Clinical Insights

SUMMARY OF CLINICAL DATA

PORTICO™ TRANSCATHETER AORTIC HEART VALVE

PORTICO I and Portico CE Mark Studies

PERSPECTIVE

Transcatheter aortic valve implantation (TAVI) is establishing itself as a strong therapeutic alternative to surgery in intermediate risk and high risk patients with severe symptomatic aortic valve stenosis. Portico was approved in Europe in 2012 for high risk patients and was the first repositionable self-expanding TAVI device.

This clinical insight summarizes the predominantly European clinical assessment starting with an initial operators' use in the Portico CE Mark study through the multinational post-market PORTICO I study. Both study populations are clinically comparable and the results are consistent at 30 days and through 1 year.

HIGHLIGHTS

- Portico is shown to be safe and effective. Results are consistent between the Portico CE Mark and PORTICO I post-market studies.
- Low rates of all-cause mortality and cardiovascular mortality are observed through 1 year.
- Single digit mean aortic gradients, large effective orifice areas and low rates of PVL rates persist out to 1 year.
- Portico outcomes are within the range of other leading TAVI devices.

PORTICO DESIGN FEATURES

Portico is a self-expanding TAVI valve designed to achieve:

- Optimal placement with ability to recapture, resheath, and reposition in situ.[1]
- Low rates of paravalvular leak (PVL) with a conformable stent frame to treat variations in annulus geometry and large stent cells to conform around calcific nodules.
- Low pacemaker implantations with a non-flared stent frame for reduced protrusion into the left ventricular outflow track.
- Controlled and relaxed deployment due to hemodynamic stability with an intra-annular valve position providing early valve functionality.[1,2]
- No rapid pacing required during valve deployment.[1,2]
- Future coronary access preservation with large open-cell geometry and a low intra-annular valve position.[1]

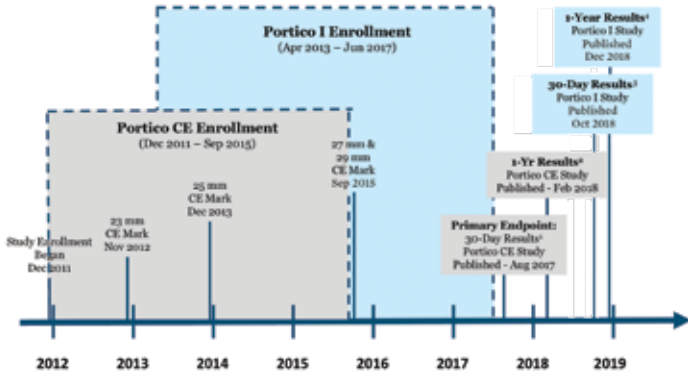
THE PORTICO CE MARK AND PORTICO I STUDY DESIGNS

TABLE 1: PORTICO STUDY DESIGNS

	PORTICO CE MARK[1]	PORTICO I[3]
Study Design	Prospective, multi-center, non-randomized study	Prospective, multi-center, non-randomized study
Patients Attempted	n=222	n=941
# of Sites	12 (EU & AUS)	61 (EU, Canada & US)
Devices Studied	23, 25, 27, 29 mm	23, 25, 27, 29 mm
Patient Population	Symptomatic, severe aortic stenosis High risk for surgical AVR	Symptomatic, severe aortic stenosis High risk for surgical AVR
Primary Endpoint	All-Cause Mortality at 30 days	All-Cause Mortality at 1 year
Follow-up	30 days and 1 year	30 days, 1, 2, 3, 4, and 5 years

- Portico received CE Mark for all valve sizes in a staged manner [FIGURE 1] as the study enrolled from Dec 2011 to Sep 2015.
- PORTICO I enrolled patients from April 2013 to June 2017 and will provide the first long-term (5 year) performance and safety for Portico in real world use.

FIGURE 1: PORTICO STUDY ENROLLMENT, CE MARK AND PUBLICATION TIMELINES



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BASELINE CHARACTERISTICS & PROCEDURAL RESULTS

- Patients from both studies were at high surgical risk, elderly with some functional limitations and multiple comorbidities, such as atrial fibrillation and renal dysfunction [Table 2].
- Portico TAVI yielded a high device success rate [Table 2].
- Pre- and post-dilatation was not required in either study and results reflect operator practice preference.

TABLE 2: PATIENT BASELINE CHARACTERISTICS AND PROCEDURAL OUTCOMES

PATIENT DEMOGRAPHICS	PORTICO CE MARK[1] N = 222	PORTICO I[3] N = 941
Mean Age	83.0	82.4
Female	74.3%	65.7%
Mean STS Score	5.8%	5.8%
NYHA Class III & IV	78.8%	64.0%
Atrial Fibrillation	38.3%	30.0%
Permanent Pacemaker	10.8%	8.5%
Prior Stroke	8.1%	6.1%
Renal Disease	32.9%	30.1%
PROCEDURAL OUTCOMES		
Device Success*	97.3%	98.0%
Valves Resheathed	33.0%	41.4%

* Device success: Successful vascular access, delivery, deployment in the proper anatomic location, and removal of the delivery system."

ALL-CAUSE MORTALITY

- The 30 day all-cause mortality rate from Portico CE Mark study (3.6%) was consistent with PORTICO I (2.7%), and comparable to rates observed for leading TAVI devices in their pivotal and post-market studies [Table 3].
- At 1 year, both Portico studies reflect favorable all-cause mortality rates that are within the 6.7%-14.4% reported from other trials [Table 4].

KEY RESULTS

- Portico was shown to be safe and effective in both studies at 30 days and 1 year [Tables 3 and 4].
  - Low incidence of all-cause death and disabling stroke.
  - Significant improvement in NYHA class [Figures 2 and 3].
  - Low moderate to severe PVL that is sustained out to 1 year [Figures 2 and 3].
  - Competitive hemodynamic performance with single-digit mean transaortic gradient that persisted out to 1 year.
  - Effective orifice area of 1.74 cm^2 at 1 year for Portico CE Mark and 1.75 cm^2 for PORTICO I.
- Clinical performance of Portico is consistent in both trials, and comparable to the Sapien 3 and Evolut™ R results [Tables 3 and 4].
- Conduction disturbances associated with aortic valve implantation is not uncommon, but resolvable with permanent pacemaker implant (PPI) [Tables 3 and 4].
  - The 30-day and 1-year overall PPI rates from Portico CE Mark and PORTICO I are within competitive range of Evolut R and Sapien 3.
- New PPI rates in these Portico patients without pre-existing pacemakers are comparable to new PPI rates reported by current TAVI devices on the market [Tables 3 and 4].
  - No intraprocedural factors were independent predictors of new PPI at 30 days in Portico CE Mark.[13]
  - Consistent with other TAVI studies, presence of pre-existing conduction disturbances (right bundle branch block, AV block, and QRS duration) are shown to be strong independent predictors for a new PPI.[14]

TABLE 3: 30-DAYS CLINICAL & VALVE PERFORMANCE FOR PORTICO, EVOLUT R AND SAPIEN 3

	PORTICO CE MARK, (N=222)[1]	PORTICO I (N=941)[3]	EVOLUT R CE MARK, (N=60)[5]	EVOLUT R FORWARD (N=1038)[6, 10]	SAPIEN 3 PARTNER II (N=583)[7, 11]	SAPIEN 3 SOURCE (N=1947)[8, 12]
All-cause Death	3.6%	2.7%	0%	1.9%	2.2%	2.2%
Cardiovascular Death	3.6%	2.4%	0%	1.8%	1.4%	1.6%
Life-threatening or disabling bleeding	3.6%	3.1%	5.0%	3.7%	10.2%	5.0%
Disabling (major) **stroke**	3.2%	1.6%	0%	1.7%	0.9%	0.5%
Major Vascular Complication	7.2%	5.5%	8.3%	6.9%	4.1%	4.1%
Overall PPI (all patients)	13.5%	17.1%	11.7%	17.8%	13.3%	12.1%
New PPI (no pre-existing pacemaker)	15.2%	18.7%	13.2%	20.2%	15.8%	13.7%
Moderate to Severe PVL	5.7%	3.9%	3.4%	2.0%*	3.4%	3.1%
Mean Aortic Gradient	8.3 mmHg	8.6 mmHg	8.1 mmHg	8.5 mmHg*	11.1 mmHg	11.8 mmHg
Effective Orifice Area (EOA)	1.9 cm^2	1.8 cm^2	1.9 cm^2	1.9 cm^{2*}	1.63 cm^2	1.64 cm^2

*Data at discharge

NOTE: Results from clinical studies are not directly comparable. Information provided for educational purposes only.

TABLE 4: 1 YEAR CLINICAL & VALVE PERFORMANCE FOR PORTICO, EVOLUT R AND SAPIEN 3

	PORTICO CE MARK, (N=222)[2]	PORTICO I (N=941)[4]	EVOLUT R CE MARK, (N=60)[9]	EVOLUT R FORWARD (N=1040)[10]	SAPIEN 3 PARTNER II (N=583)[11]	SAPIEN 3 SOURCE (N=1946)[12]
All-cause Death	13.8%	12.1%	6.7%	8.9%	14.4%	12.6%
Cardiovascular Death	9.4%	6.6%	5.0%	6.9%	8.1%	8.0%
Disabling (major) **stroke**	5.8%	2.2%	3.4%	2.1%	2.4%	1.4%
Overall PPI (all patients)	14.7%	19.5%	15.2%	19.7%	16.8%	13.2%
New PPI (no pre-existing pacemaker)	16.7%	21.3%	17.0%	22.1%	19.7%	15.0%
Moderate to Severe PVL	7.5%	2.6%	4.3%	1.2%	2.7%	2.6%
Mean Aortic Gradient	8.4 mmHg	8.7 mmHg	7.5 mmHg	8.1 mmHg	11.3 mmHg	12.3 mmHg
Effective Orifice Area	1.74 cm^2	1.8 cm^2	1.9 cm^2	1.9 cm^2	1.67 cm^2	1.7 cm^2

NOTE: Results from clinical studies are not directly comparable. Information provided for educational purposes only.

FIGURE 2: PORTICO CE MARK: NYHA AND PVL AT 30 DAYS AND 1 YEAR FOLLOW-UP (UNPAIRED)[2]

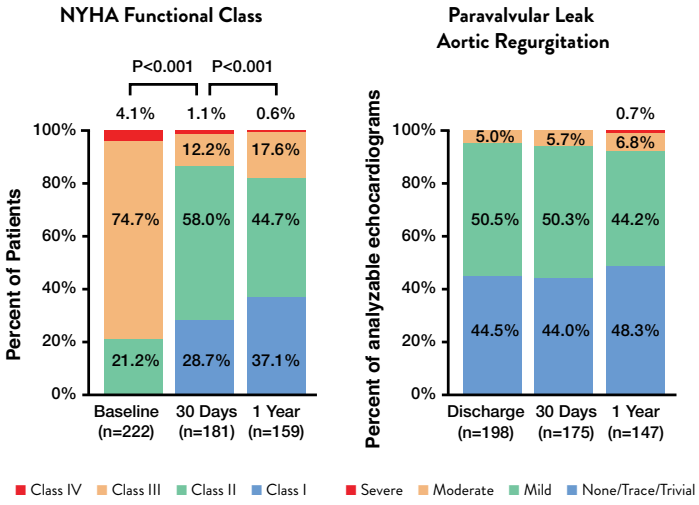
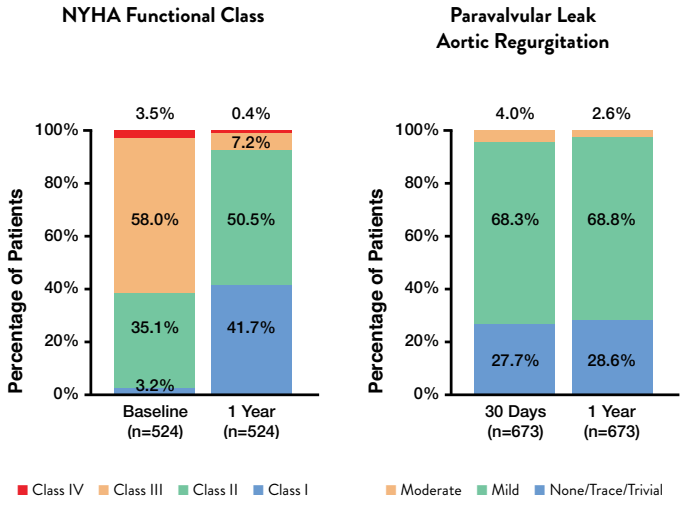


FIGURE 3: PORTICO 1: NYHA (N=673) AND PVL (N=524) THROUGH 1 YEAR FOLLOW-UP (PAIRED)[4]



CONCLUSIONS

Results You Expect

- PORTICO I, the largest reported Portico™ valve series, demonstrates excellent clinical outcomes in a global, post-market, real-world, high-risk, multicenter, prospective, single-arm, and core-lab adjudicated study.
- 30 day and 1 year Portico outcomes are consistent and repeatable as demonstrated by Portico CE Mark and PORTICO I.
- Portico has demonstrated low rates of all-cause mortality and cardiovascular mortality in Portico CE Mark and the PORTICO I.
- Portico outcomes are within the range of other leading TAVI devices.

Deliverability You Deserve

- Portico valve delivery system is easy to use and predictable as evidenced by the 97.3% and 98.0% implant success rates in Portico CE Mark and PORTICO I, respectively.

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