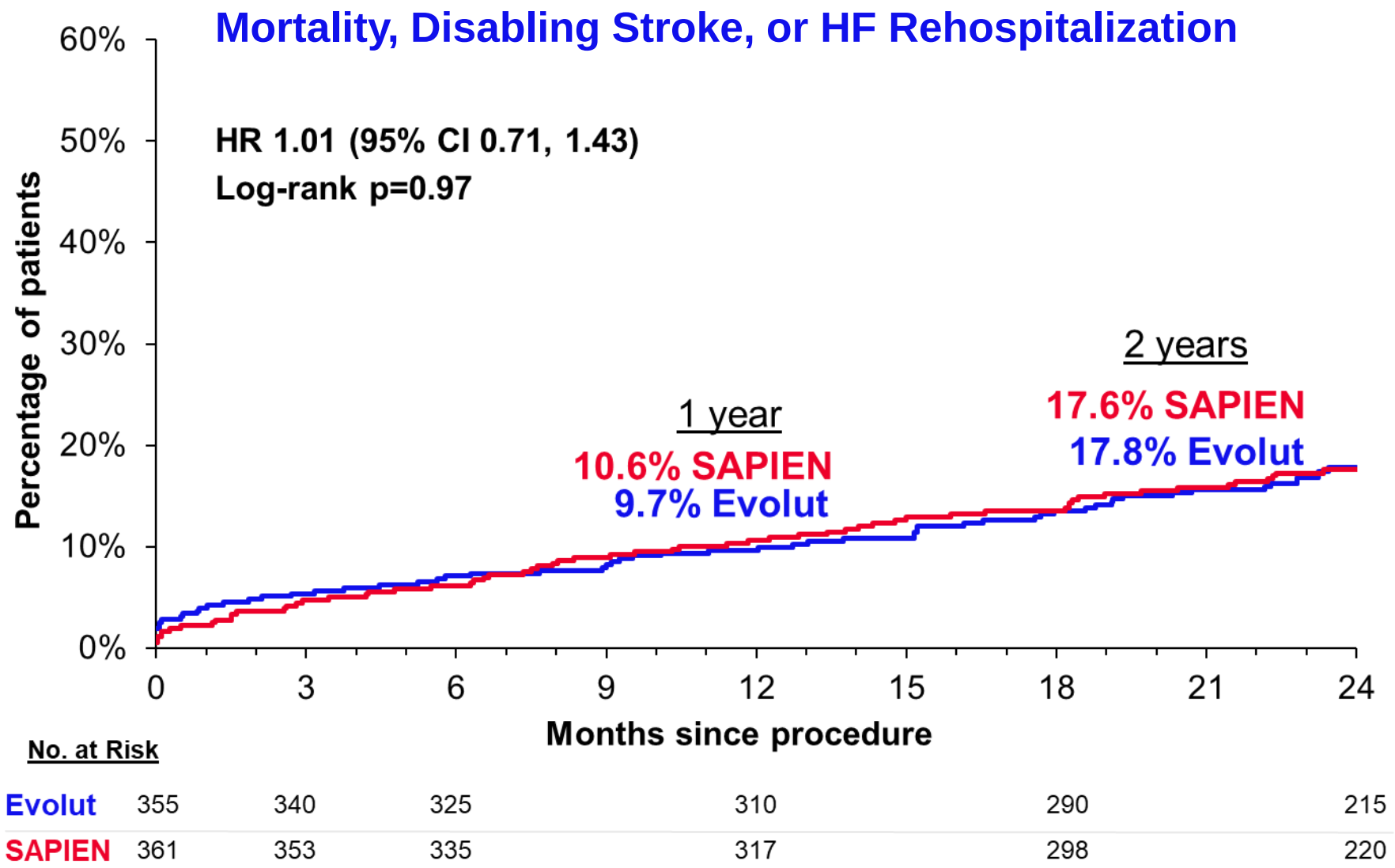
Results at 2 Years

Population and Follow-up Flowchart



2-year follow-up: Data available for 95% of patients
Echo compliance >87%

Clinical outcome composite & components through 2 years



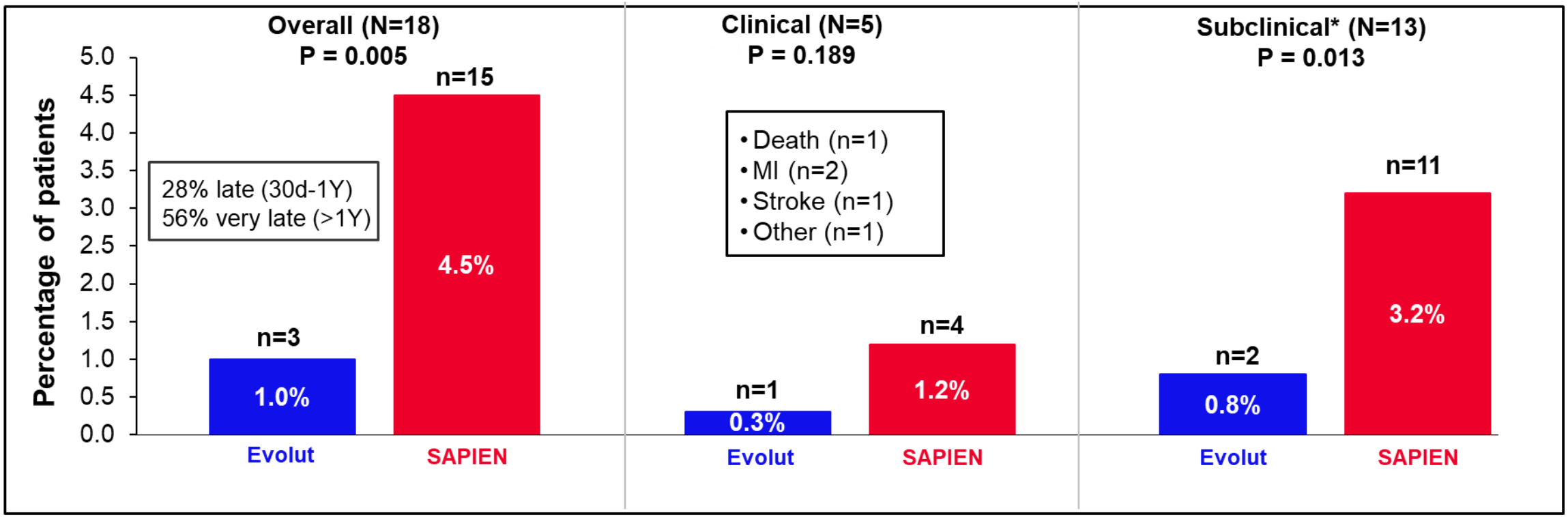
Safety events

KM%	1 Year			2 Years		
	Evolut (N=355)	SAPIEN (N=361)	Log-Rank P Value	Evolut (N=355)	SAPIEN (N=361)	Log-Rank P Value
All-cause mortality	5.1%	5.9%	0.676	12.7%	11.4%	0.657
Cardiovascular mortality	3.4%	3.7%	0.882	7.2%	6.4%	0.706
Heart failure rehospitalization	4.1%	3.5%	0.661	6.1%	6.0%	0.951
Aortic valve reintervention	0.9%	0.6%	0.637	0.9%	0.9%	0.978
New pacemaker implant[a]	14.0%	9.3%	0.052	15.4%	11.4%	0.097
Total pacemaker implant[b]	12.8%	8.7%	0.064	14.1%	10.6%	0.118
All stroke	5.4%	4.2%	0.439	7.3%	6.2%	0.487
Disabling stroke	3.1%	2.6%	0.616	4.7%	3.2%	0.302
Transient ischemic attack	0.9%	2.6%	0.087	1.2%	4.2%	0.020
Prosthetic valve thrombosis	0.3%	2.0%	0.035	1.0%	4.5%	0.005
Clinical valve thrombosis	0.3%	0.3%	0.990	0.3%	1.2%	0.189
Subclinical valve thrombosis	0.0%	1.7%	0.015	0.8%	3.2%	0.013

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

Values based on independent Clinical Events Committee adjudication.

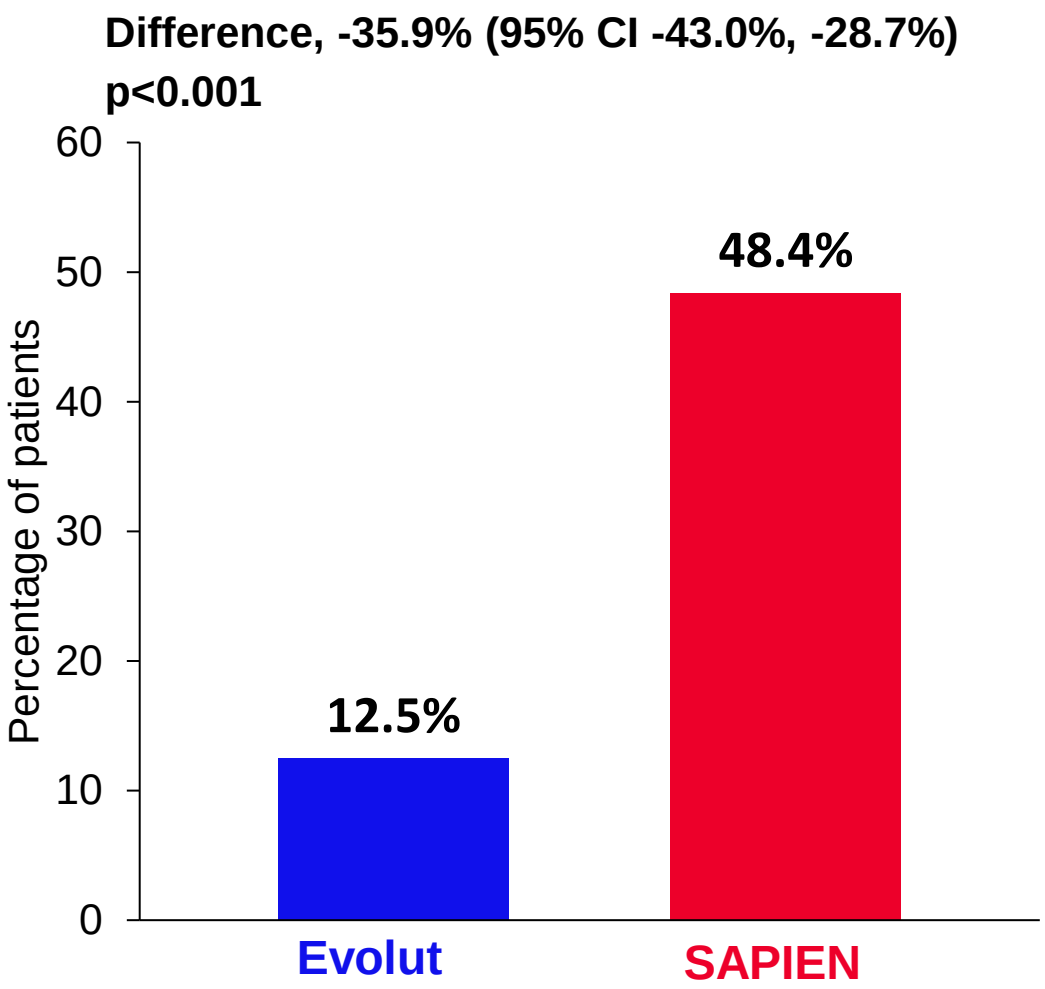
Prosthetic Valve Thrombosis Through 2 Years (CEC adjudicated)



All thrombosis events, including subclinical ones, affected patient management (hospitalization or unscheduled visits, additional imaging, or medication augmentation)

*Protocol (modified VARC 2): thrombus causing ≥50% increase in mean gradient to ≥30 mmHg or a decrease in DVI ≥50% or increase in AR to ≥ moderate

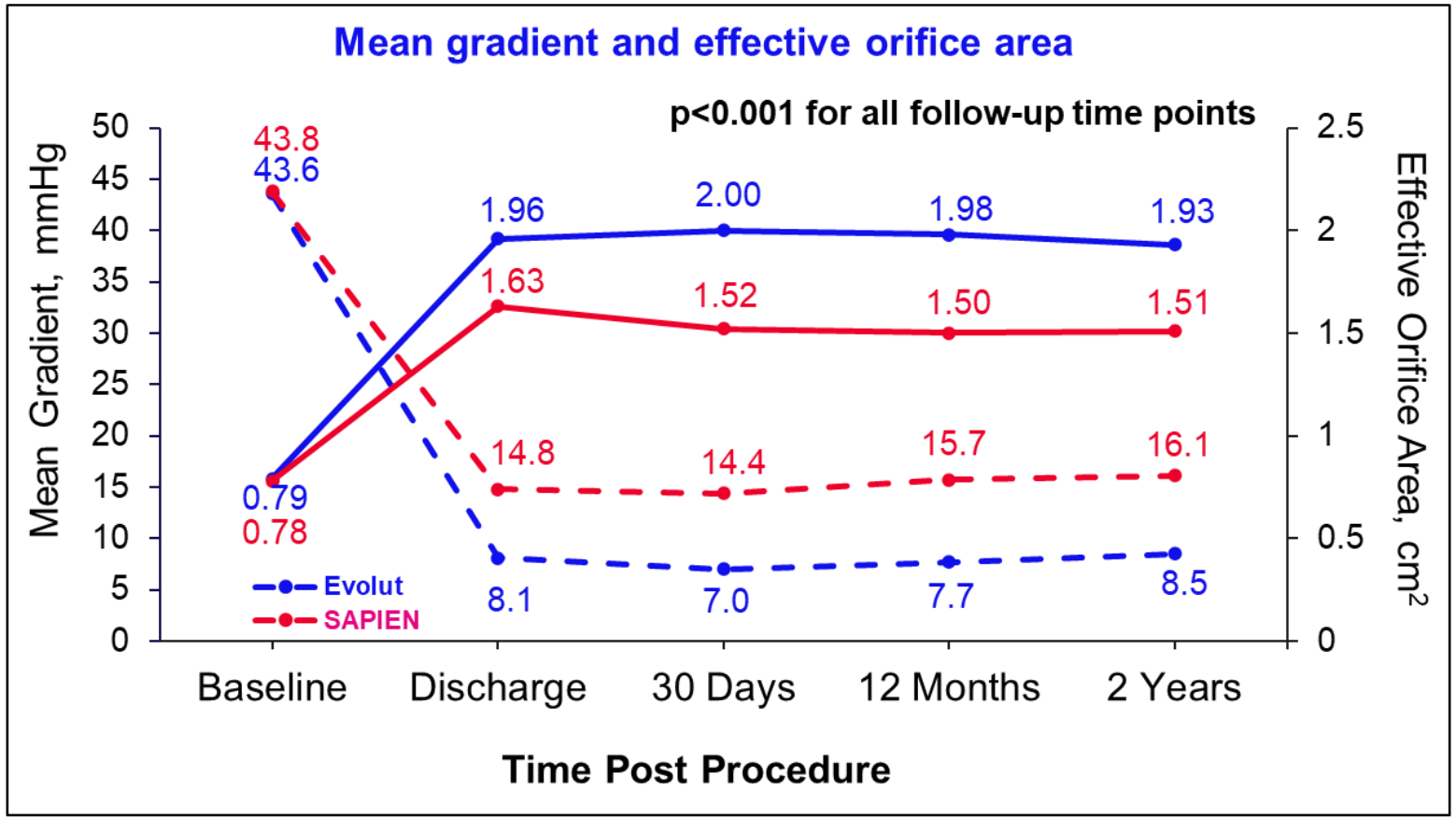
Bioprosthetic valve dysfunction through 2 years



	Evolut (N=350)	SAPIEN (N=365)	P Value
BVD composite	**12.5%**	**48.4%**	**<0.001**
HSVD	4.7%	42.4%	<0.001
NSVD	6.7%	18.0%	<0.001
Thrombosis (clinical)	0.3%	1.2%	0.17
Endocarditis	2.2%	2.6%	0.76
AV Reintervention	0.9%	0.9%	>0.99

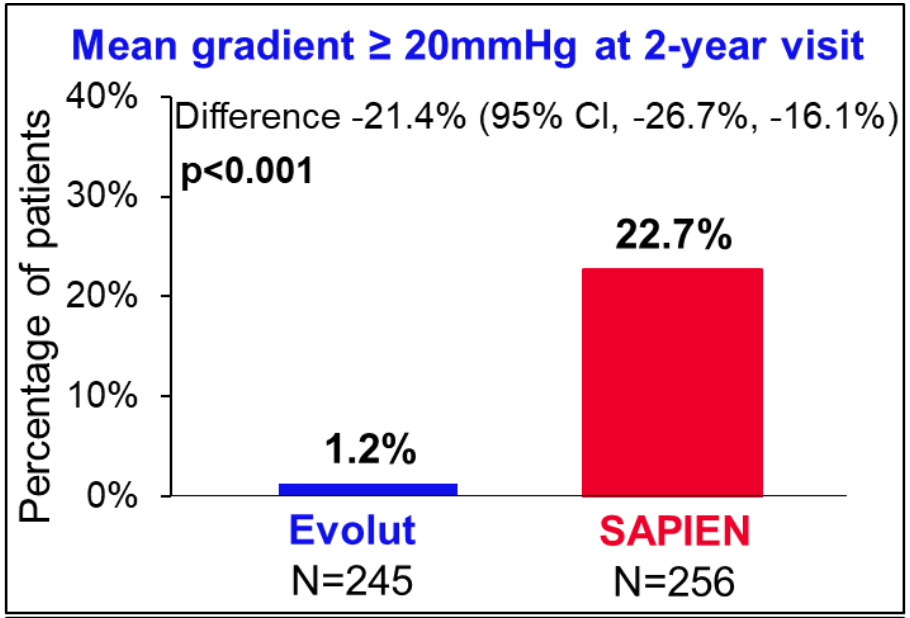
HSVD = Mean gradient ≥ 20 mmHg
NSVD = Severe PPM through 1 year per VARC-3 or ≥moderate total AR

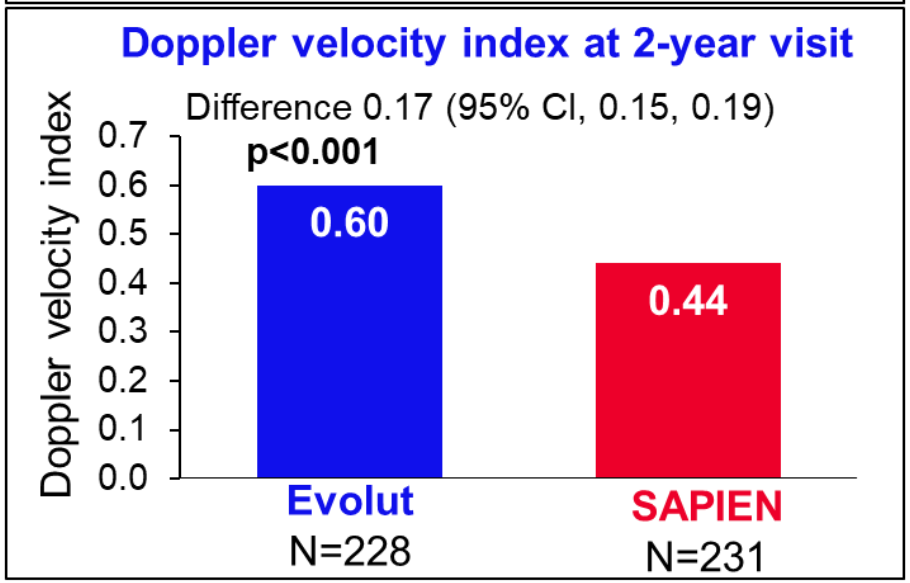
SMART Trial results at 2 years: Hemodynamics



Number of patients with echo data

Evolut MG	347	330	325	298	245
SAPIEN MG	359	348	331	301	256
Evolut EOA	264	250	273	267	215
SAPIEN EOA	281	304	296	266	223

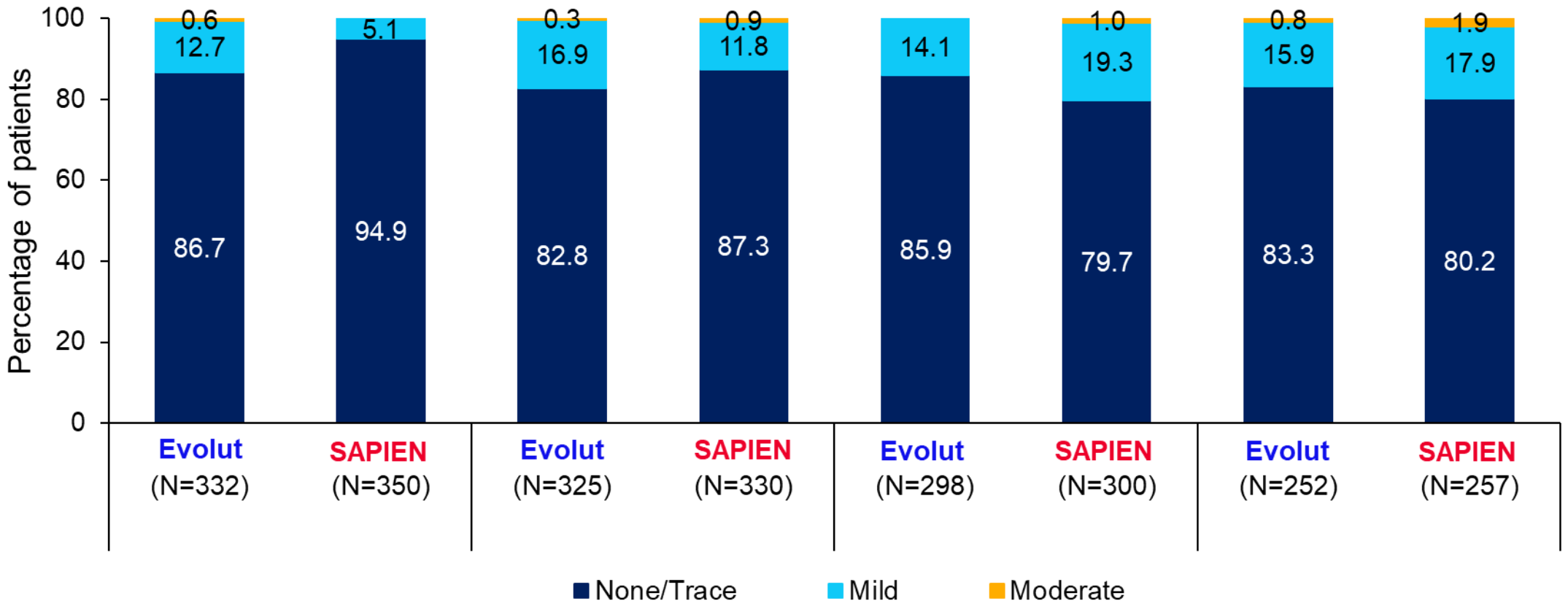




Values based on independent Echocardiography Core Laboratory (Mayo) assessment.

Total Aortic Regurgitation

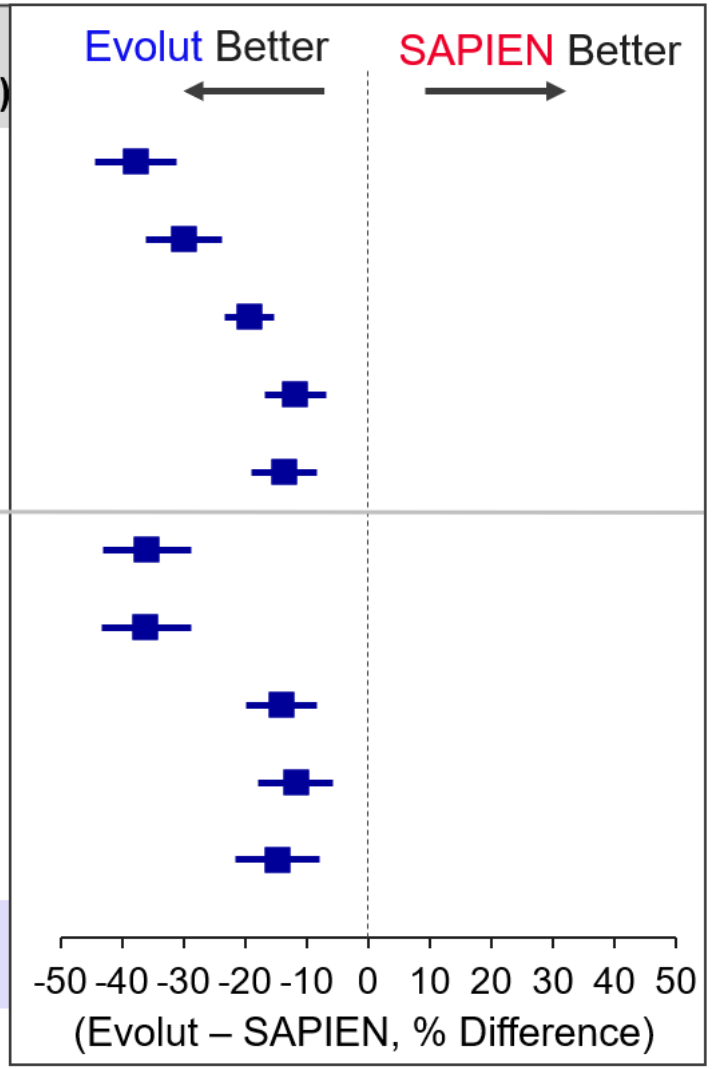
	Discharge		30 Days		1 Year		2 Years	
≥Mild Total AR	13.3%	5.1%	17.2%	12.7%	14.1%	20.3%	16.7%	19.8%
P value	P<0.001		P=0.106		P=0.043		P=0.354	



Values based on independent Echocardiography Core Laboratory (Mayo) assessment.

Alternative valve dysfunction definitions through 2 years

Alternative definition (Cumulative rates through 2 years)		Evolut (N=350)	SAPIEN (N=365)	Difference	P Value (Superiority)
Individual Component Definitions	Mean gradient ≥20 mmHg	4.7%	42.4%	-37.7%	<0.001
	Mean gradient ≥22.5 mmHg[1]	2.6%	32.5%	-29.9%	<0.001
	Mean gradient ≥25 mmHg	2.4%	21.7%	-19.2%	<0.001
	Severe PPM through 1Y (VARC-3)[2]	4.9%	16.7%	-11.8%	<0.001
	Severe PPM through 1Y (VARC-2)[3]	5.9%	19.6%	-13.6%	<0.001
Composite Definitions	SMART BVD[4]	12.5%	48.4%	-35.9%	<0.001
	EAPCI/ESC/EACTS BVD[5]	14.5%	50.6%	-36.1%	<0.001
	VARC-3 Mod Hemo[2]	10.1%	24.2%	-14.1%	<0.001
	Evolut SVD[6]	1.3%	12.9%	-11.7%	<0.001
	Evolut BVD[7]	5.3%	20.1%	-14.7%	<0.001

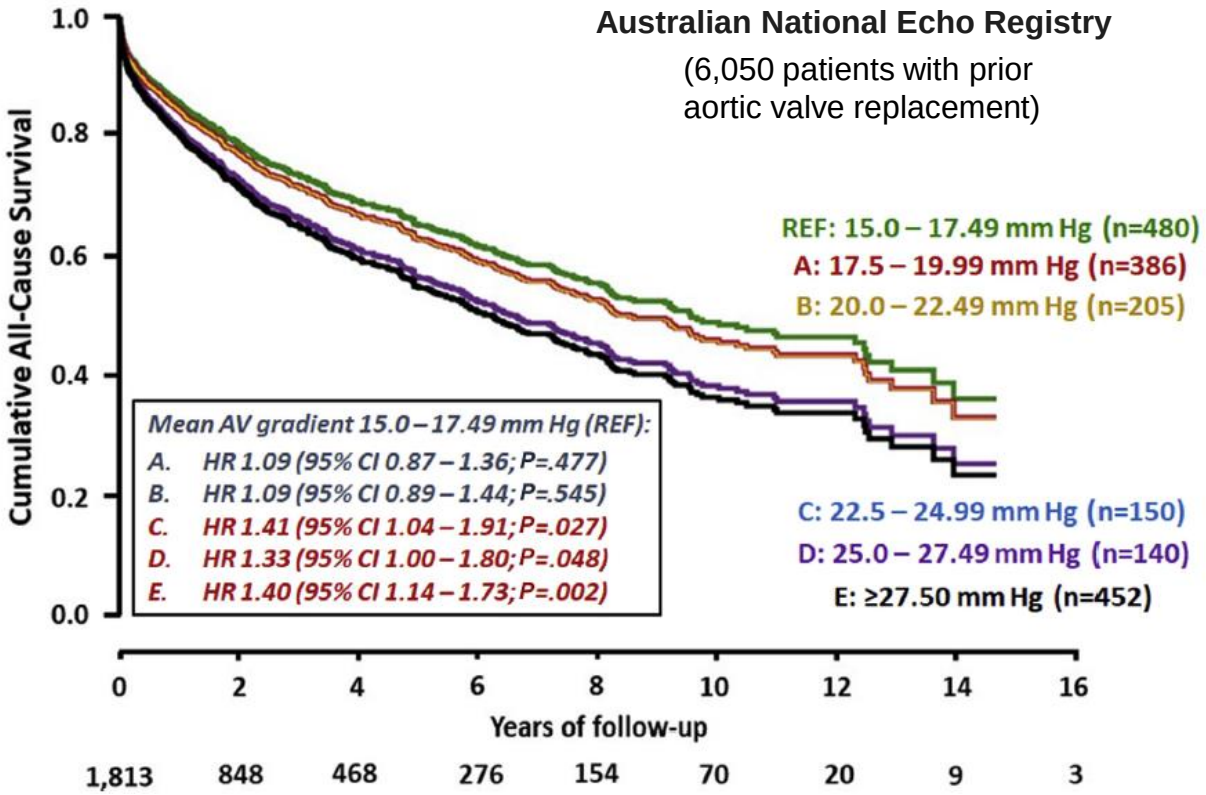


Evolut was superior to SAPIEN for all hemodynamic and composite BVD endpoint definitions tested

[1]Playford D, et al. J Am Soc Echocardiogr 2020;33(9):1077-1086.e1. [2]Genereux P, et al. J Am Coll Cardiol 2021;77(21):2717-2746. [3]Kappetein AP, et al. Eur J Cardio-Thorac Surg 2012;42:S45-S60. [4]Herrmann HC, et al. NEJM 2024;390(21):1959-1971. [5]Capodanno D, et al. Eur Heart J 2017;38(45):3382-3390. [6]O'Hair D, et al. JAMA Cardiol 2023;8(2):111-119. [7]Yakubov SJ, et al. 2024, Presentation NY Valve 2024, Manuscript in press.

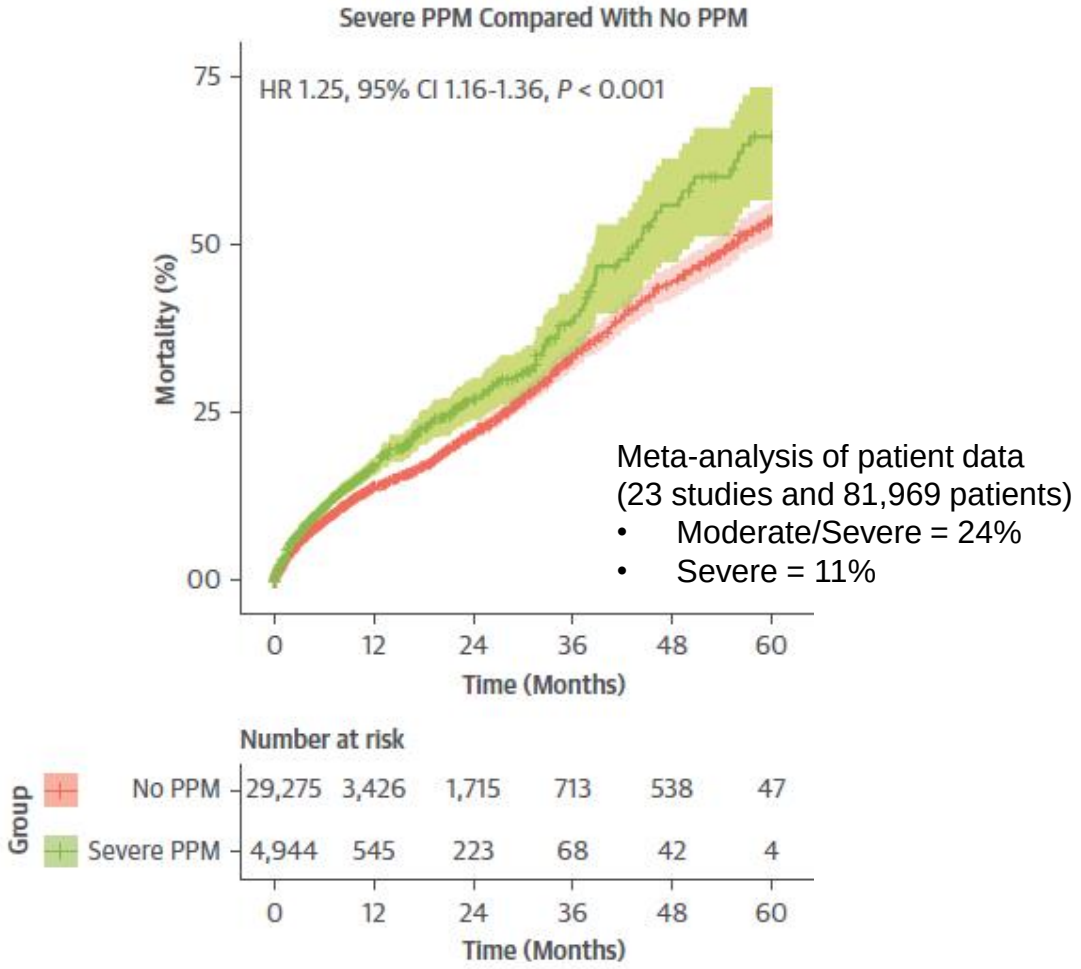
Adverse hemodynamics affect clinical outcomes

Elevated mean gradient after surgical and transcatheter aortic valve replacement reduces survival



Playford et al. J Am Soc Echocardiogr. 2020;33(9):1077-1086.e1.

Severe prosthesis-patient mismatch after TAVR increases mortality



Meta-analysis of patient data
(23 studies and 81,969 patients)

- Moderate/Severe = 24%
- Severe = 11%

Sá MP, et al. JACC Cardiovasc Imaging. 2023 Mar;16(3):298-310.

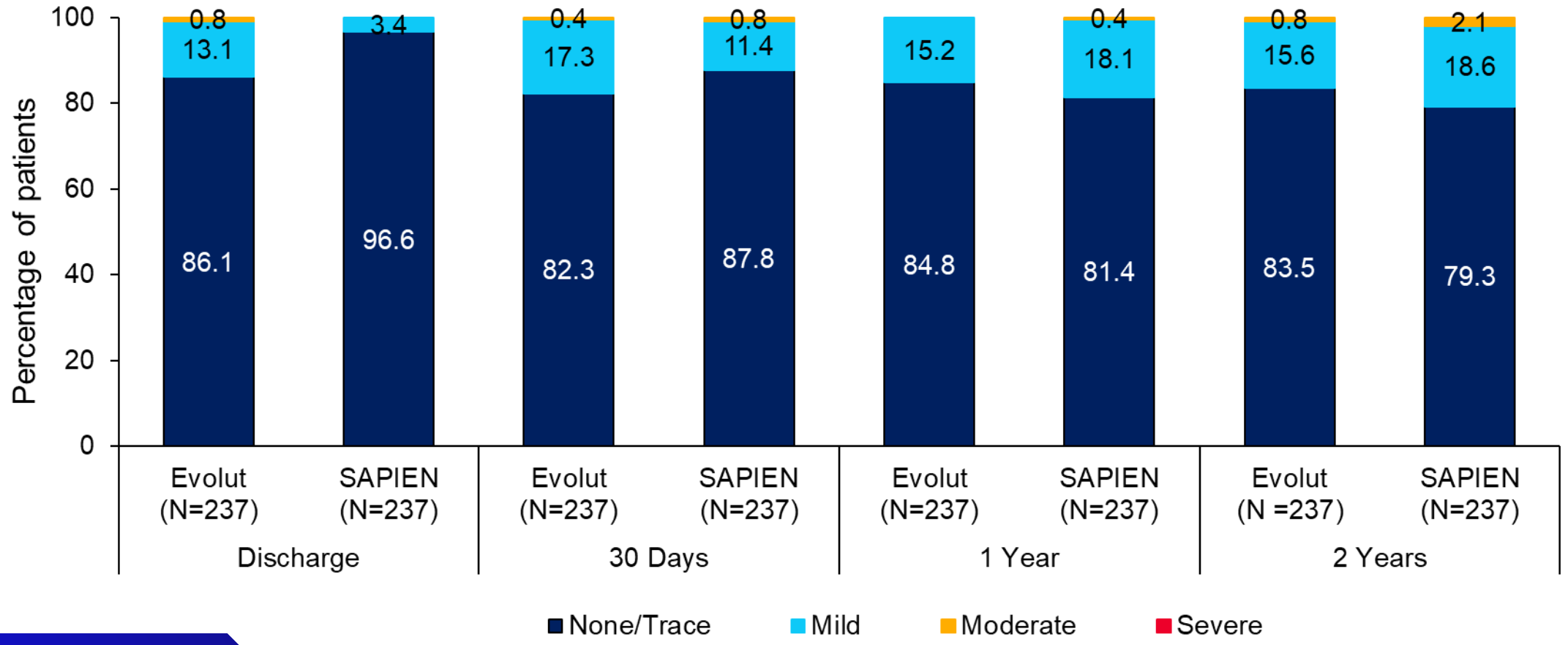
Summary

- The randomized SMART trial compared the Evolut and SAPIEN TAVR valves in 716 patients (87% women) with a small aortic annulus.
- After 2 years of follow up, we observed similar rates for the clinical outcome composite of death, disabling stroke, and HF hospitalization.
- All individual and composite hemodynamic measures continue to demonstrate the superiority of the Evolut platform.
- These findings emphasize the importance of the planned comparison through 5 years of follow-up.

Backup

Total Aortic Regurgitation (paired)

	Discharge		30 Days		1 Year		2 Years	
≥Mild Total AR	13.9%	3.4%	17.7%	12.2%	15.2%	18.6%	16.5%	20.7%
P value	P<0.001		P=0.094		P=0.327		P=0.238	

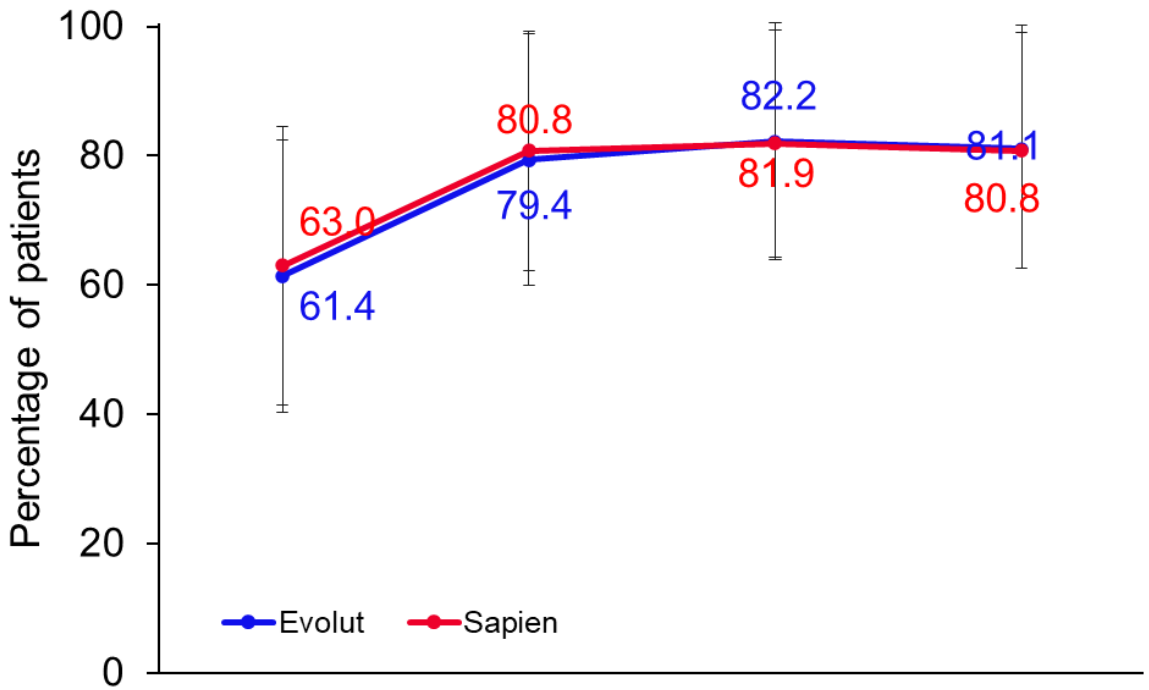


SMART Trial

Values based on independent Echocardiography Core Laboratory (Mayo) assessment.

Quality of life

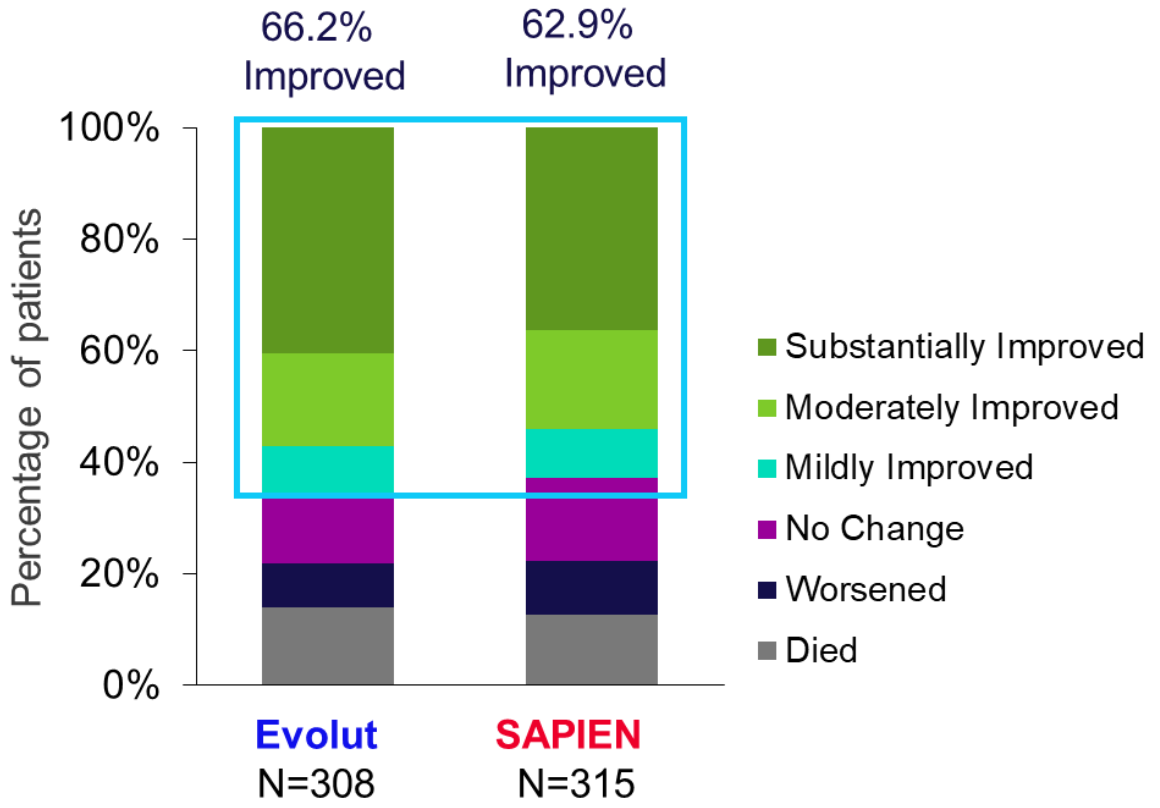
KCCQ Overall Summary Score, Mean ± SD



	Baseline	30 Days	1 Year	2 years
Evolut	354	338	300	266
SAPIEN	358	343	317	275

VARC-3 KCCQ ordinal outcome at 2 years

Evolut vs SAPIEN, p=0.388



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

Thank You to All of Our Patients, Trial Investigators, Research Coordinators, the 83 Global Sites, Committee Members & Core Laboratories!

Trial Leadership/Committees:

- Executive Committee
- Steering Committee
- Case Planning Committee
- Training & Education Committee
- Publication Committee

Independent Safety Committees:

- Clinical Events Committee
- Data Safety Monitoring Board
- Administrator: Baim Institute for Clinical Research

Independent Core Laboratories:

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

Sponsor:

- Medtronic (Minneapolis, MN)

Definitions

MG ≥20 (SMART HSVD): Based on SVD, defined as mean gradient ≥20 mmHg at any follow-up echo from discharge through the 2-year study visit

MG ≥22.5 (Playford): Based on SVD, defined as mean gradient ≥22.5 mmHg at any follow-up echo from discharge through the 2-year study visit

MG ≥25: Based on SVD, defined as mean gradient ≥25 mmHg at any follow-up echo from discharge through the 2-year study visit

VARC-3 Severe PPM (Genereux): defined as (BMI<30 and EOAI ≤0.65) OR (BMI≥30 and EOAI ≤0.55)

VARC-2 Severe PPM (Kappetein): defined as (BMI<30 and EOAI<0.65) OR (BMI≥30 and EOAI<0.60)

SMART BVD (Herrmann): Based on a composite of (1) SVD, defined as mean gradient ≥20 mmHg at any follow-up echo from discharge through 2 years; (2) NSVD, defined as severe PPM through the 1 year study visit, 395 days or moderate/severe paravalvular regurgitation at any follow-up echo from discharge through the 2-year study visit; (3) thrombosis (time to first event, ≤730 days); (4) endocarditis (time to first event, ≤730 days); and (5) reintervention (time to first event, ≤730 days).

EAPCI/ESC/EACTS BVD (Capodanno): Based on a composite of (1) SVD, defined as mean gradient ≥20 mmHg at any follow-up echo from discharge through the 2-year study visit; (2) NSVD, defined as severe PPM using the VARC-2 definition without the obesity correction through the 1 year study visit or moderate/severe total AR at any follow-up echo from discharge through the 2-year study visit; (3) thrombosis (time to first event, ≤730 days); and (4) endocarditis (time to first event, ≤730 days).

VARC-3 Mod Hemo (Genereux): Based on a composite of (1) SVD, defined as mean gradient ≥20 mmHg with a change from the reference echo of ≥10 mmHg, AND an EOA decrease of ≥0.3 OR percent EOA decrease of ≥25% OR DVI decrease of ≥0.1 OR percent DVI decrease of ≥20%, OR moderate/severe transvalvular AR with an increase from the reference echo; (2) NSVD, defined as severe PPM through 1 year or moderate/severe total AR at any follow-up echo from discharge through 2 year; (3) thrombosis (time to first event, ≤730 days); and (4) endocarditis (time to first event, ≤730 days).

SEV SVD (O'Hair): Based on SVD, 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.

SEV BVD (Yakubov): Based on a composite of (1) HSVD: mean gradient ≥20 with change from reference echo >=10 mmHg OR moderate/severe transvalvular AR with increase from reference echo (note: there were no such cases of transvalvular AR in SMART, so this was entirely driven by mean gradient); (2) NSVD: severe PPM on the reference echo (30 days if available; else use discharge echo) or severe paravalvular AR at any echo from follow-up through 2-year visit echo; (3) endocarditis: time to first (<=730 days); (4) thrombosis: time to first (<=730 days); NOTE: Core lab only. SVD includes any post 30-day echo with a gradient of ≥20 mmHg and ≥10 mmHg increase from 30 days. When the 30-day echo was not available, discharge was used. Expert adjudication of SVD was not performed.

[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.

SMART Trial Clinical Sites

- The Leeds Teaching Hospitals NHS, Leeds, UK
- Allegheny General Hospital, Pittsburgh, PA
- Kath Saint Johannes-Gesellschaft, Dortmund, Germany
- Helios Health Institute Standort Leipzig, Germany
- Montreal Heart Institute, Montreal, Canada
- Sentara Norfolk General Hospital, Norfolk, VA, USA
- Deutsches Herzzentrum München, Germany
- Hospital of the University of Pennsylvania, Philadelphia, PA
- Saint Paul's Hospital, Vancouver, Canada
- Herz- und Diabeteszentrum NRW - Ruhr-Universität Bochum, Bad Oeynhausen, Germany
- Lankenau Medical Center, Wynnewood, PA
- UPMC Pinnacle Harrisburg Campus, Mechanicsburg, PA
- Azienda Ospedaliero-Universitaria Pisana – Stabilimento di Cisanello, Pisa, Italy
- Tufts Medical Center, Boston, MA
- Clinique Pasteur, Toulouse, France
- Hospital Vall D'Hebron, Barcelona, Spain
- Spectrum Health Hospitals, Grand Rapids, MI
- Hillcrest Medical Center, Tulsa, OK
- Azienda Ospedaliera Universitaria Integrata Verona, Italy
- Centre Hospitalier Universitaire de Clermont-Ferrand - Gabriel-Montpied, Clermont Ferrand, France
- University Hospitals Cleveland Medical Center, OH
- Morton Plant Hospital, Clearwater, FL
- The Mount Sinai Hospital, NY, NY
- Saint Michaels Hospital, Toronto, Canada
- Sheba Medical Center, Ramat Gan, Israel
- The Heart Hospital Baylor Plano, TX
- J.W. Ruby Memorial Hospital, Morgantown, WV
- Saint Cloud Hospital, Saint Cloud, MN
- University of Florida, Gainesville, FL
- Toronto General Hospital, Toronto, Canada
- University of Pittsburgh Medical Center UPMC Presbyterian, Pittsburgh, PA
- NorthShore University Health System, Evanston, IL
- WellStar Kennestone Hospital, Marietta, GA
- Centro Hospitalar de Lisboa Ocidental, E.P.E. Hospital de Santa Cruz, Carnaxide, Portugal
- Ascension Saint John Hospital, Detroit, MI
- Rigshospitalet, København, Denmark
- MedStar Washington Hospital Center, Washington, DC
- Seton Medical Center Austin, TX
- WellSpan York Hospital, York, PA
- Emory University Hospital Midtown, Atlanta, GA
- Mission Hospital, Asheville, NC
- Universitätsklinikum Düsseldorf, Düsseldorf, Germany
- Yale New Haven Hospital, New Haven, CT
- University of Michigan Health System - University Hospital, Ann Arbor, MI
- Mayo Clinic, Rochester, MN
- Intermountain Saint George Regional Hospital, Saint George, UT
- University of Texas Health Sciences Center at Houston - Center for Advanced Heart Failure, Houston, TX
- Policlinico Di Sant'Orsola Malpighi, Bologna, Italy
- Advocate Christ Medical Center, Oak Lawn, IL
- Maastricht Universitair Medisch Centrum, Maastricht, Netherlands
- Vancouver Island Health Authority / Royal Jubilee Hospital, Victoria, Canada
- Helsinki University Hospital, Helsinki, Finland
- HealthPark Medical Center, Fort Myers, FL
- Hôpital Haut-Lévêque - CHU de Bordeaux, Pessac, France
- Missouri Baptist Medical Center, Saint Louis, MO
- Ichilov Medical Center Tel Aviv, Tel Aviv, Israel
- Morristown Medical Center, Morristown, NJ
- Los Robles Hospital & Medical Center, Thousand Oaks, CA
- Catharina Ziekenhuis, Eindhoven, Netherlands
- University of Iowa Hospitals and Clinic, Iowa City, IA
- Inova Fairfax Hospital, Falls Church, VA
- Cleveland Clinic, Cleveland, OH
- Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX
- Inselspital - Universitätsspital Bern, Bern, Switzerland
- Piedmont Atlanta Hospital, Atlanta, GA
- Ascension Via Christi Saint Francis, Wichita, KS
- Cedars Sinai Medical Center, Los Angeles, CA
- Universitätsklinikum Schleswig-Holstein - Campus Lübeck, Lübeck, Germany
- Scripps Green Hospital, La Jolla, CA
- NYU Langone Medical Center, NY, NY
- University of Virginia, Charlottesville, VA
- University of Kansas Medical Center, Kansas City, KS
- University of Colorado Hospital, Aurora, CO
- Saint Vincent Heart Center of Indiana, Indianapolis, IN
- Bethesda North Hospital, Cincinnati, OH
- Mount Sinai Medical Center, Miami Beach, FL
- TriStar Centennial Medical Center, Nashville, TN
- Royal Infirmary of Edinburgh, Edinburgh, UK
- The University of Texas Health Science Center at Houston, Houston, TX
- Charité – Universitätsmedizin Berlin, Berlin, Germany
- Universitätsklinikum Schleswig-Holstein - Campus Kiel, Kiel, Germany
- New York-Presbyterian Hospital/Weill Cornell Medical Center, NY, NY
- University of North Carolina Memorial Hospital, Chapel Hill, NC

Indications
The Medtronic Evolut™ PRO+, Evolut™ FX, and Evolut™ FX+ Systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Medtronic Evolut PRO+, Evolut FX, and Evolut FX+ Systems are indicated for use in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (e.g., STS predicted risk of operative mortality score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Contraindications
The Medtronic Evolut PRO+, Evolut FX, and Evolut FX+ Systems are contraindicated in patients who cannot tolerate Nitinol (titanium or nickel), gold (for Evolut FX and Evolut FX+ Systems alone), an anticoagulation/antiplatelet regimen, or who have active bacterial endocarditis or other active infections.

Warnings
General Implantation of the Evolut PRO+, Evolut FX, and Evolut FX+ Systems should be performed only by physicians who have received Medtronic Evolut PRO+, Evolut FX, or Evolut FX+ training. This procedure should only be performed where emergency aortic valve surgery can be performed promptly. Mechanical failure of the delivery catheter system and/or accessories may result in patient complications. *Transcatheter aortic valve (bioprosthesis)* Accelerated deterioration due to calcific degeneration of the bioprostheses may occur in: children, adolescents, or young adults; patients with altered calcium metabolism (e.g., chronic renal failure or hyperthyroidism).

Precautions
General Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up. The safety and effectiveness of the Evolut PRO+, Evolut FX, and Evolut FX+ Systems have not been evaluated in the pediatric population. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in the following patient populations: Patients who do not meet the criteria for symptomatic severe native aortic stenosis as defined: (1) symptomatic severe high-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient ≥ 40 mm Hg, or a peak aortic-jet velocity ≥ 4.0 m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient < 40 mm Hg, and a peak aortic-jet velocity < 4.0 m/s; with untreated, clinically significant coronary artery disease requiring revascularization; with a preexisting prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position if either the preexisting prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the preexisting prosthetic heart valve; patients with liver failure (Child-Pugh Class C); with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support; patients who are pregnant or breastfeeding. The safety and effectiveness of an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis have not been demonstrated. Implanting an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis in a degenerated surgical bioprosthetic valve (transcatheter aortic valve in surgical aortic valve [TAV-in-SAV]) should be avoided in the following conditions: The degenerated surgical bioprosthetic valve presents with: a significant concomitant paravalvular leak (between the prosthesis and the native annulus), is not securely fixed in the native annulus, or is not structurally intact (e.g., wire form frame fracture); partially detached leaflet that in the aortic position may obstruct a coronary ostium; stent frame with a manufacturer-labeled inner diameter < 17 mm. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in patient populations presenting with the following: Blood dyscrasias as defined as leukopenia (WBC < 1,000 cells/mm^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states; congenital unicuspid valve; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation [3-4+]); moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation; hypertrophic obstructive cardiomyopathy; new or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation; native aortic annulus size < 18 mm or > 30 mm per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size < 17 mm or > 30 mm; transarterial access unable to accommodate an 18 Fr introducer sheath or the 14 Fr equivalent Evolut PRO+ inline sheath when using model D-EVPROP2329US or Evolut FX Delivery Catheter System with inline sheath when using model D-EVOLUTFX-2329 or transarterial access unable to accommodate a 22 Fr introducer sheath or the 18 Fr equivalent Evolut PRO+ inline sheath when using model D-EVPROP34US or Evolut FX Delivery Catheter System with inline sheath when using model D-EVOLUTFX-34; prohibitive left ventricular outflow tract calcification; sinus of Valsalva anatomy that would prevent adequate coronary perfusion; significant aortopathy requiring ascending aortic replacement; moderate to severe mitral stenosis; severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%; symptomatic carotid or vertebral artery disease; and severe basal septal hypertrophy with an outflow gradient.

Before Use Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors. Damage may result from forceful handling of the catheter. Prevent kinking of the catheter when removing it from the packaging. The bioprosthesis size must be appropriate to fit the patient's anatomy. Proper sizing of the devices is the responsibility of the physician. Refer to the Instructions for Use for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed below. Patients must present with transarterial access vessel diameters of ≥ 5 mm when using models D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6 mm when using models D-EVPROP34US/D-EVOLUTFX-34, or patients must present with an ascending aortic (direct aortic) access site ≥ 60 mm from the basal plane for both systems. Implantation of the bioprosthesis should be avoided in patients with aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) of > 30° for right subclavian/axillary access or > 70° for femoral and left subclavian/axillary access. For subclavian access, patients with a patent left internal mammary artery (LIMA) graft must present with access vessel diameters that are either ≥ 5.5 mm when using models D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6.5 mm when using models D-EVPROP34US/D-EVOLUTFX-34. Use caution when using the subclavian/axillary approach in patients with a patent LIMA graft or patent RIMA graft. For direct aortic access, ensure the access site and trajectory are free of patent RIMA or a preexisting patent RIMA graft. For transfemoral access, use caution in patients who present with multiplanar curvature of the aorta, acute angulation of the aortic arch, an ascending aortic aneurysm, or severe calcification in the aorta and/or vasculature. If ≥ 2 of these factors are present, consider an alternative access route to prevent vascular complications. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established.

During Use If a misload is detected during fluoroscopic inspection, do not attempt to reload the bioprosthesis. Discard the entire system. Inflow crown overlap that has not ended before the 4th node within the capsule increases the risk of an infold upon deployment in constrained anatomies, particularly with moderate-severe levels of calcification and/or bicuspid condition. Do not attempt to direct load the valve. After the procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. After the procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Prior to the procedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. Fluoroscopic procedures are associated with the risk of radiation damage to the skin, which may be painful, disfiguring, and long-term. The safety and efficacy of an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events
Potential risks associated with the implantation of the Evolut PRO+, Evolut FX, or Evolut FX+ transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, or cardiac tamponade • coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) • cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention) • emergent surgical or transcatheter intervention (e.g., coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty) • prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement – prosthetic valve migration/embolization • prosthetic valve endocarditis • prosthetic valve thrombosis • delivery catheter system malfunction resulting in the need for additional recrossing of the aortic valve and prolonged procedural time • delivery catheter system component migration/embolization • stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits • individual organ (e.g., cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure • major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding) • vascular access-related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, or stenosis) • mitral valve regurgitation or injury • conduction system disturbances (e.g., atrioventricular node block, left bundle-branch block, asystole), which may require a permanent pacemaker • infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • General surgical risks applicable to transcatheter aortic valve implantation: • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

Please reference the Evolut PRO+, Evolut FX, and Evolut FX+ Instructions for Use for more information regarding indications, warnings, precautions, and potential adverse events.

Caution: Federal Law (USA) restricts these devices to the sale by or on the order of a physician.

The commercial name of the Evolut™ PRO+ device is Medtronic Evolut™ PRO+ System, the commercial name of the Evolut™ FX device is Medtronic Evolut™ FX System, and the commercial name of the Evolut™ FX+ device is Medtronic Evolut™ FX+ System.

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