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Medical Technology

Getting smarter on the SMART trial – data coming April 7th at ACC

Industry Overview

What we know about SMART trial and what matters

With the SMART trial 1-year results coming up as a late-breaking session at ACC on April 7th, we go over trial details and our expectations based on prior trials and doc feedback. MDT designed the SMART trial to try and demonstrate clinical non-inferiority and hemodynamic superiority of its Evolut TAVR vs EW's Sapien TAVR. Our doctor feedback suggests these data at 1 year are unlikely to change share and it will take longer term data with benefits on hard endpoints to drive meaningful share shifts.

Hemo good but hard end points will take more time

Based on data we have seen from previous trials/registries MDT could demonstrate superior 1 year hemodynamics (bioprosthetic valve dysfunction endpoint). The hard end point (mortality, disabling stroke, heart failure rehospitalizations) is likely statistically non-inferior; however, numerically if MDT is better/worse is harder to call at 1 year based on other data. We looked at every head-to-head study/registry we could find.

Other trials to look at - see inside for a lot more details

FRANCE-TAVI registry showed superior hemodynamic performance with CoreValve at 1-year in patients with small annuli vs Sapien. In **CHOICE study** MDT's hemodynamic endpoints were better with one metric hitting stat sig at 1 year and both at 5 years. CHOICE showed no statistically significant difference in hard endpoints but numerically, at 1-year, MDT was better on deaths and strokes but worse on hospitalizations. **PRAGMATIC Plus Initiative** showed no stat sig difference in hard endpoints but numerically MDT was higher in deaths. A **French hospital database** showed higher deaths and rehospitalizations in MDT's Evolut (strokes were same).

Doctor perspectives on SMART; longer term data needed

We recently spoke with an interventional cardiologist who expects the SMART trial to show EW's Sapien having a higher gradient at 1-year but doesn't think results will translate to more use of MDT's Evolut because to see a clinically meaningful impact of a high gradient longer term data is needed. He notes no study so far has shown gradient post-procedure affecting mortality at 1-year. Other quotes we found from TCT presentations talk about the 5-year SMART results giving us a sense of more definitive answers but not the 1-year results.

SMART trial details – 700 patients at 90 sites globally

SMART is a prospective, multi-center, international, randomized controlled post-market trial. The trial will be conducted in ~700 subjects at 90 sites globally. Patients were randomized 1:1 to receive TAVR with either Medtronic's self-expanding Evolut valve, or an Edwards balloon-expandable Sapien valve. The primary clinical outcome composite endpoint is defined as mortality, disabling stroke or heart failure rehospitalization and the co-primary valve function composite endpoint is defined as bioprosthetic valve dysfunction at 12 months. Inclusion criteria include severe aortic stenosis and aortic valve annulus area of ≤430 mm2 based on multi-detector computed tomography.

We have a Buy on Medtronic (MDT) and are Neutral on Edwards Lifesciences (EW).

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Glossary
ACC = American College of Cardiology
EW = Edwards Lifesciences
MDT = Medtronic
SMART = SMall Annuli Randomized To Evolut or SAPIEN
TAVR = transcatheter aortic valve replacement

Refer to important disclosures on page 13 to 17. Analyst Certification on page 12. Price Objective Basis/Risk on page 11.
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Summary of what to expect from SMART

SMART trial ... MDT vs EW TAVR head to head for small aortic valve annulus

Medtronic's Evolut, a self-expanding valve (SEV), and Edwards' Sapien, a balloon expandable valve (BEV), are the most widely available commercial TAVR devices. The SMART trial is being conducted to compare MDT's self-expanding Evolut Pro/Pro+ vs EW's balloon expanding Sapien 3/Sapien 3 Ultra in patients with symptomatic severe native aortic stenosis with a small aortic valve annulus to better understand the performance of these more recent devices in this population. Since SMART is the first of its kind head-to-head randomized control trial of these newer valves, the results could be used to help physicians select appropriate TAVR devices for patients with small annuli.

The population in SMART roughly a third of TAVR market

Patients with small aortic valve annuli are typically female and are often underrepresented in clinical trials but represent one third of the TAVR population (MDT has even said its closer to 40%).

Why did MDT decide to run this trial?

Hemodynamic differences have been shown to be more pronounced in patients with small annuli. And previous studies/registries have shown improved hemodynamics with self-expanding valves vs balloon-expandable valves. MDT likely has the belief that over time the better hemodynamics will lead to better outcomes on hard endpoints. And the population this is likely most seen in is the small annuli population (hence why the study was focused on this population only).

1-year SMART data: both hard endpoints and valve function composite

At ACC in April we will see the 1-year data from the SMART trial on the primary endpoints. The primary clinical outcome composite endpoint is defined as mortality, disabling stroke or heart failure rehospitalization represented as a percent of participants at 1-year. The co-primary valve function composite endpoint is defined as bioprosthetic valve dysfunction at 12 months.

Other trials suggest MDT better hemodynamics but not in hard endpoints

Below we look at other trials to get a sense for what to expect. Based on data we have seen from previous trials/registries we expect Evolut to show better hemodynamics vs Sapien but no statistically significant difference in hard clinical end points. We note it is difficult to compare different trials/registries for multiple reasons including but not limited to older-generation devices studied, differences in how the trials were conducted, and differences in endpoints.

CHOICE study: MDT's hemodynamic endpoints better; no stat sig difference in hard endpoints but numerically, at 1-year, MDT was better on deaths and strokes but worse on hospitalizations.

CHOICE: The CHOICE trial was designed to compare device performance of Edwards' valve (Sapien XT) vs Medtronic's valve (CoreValve). At one-year the Edwards' valve group had a higher device success rate but clinical outcomes (including all-cause death, cardiovascular death, stroke, and repeat hospitalizations for heart failure) after TAVR with Edwards' valve and Medtronic's were not statistically significant. Five-year results also showed clinical outcomes after between the two groups were not statistically significantly different, with limited statistical power. At 5-years forward flow hemodynamics were significantly better with Medtronic's valve.

At 1 year the rates of death of any cause (Edwards: 17.4% vs Medtronic: 12.8%; p=0.37) and of cardiovascular causes (Edwards: 12.4% vs Medtronic: 9.4%; p=0.54) were not statistically significantly different in the Edwards vs Medtronic groups. The frequencies of all strokes (Edwards: 9.1% vs Medtronic: 3.4%; p=0.11) and repeat hospitalization for heart failure (Edwards: 7.4% vs Medtronic: 12.8%; p=0.19) did not statistically significantly differ between the 2 groups. At five years there were no statistically

significant differences between Edwards and Medtronic in the cumulative incidence of death from any cause (Edwards 53.4% vs Medtronic 47.6%; p = 0.38), death from cardiovascular causes (Edwards 31.6% vs Medtronic 21.5%; p = 0.12), all strokes (Edwards 17.5% vs Medtronic 16.5%; p = 0.73) and repeat hospitalization for heart failure (Edwards 28.9% vs Medtronic 22.5%; p = 0.75). However, forward flow hemodynamics were significantly better with Medtronic. Medtronic patients had larger prosthetic valve area (Edwards 1.6 ± 0.5 cm2 vs Medtronic 1.9 ± 0.5 cm2; p = 0.02) with a lower mean transprosthetic gradient (Edwards 12.2 ± 8.7 mm Hg vs Medtronic 6.9 ± 2.7 mm Hg; p = 0.001) at 5 years.

PRAGMATIC Plus: 1 year no difference in hard endpoints but numerically MDT was higher in deaths

PRAGMATIC Plus Initiative: The aim of this study was to compare outcomes after TAVR with Medtronic CoreValve versus the Edwards Sapien/Sapien XT for severe aortic stenosis. The data from databases of 4 experienced European centers were pooled and analyzed. At 1 year, there were no differences in all-cause mortality (CoreValve 16.2% vs Sapien 12.3%; p = 0.266) or cardiovascular mortality (CoreValve 8.3% vs Sapien 7.4%; p = 0.713). No difference was also observed in the combined efficacy endpoint (CoreValve 32.4% vs Sapien 25.6%; p=0.135).

French database: EW arm had fewer deaths and hospitalizations at 1 year

French administrative hospital-discharge database: This study collected data from the French administrative hospital-discharge database for all consecutive patients treated with a TAVR device commercialized in France between 2014 and 2018. The objective of this study was to analyze the outcomes of TAVR with Sapien 3 versus Evolut R at a nationwide level in France. The mean follow-up duration was 358 days. All-cause death was lower in the Sapien group with an incidence rate of 14.4% vs 16.4% in the Evolut R group. The incidence of cardiovascular death was also lower in the Sapien group, incidence rate of 6.4% vs 7.9% in the Evolut R group. The rehospitalization rate for heart failure was also lower in the Sapien group with an incidence rate of 19.5% vs 23.2% in the Evolut R group. Rates of all-cause stroke were similar (5% in Sapien vs 5.3% in Evolut R groups).

France TAVI - MDT had superior hemodynamics at 1-year

FRANCE-TAVI Registry sub-study: In September 2022, a sub-study of results from the FRANCE-TAVI registry were presented at TCT on small aortic annulus patients who received either a Evolut R/Pro or Sapien 3. The Evolut group showed superior 1-year hemodynamic valve performance. At 1 year, those with Sapien had a higher mean gradient (13.74 mmHg) than those with a Evolut (8.62 mmHg, p<0.001). The Sapien group had smaller indexed EOA (0.9 cm2/m2) compared with the Evolut group (1.11 cm2/m2, p<0.001).

Expert feedback to France TAVI data presentation at TCT 2022

When results were presented at TCT 2022, expert feedback suggested these findings were not enough to suggest all patients with small annuli should be treated with SEV. Doctors noted it is difficult to make definitive decisions on propensity-matched analysis and it should be validated with long-term follow up in a prospective trial. On patient prosthesis mismatch specifically one doc noted "And while patient-prosthesis mismatch may not be so important in very elderly patients, many of whom are in this registry, we know from the surgical data that PPM is important in younger patients." Panelists agreed that the SMART trial will hopefully give more definitive answers. David Cohen, MD, said the data places added pressure on the SMART trial noting "And not of the 1-year results, which are going to be presented first from that trial, but the 5-year results which will give us a sense of whether this really makes a difference for patients, especially patients who are not in the extreme elderly group who may expect to live for 5-10 years," he clarified. "We need that desperately to really know what is best for that challenging group because the PPM rates here are not trivial."

SMART trial rationale and design paper highlights

Endpoints

The SMART trial has two powered primary endpoints:

1. Clinical outcome composite endpoint at 12 months:
    a. Mortality, disabling stroke or heart failure rehospitalization
2. Valve function composite endpoint of bioprosthetic valve dysfunction at 12 mo. Any of the following:
    a. Hemodynamic structural valve dysfunction (HSVD): hemodynamic mean gradient ≥20 mmHg
    b. Non-structural valve dysfunction (NSVD): severe prosthesis-patient mismatch (PPM), ≥moderate aortic regurgitation
    c. Thrombosis
    d. Endocarditis
    e. Aortic valve re-intervention
    f. MDCT, multidetector computed tomography; SMART, SMall Annuli Randomized To Evolut or SAPIEN
    g. NYHA, New York Heart Association; TAVR , transcatheter aortic valve replacement; KCCQ, Kansas City Cardiomyopathy Questionnaire

The powered secondary endpoints assessed hierarchically for the trial are: (1) Hemodynamic mean gradient as a continuous variable at 12 months, (2) Effective orifice area (EOA) as a continuous variable at 12 months, (3) HSVD at 12 months, (4) BVD in female subjects at 12 months, and (5) Moderate or severe prosthesis-patient mismatch. at 30 days. Non-powered secondary end- points include device success at 30 days, hospital read- mission at 30 days, 6-minute walk test, quality of life measures (Kansas City Cardiomyopathy Questionnaire [KCCQ] and EQ-5D), and echocardiographic measurements, all through 5 years.

Sample size and methodology

The trial sample size will include up to 700 as-treated subjects. Non-inferiority of the first primary composite clinical event rate will be evaluated using the Z-test based on the event rates and Greenwood standard errors estimated from the Kaplan-Meier method with one-sided alpha 0.05 and non-inferiority margin of 8%, assuming a rate of 16% for the primary composite clinical endpoint.

The second co-primary efficacy endpoint is the valve function composite endpoint including BVD at 12 months. The hypothesis is that the Medtronic self-expanding valve (SEV) is superior to the Edwards balloon-expandable valve (BEV) and will be evaluated with a Z-test based on the event rates and Greenwood standard errors estimated from the Kaplan-Meier method with one-sided alpha 0.025. Hypothesis testing of the powered secondary endpoints will only occur when both primary endpoints are met. Each of the powered secondary endpoints will evaluate the superiority of the Medtronic SEV to Edwards BEV and will be tested hierarchically in a pre-specified order at one-sided alpha 0.025 to control the overall type I error. Order of testing of the powered secondary endpoints is as follows: hemodynamic mean gradient as continuous variable at 12 months, effective orifice area as continuous variable at 12 months, HSVD at 12 months, BVD at 12 months, followed by moderate or severe PPM at 30 days.

What prior trials/registries have shown

CHOICE trial and CHOICE-Extend registry

CHOICE trial overview

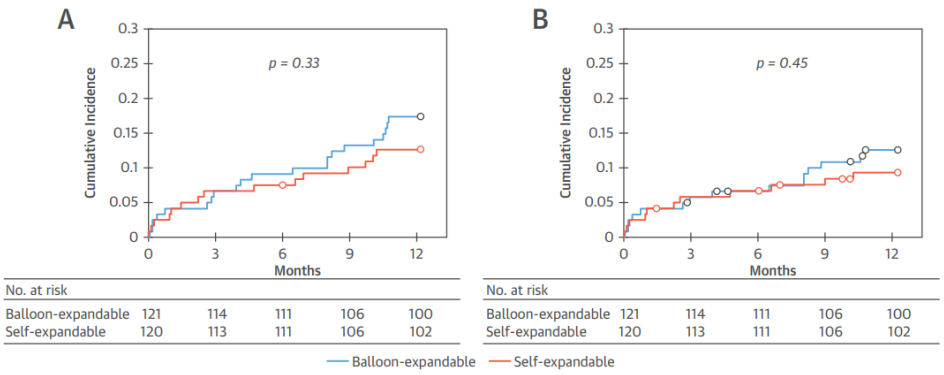
The CHOICE trial was designed to compare device performance of a balloon-expandable valve (BEV) vs a self-expanding valve (SEV). The trial was an open-label, multicenter randomized trial in Germany that enrolled 241 high risk patients with severe symptomatic aortic stenosis undergoing TAVR with either Medtronic's CoreValve (BEV) or Edwards Sapien XT (SEV). The primary end point was device success, which is a composite end point including successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only 1 valve implanted in the proper anatomical location. Secondary end points included cardiovascular mortality, bleeding and vascular complications, postprocedural pacemaker placement, and a combined safety end point at 30 days, including all-cause mortality, major stroke, and other serious complications. Patients were followed up to 5 years with assessment of clinical outcomes, and echocardiographic evaluation of valve function and durability.

At one-year the BEV group had a higher device success rate but clinical outcomes after TAVR with BEV and SEV were not statistically significant. Five-year results showed clinical outcomes after TAVR with BEV and SEV were not statistically significantly different, with limited statistical power. Forward flow hemodynamics were significantly better with Medtronic's SEV. Moderate or severe structural valve deterioration was uncommon but occurred more frequently with the BE valve.

CHOICE 1-year results show not stat sig different clinical outcomes in BEV vs SEV

At 1 year the rates of death of any cause (BEV: 17.4% vs SEV: 12.8%; p=0.37) and of cardiovascular causes (BEV: 12.4% vs SEV: 9.4%; p=0.54) were not statistically significantly different in the BEV vs SEV groups. The frequencies of all strokes (BEV: 9.1% vs SEV: 3.4%; p=0.11) and repeat hospitalization for heart failure (BEV: 7.4% vs SEV: 12.8%; p=0.19) did not statistically significantly differ between the 2 groups. Results suggest mortality was not statistically significantly different at 1 year, but clinical events with a strong impact on mortality tended to be different between both devices (numerically lower repeat hospitalizations for heart failure but higher stroke rates with BEV). Elevated transvalvular gradients during follow-up were observed in 4 patients in the BEV group (BEV: 3.4% vs SEV: 0%; p=0.12) and all were resolved with anticoagulant therapy, suggesting a thrombotic etiology. More than mild paravalvular regurgitation was more frequent in the SEV group (BEV: 1.1% vs SEV: 12.1%; p=0.005).

Exhibit 1: CHOICE 1-year time to event curves for all-cause and cardiovascular mortality
The chart on the left shows cumulative incidence curves for all-cause mortality by device type. The chart on the right shows cumulative incidence curves for cardiovascular mortality by device type. At 1 year the rates of death of any cause (BEV: 17.4% vs SEV: 12.8%; p=0.37) and of cardiovascular causes (BEV: 12.4% vs SEV: 9.4%; p=0.54) were not statistically significantly different in the BEV vs SEV groups.



Source: JACC. 1-Year Outcomes After Transcatheter Aortic Valve Replacement With Balloon-Expandable Versus Self-Expandable Valves
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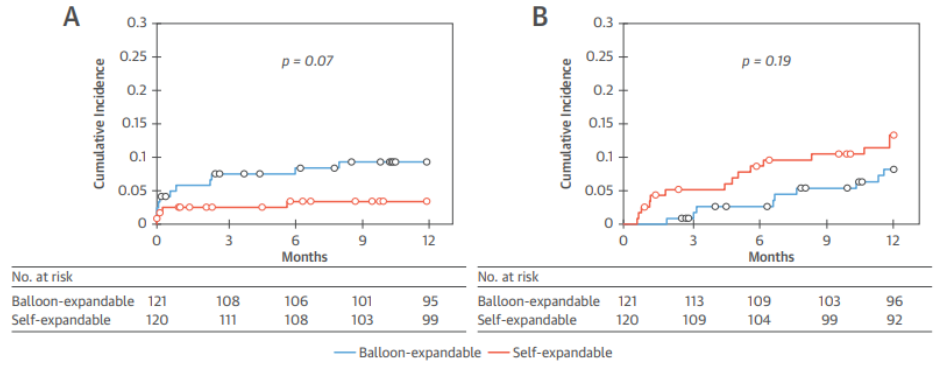
Exhibit 2: CHOICE 1-year time to event curves for all strokes and rehospitalization for heart failure
The chart on the left shows cumulative incidence curves for stroke by device type. The chart on the right shows cumulative incidence curves for rehospitalization for heart failure by device type. The frequencies of all strokes (BEV: 9.1% vs SEV: 3.4%; p=0.11) and repeat hospitalization for heart failure (BEV: 7.4% vs SEV: 12.8%; p=0.19) did not statistically significantly differ between the 2 groups.



Source: JACC. 1-Year Outcomes After Transcatheter Aortic Valve Replacement With Balloon-Expandable Versus Self-Expandable Valves.
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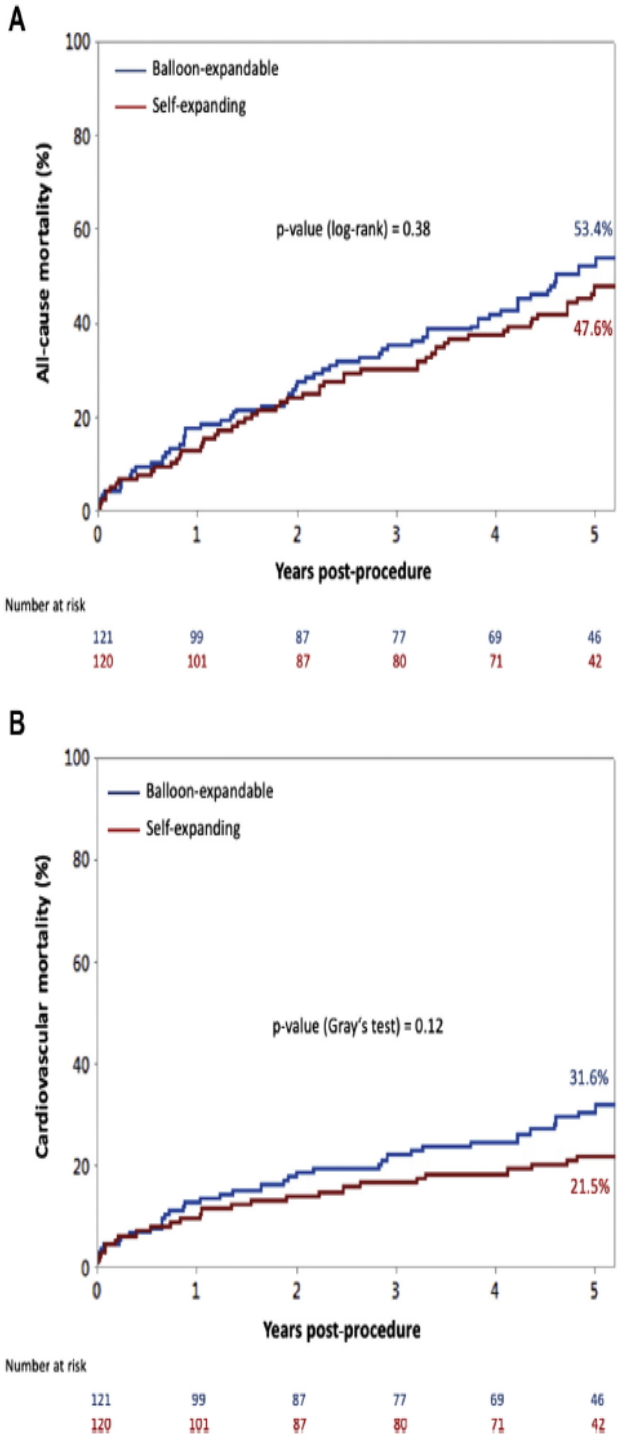
CHOICE 5-year data showed no stat sig difference in clinical outcomes but significantly better hemodynamics with SEV

At five years there were no statistically significant differences between BEV and SEV in the cumulative incidence of death from any cause (BEV 53.4% vs. SEV 47.6%; p = 0.38), death from cardiovascular causes (BEV 31.6% vs. SEV 21.5%; p = 0.12), all strokes (BSV 17.5% vs. SEV 16.5%; p = 0.73) and repeat hospitalization for heart failure (BEV 28.9% vs. SEV 22.5%; p = 0.75). However, forward flow hemodynamics were significantly better with SEV. SEV patients had larger prosthetic valve area (BEV 1.6 ± 0.5 cm2 vs. SEV 1.9 ± 0.5 cm2; p = 0.02) with a lower mean transprosthetic gradient (BEV 12.2 ± 8.7 mm Hg vs SEV 6.9 ± 2.7 mm Hg; p = 0.001) at 5 years. No differences were observed in the rates of paravalvular regurgitation.

Exhibit 3: CHOICE 5-year time to event curves for all-cause mortality and cardiovascular mortality

The chart on top shows all-cause mortality and the chart on the bottom shows cardiovascular mortality. At five years there were no statistically significant differences between BEV and SEV in the cumulative incidence of death from any cause (53.4% vs. 47.6%; p = 0.38) or death from cardiovascular causes (31.6% vs. 21.5%; p = 0.12).



Source: JACC. 5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves

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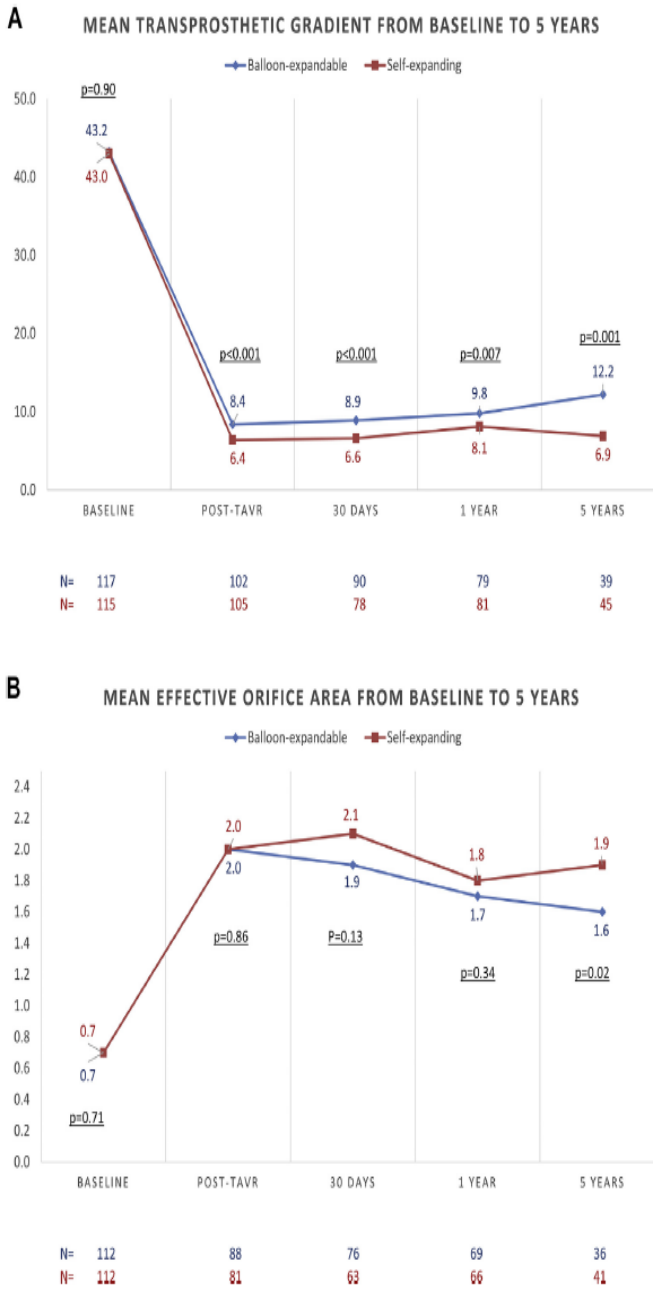
Exhibit 4: CHOICE forward flow hemodynamics from baseline to 5 years

Forward flow hemodynamics were significantly better with SEV. SEV patients had larger prosthetic valve area (1.6 ± 0.5 cm2 vs. 1.9 ± 0.5 cm2; p = 0.02) with a lower mean transprosthetic gradient (12.2 ± 8.7 mm Hg vs. 6.9 ± 2.7 mm Hg; p = 0.001) at 5 years



Source: JACC. 5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves

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Insights from CHOICE and CHOICE-Extend registry in small annuli patients

A study was conducted to compare SEV and BEV in large versus small aortic valve annuli. The study looks at patients undergoing TAVR in the randomized CHOICE trial and the non-randomized CHOICE-Extend registry. Patients were stratified according to aortic valve annular mean diameter into those with large (>23 mm) or small (≤23 mm) annuli. The CHOICE-Extend registry is a nonrandomized, prospective registry enrolling patients undergoing TAVR using a third-generation Evolut R (n=100) or Sapien 3 (n=334). The choice of valve was left to the discretion of the operator. The results concluded bioprosthetic valve performance in patients with small aortic valve annuli seems to be better with SEV than with BEV. The improved performance includes comparable prosthetic valve regurgitation (PVR) and less patient prosthesis mismatch (PPM).

The results from the CHOICE trial show the SAPIEN XT is associated with less PVR than the CoreValve in patients with a large annulus, but not in those with a small annulus. In the CHOICE-Extend registry the rate of PVR did not significantly differ between Sapien 3 vs Evolut R, regardless of the annulus size. However, the rate of PPM was indeed 2-fold higher in the SAPIEN 3 versus the Evolut R in both small and large annulus categories. These findings suggest that the type and generation of THV as well as the size of the patient's aortic annulus are the main factors determining the incidence of PVR and PPM following TAVR.

Exhibit 5: CHOICE and CHOICE-Extend: Rates of PVR and PPM According to Aortic Annulus Size
These trials showed bioprosthetic valve performance in patients with small aortic valve annuli seems to be better with SEV than with BEV. The improved performance includes comparable prosthetic valve regurgitation (PVR) and less patient prosthesis mismatch (PPM).

CHOICE Trial						
	Small Annuli			Large Annuli		
Outcome Measurement	CoreValve	SAPIEN XT	p-value	CoreValve	SAPIEN XT	p-value
Paravalvular Regurgitation (PVR)	56.7%	46.7%	0.22	60.4%	47.5%	0.006
Prosthesis Patient Mismatch (PPM)	15.4%	23.3%	0.52	16.2%	26.1%	0.30
CHOICE-Extend Registry						
	Small Annuli			Large Annuli		
Outcome Measurement	Evolut R	Sapien 3	p-value	Evolut R	Sapien 3	p-value
Paravalvular Regurgitation (PVR)	47.1%	43.8%	0.84	41.7%	32.6%	0.35
Prosthesis Patient Mismatch (PPM)	33.3%	59.2%	0.029	21.7%	43.2%	0.008

Source: JACC

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PRAGMATIC Plus Initiative

The aim of this study was to compare outcomes after TAVR with Medtronic CoreValve versus the Edwards Sapien/Sapien XT for severe aortic stenosis. The data from databases of 4 experienced European centers were pooled and analyzed. Due to differences in baseline clinical characteristics, propensity score matching was performed. In total, 793 patients were included with 453 (57.1%) patients treated with CoreValve and 340 (42.9%) with Sapien. After propensity matching, 204 patients were identified in each group. Study objectives were Valve Academic Research Consortium outcomes at 30 days and 1 year.

At 1 year, there were no differences in all-cause mortality (CoreValve 16.2% vs Sapien 12.3%; p = 0.266) or cardiovascular mortality (CoreValve 8.3% vs Sapien 7.4%; p = 0.713). No difference was also observed in the combined efficacy endpoint (CoreValve 32.4% vs Sapien 25.6%; p=0.135). Results show no differences between the 2 devices at the adjusted analysis in Valve Academic Research Consortium outcomes.

French administrative hospital-discharge database

This study collected data from the French administrative hospital-discharge database for all consecutive patients treated with a TAVR device commercialized in France between 2014 and 2018. Propensity score matching was used for the analysis of outcomes during follow-up. The objective of this study was to analyze the outcomes of TAVR according to Sapien 3 versus Evolut R at a nationwide level in France. A total of 31,113 patients

treated with either Sapien 3 or Evolut TAVR were found in the database. After matching on baseline characteristics, 20, 918 patients were analyzed or 10,459 in each group. The mean follow-up duration was 358 days.

All-cause death was lower in the Sapien group with an incidence rate of 14.4% vs 16.4% in the Evolut R group. The incidence of cardiovascular death was also lower in the Sapien group, incidence rate of 6.4% vs 7.9% in the Evolut R group. The rehospitalization rate for heart failure was also lower in the Sapien group with an incidence rate of 19.5% vs 23.2% in the Evolut R group. Rates of all-cause stroke were similar (5% in Sapien vs 5.3% in Evolut R groups).

FRANCE-TAVI registry

Summary of FRANCE-TAVI sub-study in small annuli patients

In September 2022, a sub-study of results from the FRANCE-TAVI registry were presented at TCT on small aortic annulus patients. This was the first large all-comer real-world study comparing self-expanding valves (SEV) with Evolut R/Pro and balloon-expanding valves (BEV) with Sapien 3 in small aortic annuli in terms of hemodynamic performances and impact on clinical outcomes. Supra-annular SEV showed superior 1-year hemodynamic valve performance and BEV was an independent predictor of 1-year moderate or severe patient prosthesis mismatch (PPM). 1-year severe PPM was an independent predictor of 3-year all-cause mortality. Results suggest patients with severe PPM at 1-year have a twofold relative hazard for all-cause mortality at 3 years.

Sub-study details and design

The France-TAVI Registry included 47,494 patients of whom 19,204 had small annuli and data was presented on 1,195 patients (data was not available for all small annuli patients and those with valves other than Evolut and Sapien were excluded). A small aortic annulus was defined as < 23 mm diameter or indexed diameter <12 mm/m2. The sub-study looked at third-generation valves including EvolutR/Pro from Medtronic or Sapien 3 from Edwards. The primary endpoint was moderate or severe patient-prosthesis mismatch at 1-year (predictors) and secondary endpoint was 3-year all-cause mortality (predictors), mean gradient, and effective orifice area at 1-year. The study used a propensity score analysis including 10 anatomical, clinical and procedural variables. Patients treated with Medtronic's self-expanding valve were matched 1:3 with patients treated with balloon-expanding. Propensity matching was also conducted by using the propensity score to generate an inverse probability treatment weighting (IPTW) as a sensitivity analysis. After matching, both cohorts were comparable in terms of demographics and basic echocardiographic and CT data as well as procedural and postprocedural results.

Detailed results showing superior SEV hemodynamic performance vs BEV

The hemodynamic performance was significantly better with the supra-annular SEV compared with BEV in terms of lower mean gradient and larger index effective orifice area. At 1 year, those with BEV had a higher mean gradient (13.74 mmHg) than those with a SEV (8.62 mmHg, p<0.001). The BEV group had smaller indexed EOA (0.9 cm2/m2) compared with the SEV group (1.11 cm2/m2, p<0.001).

The rates of severe PPM at 1 year were significantly higher in the BEV group (8.5%) than in the SEV (3,0%, p<0.001) group before and after matching. The significance also held in the matched population (SEV 3.5% vs. BEV 8.0%, p<0.001). In both the matched and IPTW populations, implantation of a BEV was an independent predictor of moderate to severe PPM at 1 year compared with a SEV (matched: HR 2.94, 95% CI 1.79-4.76, p=0.01; IPTW: HR 2.86, 95% CI 1.92-4.35, p=0.01). Severe PPM at 1 year was an independent predictor of 3-year all-cause mortality in both the matched (HR 2.01, 95% CI 1.02-3.95; p=0.04) and IPTW (HR 2.41; 95% CI 1.31-4.44; p=0.004) analyses. Overall, BEV was an independent predictor of moderate or severe PPM.

Expert feedback to data presentation at TCT 2022

When results were presented at TCT 2022, expert feedback suggested these findings were not enough to suggest all patients with small annuli should be treated with SEV. Doctors noted it is difficult to make definitive decisions on propensity-matched analysis and it should be validated with long-term follow up in a prospective trial. On patient prosthesis mismatch specifically one doc noted: "And while patient-prosthesis mismatch may not be so important in very elderly patients, many of whom are in this registry, we know from the surgical data that PPM is important in younger patients." Panelists agreed that the SMART trial will hopefully give more definitive answers. David Cohen, MD, said the data places added pressure on the SMART trial noting "And not of the 1-year results, which are going to be presented first from that trial, but the 5-year results which will give us a sense of whether this really makes a difference for patients, especially patients who are not in the extreme elderly group who may expect to live for 5-10 years," he clarified. "We need that desperately to really know what is best for that challenging group because the PPM rates here are not trivial."

SOLVE-TAVI trial

SOLVE-TAVI is a multicenter, open-label, 2x2 factorial, randomized trial of 447 patients with aortic stenosis undergoing TAVR comparing Medtronic's self-expanding valve (SEV), Evolut R, with Edwards balloon-expandable (BEV) Sapien 3. The primary efficacy composite endpoint of all-cause mortality, stroke, moderate/severe prosthetic valve regurgitation, and permanent pacemaker implantation at 30 days was powered for equivalence (equivalence margin 10% with significance level 0.05). The primary composite endpoint occurred in 28.4% of SEV patients and 26.1% of BEV patients meeting the prespecified criteria of equivalence. Event rates for the individual components were as follows in SEV vs BEV: all-cause mortality 3.2% vs. 2.3%; p-equivalence<0.001, stroke 0.5% vs. 4.7%; p-equivalence=0.003, moderate/severe paravalvular leak 3.4% vs. 1.5%; p-equivalence=0.0001, and permanent pacemaker implantation 23.0% vs 19.2%; p-equivalence=0.06. The results conclude In patients with aortic stenosis undergoing transfemoral TAVI, newer generation SEV and BEV are equivalent for the primary valve-related efficacy endpoint.

Exhibit 6: Stocks mentioned
Prices and ratings for stocks mentioned in this report

BofA Ticker	Bloomberg ticker	Company name	Price	Rating
EW	EW US	Edwards Lifesciences	US$ 86.04	B-2-9
MDT	MDT US	Medtronic	US$ 84.72	B-1-7

Source: BofA Global Research

BofA GLOBAL RESEARCH

Price objective basis & risk

Edwards Lifesciences (EW)

Our PO of $97 is based on a 32x PE multiple on our 2025E EPS. We assume with high single digit revenue growth, good margins/cash flow/balance sheet and some upside TAM potential, EW deserves a 32x forward EPS (two turn premium to SYK).

Risks to our PO are: 1) the TAVR market slows if the TAM is not as big as we expect or new populations do not benefit from TAVR, 2) the mitral/tricuspid market does not materialize, 3) EW faces setbacks with its clinical trials or pipeline, 4) the TAVR market becomes more competitive.

Medtronic (MDT)

Our $100 price objective for MDT is based on 18.5x our calendar 2024E EPS. This multiple is in line with the average medtech multiple 2023 EPS and is warranted for a company with a mid single digit (MSD) growth profile that competes in MDT's markets.

Downside risks to our price objective are 1) RDN data disappoints, 2) slower-than-expected revenue growth from new products, 3) other pipeline setbacks, 4) increased competition or share losses, and 5) China VBP.

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I, Travis Steed, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Medical Technology & Devices Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
BUY				
	Abbott Laboratories	ABT	ABT US	Travis Steed
	Axonics	AXNX	AXNX US	Travis Steed
	Bausch & Lomb	BLCO	BLCO US	Craig Bijou
	Becton Dickinson	BDX	BDX US	Travis Steed
	Boston Scientific	BSX	BSX US	Travis Steed
	Dexcom	DXCM	DXCM US	Travis Steed
	Inari Medical	NARI	NARI US	Travis Steed
	Inspire Medical	INSP	INSP US	Travis Steed
	Insulet	PODD	PODD US	Travis Steed
	Intuitive Surgical	ISRG	ISRG US	Travis Steed
	Medtronic	MDT	MDT US	Travis Steed
	Paragon 28	FNA	FNA US	Craig Bijou
	Procept BioRobotics Corporation	PRCT	PRCT US	Craig Bijou
	RxSight	RXST	RXST US	Craig Bijou
	Shockwave Medical	SWAV	SWAV US	Travis Steed
	Si-Bone	SIBN	SIBN US	Craig Bijou
	Stryker	SYK	SYK US	Travis Steed
	The Cooper Companies	COO	COO US	Craig Bijou
NEUTRAL				
	Baxter International Inc	BAX	BAX US	Travis Steed
	Conmed	CNMD	CNMD US	Travis Steed
	Edwards Lifesciences	EW	EW US	Travis Steed
	Integer Holdings Corporation	ITGR	ITGR US	Craig Bijou
	Merit Medical	MMSI	MMSI US	Craig Bijou
	Teleflex Incorporated	TFX	TFX US	Craig Bijou
	Zimmer Biomet	ZBH	ZBH US	Travis Steed
UNDERPERFORM				
	Embecta	EMBC	EMBC US	Travis Steed
	Globus Medical	GMED	GMED US	Craig Bijou
	Integra Lifesciences	IART	IART US	Craig Bijou
	Nevro	NVRO	NVRO US	Travis Steed
	Outset Medical	OM	OM US	Travis Steed
	Silk Road Medical	SILK	SILK US	Travis Steed
	Tandem Diabetes Care	TNDM	TNDM US	Travis Steed
RSTR				
	GE HealthCare	GEHC	GEHC US	Craig Bijou

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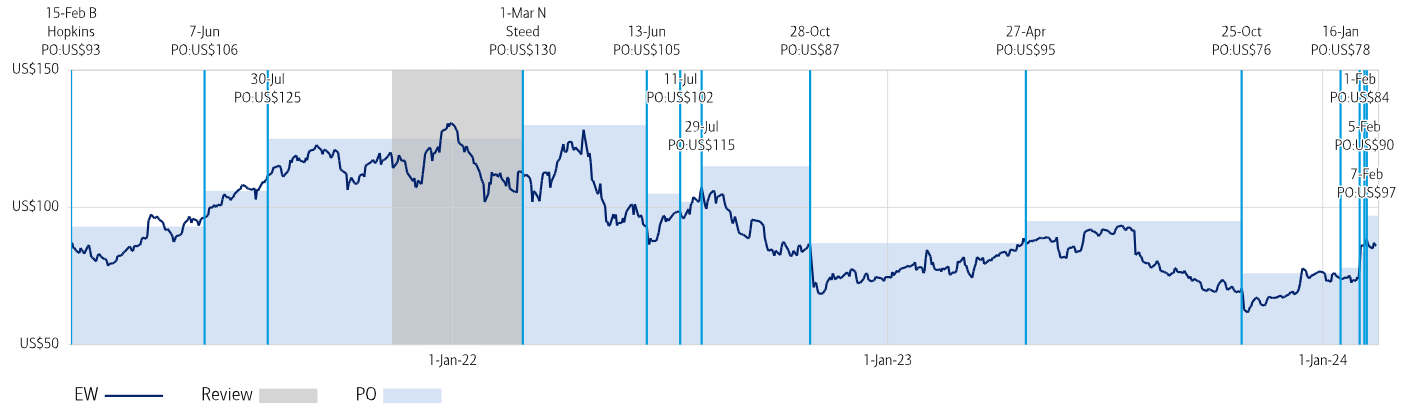
Important Disclosures

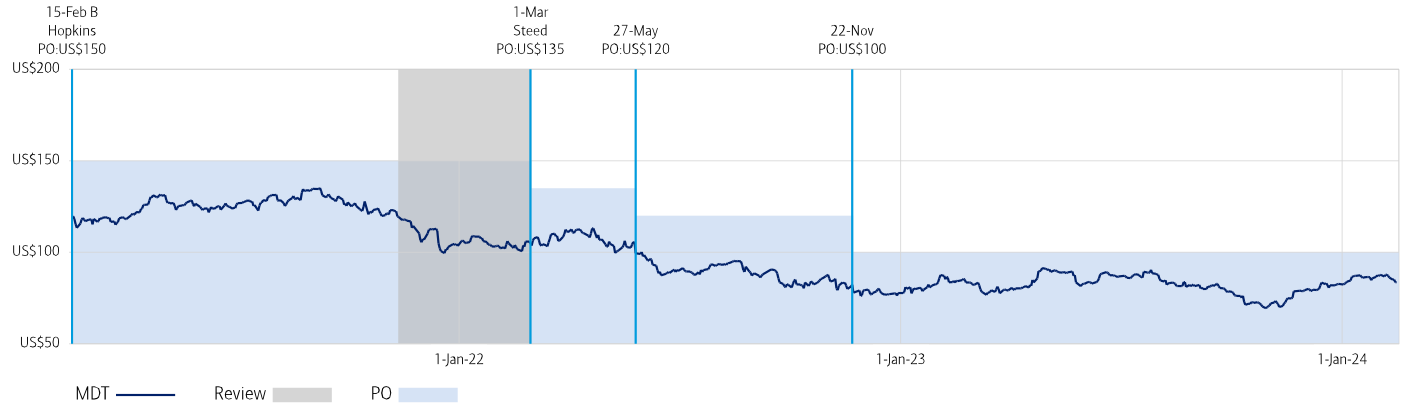
Edwards Lifesciences (EW) Price Chart



B: Buy, N: Neutral, U: Underperform, PO: Price Objective, NA: No longer valid, NR: No Rating

The Investment Opinion System is contained at the end of the report under the heading "Fundamental Equity Opinion Key". Dark grey shading indicates the security is restricted with the opinion suspended. Medium grey shading indicates the security is under review with the opinion withdrawn. Light grey shading indicates the security is not covered. Chart is current as of a date no more than one trading day prior to the date of the report.

Medtronic (MDT) Price Chart



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Equity Investment Rating Distribution: Health Care Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	234	60.94%	Buy	115	49.15%
Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

Equity Investment Rating Distribution: Global Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1895	53.62%	Buy	1083	57.15%
Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

[R1] Issuers that were investment banking clients of BofA Securities or one of its affiliates within the past 12 months. For purposes of this Investment Rating Distribution, the coverage universe includes only stocks. A stock rated Neutral is included as a Hold, and a stock rated Underperform is included as a Sell.

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Investment rating	Total return expectation (within 12-month period of date of initial rating)	Ratings dispersion guidelines for coverage cluster[R2]
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Neutral	≥ 0%	≤ 30%
Underperform	N/A	≥ 20%

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