February 20, 2024

Tamara Syrek-Jensen, JD, Acting Director
Center for Clinical Standards and Quality, Coverage & Analysis Group
Centers for Medicare and Medicaid Services (CMS)
7500 Security Boulevard
Baltimore, MD 21244

REQUEST FOR TRANSCATHETER TRICUSPID VALVE REPLACEMENT (TTVR)
MEDICARE NATIONAL COVERAGE DETERMINATION (NCD)

Dear Ms. Syrek-Jensen:

Edwards Lifesciences (Edwards) requests a National Coverage Determination (NCD) for the coverage of transcatheter tricuspid valve replacement (TTVR). Edwards was accepted into the Parallel Review Program, by which there is concurrent review by CMS and the U.S. Food and Drug Administration (FDA), for the Edwards EVOQUE tricuspid valve replacement system (EVOQUE system). Edwards appreciates the engagement and input from CMS and the FDA on the design of the pivotal trial, TRISCEND II, and the continued engagement since then. On February 1, 2024, the FDA completed its review of the Premarket Approval (PMA) application and approved the EVOQUE system for the improvement of health status in patients with symptomatic severe tricuspid regurgitation despite optimal medical therapy, for whom tricuspid valve replacement is deemed appropriate by a heart team.

We are pleased by our shared commitment to advance appropriate coverage for TTVR, ensuring Medicare beneficiaries with tricuspid regurgitation have access to this innovative technology. As CMS considers the coverage policy options for TTVR, we urge the agency to consider the evolution of clinical practice using transcatheter therapies. The first transcatheter technology NCD was implemented in 2012 for the coverage of transcatheter aortic valve replacement (TAVR). The introduction of this novel transcatheter technology, along with the NCD, drove hospital infrastructure adapting to provide transcatheter technologies, clinical practice evolving to improve outcomes, technologies maturing, and this once novel procedure becoming a well-established treatment modality that improves the quality of life of nearly 100,000 U.S. patients each year. Similarly, mitral valve transcatheter technologies have been incorporated into clinical practice, furthering the life of Medicare beneficiaries every day.

As such, when considering the appropriate coverage criteria for TTVR, we ask that CMS apply the learnings from the TAVR and mitral valve transcatheter edge-to-edge (M-TEER) coverage policies and develop a TTVR coverage policy that balances optimal patient outcomes with adequate patient access. It is our recommendation that the M-TEER coverage policy (20.33) is a starting point from which to base the TTVR coverage policy, modifying the M-TEER requirements as appropriate to reflect the patient population with tricuspid regurgitation and the existing treatment modalities. Specifically, we believe the site and operator procedural experience and volume requirements for M-TEER serve as an appropriate starting point for TTVR requirements. This approach will ensure that Medicare beneficiaries with tricuspid regurgitation benefit from the current strengths of existing coverage policy, evidence development capabilities, and existing infrastructures of collaborative heart teams at high quality facilities.

The urgency with which to ensure Medicare beneficiaries have consistent and equitable access to this technology is paramount. TRISCEND II was one of the fastest enrolling trials Edwards has sponsored, and since the FDA approval, many patients and physicians are eagerly seeking use of this breakthrough

and since the FDA approval, many patients and physicians are eagerly seeking use of this breakthrough treatment option, which reflect the magnitude and urgency of the patient population with limited or no current therapeutic treatment options.

We look forward to your engagement. Please reach out to me with any questions or for additional information or clarification.

Sincerely,

Daveen Chopra
Corporate Vice President
Transcatheter Mitral and Tricuspid Therapies (TMTT)

Table of Contents

Acronyms

6MWD: 6-minute walk distance

6MWT: 6-minute walk test

ACC: American College of Cardiology

AHA: American Heart Association

CED: Coverage with Evidence Development

CMS: Centers for Medicare & Medicaid Services

CS: Cardiogenic shock

FDA: U.S. Food & Drug Administration

ICD: Implantable cardioverter defibrillator

KCCQ: Kansas City Cardiomyopathy Questionnaire

MAE: Major adverse event

M-TEER: Mitral valve transcatheter edge-to-edge repair

NCD: National Coverage Determination

NYHA: New York Heart Association

OMT: Optimal medical therapy

PH: Pulmonary hypertension

PMA: Pre-market application

QoL: Quality of life

RV: Right ventricle

RVD: Right ventricular dysfunction

SCAI: Society for Cardiovascular Angiography and Interventions

STS: Society of Thoracic Surgeons

TAVR: Transcatheter aortic valve replacement

TEE: Transesophageal echocardiography

TTE: Transthoracic echocardiography

T-TEER: Tricuspid valve transcatheter edge-to-edge repair

TTVI: Transcatheter tricuspid valve intervention (Note: TTVI is also an acronym used for transcatheter tricuspid valve implantation. For purposes of this request, TTVI refers to transcatheter tricuspid valve intervention)

TTVR: Transcatheter tricuspid valve replacement

TVT: Transcatheter valve therapies

ViV: Valve-in-Valve

1. Requesting Organizations

Edwards Lifesciences, LLC

2. Development Track

Request for a National Coverage Determination (NCD) under Parallel Review

3. Benefit Categories

Physician services

Inpatient hospital services

4. Description of the Transcatheter Tricuspid Valve Replacement (TTVR) System

TTVR procedures involve the replacement of the native tricuspid valve with a prosthetic valve via a catheter in a transfemoral venous approach. TTVR has several potential benefits: TTVR has the potential to reduce and/or eliminate tricuspid regurgitation, TTVR is less dependent on tricuspid valve morphology compared to tricuspid valve transcatheter edge-to-edge repair (T-TEER), and implantation of a valve within the tricuspid annulus allows for potential future valve-in-valve (ViV) procedures, if needed.[1,2]

TTVR could reduce and/or eliminate tricuspid regurgitation without the need for open heart surgery and offers an alternative treatment option for patients with significant tricuspid regurgitation who are only medically managed for their symptoms.[3, 4, 5, 6, 7, 8, 9, 10] EVOQUE is currently the only FDA approved transcatheter tricuspid valve replacement device in the United States. The Edwards EVOQUE Tricuspid Valve Replacement System (EVOQUE system), granted breakthrough designation by the FDA, fills an unmet need by providing a novel, transcatheter treatment option for patients with tricuspid regurgitation.

Data from the Edwards TRISCEND study (NCT04221490) and early human use suggest that TTVR with the EVOQUE system is feasible, has acceptable safety, reduces and/or eliminates tricuspid regurgitation, and improves functional status and QoL.[11,12,13,14,15,16]

The Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device (“TRISCEND II pivotal trial”) is the first confirmatory randomized controlled trial in the United States to evaluate the safety and effectiveness of TTVR for treatment of at least severe tricuspid regurgitation (NCT04482062). In the TRISCEND II pivotal trial, selection of sites was based on their experience in managing patients with tricuspid regurgitation and with performing transcatheter structural heart procedures. In the Breakthrough Pathway Cohort, the primary safety was Major Adverse Events at 30 days. The primary effectiveness endpoints for the Breakthrough Pathway were: (1) TR grade reduction to moderate or less at 6 months, and (2) a hierarchical composite endpoint at 6 months of the following components: KCCQ overall summary score of ≥ 10 points, NYHA functional class improvement of ≥ 1 class, and 6MWD improvement of ≥ 30 meters. The primary safety and effectiveness endpoints were met.

Publications on TTVR are summarized in Section 12 below.

Detailed description of the procedure
After general anesthesia is induced, the patient is intubated. A transesophageal echocardiography (TEE) probe is inserted and positioned. Femoral vein access is obtained, after which, under

fluoroscopic guidance, a guidewire is inserted and advanced across the tricuspid valve. After the access site is dilated to accommodate the 28 French delivery system, the delivery system (with valve) is advanced over the guidewire into the right atrium of the heart.

A combination of fluoroscopic and echocardiographic guidance is used to advance the valve delivery catheter via the vena cava to the right atrium. Entry is confirmed and the system is advanced into the right atrium and the appropriate position for deployment of the valve within the tricuspid plane is determined by fluoroscopy and TEE.

The selected echocardiographic modality and fluoroscopic guidance are used to monitor expansion of the prosthesis, leaflet capture, and assure proper positioning throughout the deployment process.

After deployment of the new valve prosthesis, the delivery catheter is withdrawn across the valve and from the right atrium. The catheter is retracted and removed from the access site; venous access is closed. Proper positioning and functioning of the valve, including the assessment of any paravalvular leakage, is confirmed by TEE. Measurement of regurgitation and resultant gradients is taken.

5. Target Medicare population and medical conditions for which TTVR can be used

The reduction or elimination of tricuspid regurgitation may slow the progression of heart failure and improve patient outcomes and quality of life. In the United States, more than 1.6 million people suffer from significant tricuspid regurgitation (moderate and above).[17, 18] The prevalence of moderate or greater TR is more frequent in women than men, with approximately four times as many women with the disease.[19] The prevalence of tricuspid regurgitation increases with age and the incidence of tricuspid regurgitation is expected to increase with an aging population.[20] When tricuspid regurgitation is severe, it is typically associated with right-sided heart failure and symptoms usually include neck palpitations, lower limb edema, ascites, fatigue, and dyspnea. Twelve-month mortality in patients who were diagnosed with isolated severe tricuspid regurgitation between 2001 and 2016 and were medically managed is reported to be 31%.[21]

The only commercially available treatments for significant tricuspid regurgitation in the United States are medical management and surgical tricuspid valve repair (surgical replacement is performed using off-label devices). With high in-hospital mortality rates for isolated tricuspid regurgitation surgery, ranging between 6 and 12%, patients with tricuspid regurgitation tend to be conservatively managed with medical therapy due to the significant risks associated with current surgical treatment options.[22, 23, 24, 25, 26] Tricuspid regurgitation patients are commonly managed with diuretics to treat symptoms of systemic congestion and are typically only considered for surgery after advanced right ventricle (RV) dysfunction, liver dysfunction, and/or cirrhosis have developed. For patients with significant tricuspid regurgitation, medical therapy may only provide temporary symptom relief, and its effectiveness may decrease as tricuspid regurgitation progresses, heart failure worsens, and risk of death increases.[27, 28, 29] While a majority of patients rely on medical management alone to treat the symptoms of tricuspid regurgitation, there remains no class I recommendation for medication management in clinical guidelines.[30]

In response to this significant unmet need for patients suffering from tricuspid regurgitation, Edwards sponsored the TRISCEND and TRISCEND II clinical studies to evaluate the safety and efficacy of the EVOQUE system. The first study, the single-arm TRISCEND study, included patients with at least moderate tricuspid regurgitation (9.6% moderate, 50.0% severe, 25.0% massive, 15.4% torrential) with an average age of 79.3 ± 7.7.[31] The randomized controlled trial, TRISCEND II, included patients with at least severe tricuspid regurgitation (43.8% severe, 21.9% massive, 34.4% torrential) who were deemed candidates for transcatheter tricuspid valve

replacement with the EVOQUE system by their multidisciplinary local heart team. The TRISCEND II pivotal trial is a randomized study that compares patients implanted with the EVOQUE system while being on optimal medical therapy (OMT) with patients treated with OMT alone. The average age was 79.4 ± 7.71years in the EVOQUE+OMT group and 78.2 ± 8.32 years in the OMT alone group.

With the advanced age of patients with at least severe tricuspid regurgitation in the clinical trials,, we believe the results of the TRISCEND studies are generalizable to the Medicare population.

The EVOQUE system is indicated for the improvement of health status in patients with symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy for whom tricuspid valve replacement is deemed appropriate by a Heart Team. Tricuspid regurgitation severity is evaluated via echocardiography and defined by a combination of physiologic criteria[32] as assessed by the local heart team. Additional parameters may be utilized to determine suitability for TTVR, based on echocardiographic and computed tomography evaluation (e.g., tricuspid annular size, RV function).

The American Society of Echocardiography (ASE) developed a three-tier grading scale to describe different stages of TR including "Mild," "Moderate," and "Severe."[33] This grading scale is based off structural, semi-quantitative, and quantitative echocardiographic parameters. To better characterize the variability of TR seen in patients with transcatheter devices, an expanded grading scale for assessing TR severity was proposed by Hahn & Zamorano; the scale further expands the "severe" grade to include "massive" and "torrential" grades.[32] This expansion of the ASE "Severe" TR grade would allow for the more precise assessment of the impact of TR intervention. Table 1 provides a comparison of the quantitative echocardiographic parameters used in each grading scale. While quantitative echocardiographic parameters are frequently used to identify a patient's TR grade, other factors can be used to determine TR grade, including tricuspid valvular structure, qualitative doppler characteristics, and semiquantitative measures, such as color flow jet area, hepatic vein flow, and tricuspid inflow.

While echocardiographic parameters are used to define the different grades of TR, in clinical practice physicians will consider these quantitative measures, as well as unique patient characteristics, existing comorbidities, and risk factors, to determine the most appropriate treatment pathway for patients with TR, including consideration for transcatheter edge-to-edge repair (TEER) or TTVR.

Table 1 Comparison of TR Grading Schemes, Quantitative Echocardiographic Parameters

ASE Guidelines and Standards: TR Grading[33]	Mild	Moderate	Severe		
VC Width (cm)	< 0.3 cm	0.3 – 0.69 cm	≥ 0.7 cm		
EROA by PISA (cm^2)	< 0.2 cm^2	0.2 – 0.39 cm^2	> 0.4 cm^2		
RVol (mL)	< 30 mL	30 – 44 mL	≥ 45 mL		
Expanded TR Grading (Hahn & Zamorano)[32]	**Mild**	**Moderate**	**Severe**	**Massive**	**Torrential**
VC Width (cm)[a]	< 0.30 cm	0.30 – 0.69 cm	0.70 – 1.3 cm	1.4 – 2.0 cm	≥ 2.1 cm
EROA by PISA (cm^2)[a]	< 0.20 cm^2	0.20 – 0.39 cm^2	0.40 – 0.59 cm^2	0.60 – 0.79 cm^2	≥ 0.8 cm^2
3D VCA or quantitative EROA (cm^2)[a,b]	-	-	0.75 – 0.94 cm^2	0.95 – 1.14 cm^2	≥ 1.15 cm^2

[a] Measurements reported in mm and mm^2; cited measurements have been converted to cm and cm^2
[b] 3D VCA and quantitative Doppler EROA cut-offs may be larger than PISA EROA

VC, vena contracta; EROA, effective regurgitant orifice area; RVol, regurgitant volume 3D VCA, three-dimensional vena contracta area

In addition to evaluating these clinical parameters, it is important that clinicians consider and evaluate the important functional and QoL improvements the patient is seeking in the treatment of tricuspid regurgitation.

The multidisciplinary heart team will play a critical role in identifying patients who are likely to have clinically meaningful benefits from receiving TTVR with the EVOQUE system. The multidisciplinary heart team should have specific protocols for care related to pre-procedure assessment and screening. These protocols should be implemented and executed jointly by the multidisciplinary team, and will involve screening for the presence, degree, and severity of comorbidities, and identification of patient management strategies and other procedures that may be required to ensure good outcomes.

Both T-TEER and TTVR are expected to contribute to the toolbox of treatment options for patients with tricuspid regurgitation. Selection of repair versus replacement depends on various anatomic and patient factors.[34, 35, 36, 37, 38, 39, 40, 41, 42] For example, replacement may be more suitable for patients with large coaptation gaps (i.e., > 8.5 mm), pacemaker leads, or severe leaflet tethering. As manufacturers continue to innovate and introduce technologies to the toolbox of treatment modalities for tricuspid regurgitation, patient clinical suitability, patient preference, and patient-centered care must continue to be championed. Treatment selection must determined by the physician and patient.

6. Supporting medical and scientific information

Overview of the technology

TTVR utilizes a bioprosthetic valve that is inserted using a catheter-based technology. Delivery can be accomplished via a transfemoral venous approach. Evidence from the randomized controlled trial TRISCEND II indicates that when used in experienced centers with qualified operators, the results of TTVR have been positive – showing greater improvement in tricuspid regurgitation grade, symptoms, and overall patient quality of life as compared to medical therapy.

Medical management for the treatment of tricuspid regurgitation is likely to provide only temporary symptom relief for most patients, despite being the most frequent treatment modality for this patient population. Patients with severe tricuspid regurgitation are typically only considered for surgical intervention when undergoing left-sided valve surgery or after symptoms of progressive RV dilation/dysfunction have developed.[43, 44] Isolated tricuspid regurgitation

surgery is performed for only a very small subset of patients due to lack of clinical guidelines, high surgical risk, and high in-hospital mortality rates.

The lack of sustained benefit from medical therapies and the limited number of patients treated surgically for tricuspid regurgitation has prompted research and development of alternative transcatheter repair and replacement therapies.[45]

We believe patients eligible to receive TTVR represent a patient population who currently have limited treatment options. The TTVR procedure will be performed on patients who meet rigorous selection criteria based on age, comorbidities, and who are identified as appropriate candidates as determined by the multidisciplinary heart team. The FDA approved indication for EVOQUE is for the improvement of health status in patients with symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy for whom tricuspid valve replacement is deemed appropriate by a Heart Team.

While TTVR presents a treatment option for many patients with few effective alternatives, there may be an overlap in the patient population that will be clinically eligible to receive TTVR, the patient population that will be clinically eligible to receive T-TEER, and those who are eligible, based on existing guidelines, for surgical tricuspid valve intervention. When selecting the most appropriate modality for treatment, patient preference and patient-centered care should determine which modality will be most beneficial for the patient.

Devices
TTVR devices are similar in that they allow for transcatheter deployment of a bioprosthetic tricuspid valve utilizing a percutaneous approach. There are seven companies that are involved in the development of TTVR devices. Some of the companies that are involved in the development of TTVR devices include: the EVOQUE system (Edwards Lifesciences), Intrepid (Medtronic), LuX-Valve (Jenscare Biotechnology), GATE (Navigate Cardiac Structures, Inc.), Topaz (TRiCares), VDYNE valve (VDYNE), and TRISOL Valve (Trisol Medical). As of February 1, 2024, the EVOQUE system is the only device that has been approved by the FDA for treatment of patients with symptomatic severe TR in the United States.

Clinical experience
Early clinical experience
A retrospective analysis of symptom burden, echocardiographic outcomes, adverse events, and survival through 2 years among patients who were treated with the EVOQUE system under compassionate use between 2019 and 2021 was published by Stolz L, et al (2023).[46] The 38 patients studied had an average age of 77 ± 12 years, 28 (74%) of the patients were female, and all patients had at least severe tricuspid regurgitation at the time of intervention.

Tricuspid regurgitation was successfully reduced to mild or trace/none in 97% of patients following the procedure and results were durable in 94% of patients at the latest available follow-up (median of 520 days based on 92% of patients with follow-up data). Survival rates for the patients were 86% at 1 year and 71% at 2 years. Prior to intervention, 92% of patients were NYHA functional class ≥ III, compared to 20% after intervention.

TTVR with the EVOQUE system reduced symptoms of right-sided heart failure: reduction in peripheral edema from 71% to 37% and ascites from 50% to 14% of patients. In this cohort of patients, echocardiographic signs of RV reverse remodeling have been observed as soon as 30 days post-procedure and have been maintained in long-term follow-up.[47]

One patient underwent surgical TV replacement after early device migration (5 days after TTVR). New conduction disturbances (primarily right bundle branch block or complete heart block) occurred in 4 patients, requiring permanent pacemaker implantation in 3 patients within the first week after TTVR. Major bleeding events were reported in 4 patients (11%: 2 retroperitoneal hematoma, 1 scrotal hematoma, 1 upper gastrointestinal bleeding; 2 events occurred in-hospital and 2 occurred late).

Early clinical use with the EVOQUE system in the treatment of tricuspid regurgitation shows high procedural success and durable reduction of tricuspid regurgitation and associated symptoms at 2-year follow-up.

TRISCEND Single-arm study
The TRISCEND study is the first in a series of clinical trials to evaluate the safety and performance of the EVOQUE system (Kodali S, et al. 2022, Kodali S, et al. 2023). The study is a prospective, single-arm, multi-center study evaluating patients with symptomatic moderate or greater tricuspid regurgitation, despite medical therapy. Thirty-day and one-year outcomes, including echocardiographic parameters, clinical, functional, and qualify-of-life measures, and a composite rate of major adverse events (MAEs) have been published in peer-reviewed journals. 6-month and 2-year results have been presented at cardiovascular conference podium presentations (TCT 2021, LondonValves 2023).

TRISCEND: 30-day Results
Enrolled patients were predominantly women (76.8%) and had a mean age of 79.3 ± 7.7 years. Ninety-one percent of patients presented with torrential, massive, or severe tricuspid regurgitation. A majority of patients (87.5%) had significant functional impairment (class III or IV) based on NYHA assessment. The most prevalent comorbidities among the patient population included atrial fibrillation (91.1%), systemic hypertension (87.5%), and pulmonary hypertension (80.4%). Prior cardiac treatments included valve surgery or intervention (39.3%) and pacemaker or implantable cardioverter-defibrillator (ICD) implantation (33.9%) with leads crossing the tricuspid valve annulus in 32%.

Device success, the successful device deployment and retrieval of the delivery system, was achieved in 98.2% of patients and procedural success, defined as successful device performance with absence of paravalvular leak via TTE at discharge, was achieved in 96.4%. At discharge 98.1% of patients had a reduction of at least 2 tricuspid regurgitation grades.

At 30 days, 53 of the 56 enrolled patients completed follow-up in the study (missed visit n=1; all-cause mortality n=2). Observed study outcomes included:

- Clinical success, defined as procedural success without any MAEs, was achieved in 73.2% of patients.
- Fifteen (26.8%) patients experienced MAEs: 1 cardiovascular death, 2 non-elective TV reinterventions, 1 major access site or vascular complication, and 15 severe bleeding events (none were life-threatening). All patients who experienced severe bleeding were on anticoagulation or antiplatelet medication before the procedure.
- Most patients (87.5%) were in NYHA functional class III or IV at baseline, and 78.8% of patients were in NYHA functional class I or II at 30 days.
- The 6-minute walk distance (6MWD) increased a mean of 49.8 ± 80.5 m at 30 days from 199.1 ± 128.6 m at baseline to 248.9 ± 127.5 m.
- The KCCQ score increased from a mean of 46.5 ± 23.1 points at baseline to 65.6 ± 21.6 points, a mean improvement of 19.0 ± 20.5 points at 30 days. A change of 10 points in KCCQ score is indicative of moderate to large clinical improvement.

- Edema assessed by standard pitting test significantly improved at 30 days ($P < 0.001$); 13.7% reported ankle swelling with moderate to extreme activity limitations at 30 days compared with 35.7% at baseline. Ankle circumference improved, and body weight decreased.

At 30 days, 96% of patients had none/trace or mild tricuspid regurgitation. Additional clinical improvements were observed at 30 days with measures of right-sided heart remodeling showing significant improvement. Overall, acute clinical outcomes were associated with improved functional status and QoL at 30 days.

TRISCEND: One-Year Results

The TRISCEND study (Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device) is a prospective, multicenter, single-arm, open-label, interventional study evaluating the safety and performance of transfemoral transcatheter tricuspid valve replacement in patients with clinically significant TR. Kodali et al. published 1-year results for this study (Kodali et al. 2023).

Among 176 patients enrolled at 20 centers in North America and Europe, 71.0% were female, mean age 78.7 years, Society of Thoracic Surgeons mortality scores of 7.4% (mitral valve repair) and 10.0% (mitral valve replacement), and EuroSCORE II 5.1% (Table 1). Tricuspid regurgitation grade was ≥severe in 88.0%, with etiologies of secondary (68.2%), mixed (14.2%), primary (9.7%), indeterminate (5.1%), and pacer related (2.8%). Three-quarters (75.4%) of patients were in NYHA class III or IV, and significant comorbidities included atrial fibrillation (92.0%), hypertension (84.1%), pulmonary hypertension (75.0%), hyperlipidemia (65.3%), renal insufficiency or failure (58.5%), and ascites (22.2%). At baseline, 32.4% had a preexisting cardiac implantable electronic device, 37.5% had a history of valve surgery or intervention, and 16.5% had prior coronary artery bypass grafting.

Successful femoral access was achieved in 99.4% of patients (one case was aborted due to stenosis in right and left iliac veins), with a right-femoral-vein approach used in 93.8% of cases and pre-dilatation performed in 84.7%. New permanent pacemakers (not included in the pre-defined composite MAE definition) were implanted in 15 patients (13.3% of patients without a pre-existing pacemaker), all within 9 days post-procedure. No patients received a new pacemaker after 30 days. Of those receiving new pacemakers, 14 had baseline atrial fibrillation, eight with additional conduction disturbances (i.e. left bundle branch block, right bundle branch block, prolonged QT interval, and atrioventricular block).

At one year, the all-cause cause mortality rate (n = 176) was 9.1%, and the rate of hospitalization for HF was 10.2%. Kaplan Meier estimates for all-cause mortality and HF hospitalization were 9.9 ± 2.3% and 11.6 ± 2.6%, respectively (Figure 2), and there was a 74.9% relative reduction in the rate of HF hospitalization in the 12 months before vs. after the procedure ($P <.001$). All patients (100%) experienced at least one grade reduction in TR severity, 97.6% had ≥two grade reductions, and 33.3% ≥four grade reductions. The majority (88.2%) of patients had no or trace paravalvular leak, with 10.6% mild and 1.2% moderate. Changes from baseline to one-year follow-up TTE (Table 3) included reductions in RV mid-ventricular end-diastolic diameter (−6.3 ± 9.5 mm, $P < .001$) and IVC diameter at end-expiration (−7.2 ± 5.9 mm, $P < .001$). In the setting of a stable LV ejection fraction ($P = .197$), there were significant increases in LV outflow tract stroke volume (10.5 ± 16.8 mL, $P < .001$) and cardiac output (0.6 ± 1.2 L/min, $P < .001$). Several parameters associated with RV systolic function decreased, including RV FAC (−8.4 ± 13.8%, $P < .001$) and TAPSE (−2.8 ± 6.5 mm, $P = .006$). Pulmonary artery systolic pressure also decreased (−6.8 ± 13.6 mmHg, $P = .003$).

At one year, 93.3% of patients were in NYHA class I or II, compared with 25.8% at baseline (P < .001). The mean KCCQ overall summary score increased from 46.0 ± 21.8 points to 71.7 ± 22.0 points (P < .001), with 54.9% of patients improving by at least 20 points and 21.6% by 10–19 points; 50.0% had scores in the range of 75 to 100 points at one year. There was also a significant improvement in mean 6MWD, which increased by 56.2 ± 117.0 m (P < .001). Patients lost body weight by a mean of 1.8 ± 6.3 kg (P = .005), and the proportion of patients with absent or grade 1 + edema (assessed by standard pitting) improved from 63.9% at baseline to 86.6% at one year (P < .001).

Overall, key findings included high rates of device and procedural success, with low mortality and significant TR reduction, as well as significant improvements in functional status and quality of life. The 56 patients treated in this study had a mean age of 79.3 (SD: 7.7) years, were majority female (76.8%), and had predominantly functional TR (67.9%), with severity classified as torrential/Grade 5 (18.2%), massive/Grade 4 (27.3%), severe/Grade 3 (45.5%), or moderate/Grade 2 (9.1%). All patients had symptomatic moderate or greater TR despite medical therapy or with prior heart failure hospitalization for TR, and most were in NYHA functional class III or IV (87.%).

A range of comorbidities were recorded, the most common being AF (91.1%), systemic hypertension (87.5%), pulmonary hypertension (80.4%), chronic kidney disease (66.1%), previous valves surgery/intervention (39.3%), and pacemaker or implantable cardioverter-defibrillator implantation (33.9%).

TRISCEND II Pivotal Trial

The results from the Breakthrough Pathway Cohort of the TRISCEND II Pivotal Trial were the basis for the FDA approval of the EVOQUE system. A summary of the results can be accessed in the EVOQUE system FDA Labeling (P230013) and Summary of Safety and Effectiveness Data (link). Patients in the Breakthrough Pathway Cohort were enrolled in the trial between May 2021 and April 2022. A total of 153 patients were randomized to either the EVOQUE+OMT (device) group or the OMT-only (control) group and 150 patients were included in the modified Intent-to-Treat (mITT) analyses for safety and effectiveness (EVOQUE+OMT N=96, OMT-only N=54).

Baseline Characteristics

Overall, the cohorts had similar baseline characteristics. The average age in the device group was 79.4 and 78.2 in the control group. A majority of the enrolled patients were female (120/150). Compared to the control group, more patients in the device group were in New York Heart Association (NYHA) class III/IV or had a prior stroke and fewer device group patients had myocardial infarction or had ≥1 prior open-heart surgeries. At baseline, all patients had severe TR using the American Society of Echocardiography TR grading scale based on echocardiographic quantitative measures (i.e., VC width, EROA by PISA, and 3D VCA or quantitative EROA). However, to better characterize the severity of TR, the TRISCEND II echocardiographic core lab used the Hahn & Zamorano 5-level TR grading scale ("Mild," "Moderate," "Severe," "Massive," and "Torrential"). In the device group 43.8% were classified as having severe TR, 21.9% with massive, and 34.4% with torrential.

Primary Safety Endpoint

The TRISCEND II pivotal trial met its pre-specified primary safety endpoint. The 30-day composite MAE rate in the EVOQUE+OMT group was 27.4% with a one-sided 97.5% upper confidence bound of 36.9%, which is less than the pre-specified performance goal of 70.0% based on a surgical predicate. At 30 days, the proportion of patients treated with the EVOQUE system who experienced a MAE was less than the pre-specified objective performance goal. Beyond the 30-day peri-procedural period, the rate of serious adverse events was comparable

among patients treated with EVOQUE+OMT and those receiving OMT alone, and no unanticipated risks were identified.

Table 2. MAEs at 30 Days – Breakthrough Pathway Cohort mITT (Safety) Population

Endpoint	No. Events	Event Rate*	One-sided 97.5% Upper Confidence Bound†	Endpoint Result
Composite MAEs	36	27.4% (26/95)	36.9% < 70%	Endpoint met
Cardiovascular mortality	3	3.2% (3/95)	-	-
Myocardial infarction	1	1.1% (1/95)	-	-
Stroke	0	0.0% (0/95)	-	-
New need for renal replacement therapy	1	1.1% (1/95)	-	-
Severe bleeding‡	10	10.5% (10/95)	-	-
Non-elective tricuspid valve re-intervention, percutaneous or surgical	0	0.0% (0/95)	-	-
Major access site and vascular complications	3	3.2% (3/95)	-	-
Major cardiac structural complications due to access-related issues	2	2.1% (2/95)	-	-
Device-related pulmonary embolism	1	1.1% (1/95)	-	-
Arrhythmia and conduction disorder requiring permanent pacing	14	14.7% (14/95)	-	-

MAEs: major adverse events

*% (no./total no.). Denominator included patients who had been in the trial for ≥30 days or had an MAE prior to 30 days. One patient had an aborted procedure and withdrew from the trial on post operative day (POD) 22 without experiencing an MAE and thus was not included in the denominator.

†Based on the normal approximation method with continuity correction for the proportion of patients with the MAEs and compared to the pre-specified performance goal of 70%.

‡Fatal, life-threatening, extensive, or major bleeding, as defined by Mitral Valve Academic Research Consortium (MVARC; Stone et al. 2015).

Co-Primary Effectiveness Endpoints

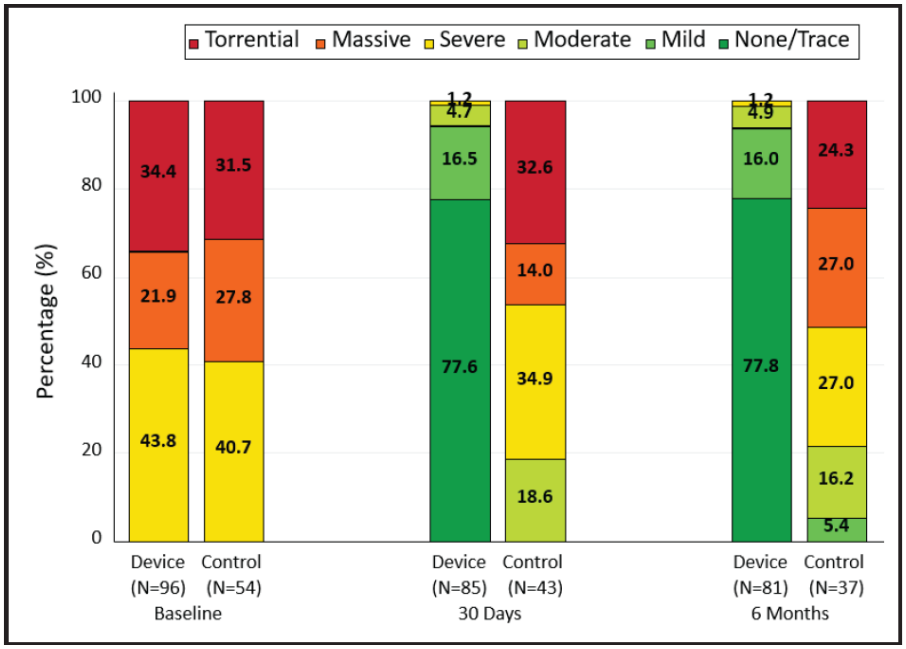
Based on 6-month primary effectiveness endpoints, treatment with EVOQUE system and OMT provides superior benefits compared to OMT alone, the accepted standard of care for patients with severe (or greater) TR. The TRISCEND II pivotal trial met both of its co-primary effectiveness endpoints, demonstrating that the EVOQUE system with OMT is superior to OMT alone with regards to tricuspid regurgitation reduction and a hierarchical endpoint that assessed clinically meaningful quality of life (QoL) and functional improvements at 6 months.

1. **Tricuspid Regurgitation Reduction**

   The first co-primary endpoint assessed TR grade reduction from severe or greater TR at baseline to moderate or less at 6 months. The proportion of patients who achieved a reduction in TR grade from severe or greater at baseline to moderate, mild or trace/none at 6 months was significantly higher in the EVOQUE+OMT group compared to optimal medical therapy alone:

   - 98.8% of patients in the EVOQUE+OMT group experienced this reduction in TR grade, compared to 21.6% of patients in the OMT alone group. This difference of 77.1% was statistically significant (p-value of < 0.001).
   - 93.8% of patients in the EVOQUE + OMT group achieved reductions in TR grade from severe to mild or less at 6 months, including 77.8% with none/trace TR. Nearly all patients in the EVOQUE+OMT group (>97%) had TR grades classified as moderate, mild, or none/trace at discharge, 30 days, and 6 months.

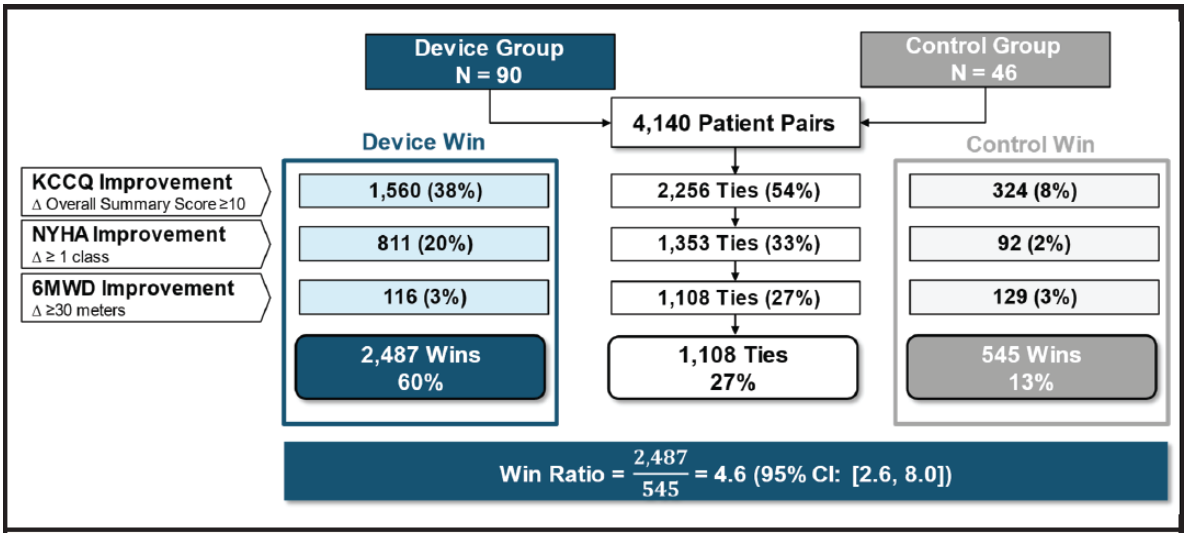
Figure 1 TR Severity Grade by Visit -- mITT (Effectiveness) Population



2. Symptomatic and Functional Outcomes

The second co-primary effectiveness endpoint was a hierarchical composite endpoint that assessed three established symptomatic and functional outcome measures for heart failure; included patient-reported (KCCQ), clinician-reported (NYHA), and performance (6MWT) outcomes; and incorporated clinically meaningful thresholds for improvement. The unmatched win ratio for this endpoint is 4.6, in favor of the EVOQUE+OMT group. If the results of any EVOQUE+OMT patient are compared with any OMT alone patient, and the results from the comparison are not tied, the odds of the EVOQUE+OMT patient being the "winner" are 4.6 times that of an OMT alone patient (one-sided 97.5% lower bound of 2.6), with respect to KCCQ, NYHA, and 6MWD improvement at the same thresholds used in the Finkelstein-Schoenfeld analysis.

Figure 2 Win Ratio Analysis of Co-Primary Effectiveness Endpoint #2 Result - mITT Effectiveness Population



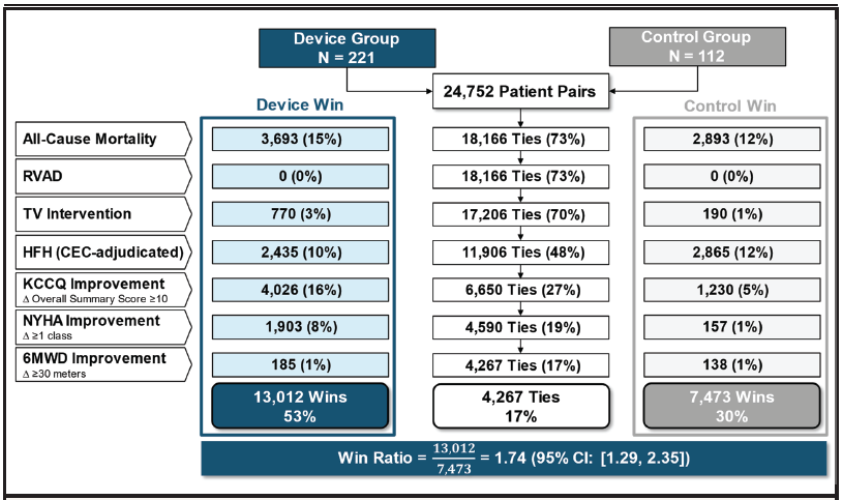
KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; 6MWD: 6-minute walk distance; CI: confidence interval

One-year Outcomes for Available Full Cohort Patients

During FDA's PMA review, a total of 259 patients were randomized to the device group and had an attempted procedure, and 133 patients were randomized to the control group (Full Cohort mITT Safety Population), of which 220 (84.9%) device patients and 98 (73.7%) control patients completed the 1-year visit as of December 15, 2023.

The results showed favorable trends in the device group compared to the control group in the win ratio result of the primary endpoint and in the descriptive results of all the primary endpoint components with observed events.

Figure 3 Win Ratio Analysis of Primary Safety and Effectiveness Endpoint - Available Full Cohort mITT Effectiveness Population



RVAD: right ventricular assist device; TV: tricuspid valve; HFH: heart failure hospitalization; CEC: Clinical Events Committee; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; 6MWD: 6-minute walk distance; CI: confidence interval.

Figure 4 Kaplan-Meier Analysis of Site-Reported All-Cause Mortality – Available Full Cohort mITT Safety Population

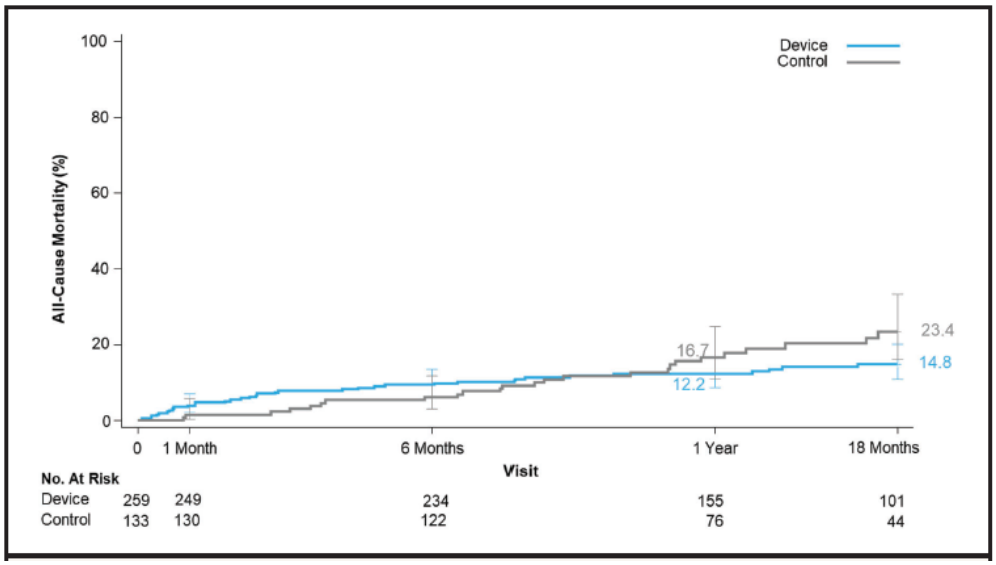


Figure 5 Kaplan-Meier Analysis of Sited Reported Tricuspid Valve Surgical or Percutaneous Intervention – Available Full Cohort mITT Safety Population

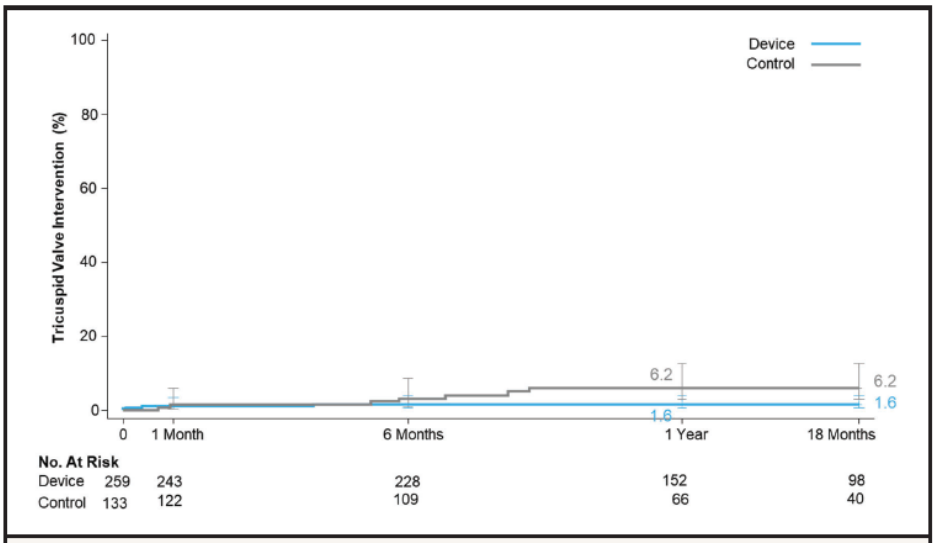
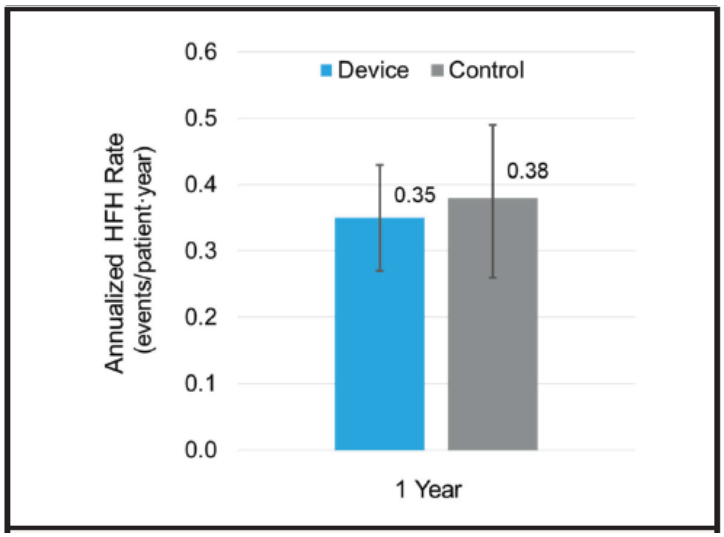
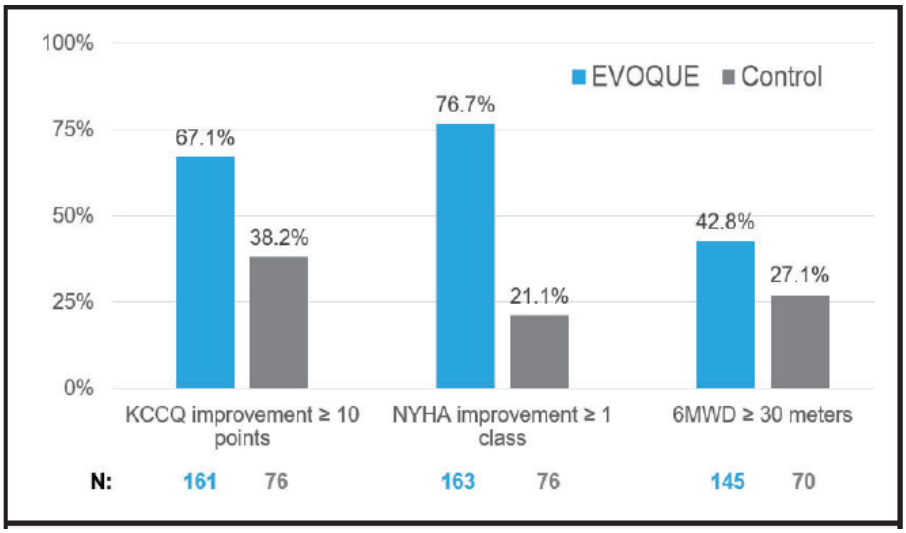


Figure 6 Annualized HF Hospitalization Rate – Available Full Cohort mITT Safety Population



HFH: heart failure hospitalization. The error bars represent the 95% confidence interval (CI). The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

Figure 7 KCCQ, NYHA, and 6MWD Improvements at 1 Year – Available Full Cohort mITT Safety Population



KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; 6MWD: 6-minute walk distance

Patient Preference

The patient perspective on goals of treatment is growing increasingly important in clinical research. Prior to 2007, patient reported outcomes were only reported in approximately 14% of clinical trials, however between 2007 and 2013, this rate increased to 27% of trials.[48] In an effort to support patient-centered care and better reflect the impact of severe TR in this patient population, Edwards incorporated a novel patient preference survey in the TRISCEND II pivotal trial.

This patient preference survey developed by Edwards Lifesciences in partnership with patient preference researchers was administered at baseline to all patients participating in the TRISCEND II pivotal trial to understand the patient priorities for relief from TR symptoms and patient disease burden and experience. Patients were asked to rank activities or symptoms on a scale of 1 to 6, with 1 being the "most important" and 6 being the "least important" activity or symptom to

improve. Fifty-three percent (53%; 76/144) of the patients ranked "caring for yourself"' as the most important activity for improvement, and 41% (59/144) of patients rated "shortness of breath" as the most important symptom to see improvement.

7. FDA Documentation/Information

On February 1, 2024, Edwards received FDA approval for the EVOQUE system for the improvement of health status in patients with symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy for whom tricuspid valve replacement is deemed appropriate by a Heart Team.

Explanation of the design, purpose, and method of using the item or equipment, including whether the item or equipment is for use by healthcare practitioners or patients

Establishment of clinical expertise to predict positive patient outcomes and ensure adequate access

The specialized expertise, experience, imaging equipment, and facilities equipped to optimize outcomes for TTVR patients are not available in all hospital programs. However, while TTVR is a novel procedure, transcatheter expertise with structural heart procedures has been built and developed by centers for over a decade with experience in transcatheter aortic valve replacement (TAVR) and mitral valve transcatheter edge-to-edge repair (M-TEER) technologies. The procedural experience from TAVR and M-TEER has established a foundation of specialists, imaging equipment, procedural facilities, and support infrastructure for transcatheter procedures in hospital programs across the country.

While we maintain that the deployment of TTVR technologies must be implemented in a controlled and regulated fashion to ensure positive patient outcomes, we recommend that CMS recognize the maturity of the cardiac transcatheter procedural landscape in which TTVR is being introduced. In addition to the technical expertise and infrastructure needed to provide TTVR safely and effectively to Medicare patients, Edwards also recommends CMS consider the impact any site criteria will have on patient access (e.g., geographic distance and transportation barriers) to this innovative technology. There have been multiple analyses and publications regarding TAVR access demonstrating that underserved communities have lower rates of intervention, resulting in inequities in access to care.[49,50]

Multidisciplinary heart teams

The concept of a multidisciplinary professional heart team was formally introduced beginning with the SYNTAX (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries, 2010) trial for patients with advanced coronary artery disease. Since then, the concept of a multidisciplinary heart team has been endorsed and recommended in clinical guidelines published by the American College of Cardiology (ACC) and the American Heart Association (AHA) and incorporated more broadly in clinical practice within the structural heart space.

Both the TAVR and M-TEER coverage determinations incorporate the coordination amongst a "heart team," reflective of the clinical expertise needed for each treatment modality. As evidence evolves and innovations mature and become standards of care for patients, heart teams may evolve and be adapted to better meet the needs of patients, institutional protocols, and minimize access barriers for underserved geographic regions. As such, as experience with innovation deepens, the defined heart team may gradually look different for established therapies, such as TAVR, compared to the requirements incorporated into novel procedures, as with TTVR.

Within the TRISCEND II pivotal trial, patient evaluation was typically conducted by the interventional cardiologist, with consultation and final determination of eligibility and patient benefit in collaboration with the local heart team, inclusive of a cardiologist, cardiac surgeon, heart failure specialist, and echocardiographer. Local heart team collaboration consisted of pre-procedural evaluation in valvular heart disease clinics and multidisciplinary team conferences. Key expertise within the multidisciplinary team managing patients with tricuspid valve disease within the trial included primary cardiology, interventional cardiology, cardiac surgery, noninvasive and heart failure cardiology, echocardiography, cardiac imaging, and cardiac anesthesiology, as well as other support staff to care for complex patient needs inclusive of nurse practitioners, physician assistants, research coordinators, administrators, dietary and rehabilitation specialists, and social workers.

Primary cardiology

Primary cardiologists typically care for these patients longitudinally over the course of their diseases and have a unique perspective of patient and family dynamics. These physicians coordinate care, ensure complete evaluation, order and evaluate diagnostic studies, implement medical care, and ensure involvement of patients and families in the decision-making process. Primary cardiologists also resume care of the patient after the procedure and need to be cognizant of the follow-up needs and protocols; accordingly, individuals with this type of clinical experience are an essential component of the heart team to enhance patient-centered care. The patient's values and goals need to be central in benefit-risk assessment and treatment decisions.

Interventional cardiology and cardiac surgery

Interventional cardiologists or cardiac surgeons who have had appropriate training and experience will provide treatment and management for TTVR patients. In some cases, at the discretion of the heart team, two physicians may evaluate and perform the procedure together. In other cases, only one physician will evaluate and perform the procedure. In the context of the TRISCEND II trial, an interventional cardiologist and cardiac surgeon frequently performed the intra-operative components of the procedure, which was appropriate given the procedures were performed as a part of a clinical trial. In either situation, the physician who performs the procedure (alone or jointly) will have responsibility in the technical aspect of the procedure. Minimum ongoing case volumes should be established to ensure that cardiac surgeons and interventional cardiologists continue to have the required skills to participate in the use of this technology and that they have the required experience to make patient-centric and safe decisions about which Medicare beneficiaries are acceptable candidates for TTVR.

Echocardiography and imaging specialty

Imaging modalities necessary for a structural heart disease program include 2- and 3-dimensional transthoracic and transesophageal echocardiography. While TTE and TEE are frequently used imaging modalities in transcatheter procedures, 3D ICE is an alternative technique used to identify cardiac anatomy and provide guidance for intracardiac procedures. Both traditional TTE/TEE and 3D ICE can be appropriately leveraged by the experienced imager performing the imaging for the TTVR procedure.

An important assessment for determining the severity of TTVR involves a TTE that establishes the severity of tricuspid regurgitation using the guidelines based on echocardiography ACC/AHA guidelines and the American Society of Echocardiography Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation. Individuals with this level of knowledge and experience will be Level 3 echocardiographers. The echocardiography is used to determine that

the patient has at least severe tricuspid regurgitation as defined echocardiographically by a combination of physiologic, structural, and functional criteria.[51]

Heart failure specialty

Identification of appropriate patients with tricuspid regurgitation and heart failure who may benefit from a catheter-based approach is best accomplished by consultation with a cardiologist experienced in treating advanced heart failure. Additionally, physicians with experience in treating advanced heart failure will be critical for fluid management of TTVR patients prior to the procedure. Fluid optimization in patients undergoing TTVR is critically important as these patients often have significant fluid overload pre-operatively. Chronic excess volume in the presence of tricuspid regurgitation is typically well-tolerated by the RV. However, following the immediate reversal of the regurgitation with TTVR, the resulting increase in afterload pressure, preload and contractility of the RV may be unable to compensate resulting in a reduction of the stroke volume.[52] As such, cardiologists with experience managing tricuspid regurgitation and heart failure patients are a critical component of the heart team in ensuring adequate fluid volumes pre- and post-operatively.

Anesthesiology

The anesthesiologist determines the most appropriate anesthesia and monitoring techniques for the patient and may provide technical expertise in advanced imaging.

Establishment of a national registry for valvular heart disease

The Society for Thoracic Surgery (STS) and ACC Transcatheter Valve Therapy (TVT) registry is an established registry that has been critical for the ongoing collection of data for TAVR and M-TEER. A registry module to supplement the existing TVT registry for transcatheter tricuspid valve procedures has been developed by the STS and ACC in conjunction with input from other relevant stakeholders.

There is infrastructure and experience within the TVT registry, which has been critical for the collection of data for other transcatheter procedures and can be leveraged for the ongoing data collection for TTVR. While supportive of the need for ongoing data collection, it is necessary to balance the need for clinical data demonstrating procedural outcomes with the workload placed on those who report and collect the data. Additionally, not only will the data collected via the TVT Registry support the establishment of clinical expertise to predict positive patient outcomes and ensure adequate access, but we also believe the data from the registry will provide deep insights for patients to support informed choices about treatment.

Registry data, such as data from the TVT Registry, may be merged with Medicare and potentially other claims databases to study the effectiveness of TTVR in the real-world.

Training and credentialing criteria

Operator training is a crucial component for treating structural valvular heart disease using a TTVR approach. Training for proceduralists and echocardiographers is required for the use of the EVOQUE system, as defined by the FDA label. Initial training requirements consist of a didactic training session and hands-on product training.

There will be transcatheter case volume requirements for TTVR proceduralists. Either the interventional cardiologist or surgeon performing the procedure will need to have appropriate training in order to establish a TTVR program. Following the establishment of a program, all members of the multidisciplinary team will need to maintain volume requirements for continued

participation and will be monitored on an ongoing basis to ensure acceptable outcomes using real-world evidence collected via a prospective, national, audited registry. The institutional structural requirements and interventional cardiologist, cardiac surgeon, and echocardiographer volume and outcomes criteria for TTVR will be modeled after the CMS criteria for TAVR and M-TEER, with appropriate modifications based on the clinical differences of the TTVR procedure supported by society recommendations and clinical practice.

8. Benefits and relevance of procedure to the Medicare population

An explanation of the relevance of the evidence selected
Prior to the introduction of TTVR technology, there were Medicare beneficiaries who were not considered to have any effective treatment for their tricuspid regurgitation other than medical management. Surgical intervention is currently only performed in a very narrow patient population, and surgical replacement is performed with off-label use of devices.

The evidence summarized within this request from early clinical experience and the single arm TRISCEND and randomized pivotal TRISCEND II studies demonstrates that TTVR now offers a safe and effective alternative to medical management alone.

Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population
The evidence presented in this request demonstrates that, based on the FDA approval of the EVOQUE system, Medicare patients with at least severe tricuspid regurgitation will have access to a safe and effective therapy for tricuspid regurgitation. The safe and appropriate application of TTVR in the Medicare population should be limited to structural heart valve centers with appropriately trained surgeons, interventional cardiologists, and other members of the identified multidisciplinary team. The results of the TRISCEND II pivotal trial in such established centers have demonstrated that this technology can be used in the Medicare population with acceptable results.

Information that examines the magnitude of the medical benefit
The results of the Breakthrough Pathway Cohort of the TRISCEND II pivotal trial demonstrate the following benefits associated with TTVR using EVOQUE in conjunction with OMT:

i) An acceptable 30-day safety profile, as a composite of MAEs for the EVOQUE system compared to isolated tricuspid valve replacement surgery,
ii) Superiority of EVOQUE+OMT versus OMT alone in tricuspid regurgitation grade reduction at 6 months, and
iii) Superiority of EVOQUE+OMT versus OMT alone in an analysis of a hierarchical composite of clinically meaningful symptomatic and functional improvement measures (KCCQ, NYHA functional classification, and 6MWT) at 6 months.
iv) The available 12-month data for the Randomized Cohort show positive trending for reduced all-cause mortality and heart failure hospitalization, a reduced rate of tricuspid valve surgery and intervention, and sustained symptomatic and functional improvement for patients with severe or greater tricuspid regurgitation in the EVOQUE+OMT group compared to the OMT alone group.

The study populations in which EVOQUE was evaluated (early clinical use, TRISCEND, and TRISCEND II) all involved patients primarily of Medicare age. Therefore, the results are fully applicable to the Medicare population at large with at least severe tricuspid regurgitation not adequately managed with medical therapy. Given the demographics of patients with at least severe tricuspid regurgitation and the progressive nature of the condition, most cases in the United States will likely be performed in the Medicare population.

Reasoning for how coverage of the item or service will help improve the medical benefit to the target population

Delaying coverage for this novel therapy will likely result in a significant patient population to remain without effective treatment for tricuspid regurgitation, which is particularly impactful given the progressive nature of the disease and its symptoms. The benefits associated with TTVR, as described in the summary of the clinical evidence in section 12, should be considered relative to the fact that medical management is palliative and likely to provide only temporary symptom relief for most patients. Coverage of the TTVR procedure will allow previously untreated Medicare patients with a diagnosis of tricuspid regurgitation to receive safe and effective treatment of their disease that has not been available until now. This allows the target Medicare population with tricuspid regurgitation to have an improvement in their tricuspid regurgitation grade and improve their quality of life.

9. A description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service

There are currently two ongoing clinical trials in the U.S. evaluating the use of the EVOQUE system:

1. TRISCEND single-arm study
2. TRISCEND II pivotal trial

The TRISCEND single-arm study (NCT04221490) has completed enrollment in the U.S. Thirty-day (N=53) and 1-year (N=176) results have been published. Outcomes will be measured in the full cohort annually through 5-years.

The primary outcome measured at 30-days is freedom from device or procedure related adverse events. Secondary outcome measures (measured at 30-days, six months, 12 months, and annually for five years) include:

- Reduction in tricuspid regurgitation grade from baseline
- NYHA functional class improvement
- 6MWD improvement
- QoL improvement (KCCQ overall summary score)
- Improvement in health status (36 item short form survey)

TRISCEND II pivotal trial (NCT04482062) is a prospective, multi-center, randomized controlled pivotal clinical trial to evaluate the safety and effectiveness of the EVOQUE system with OMT compared to OMT alone in the treatment of patients with at least severe tricuspid regurgitation. Subjects are followed at discharge, 30 days, 3 months, 6 months and annually through 5 years. Enrollment in the randomized cohort concluded in 2023.

Enrollment in the clinical trial included 400 randomized patients over 23 months, with a 2:1 treatment assignment ratio to the EVOQUE system + OMT or OMT alone at 45 study sites in the U.S. and Germany. The Breakthrough Pathway Cohort included 150 patients (96 EVOQUE system + OMT and 54 OMT alone) enrolled at 30 sites (26 U.S. / 4 EU). Of the 150 patient cohort, 136 received treatment in the U.S.

As submitted in the FDA pre-market approval (PMA) submission based on the Breakthrough Pathway Cohort, the primary safety and effectiveness endpoints to evaluate the EVOQUE tricuspid replacement system include:

- Co-Primary effectiveness endpoints:

At 6 months post-implant, the following endpoints are assessed for the randomized cohort:
    - Tricuspid regurgitation grade reduction to moderate, mild, or trace/none
    - A hierarchical composite endpoint determined by pair-wise comparisons among all randomized patients according to the following pre-specified hierarchy of outcomes:
        1. QoL improvement (KCCQ overall summary score)
        2. NYHA functional class improvement
        3. 6MWD improvement
- Primary safety endpoint
  At 30 days, safety will be analyzed in the test group as a composite endpoint of the following MAEs:
    - Cardiovascular mortality
    - Myocardial infarction
    - Stroke
    - New need for renal replacement therapy
    - Severe bleeding
    - Non-elective tricuspid valve re-intervention, percutaneous or surgical
    - Major access site and vascular complications
    - Major cardiac structural complications due to access-related issues
    - Device-related pulmonary embolism
    - Arrhythmia and conduction disorder requiring permanent pacing

Descriptive analyses for components of the 12-month primary safety and effectiveness endpoint for available randomized cohort data were also submitted in the PMA. At 12 months, a pre-specified hierarchical composite endpoint will be assessed in the full randomized cohort:

- All-cause mortality
- RVAD implantation or heart transplant
- Tricuspid valve surgery or percutaneous tricuspid intervention
- Annualized rate of heart failure hospitalizations
- QOL improvement (by KCCQ overall summary score)
- NYHA functional class improvement
- 6MWD improvement

10. Use of device subject to FDA regulations and the status of the current FDA regulatory review

There are currently multiple companies involved in the development of TTVR devices. Some of the companies that are involved in the development of TTVR devices include the following: EVOQUE System (Edwards Lifesciences), Intrepid (Medtronic), LuX-Valve (Jenscare Biotechnology), GATE bioprothesis (Navigate Cardiac Structures), Topaz (TRiCares), VDyne valve (VDYNE), and TRISOL Valve (Trisol Medical). Many of these companies are currently sponsoring trials to evaluate the replacement systems. To the best of our knowledge, the EVOQUE Tricuspid Valve Replacement System is the first tricuspid valve replacement device that has completed a clinical trial evaluating safety and efficacy, and is the first to receive FDA approval in the U.S.

Product information and descriptions provided below (Accessed June 29, 2023).[53, 54]

EVOQUE (Edwards Lifesciences)
The EVOQUE tricuspid valve replacement system (Edwards Lifesciences, Irvine, CA, USA) is a new, transcatheter treatment option indicated for the improvement of health status in patients with

symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy for whom tricuspid valve replacement is deemed appropriate by a Heart Team. The EVOQUE system is designed to replace the native tricuspid valve without the need for conventional open-heart surgery. The valve consists of a trileaflet bovine pericardial tissue valve, nitinol frame, and fabric skirt. Edwards received FDA approval for the EVOQUE valve in 3 sizes with outer frame diameters of 44mm, 48mm, and 52mm. While a larger 56mm size valve was approved for use in the TRISCEND II trial, it was not in scope for the FDA approval issued on February 1, 2024. Valve size selections are based on native valve annulus size, as measured by computed tomography.

The EVOQUE system is currently being evaluated in two ongoing clinical trial in the United States (NCT04482062; NCT04221490) and one in Japan (NCT05760989).

Intrepid™ TTVR System (Medtronic)
The Intrepid™ System (Medtronic, Minneapolis, MN, USA) is available in 42mm and 48 mm sizes and received Breakthrough Device Designation by the FDA. The Intrepid valve is composed of a nitinol frame with trileaflet bovine pericardial valve. The frame has two constituents: (1) Outer fixation rim that comes two sizes (42mm or 48mm diameter); (2) Inner 27mm frame, which houses the valve. The valve uses simple anchors to stabilize the valve without leaflet or chord capture. The delivery system is through a 35 Fr sheath.

The Intrepid TTVR System is currently recruiting for an early feasibility study in the United States to gain early clinical insight into the performance of the Intrepid transcatheter tricuspid valve replacement system intended for transfemoral access to deliver a self-expanding bioprosthetic valve within the tricuspid valve (NCT04433065).

LuX-Valve (Ninbo Jenscare Biotechnology)
The LuX-Valve (Ningbo Jenscare Biotechnology Co. Ltd., Ningbo, China) is a radial force independent orthotopic transcatheter TV consisting of four components: (1) trileaflet prosthetic valve with bovine pericardium, (2) self-expanding nitinol alloy frame, (3) interventricular septal anchor or tongue, (4) polytetrafluoroethylene-covered grasper. The LuX-valve is delivered via a 32 Fr system via right thoracotomy and transapical approach.

The LuX-Valve system is currently recruiting for several early feasibility trials in China and France. No clinical trials have been initiated in the United States. (NCT04436653; NCT05436028; NCT05194423)

GATE (Navigate Cardiac Structures, Inc.)
The GATE™ bioprosthesis (NaviGate Cardiac Structures, Inc., Lake Forest, CA, USA) is a self-expanding nitinol alloy prosthesis into which equine pericardium is mounted. The valve is designed to engage both the tricuspid annulus as well as tricuspid leaflets via 12 atrial winglet and 12 ventricular tines. The inferior diameter is configured to match the dilated annulus commonly encountered in the functional tricuspid regurgitation. The valve comes in four sizes ranging from 36mm to 52mm with oversizing of around 2%–5%.

There are currently no clinical trials underway to evaluate the safety and efficacy of the GATE bioprothesis tricuspid valve replacement system.

Topaz (TRiCares)
The Topaz Transfemoral Tricuspid Heart Valve Replacement System (TRiCares, Aschheim, Munich, Germany) is bovine pericardial valve mounted on a self-expanding nitinol stent frame with both atrial and ventricular widening to ensure adequate anchoring of the valve.

The Topaz replacement system is currently recruiting for a first in human trial in Europe (Belgium & France). (NCT05126030)

VDyne System (VDyne, Inc.)
The VDyne Transcatheter Tricuspid Valve Replacement System (VDyne, Inc., Maple Grove, Minnesota, USA) consists of a bioprosthetic implantable tricuspid valve, the VDyne Delivery System, Drop Tether, accessories that facilitate the placement of the valve and the VDyne Retrieval System. The VDyne Valve is deployed by transfemoral implantation within the native tricuspid valve and is implanted under fluoroscopic and transesophageal echocardiography (TEE) guidance, while the heart remains beating, without the use of CPB. The valve is repositionable and fully retrievable intraoperatively. Repositioning allows optimization of the valve position following deployment, and retrieval, with the VDyne Retrieval System, allows use of an alternative valve size or removal of the index VDyne Valve in the event of suboptimal valve delivery or other intraoperative complication. (Source: https://clinicaltrials.gov/ct2/show/NCT05797519)

The VDyne system is currently recruiting for an early feasibility study in Australia and Czechia to evaluate the safety and clinical efficacy of the VDyne System in the treatment of moderate to severe tricuspid regurgitation (NCT05797519).

Trisol (Trisol Medical)
The Trisol valve (Trisol Medical, Yokneam, Israel) consists of a atrial polyester skirt and a ventricular porcine pericardial skirt. The dome shaped leaflet of the valve is made of the bovine pericardium and creates a bileaflet valve. The valve framework is constructed from the nitinol self-expanding framework with a conical shape to accommodate all annular sizes. Additionally, the conical arms help in anchoring via a sandwich effect. The valve is delivered via a 30 Fr steerable delivery system and is valve is retrievable and repositionable.

An early feasibility study is currently underway and recruiting in the United States to evaluate the safety and effectiveness of the Trisol replacement system. (NCT04905017)

11. Relevant literature to support the coverage of TTVR

To support the FDA approval of the EVOQUE system, Edwards sponsored TRISCEND and TRISCEND II clinical studies. The results from the TRISCEND II pivotal randomized clinical trial were evaluated by the FDA to support its approval determination of the EVOQUE tricuspid valve replacement system.

This presentation of evidence summarizes the current data available related to TTVR treatment. The evidence summarized focuses on the health outcomes, such as procedural success, mortality, reoperations, and adverse events, and impact on patient quality of life. It is noted where the evidence may be generalizable to the Medicare population based on age and overall patient demographics.

Edwards performed a literature search on June 9, 2023, utilizing PubMed, Cochrane, and Embase. Search terms included “EVOQUE”, “transcatheter tricuspid valve replacement,” and “transcatheter tricuspid valve intervention.” The literature search was limited to the English language, but included studies published in all journals, regardless of country.

The search found 214 unique publications. Case studies and commentary were excluded; transcatheter tricuspid valve intervention (TTVI) articles that did not include TTVR as a studied modality were excluded; and studies with sample sizes that were less than 25 were also excluded. We supplemented the search with a review of the reference lists of the systematic review and

publications demonstrating clinical experience with the EVOQUE system irrespective of sample size or article type. In total, we identified eleven articles evaluating the clinical impact of TTVR on patient outcomes. There was one prospective single-arm study, two systematic reviews, and eight observational studies.

Below are references, links, and abstracts from each of the identified supporting literature grouped by EVOQUE-specific literature, TTVR systematic reviews, and observational studies. These publications supplement the robust evidence base beyond TRISCEND and TRISCEND II studies. We also include links to other relevant publications (inclusive of physician thought pieces and other case studies related to TTVR experience).

EVOQUE Evidence

To date, approximately 1,000 patients have been treated with the EVOQUE system, indicating a growing breadth of clinical experience and learning with the TTVR procedure. The clinical experience that has been published is summarized in the table and sections below.

Title (Year)	Authors	Sample Size	Evidence Generated
TRISCEND II Randomized Control Trial: 6-months and trending 1-year analysis			
TRISCEND II pivotal trial results: Breakthrough Pathway Cohort[55] (2024) *(Summarized in Section 6)*	Edwards EVOQUE Tricuspid Valve Replacement System FDA Labeling (P230013)	N=150	Safety and efficacy of the EVOQUE + OMT group versus OMT-alone at 6 months
TRISCEND Single-arm Study: 30-day, 6-months, and 1-year results			
Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study[56] (2023)	Manuscript submitted for peer-review; publication expected 2023	N=176**	Prospective, single-arm, multicenter study demonstrating feasibility, acceptable safety, tricuspid regurgitation reduction, and symptomatic improvement at 1-year
Transfemoral Tricuspid Valve Replacement in Patient with Tricuspid Regurgitation: TRISCEND study 30-day results[57] (2022)	Kodali S, Hahn RT, George I, et al.	N=53	…at 30 days
Early Clinical Experience			
2-Year outcomes Following Transcatheter Tricuspid Valve Replacement Using the EVOQUE System[58] (2023)	Stolz L, Weckbach LT, Hahn RT, et al.	N=38	Long-term durability (2 years) of the EVOQUE device
Transcatheter tricuspid valve replacement with the EVOQUE system: 1-year outcomes of a multicenter, first-in-human experience[59] (2022)	Webb JG, Chuang AM, Meier D, et al.	N=27	Early compassionate use of the EVOQUE system demonstrating durable efficacy and improvement in tricuspid regurgitation at one year
Right Ventricular Reverse Remodeling After Transcatheter Tricuspid Valve Replacement in Patients with Heart Failure[60] (2023)	Weckbach LT, Stolz L, Chatfield AG, et al.	N=25	RV remodeling and increased LV stroke volume following TTVR
Transfemoral transcatheter tricuspid valve replacement with the EVOQUE system: a multicenter, observational, first-in-human experience[61] (2020)	Fam NP, Bardeleben RS, Hensey M, et al.	N=25	First-in-human experience evaluating EVOQUE TTVR demonstrated high technical success, acceptable safety, and significant clinical improvement at 30-days
Transfemoral Transcatheter Tricuspid Valve Replacement[62] (2020)	Fam NP, Ong G, Deva DP, Peterson MD	N=1	Clinical experience for TTVR procedural success

Kodali S, Hahn RT, Makkar R, et al. Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. Eur Heart J. 2023 Dec 7;44(46):4862-4873.

Objectives

The TRISCEND study (Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device) is evaluating the safety and performance of transfemoral transcatheter tricuspid valve replacement in patients with clinically significant tricuspid regurgitation and elevated surgical risk.

Background
For patients with symptomatic, severe tricuspid regurgitation (TR), early results of transcatheter tricuspid valve (TV) intervention studies have shown significant improvements in functional status and quality of life associated with right-heart reverse remodeling. Longer-term follow-up is needed to confirm sustained improvements in these outcomes.

Methods
The prospective, single-arm, multicentre TRISCEND study enrolled 176 patients to evaluate the safety and performance of transcatheter TV replacement in patients with ≥moderate, symptomatic TR despite medical therapy. Major adverse events, reduction in TR grade and haemodynamic outcomes by echocardiography, and clinical, functional, and quality-of-life parameters are reported to one year.

Results
Enrolled patients were 71.0% female, mean age 78.7 years, 88.0% ≥ severe TR, and 75.4% New York Heart Association classes III-IV. Tricuspid regurgitation was reduced to ≤mild in 97.6% ($P < .001$), with increases in stroke volume (10.5 ± 16.8 mL, $P < .001$) and cardiac output (0.6 ± 1.2 L/min, $P < .001$). New York Heart Association class I or II was achieved in 93.3% ($P < .001$), Kansas City Cardiomyopathy Questionnaire score increased by 25.7 points ($P < .001$), and six-minute walk distance increased by 56.2 m ($P < .001$). All-cause mortality was 9.1%, and 10.2% of patients were hospitalized for heart failure.

Conclusions
In an elderly, highly comorbid population with ≥moderate TR, patients receiving transfemoral EVOQUE transcatheter TV replacement had sustained TR reduction, significant increases in stroke volume and cardiac output, and high survival and low hospitalization rates with improved clinical, functional, and quality-of-life outcomes to one year.

Kodali S, Hahn RT, George I, et al. Transfemoral Tricuspid Valve Replacement in Patient With Tricuspid Regurgitation: TRISCEND study 30-day results. J Am Coll Cardiol Intv. 2022; 15:471–480.

Objectives
The TRISCEND study (Edwards EVOQUE Tricuspid Valve Replacement: Investigation of Safety and Clinical Efficacy after Replacement of Tricuspid Valve with Transcatheter Device) is evaluating the safety and performance of transfemoral transcatheter tricuspid valve replacement in patients with clinically significant tricuspid regurgitation and elevated surgical risk.

Background
Transcatheter valve replacement could lead to a paradigm shift in treating tricuspid regurgitation and improving patient quality of life.

Methods
In the prospective, single-arm, multicenter TRISCEND study, patients with symptomatic moderate or greater tricuspid regurgitation, despite medical therapy, underwent percutaneous transcatheter tricuspid valve replacement with the EVOQUE system. A composite rate of major adverse events, echocardiographic parameters, and clinical, functional, and quality-of-life measures were assessed at 30 days.

Results
Fifty-six patients (mean age of 79.3 years, 76.8% female, 91.1% TR severe or greater, 91.1% atrial fibrillation, and 87.5% New York Heart Association functional class III or IV) were treated, with 3 patients lost to follow-up. At 30 days, tricuspid regurgitation was reduced to mild or less in 98% of patients. The composite major adverse events rate was 26.8% at 30 days caused by 1 cardiovascular death in a patient with a failed procedure, 2 reinterventions after device embolization, 1 major access site or vascular complication, and 15 severe bleeds, of which none were life-threatening or fatal. No myocardial infarction, stroke, renal failure, major cardiac structural complications, or device-related pulmonary embolism were observed. New York Heart Association significantly improved to functional class I or II (78.8%; $P < 0.001$), 6-minute walk distance improved 49.8 m ($P < 0.001$), and KCCQ score improved 19 points ($P < 0.001$).

Conclusions
Early experience with the transfemoral EVOQUE system in patients with clinically significant tricuspid regurgitation demonstrated technical feasibility, acceptable safety, tricuspid regurgitation reduction, and symptomatic improvement at 30 days. The TRISCEND II randomized trial (NCT04482062) is underway.

Stolz L, Weckbach LT, Hahn RT, et al. 2-Year outcomes Following Transcatheter Tricuspid Valve Replacement Using the EVOQUE System. J Am Coll Cardiol. 2023; 81:2374-2376.

Summary of Results (Abstract Unavailable)
This was a retrospective analysis of symptom burden, echocardiographic outcomes, adverse events, and survival at 2 years among patients who were treated with the EVOQUE system under compassionate use between 2019 and 2021 at 8 centers in Europe, the United States, and Canada. The 38 patients studied had an average age of 77 ± 12 years, 28 (74%) of the patients were female, and all patients had at least severe tricuspid regurgitation at the time of intervention.

Tricuspid regurgitation was successfully reduced to mild or trace/none in almost all patients (97%) following the procedure and results were durable in 94% of patients at the latest available follow-up (median 520 days). Survival rates for the patients were 86% and 71% at 1 and 2 years, respectively.

Improvement in functional patient status (as evaluated using NYHA functional class) was reported in 72% of patients. Prior to intervention, 92% of patients were NYHA functional class ≥ III; compared to 20% after intervention.

TTVR utilizing the EVOQUE system reduced symptoms of right-sided heart failure: reduction in peripheral edema from 71% to 37% and ascites from 50% to 14% of patients.

The results from the early compassionate use of the EVOQUE replacement system demonstrate strong procedural success and reduction in clinical symptoms of TR in long-term follow-up of the patient population.

Webb JG, Chuang AM, Meier D, et al. Transcatheter tricuspid valve replacement with the EVOQUE system: 1-year outcomes of a multicenter, first-in-human experience. J Am Coll Cardiol Intv. 2022; 15:481–491.

Objectives
The aim of this study was to report the midterm outcomes at 1 year in the expanded first-in-human experience with the transfemoral EVOQUE system (Edwards Lifesciences) for tricuspid regurgitation.

Background
Untreated tricuspid regurgitation is associated with excess mortality and morbidity. The first-in-human experience with the EVOQUE tricuspid valve replacement system reported favorable 30-day outcomes with no mortality in a compassionate use population.

Methods
Twenty-seven patients with severe tricuspid regurgitation were treated with the EVOQUE system in a compassionate use experience at 7 centers between May 2019 and July 2020. All patients had clinical right-sided heart failure (HF) and were deemed inoperable and unsuitable for transcatheter edge-to-edge repair by the institutional heart teams. The clinical outcomes collected included all-cause mortality, symptom status, tricuspid regurgitation severity, HF hospitalization, and major adverse cardiovascular events.

Results
At baseline, all patients (age: 77 ± 8 years, 89% female) were at high surgical risk (mean Society of Thoracic Surgeons score: 8.6% ± 5.5%), with 89% New York Heart Association functional class III/IV. Tricuspid regurgitation was predominantly functional in etiology (19/27, 70%). At 1 year, mortality was 7% (2/27), 70% of patients were New York Heart Association functional class I/II, and 96% and 87% of patients had a TR grade ≤2+ and ≤1+, respectively. Between 30 days and 1 year, two patients experienced HF hospitalizations, and one patient required a new pacemaker implantation.

Conclusions
In this early, compassionate use experience, the transfemoral transcatheter EVOQUE tricuspid valve replacement system demonstrated durable efficacy, persistent improvement in symptom status, and low rates of mortality and HF hospitalizations at a 1-year follow-up. Further studies are underway to validate its efficacy.

Fam NP, et al. Transfemoral transcatheter tricuspid valve replacement with the EVOQUE system: a multicenter, observational, first-in-human experience. JACC Cardiovasc Interv. 2021; 14:501-11.

Objectives
The purpose of this observational first-in-human experience was to investigate the feasibility and safety of the EVOQUE tricuspid valve replacement system and its impact on short-term clinical outcomes.

Background
Transcatheter tricuspid intervention is a promising option for selected patients with severe tricuspid regurgitation. Although transcatheter leaflet repair is an option for some, transcatheter tricuspid valve replacement (TTVR) may be applicable to a broader population.

Methods
Twenty-five patients with severe tricuspid regurgitation underwent EVOQUE TTVR in a compassionate-use experience between May 2019 and February 2020. The primary outcome was technical success, with NYHA functional class, tricuspid regurgitation grade, and major adverse cardiac and cerebrovascular events assessed at 30-day follow-up.

Results
All patients (mean age 76 ± 3 years, 88% women) were at high surgical risk (mean Society of Thoracic Surgeons risk score 9.1 ± 2.3%), with 96% in NYHA functional class III or IV. Tricuspid regurgitation etiology was predominantly functional, with mean tricuspid annular

diameter of 44.8 ± 7.8 mm and mean tricuspid annular plane systolic excursion of 16 ± 2 mm. Technical success was 92%, with no intraprocedural mortality or conversion to surgery. At 30-day follow-up, mortality was 0%, 76% of patients were in NYHA functional class I or II, and tricuspid regurgitation grade was ≤2+ in 96%. Major bleeding occurred in 3 patients (12%), 2 patients (8%) required pacemaker implantation, and 1 patient (4%) required dialysis.

Conclusions
This first-in-human experience evaluating EVOQUE TTVR demonstrated high technical success, acceptable safety, and significant clinical improvement. Larger prospective studies are needed to confirm durability and safety and the impact on long-term clinical outcomes.

Weckbach LT, et al. Right Ventricular Reverse Remodeling After Transcatheter Tricuspid Valve Replacement in Patients With Heart Failure. JACC. 2023; 81(7):708-710.

The authors conducted a retrospective analysis of the patient population (n=25) studied in Fam, et al., 2022, evaluating first-in-human experience with the EVOQUE system to identify the impact of the TTVR intervention on RV reverse remodeling. It was found that there was a substantial (35%) reduction of RV end-diastolic volumes, suggesting RV reverse remodeling following the intervention.

In the context of T-TEER and TV surgical intervention, RV reverse remodeling is associated with increased survival following intervention. As such, these results of remodeling following TTVR may have similar impact on survival.

Fam NP, et al. Transfemoral transcatheter tricuspid valve replacement. JACC Cardiovasc Interv. 2020;13:e93-e94.

In a case study evaluating the use of the EVOQUE system to treat a 75-year-old heart failure patient with severe tricuspid regurgitation, Fam, et al., describe the distinction between the potential patient population eligible for T-TEER versus TTVR.

Systematic Reviews
Buğan B, Çekirdekçi EI, Onar LC, and Barçin C. Transcatheter Tricuspid Valve Replacement for Tricuspid Regurgitation: A Systematic Review and Meta-analysis. Anatolian Journal of Cardiology (2022) 26:7 (505-519).

Background
The present data aim to evaluate the feasibility of the orthotopic transcatheter tricuspid valve replacement devices, echocardiographic, functional improvements, and mortality rates following replacement in patients with significant tricuspid valve regurgitation.

Methods
The authors systematically searched for studies evaluating the efficacy and safety of transcatheter tricuspid valve replacement for significant tricuspid valve regurgitation. The efficacy and safety outcomes were the improvements in New York Heart Association functional class, 6-minute walking distance, all-cause death, and periprocedural and long-term complications. In addition, a random-effect meta-analysis was performed comparing outcomes before and after transcatheter tricuspid valve replacement.

Results
Nine studies with 321 patients were included. The mean age was 75.8 years, and the mean European System for Cardiac Operative Risk Evaluation II score was 8.2% (95% CI: 6.1 to 10.3). Severe, massive, and torrential tricuspid valve regurgitation was diagnosed in 95% of patients

(95% CI: 89% to 98%), and 83% (95% CI: 73% to 90%) of patients were in New York Heart Association functional class III or IV. At a weighted mean follow-up of 122 days, New York Heart Association functional class (risk ratio = 0.20; 95% CI: 0.11 to 0.35; P < .001) and 6-minute walking distance (mean difference = 91.1 m; 95% CI: 37.3 to 144.9 m; P < .001) significantly improved, and similarly, the prevalence of severe or greater tricuspid valve regurgitation was significantly reduced after transcatheter tricuspid valve replacement (baseline risk ratio = 0.19; 95% CI: 0.10 to 0.36; P < .001). In total, 28 patients (10%; 95% CI: 6% to 17%) had died. Pooled analyses demonstrated non-significant differences in hospital and 30-day mortality and >30-day mortality than predicted operative mortality (risk ratio = 1.03; 95% CI: 0.41 to 2.59; P = .95, risk ratio = 1.39; 95% CI: 0.69 to 2.81; P = .35, respectively).

Conclusion
Transcatheter tricuspid valve replacement could be an emerging treatment option for patients with severe tricuspid regurgitation who are not eligible for transcatheter repair or surgical replacement because of high surgical risk and poor prognosis.

Edwards Note: This systematic review included publications that studied the following devices: Evoque (Edwards Lifescience, Irvine, CA, USA), LuX-Valve (Jenscare Biotechnology, Ningbo, China), NaviGate (NaviGate Cardiac Structures Inc., Lake Forest, CA, USA). LuX-Valve and NaviGate are not under clinical study in the United States. The concluding statement in this study indicates a narrower patient population than what has been submitted to the FDA as the proposed indication for use. Patients in the TRISCEND II trial were not required to be surgery-ineligible.

Ricci F, Bufani G, Galusko V., et al. Tricuspid regurgitation management: a systematic review of clinical practice guidelines and recommendations. European heart journal. Quality of care & clinical outcomes (2022) 8:3 (238-248).

Tricuspid regurgitation is a highly prevalent condition and an independent risk factor for adverse outcomes. Multiple clinical guidelines exist for the diagnosis and management of tricuspid regurgitation, but the recommendations may sometimes vary. The authors systematically reviewed high-quality guidelines with a specific focus on areas of agreement, disagreement, and gaps in evidence. The authors searched MEDLINE and EMBASE (1 January 2011 to 30 August 2021), the Guidelines International Network International, Guideline Library, National Guideline Clearinghouse, National Library for Health Guidelines Finder, Canadian Medical Association Clinical Practice Guidelines Infobase, Google Scholar, and websites of relevant organizations for contemporary guidelines that were rigorously developed (as assessed by the Appraisal of Guidelines for Research and Evaluation II tool). Three guidelines were finally retained. There was consensus on a TR grading system, recognition of isolated functional tricuspid regurgitation associated with atrial fibrillation, and indications for valve surgery in symptomatic vs. asymptomatic patients, primary vs. secondary tricuspid regurgitation, and isolated tricuspid regurgitation forms. Discrepancies exist in the role of biomarkers, complementary multimodality imaging, exercise echocardiography, and cardiopulmonary exercise testing for risk stratification and clinical decision-making of progressive TR and asymptomatic severe tricuspid regurgitation, management of atrial functional tricuspid regurgitation, and choice of TTVI. Risk-based thresholds for quantitative tricuspid regurgitation grading, robust risk score models for tricuspid regurgitation surgery, surveillance intervals, population-based screening programs, TTVI indications, and consensus on endpoint definitions are lacking.

Edwards Note: The expedited phase of the TRISCEND II pivotal trial establishes the EVOQUE system as a safe and effective treatment option for patients with at least severe tricuspid regurgitation. The EVOQUE device provides an effective treatment option to significantly reduce or eliminate tricuspid regurgitation, which is a life-threatening and/or debilitating condition, and

where no approved alternatives exist. It is anticipated that clinical guidelines and consensus will evolve as experience and evidence associated with the procedure grows.

Observational Studies

Muntane-Carol G, Taramasso M, Miura M, et al. Transcatheter Tricuspid Valve Intervention in Patients with Right Ventricular Dysfunction or Pulmonary Hypertension. Circulation: Cardiovascular Interventions (2021) 14:2 (E009685).

Background

Scarce data exist on patients with right ventricular dysfunction (RVD) or pulmonary hypertension (PH) undergoing transcatheter tricuspid valve intervention. This study aimed to determine the early and midterm outcomes and the factors associated with mortality in this group of patients.

Methods

This sub-analysis of the multicenter TriValve (Transcatheter Tricuspid Valve Therapies) registry included 300 patients with severe tricuspid regurgitation with RVD (n=244), PH (n=127), or both (n=71) undergoing transcatheter tricuspid valve intervention. RVD was defined as a tricuspid annular plane systolic excursion <17 mm, and PH as an estimated pulmonary artery systolic pressure ≥50 mm Hg.

Results

Mean age of the patients was 77±9 years (54% women). Procedural success was 80.7%, and 9 patients (3%) died during the hospitalization. At a median follow-up of 6 (interquartile range, 2–12) months, 54 patients (18%) died, and the independent associated factors were higher gamma-glutamyl transferase values at baseline (hazard ratio, 1.02 for each increase of 10 u/L [95% CI, 1.002–1.04]), poorer renal function defined as an estimated glomerular filtration rate <45 mL/min (hazard ratio, 2.3 [95% CI, 1.22–4.33]), and the lack of procedural success (hazard ratio, 2.11 [95% CI, 1.17–3.81]). The grade of RVD and the amount of PH at baseline were not found to be predictors of mortality. Most patients alive at follow-up improved their functional class (NYHA I–II in 66% versus 7% at baseline, P<0.001).

Conclusions

In patients with severe tricuspid regurgitation and RVD/PH, transcatheter tricuspid valve intervention was associated with high procedural success and a relatively low in-hospital mortality, along with significant improvements in functional status. However, about 1 out of 5 patients died after a median follow-up of 6 months, with hepatic congestion, renal dysfunction, and the lack of procedural success determining an increased risk. These results may improve the clinical evaluation of transcatheter tricuspid valve intervention candidates and would suggest a closer follow-up in those at increased risk.

Edwards Note: This study evaluates a subpopulation of patients with tricuspid regurgitation, RV dysfunction, and pulmonary hypertension. The results demonstrate procedural success in this subpopulation. The authors conclude that despite the high-risk profile of this population, high procedural success and functional improvements were observed. Hepatic congestion and renal dysfunction increased risk of mortality. Results, however, are limited in their applicability to TTVR, as ≤ 2.3% of the study population received TTVR as the treatment modality to address their tricuspid regurgitation.

Hahn, RT, et al. Early Multinational Experience of Transcatheter Tricuspid Valve Replacement for Treating Severe Tricuspid Regurgitation. JACC: Cardiovasc Interv. 2020;13:2482-2493.

Objectives

The aim of this registry was to evaluate the feasibility and safety of transcatheter TTVI in patients with extreme surgical risk.

Background
Isolated tricuspid regurgitation surgery is associated with high in-hospital mortality.

Methods
Thirty consecutive patients (mean age 75 ± 10 years; 56% women) from 10 institutions, with symptomatic functional tricuspid regurgitation, had institutional and notified body approval for compassionate use of the GATE TTVI system. Baseline, discharge, and 30-day follow-up echocardiographic data and procedural, in-hospital, and follow up clinical outcomes were collected.

Results
At baseline, all patients had multiple comorbidities, severe or greater tricuspid regurgitation, and reduced baseline right ventricular function. Technical success was achieved in 26 of 30 patients (87%). Device malpositioning occurred in 4 patients, with conversion to open heart surgery in 2 (5%). Of those who received the device, 100% had reductions in tricuspid regurgitation of ≥ 1, and 75% experienced reductions of ≥ 2 grades, resulting in 18 of 24 of patients (76%) with mild or less tricuspid regurgitation at discharge. All patients had mild or less central tricuspid regurgitation. There was continued improvement in tricuspid regurgitation grade between discharge and 30 days in 15 of 19 patients (79%). In-hospital mortality was 10%. At mean follow-up of 127 ± 82 days, 4 patients (13%) had died. Of patients alive at follow-up, 62% were in NYHA functional class I or II, with no late device-related adverse events.

Conclusions
Compassionate treatment of severe, symptomatic functional tricuspid regurgitation using a first-generation TTVI device is associated with significant reduction in tricuspid regurgitation and improvement in functional status with acceptable in-hospital mortality. Further studies are needed to determine the appropriate patient population and long-term outcomes with TTVI therapy.

Edwards Note: This study evaluated early clinical experience using the NaviGate (NaviGate Cardiac Structures Inc., Lake Forest, CA, USA). *The study population was limited to patients who were inoperable or at high surgical risk; patients in the TRISCEND II trial were not required to be surgery-ineligible.*

Lu FL, An Z, Ma Y, et al. Transcatheter tricuspid valve replacement in patients with severe tricuspid regurgitation. Heart (2021) 107:20 (1664-1670).

Objective
Tricuspid regurgitation is a common valvular heart disease with unsatisfactory medical therapeutics and high surgical mortality. The present study aims to evaluate the safety and effectiveness of TTVR in high-risk patients with severe tricuspid regurgitation.

Methods
This was a compassionate multicenter study. Between September 2018 and November 2019, 46 patients with TR who were not suitable for surgery received compassionate TTVR under general anesthesia and the guidance of TEE and fluoroscopy in four institutions. Access to the tricuspid valve was obtained via a minimally invasive thoracotomy and transatrial approach. Patients' data at baseline, before discharge, 30 days and 6 months after the procedure were collected.

Results

All patients had severe TR with vena contracta width of 12.6 (11.0, 14.5) mm. Procedural success (97.8%) was achieved in all but one case with right ventricle perforation. The procedural time was 150.0 (118.8, 180.0) min. Intensive care unit time was 2.0 (1.0, 4.0) days. 6-month mortality was 17.4%. Device migration occurred in one patient (2.4%) during follow-up. Transthoracic echocardiography (TTE) at 6 months after operation showed tricuspid regurgitation was significantly reduced (none/trivial in 33, mild in 4 and moderate in 1) and the primary safety end point was achieved in 38 cases (82.6%). Patients suffered from peripheral oedema and ascites decreased from 100.0% and 47.8% at baseline to 2.6% and 0.0% at 6 months.

Conclusions
The present study showed TTVR was feasible, safe and with low complication rates in patients with severe tricuspid regurgitation.

Edwards Note: This compassionate use study evaluated early experience with the LuX-Valve (Jenscare Biotechnology, Ningbo, China) in 46 patients across four facilities in China between 2018 and 2019. LuX-Valve and NaviGate are not under clinical study in the United States. Eligible patients had severe tricuspid regurgitation, however, the grading scale used only recognized mild, moderate, or severe tricuspid regurgitation.

Taramasso M, Alessandrini H, Latib A, et al. Outcomes After Current Transcatheter Tricuspid Valve Intervention: Mid-Term Results from the International TriValve Registry. JACC Cardiovasc Interv. (2019) 12:2 (155-165).

Objectives
A large, prospective international registry was developed to evaluate the initial clinical applications of TTVI with different devices.

Background
TTVI for native tricuspid valve dysfunction has been emerging during the last few years as an alternative therapeutic option to serve a large high-risk population of patients with severe symptomatic tricuspid regurgitation.

Methods
The TriValve Registry included 312 high-risk patients with severe tricuspid regurgitation (76.4 ± 8.5 years of age; 57% female; EuroSCORE II 9 ± 8%) at 18 centers. Interventions included repair at the level of the leaflets (MitraClip, Abbott Vascular, Santa Clara, California; PASCAL Edwards Lifesciences, Irvine, California), annulus (Cardioband, Edwards Lifesciences; TriCinch, 4tech, Galway, Ireland; Trialign, Mitraling, Tewksbury, Massachusetts), or coaptation (FORMA, Edwards Lifesciences) and replacement (Caval Implants, NaviGate, NaviGate Cardiac Structures, Lake Forest, California). Clinical outcomes were prospectively determined during mid-term follow-up.

Results
A total of 108 patients (34.6%) had prior left heart valve intervention (84 surgical and 24 transcatheter, respectively). Tricuspid regurgitation etiology was functional in 93%, and mean annular diameter was 46.9 ± 9 mm. In 75% of patients the regurgitant jet was central (vena contracta 1.1 ± 0.5; effective regurgitant orifice area 0.78 ± 0.6 cm2). Pre-procedural systolic pulmonary artery pressure was 41 ± 14.8 mm Hg. Implanted devices included: MitraClip in 210 cases, Trialign in 18 cases, TriCinch first generation in 14 cases, caval valve implantation in 30 cases, FORMA in 24 cases, Cardioband in 13 cases, NaviGate in 6 cases, and PASCAL in 1. In 64% of the cases, TTVI was performed as a stand-alone procedure. Procedural success (defined as the device successfully implanted and residual tricuspid regurgitation ≤2+) was 72.8%. Greater coaptation depth (odds ratio: 24.1; p = 0.002) was an independent predictor of reduced device

success. Thirty-day mortality was 3.6% and was significantly lower among patients with procedural success (1.9% vs. 6.9%; p = 0.04); Actuarial survival at 1.5 years was 82.8 ± 4% and was significantly higher among patients who had procedural success achieved.

Conclusions
TTVI is feasible with different technologies, has a reasonable overall procedural success rate, and is associated with low mortality and significant clinical improvement. Mid-term survival is favorable in this high-risk population. Greater coaptation depth is associated with reduced procedural success, which is an independent predictor of mortality.

Edwards Note: The study evaluates the clinical outcomes for different TTVI modalities, including, T-TEER, annular or coaptation reduction, and TTVR (median follow-up of 6.2 months). However, the study did not include the EVOQUE system among the studied TTVR modalities. The authors conclude that substantial reduction of tricuspid regurgitation (≥ 2+ grades) is strongly associated with improved survival at mid-term follow-up.

Other relevant literature (Summary of key findings provided)
Goldberg YH, Ho E, Chau M, Latib A. Update on Transcatheter Tricuspid Valve Replacement Therapies. Frontiers in Cardiovascular Medicine (2021) 8 Article Number: 619558.

The authors presented considerations to determine which treatment modality, TTVR or T-TEER, may be most appropriate, including a large coaptation gap, leaflet tethering, likelihood of reducing tricuspid regurgitation to none/trace or moderate, and presence of pacemaker leads. They articulate the importance of pre-operative fluid management in patients with tricuspid regurgitation, as the risk of afterload on the RV is a potential complication of the intervention.

Dreyfus GD, Essayagh B. Transcatheter treatment options for severe tricuspid regurgitation: And the winner is valve replacement? JACC Cardiovasc Interv. 2021; 14:512-4.

Physician leaders support TTVR as a treatment option that fulfills an unmet need for patients with tricuspid regurgitation. This commentary article responds to early experience with the EVOQUE system, concluding that transcatheter replacement may eventually be performed to a greater number of patients due to its elimination/great reduction of TR as compared with T-TEER procedures.

Hagemeyer D, Ong G, Peterson MD, Fam NP. Transcatheter tricuspid valve intervention: To repair or to replace? Current Opinion in Cardiology (2022) 37:6 (495-501).

In a review of available literature, the authors compare the strengths, limitations, and complications between TTVR and T-TEER. The authors conclude that TTVR holds an advantage as it effectively eliminates TR, while T-TEER typically has a shorter length of stay.

The patient populations for TTVR and T-TEER are likely overlapping, and, ultimately, treatment modality should be selected based on patient anatomy, operator experience, and device availability until additional data is available directly comparing T-TEER and TTVR.

Cammalleri V, et al. Transcatheter Tricuspid Valve Therapy: From Anatomy to Intervention. Frontiers in Cardiovascular Medicine (2021) 8 Article Number: 778445.

This article explores existing imaging techniques to support successful TTVI procedures. The authors recommend a pre-procedural imaging checklist for TTVR procedures, including dimensions and morphology of the TV annulus; RA and ventricular dimensions, anatomic

relations with surrounding structures, and analysis of vascular access route and relationship between caval veins and the TV plane.

The authors also provide recommendations as to anatomical conditions to consider when determining the most appropriate TV intervention.

Lawlor M, Kampaktsis P, Wang V, et al. TCT CONNECT-497 Incidence and Predictors of Cardiogenic Shock Following Tricuspid Valve Repair or Replacement. J Am Coll Cardiol (2022) 76:17 Supplement (B212).

The objective of this study was to evaluate the incidence of and risk factors associated with cardiogenic shock (CS) following surgery versus transcatheter tricuspid valve intervention TTVI for tricuspid regurgitation. From 2008 to 2020, a total of 122 patients underwent isolated TV surgery (n = 58, 14 TV repair, and 44 TV replacement) or TTVI (n = 64, 36 TV repair, and 28 TV replacement). Surgical patients were significantly younger than TTVI patients (67.5 vs. 80 years, $p < 0.0001$). In patients undergoing TV intervention for tricuspid regurgitation, surgery versus TTVI and elevated CVP are associated with advanced postprocedural CS. Patients developing advanced CS are at increased risk of in-hospital mortality.

Heitzinger G, et al. Contemporary insights into the epidemiology, impact and treatment of secondary tricuspid regurgitation across the heart failure spectrum. European Journal of Heart Failure (2023).

In a population-based study, the authors identified the relationship between patients with tricuspid regurgitation and heart failure. The results demonstrate that moderate and severe tricuspid regurgitation is frequent in all heart failure subtypes. The authors recommend opportunities to treat patients early in the disease pathway with a portfolio of treatment options, including TTVR.

Latib A, Scotti A. Transfemoral Transcatheter Tricuspid Valve Replacement: Will TV repair be replaced? JACC Cardiovasc Interv. 2022;15:492-495.

T-TEER may provide an appropriate treatment option for many patients, however TTVR fills a significant treatment gap for patients with tricuspid regurgitation. In response to the publication of TRISCEND 30-day results (Kodali, et al., 2022) and 1-year results from early compassionate use of the EVOQUE system (Webb, et al., 2022), the authors explore the key findings from the early experience with this treatment modality.

Mesnier J, et al. Transcatheter tricuspid valve interventions: Current devices and associated evidence. Progress in Cardiovascular Diseases (2021) 69 (89-100).

This paper outlines current TTVI devices, including T-TEER, annular reduction, and TTVR technologies. Advancements in transcatheter technologies for the treatment of tricuspid regurgitation indicate potential to intervene earlier in the progression of the disease. Real world evidence and experience with TTVI technologies will fill important gaps in the evidence and provide clinicians with additional information on patient selection criteria.

Nagraj S, et al. Transcatheter Tricuspid Valve Replacement: A Feasible Solution to a Real-world Problem. Reviews in Cardiovascular Medicine (2022) 23:5 Article Number: 163.

The authors summarize currently available TTVR technologies, patient selection factors, pre-procedural imaging to evaluate patient suitability, and existing evidence for each of the devices. In summarizing the evidence from the first in human experience with the EVOQUE system, the

authors note the significant reduction of heart failure hospitalizations observed in the patient population.

Ponna PK, et al. Transcatheter interventions for severe tricuspid regurgitation: a literature review. Journal of Geriatric Cardiology (2022) 19:7 (539-550).

This literature search outlines the different investigational transcatheter treatment modalities for patients with tricuspid regurgitation. The authors identify one of the most important considerations for TTVR is pre-procedural fluid management to reduce the effect of the immediate repair of the tricuspid valve and minimize the effects of afterload on the RV.

Russo G, et al. Challenges and future perspectives of transcatheter tricuspid valve interventions: adopt old strategies or adapt to new opportunities? European Journal of Heart Failure (2022) 24:3 (442-454).

The authors evaluate the strengths and weakness of T-TEER and TTVR as treatment options for patients with tricuspid regurgitation. Guidelines recommending timing of TV intervention are based on surgical risk. However, as transcatheter procedures are lower risk, as the evidence base supporting the technologies matures, there may be opportunity for earlier intervention for patients with tricuspid regurgitation.

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