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Austrian Institute for
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Caval valve implantation for severe tricuspid regurgitation

Systematic Review

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Conflict of interest

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

CAVI ..... caval valve implantation
CI..... confidence interval
COPD..... chronic obstructive pulmonary disease
EACTS ..... European Association for Cardio-Thoracic Surgery
ESC ..... European Society of Cardiology
EUnetHTA ..... European Network for Health Technology Assessment
FDA..... United States Food and Drug Administration
FU ..... follow up
GRADE..... Grading of Recommendations, Assessment, Development and Evaluations
GMDN ..... Global Medical Device Nomenclature
ICD-11 ..... International Classification of Diseases-11
IHE..... Institute for Health Economics
IQR..... interquartile range
KCCQ12 ..... Kansas City Cardiomyopathy Questionnaire
LKF..... leistungsorientierte Krankenanstaltenfinanzierung
MeSH ..... medical subject heading
MLHFQ..... Minnesota Living with Heart Failure Questionnaire
NYHA ..... New York Heart Association
OMT..... optimised medical therapy
PISA ..... proximal isovelocity surface area
RCT..... randomised controlled trial
RA..... right atrium
RR ..... risk ratio
RV..... right ventricle
SD..... standard deviation
TR..... tricuspid regurgitation
USA ..... United States of America
USD..... United States Dollar
VO2max ..... maximum volume of oxygen
WHO-ICTRP ..... World Health Organization-International Clinical Trials Registry Platform

Executive Summary

Introduction

Health Problem

The tricuspid valve in the heart is situated between the right atrium and right ventricle. The valve opens and closes during heart contractions to allow the one-way flow of blood from the right atrium into the right ventricle. Tricuspid regurgitation (TR) or insufficiency (TI) occurs when the valve does not close properly, allowing blood to flow backward into the right atrium when the right ventricle contracts and reducing the amount of blood that flows to the rest of the body. In chronic TR, the right atrium and ventricle gradually enlarge to maintain cardiac output and the forward flow of blood. The additional ventricular dilatation separates the valve leaflets further, leading to more regurgitation. The longstanding volume overload caused by this positive feedback loop eventually results in symptoms and potentially irreversible right ventricular dysfunction.

tricuspid insufficiency (TI): backflow of blood from right ventricle to right atrium due to incomplete closure of the tricuspid valve

The long-term prognosis for patients with severe TR is poor. Patients with severe TR can expect to live a mean 4.4 years after diagnosis and 2.3 years from the onset of symptoms. The all-cause mortality rates at two and four years after diagnosis are 50% and 69%, respectively.

life expectancy severe TI Ø 4.4 years after diagnosis, Ø 2.3 after symptom onset

Moderate or severe TR is present in 0.55% of the general population. TR affects approximately 4% of people older than 75 years, more commonly women. Symptomatic patients with severe TR have an increased risk of death, morbidity, hospitalisation and rehospitalisation, and quality of life is inversely related to TR severity.

moderate to severe TI in 0.55% of general population

Description of Technology

The recommended treatment for TR is surgical valve repair or replacement with open heart surgery. However, a large proportion of patients with TR are at high risk of or ineligible for surgery. Transcatheter TR intervention has recently emerged as a less invasive alternative for these patients. Transcatheter techniques involve inserting a catheter into a blood vessel in the groin or chest under local or general anaesthetic. The catheter is steered to the tricuspid valve under fluoroscopic or transoesophageal echocardiographic guidance. Once in position, a prosthesis is passed down the catheter and fixed into place, after which the delivery system is removed.

transcatheter TI interventions for patients ineligible for open heart surgery

One emerging transcatheter technique for TR is caval valve implantation (CAVI), in which a prosthetic valve is placed in the inferior vena cava alone (caval implantation) or in combination with a second valve in the superior vena cava (bicaval implantation). CAVI minimises the backflow of blood into the inferior vena cava (and superior vena cava), thereby reducing hepatic and renal vein congestion. CAVI valves, at present, comprise either nondedicated balloon expandable stents commonly used for transcatheter aortic or mitral valve replacement, or dedicated self-expandable devices made specifically for placement in the venae cavae.

caval valve implantation (CAVI): insertion of a prostethic valve into the inferior vena cava (or also into the superior vena cava)

Methods

The aim of this report was to assess the safety and effectiveness of CAVI, compared with other transcatheter techniques or optimised medical treatment (OMT), in patients with symptomatic severe TR who are at high risk of or ineligible for surgery.

aim: assessment of effectiveness and safety of CAVI

A systematic search was conducted to identify relevant systematic reviews, randomised controlled trials, non-randomised comparative studies and case series studies with at least ten patients published in English or German. The following databases were searched on 12 December 2022: Medline, Embase, The Cochrane Library and the INAHTA Database (International Network of Agencies for Health Technology Assessment). Study selection, data extraction and quality appraisal were carried out independently by two authors. Any disagreements were resolved by a third author. The quality of the included studies was assessed using the Cochrane Risk of Bias 2 tool (for RCTs) and the IHE checklist (for case series studies). The strength of the evidence was rated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scheme.

systematic search in 4 databases

study selection, extraction & quality assessment

Domain effectiveness

The following effectiveness-related outcomes were used as evidence to derive a recommendation: all-cause mortality, cardiovascular mortality, changes in health-related quality of life, changes in functional status and changes in exercise capacity.

effectiveness outcomes

Domain safety

Adverse events and serious adverse events were used as evidence to derive a safety recommendation.

safety outcomes

Results

Available evidence

One RCT and four case series studies (two prospective and two retrospective) met the predefined inclusion criteria.

inclusion of 1 RCT and 4 case series studies

Clinical effectiveness

One small RCT (n=28) reported outcomes for CAVI and OMT. The certainty of evidence ranged from very low to low for the outcomes reported. There were no statistically significant differences between the two treatment groups with respect to all-cause mortality, functional status or health-related quality of life twelve months after implantation. The mean change in exercise capacity was also similar for both treatments at three months' follow up. Echocardiographic examinations showed no improvement in TR severity with respect to baseline in the patients who received CAVI.

effectiveness 1 RCT: no statistically significant improvement for mortality, functional status, quality of life

Evidence from four case series studies (very low certainty evidence) indicated that CAVI improved functional status (four studies), exercise capacity (one study) and quality of life (one study) up to six months after the procedure. The rate of all-cause mortality ranged from 9% to 63% up to twelve months following the procedure, whereas the rate of cardiovascular mortality was low (2.5%).

effectiveness 4 case series: mortality up to 12 months between 9-63%, improvements in other outcomes

Safety

safety 1 RCT: premature study termination due to safety concerns – conversion to surgery in 29% of patients

In the RCT, 29% of patients receiving CAVI required conversion to surgery due to stent migration or valve dislocation. Three of these patients died in hospital due to haemorrhagic shock. These unexpected complications led to the premature termination of the study. However, the rate of hospitalisation for heart failure was identical for both groups over the twelve-month follow-up period.

safety 4 case series: hospitalisation for heart failure and kidney injury of renal failure

The rate of device migration was much lower in the case series studies (4%) and only one in-hospital death was considered procedure-related. Major bleeding complications occurred in 6% of patients up to 12 months after CAVI, 20% of patients required hospitalisation for heart failure and 9% experienced kidney injury or renal failure.

Upcoming evidence

1 ongoing RCT
4 ongoing case series

There are four ongoing open label, multicentre studies (one RCT and four prospective case series studies) assessing the bicaval application of the TricValve in patients with severe TR. It has a target enrolment of 430 patients and a primary completion date of January 2025. The sample sizes of the four case series studies range from 10 to 450. The primary completion dates cited for two of the studies are May and December 2025; a completion date has not been reported for the third study. The fourth case series study, with a primary completion date of October 2023, is assessing the bicaval implantation of the TRICENTO valve patients with carcinoid heart disease and symptomatic severe TR.

Discussion

current study populations might not be representative of future CAVI use

The evidence base for CAVI is currently limited to small feasibility studies where the procedure was conducted for compassionate reasons. Consequently, most of the patients had severe, often life-limiting comorbidities and were undergoing CAVI as a last resort, which potentially confounds the results of the studies. This also means that these patient groups may not be representative of the patients who may benefit most from this intervention.

dedicated devices and might improve outcomes

Since the technique is still evolving, there are potential improvements that can be made in terms of stent sizing, design and deployment. There is also some suggestion that better outcomes may be obtained using a dedicated self-expanding stent for implantation in the venae cavae, rather than non- dedicated balloon expandable devices that appear to be more prone to device migration and embolisation.

other issues: long-term impact, caval vs bicalval implantation, comparison with other interventions

Other issues that need to be addressed regarding the CAVI technique include: its long-term durability, particularly its long-term impact on right atrium and ventricular function; whether caval or bicaval implantation has superior outcomes for particular patient subgroups; and how the procedure compares with transcatheter interventions that address TR directly. The current evidence base is too limited and the follow-up periods are too short to answer these questions. In addition, it is unclear whether the statistically significant changes observed, particularly in the case series studies, are of meaningful benefit to patients.

Conclusion

no significant benefit with very low to low certainty evidence

CAVI is a palliative procedure that does not reverse or improve the underlying cause of TR. Very low to low certainty evidence from one RCT indicated that CAVI offers no significant benefit over OMT with respect to rates of all-cause mortality and improvement in functional status, exercise capacity or health-related quality of life, while exposing patients to potentially life-threatening procedure-related adverse events. Very low certainty evidence from four case series studies suggested that CAVI can significantly improve functional status, exercise capacity and health-related quality of life compared with baseline values, but it is unclear whether these improvements are greater than those that would be achieved with OMT.

insufficient evidence

Given the stage of development of the procedure and the fact that only two of the included studies used dedicated CAVI devices, as opposed to stents being used off label in the tricuspid valve, it is still unclear whether CAVI offers enough benefit over OMT to justify the risks.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Trikuspidalinsuffizienz (TI): Blutrückfluss aus rechter Herzkammer in rechten Vorhof durch unvollständige Schließung der Trikuspidalklappe

Die Trikuspidalklappe liegt zwischen dem rechten Vorhof und der rechten Herzkammer und reguliert durch ihr Öffnen und Schließen die Fließrichtung des Blutes. Bei einer Trikuspidalinsuffizienz (TI) schließt die Trikuspidalklappe nicht vollständig, sodass Blut aus der rechten Herzkammer in den rechten Vorhof zurückfließt und somit den Blutfluss in den Körper reduziert. Selten ist TI angeboren oder durch z. B. infektiöse Endokarditis oder rheumatische Herzerkrankungen erworben (primäre TI). Stattdessen handelt es sich in 90 % der Fälle um sekundäre TI, die z. B. durch Dilatation des rechten Ventrikels aufgrund von pulmonaler Hypertonie, oder nach einer linksseitigen Herzklappenoperation entstehen kann. Risikofaktoren für TI sind unter anderem ein Alter von ≥60 Jahren, weibliches Geschlecht, Vorhofflimmern oder auch pulmonale Hypertonie.

Unterteilung in 5 TI Schweregrade: mild, moderat, schwerwiegend, massiv, torrential

hohe Mortalitätsrate bei schwerwiegender TI

TI wird in fünf Schweregrade unterteilt: mild, moderat, schwerwiegend, massiv und torrential (sintflutartig). Um den Blutrückfluss auszugleichen, kommt es zu einer langsamen Vergrößerung des rechten Vorhofs und der Herzkammer, die jedoch oft asymptomatisch verläuft. Symptome bei moderater bis schwerwiegender TI sind unter anderem Halsvenenstauung, Erschöpfung, Atemnot beim Liegen oder Brustschmerzen. Moderate bis schwerwiegende TI tritt durchschnittlich bei 0,55 % der allgemeinen Bevölkerung und in 4 % von Personen über 75 auf. Die durchschnittliche Lebenserwartung bei schwerwiegender TI beträgt 4,4 Jahre nach der Diagnose und 2,3 Jahre nach dem Einsetzen der Symptome.

Behandlungsoptionen: medikamentöse Behandlung, Operation am offenen Herzen, transkatheter Interventionen

Für die Behandlung von TI gibt es drei Optionen: eine medikamentöse Behandlung, einen chirurgischen Herzklappenersatz am offenen Herzen oder eine transkatheterbasierte Intervention bei Patient*innen mit hohem Operationsrisiko. Die medikamentöse Behandlung stellt die Erstlinientherapie dar und besteht hauptsächlich aus Dosis-Eskalation, die jedoch das Fortschreiten der TI nicht aufhalten kann. Aufgrund von späten Diagnosen und zusätzlichen Komorbiditäten bei Patient*innen mit schwerwiegender TI erhalten weniger als 10 % chirurgische Interventionen.

Beschreibung der Technologie

transkather Interventionen bei Patient*innen mit hohem Operationsrisiko

Die Option einer chirurgischen Klappenreparatur oder ein Klappenersatz am offenen Herzen kommt bei vielen Patient*innen mit TI aufgrund hohem Operationsrisiko nicht in Frage. In jüngster Zeit wurden transkatheter-basierte TI-Interventionen als eine weniger invasive Alternative entwickelt. Bei diesen Interventionen wird unter örtlicher Betäubung oder Vollnarkose ein Katheter in ein Blutgefäß in der Leiste oder im Brustkorb eingeführt und unter fluroskopischer oder transösophagealer echokardiographischer Führung zur Trikuspidalklappe geführt. Sobald der Katheter in Position ist, wird eine Prothese durch diesen geführt und fixiert, wonach das Einführsystem wieder entfernt wird.

perkutane transfemorale heterotope Trikuspidalklappenersatz – „CAVI" als aufkommende transkatheter Intervention

Eine noch junge transkatheter Intervention ist der perkutane transfemorale heterotope Trikuspidalklappenersatz (caval valve implantation, „CAVI"). Bei CAVI wird eine Herzklappenprothese entweder nur in die Vena cava inferior, oder auch in die Vena cava superior platziert. Im Gegensatz zu anderen transkatheter Interventionen, wird bei CAVI also nicht die Trikuspidklappe selbst behandelt, sondern nur der Blutrückfluss zurück in den Körper verhindert. Zurzeit sind zwei CAVI-Produkte, die TricValve und TRICENTO zugelassen. Zusätzlich werden zwei Off-Lable Produkte SAPIEN XT/3, oder DirectFlow, verwendet. Mögliche Langzeitfolgen der Intervention sind zum einen die Vergrößerung des rechten Vorhofs, die weitere Dilatation der Trikuspidalklappe sowie die Embolisation oder die Migration des implantierten Produktes.

Methoden

Forschungsfrage

Ziel der vorliegenden Arbeit war es, die Wirksamkeit und Sicherheit von CAVI im Vergleich zur medikamentösen Behandlung bei Patient*innen mit schwerwiegender symptomatischer Trikuspidalklappeninsuffizienz, die ein hohes Operationsrisiko haben, oder die für eine offene Operation nicht geeignet sind, zu bewerten.

systematische Suche in 4 Datenbanken

Dazu wurde eine systematische Literatursuche am 12. Dezember 2023 in vier Datenbanken (Medline, Embase, The Cochrane Library die INAHTA Database) durchgeführt. Zusätzlich erfolgte eine Handsuche und Hersteller von CAVI-Produkten wurden für weitere Informationen kontaktiert. Zuletzt fand eine Suche nach derzeit laufenden Studien statt.

Studienauswahl, Datenextraktion und Bewertung der Evidenz nach GRADE

Die Studienauswahl erfolgte unabhängig von zwei Autor*innen. Die Datenextraktion sowie die Bewertung der Studienqualität wurden von einer Autorin durchgeführt und von einer zweiten verifiziert. Zur Bewertung der Studienqualität wurde je nach Studiendesign das Cochrane Risk of Bias Tool Version 2, oder die IHE-Checkliste, verwendet. Die Vertrauenswürdigkeit der Evidenz wurde mithilfe des Grading of Recommendations, Assessment, Development und Evaluation (GRADE) Schemas bewertet.

Klinische Wirksamkeit

Wirksamkeitsendpunkte: Mortalität, kardiovask. Mortalität, funktioneller Status, Leistungsfähigkeit und Lebensqualität

Die folgenden Endpunkte wurden als *entscheidend* für die Bewertung der Wirksamkeit eingestuft: Gesamtmortalität, kardiovaskuläre Mortalität, funktioneller Status, Leistungsfähigkeit und Lebensqualität.

Sicherheit

Sicherheitsendpunkte: (schwerwiegende) unerwünschte Ereignisse

Für die Bewertung der Sicherheit wurden schwerwiegende unerwünschte Ereignisse und andere wichtige unerwünschte Ereignisse als *entscheidende* Endpunkte definiert.

Ergebnisse

Verfügbare Evidenz

insgesamt 5 Studien eingeschlossen

Es wurden insgesamt fünf Studien, davon eine randomisierte kontrollierte Studie und vier Fallserien (zwei retrospektive und zwei prospektive), eingeschlossen.

Die randomisiert kontrollierte Studie untersuchte die Wirksamkeit von CAVI im Vergleich zur optimalen medikamentösen Behandlung. Dabei wurde bei CAVI die Off-Label SAPIEN XT Klappe eingesetzt. Die herstellerfinanzierte Studie wurde jedoch nach Einschluss von 28 Patient*innen aufgrund von Sicherheitsbedenken frühzeitig abgebrochen. Das durchschnittliche Alter der Patient*innen betrug 77 Jahre und der Großteil hatte torrentiale TI. Der primäre Endpunkt war die Leistungsfähigkeit nach drei Monaten.

1 RCT (n=28): CAVI vs. optimale medikamentöse Therapie (OMT)

Patient*innen mit torrentialer TI

In den vier Fallserien wurden insgesamt 105 Patient*innen mit einem Durchschnittsalter zwischen 74 und 80 Jahren eingeschlossen. Der Großteil der Patien*innen litt an schwerwiegender TI und 50 bis 76 % der Patient*innen wurden vor CAVI bereits am Herzen operiert. Der Follow-Up dauerte zwischen 61 und 332 Tage.

4 Fallserien (n=105) Patient*innen mit schwerwiegender TI

Vertrauenswürdigkeit der Evidenz

In der randomisiert kontrollierten Studie wurde das Verzerrungsrisiko je nach Endpunkt als sehr niedrig bis niedrig eingestuft. Bedenken gab es dabei vor allem bei den Aspekten „verdeckte Zuordnung“ und „Verblindung“. Die Vertrauenswürdigkeit Evidenz aus Beobachtungsstudien war sehr niedrig, was unter anderem auf eine mögliche selektive Rekrutierung der Patient*innen und fehlende Verblindung jener, die die Endpunkte in der Nachbeobachtung erhoben, zurückzuführen ist.

Vertrauenswürdigkeit RCT Endpunkte: sehr niedrig bis niedrig

Fallserien: sehr niedrig

Klinische Wirksamkeit

RCT-Evidenz

Der RCT fand einen nicht signifikanten Unterschied hinsichtlich der Mortalität zwischen CAVI-Gruppe und der Kontrollgruppe von 57 % vs. 29 % (8/14 vs. 4/14; p=0.16). Bezüglich des funktionellen Status und der Lebensqualität kam es zwar zu einer signifikanten Verbesserung in der CAVI-Gruppe im Vergleich zum Anfangswert (p=0.025 und p=0.004), jedoch waren die Gruppenunterschiede nicht signifikant. Eine signifikante Verbesserung des TI-Schweregrades im Vergleich zum Anfangswert konnte in der CAVI-Gruppe nicht festgestellt werden.

vergleichende Wirksamkeit (RCT): Mortalität 57 vs. 29 %; keine stat. signifikanten Unterschiede bei funktionellen Status und Lebensqualität

Evidenz aus Beobachtungsstudien

Die Mortalitätsrate betrug je nach Studie zwischen neun und 63 % bis zu 12 Monate nach dem Eingriff, während die kardiovaskuläre Mortalität nur bei 2.5 % lag. Nur in einer der vier Fallserien kam es im Vergleich zum Anfangswert zu einer statistisch signifikanten Verbesserung der Leistungsfähigkeit und in zwei Studien zu einer statistisch signifikanten Verbesserung des TI-Schweregrades. In zwei Studien kam es zu dem bei den meisten Patient*innen zur Verbesserung des funktionellen Status um mindestens eine NYHA-Klasse. Eine Fallserie berichtete über einen Vorher-Nachher-Vergleich der Leistungsfähigkeit im 6-Minuten-Gehtest ohne Verbesserung. Eine Fallserie berichtete über eine statistisch signifikante Verbesserung der Lebensqualität nach sechs Monaten.

Wirksamkeit in 4 Fallserien: Mortalität 9-63 %, Verbesserung der Leistungsfähigkeit in 1/4, Verbesserung des TI-Schweregrads und funktionellen Status in jeweils 2/4 Studien signifikant

Sicherheit

RCT-Evidenz

Bei vier von 14 Patient*innen der CAVI-Gruppe (29 %) der randomisiert kontrollierten Studie war eine offene Operation aufgrund von Klappenverschiebung nötig. Drei dieser Patient*innen starben im Krankenhaus an hämorrhagischen Schocks, was zur vorzeitigen Beendigung der Studie führte. Hospitalisierung aufgrund von Herzinsuffizienz trat in jeweils vier Patient*innen pro Gruppe auf.

Sicherheit (RCT): Produktmigration in 4/14 (29 %) Patient*innen → Abbruch der Studie

Evidenz aus Beobachtungsstudien

In den vier Fallserien trat nur eine Konversion zur Operation auf. Produktmigration war in 4 % der Patient*innen der Fall und ein Krankenhaustod wurde auf die Intervention zurückgeführt. Insgesamt starben 12 % der Patient*innen nach der Intervention im Krankenhaus. Zudem traten in den verschiedenen Studien bei 0 bis 8 % der Patient*innen Blutungskomplikationen auf, 20 % der Patient*innen wurden aufgrund einer Herzinsuffizienz hospitalisiert und 9 % der Patient*innen erlitten eine Nierenverletzung oder ein Nierenversagen.

Sicherheit (Fallserien): Produktmigration in 4 %; Mortalität nach Intervention bei 12 %

Laufende Studien

Insgesamt wurden fünf laufende Studien, darunter eine randomisiert kontrolliere Studie und vier prospektive Fallserien, identifiziert. Der RCT „TRICAV“, wird vom Hersteller finanziert und untersucht die Wirksamkeit der TricValve im Vergleich zur Standardtherapie mit einem zwölf Monate Follow-Up Zeitraum. Geplant ist eine Rekrutierung von 430 Patient*innen und ein primärer Studienabschluss im Jahr 2025. Die einzelnen Fallserien planen eine Rekrutierung von zehn bis 450 Patient*innen, mit Analysen nach drei und zwölf Monaten nach Produktimplantation. Zwei der Fallserien gaben ihren primären Studienabschluss im Jahr 2025 an, eine Fallserie in 2023 und eine hatte zum Studienabschluss keine Angaben gemacht.

5 laufende Studien:

1 RCT zu CAVI vs. Standardtherapie und 4 Fallserien

Diskussion

Die eingeschlossenen randomisiert kontrollierte Studie, welche CAVI mit optimaler medikamentöser Therapie verglich, konnte keinen statistisch signifikanten Unterschied zwischen den beiden Gruppen über den gesamten Follow-Up Zeitraum hinweg nachweisen. Zudem gilt zu beachten, dass diese Studie aufgrund von Produktmigration in vier von 14 Patient*innen vorzeitig abgebrochen wurde. Dagegen zeigte sich in den vier eingeschlossenen Fallserien generell eine Verbesserung der Leistungsfähigkeit, sowie der Lebensqualität. Jedoch gibt es in diesen Fällen keinen direkten Vergleich mit anderen Therapien und es ist nicht klar, inwiefern diese Verbesserungen für die Patient*innen bedeutend war.

Evidenz: 1 RCT mit einem Vergleich von CAVI mit optimaler medikamentöser Therapie und 4 Fallserien

Zusätzlich sind die vorliegenden Daten bis dato auf Patient*innen mit schwerwiegender TI beschränkt, bei denen die Therapie als letztes Mittel eingesetzt wird. Es ist jedoch davon ausgehen, dass diese Patient*innen weniger von CAVI profitieren als Patient*innen, bei denen CAVI in früheren Stadien von TI eingesetzt wird. Eine Weiterentwicklung und technische Verbesserung des Verfahrens, wie auch der vermehrte Einsatz von speziell für CAVI angefertigten Produkten, könnten ebenfalls den tatsächlichen Nutzen bzw. Vergleichbarkeit von CAVI mit anderen Behandlungen verdeutlichen. Schluss-

Limitation der Evidenz: Patient*innen mit schwerwiegender TI

endlich ist jedoch eine Wirksamkeit bzw. ein zusätzlicher Nutzen von CAVI im Vergleich zur optimalen medikamentösen Behandlung, mit der derzeitig vorhandenen Evidenz, noch ungewiss.

Schlussfolgerung

unzureichende Evidenz für zusätzlichen Nutzen von CAVI vs. optimale medikamentöse Therapie

CAVI ist ein palliativer Eingriff, der die zugrundeliegende Ursache für TI nicht behebt. Die eingeschlossenen Studien deuten auf eine ähnliche (geringfügige) Wirksamkeit von CAVI im Vergleich zur optimalen medikamentösen Behandlung hin, jedoch mit einem zusätzlichen Risiko für lebensbedrohliche verfahrensbedingte unerwünschte Ereignisse. Zudem wurde die Verlässlichkeit der Evidenz als sehr niedrig eingestuft.

In Ermangelung belastbarer vergleichender Daten sind keine Schlussfolgerungen zur relativen klinischen Wirksamkeit und Sicherheit der CAVI im Vergleich zu optimaler medikamentöser Therapie möglich.

Re-Evaluation 2026

Eine Re-Evaluierung wird für das Jahr 2026 angeraten, wenn Ergebnisse aus der derzeit laufenden Studie „TRICAV“ vorliegen.

1 Background

1.1 Overview of the disease, health condition and target population

The target population for this assessment is patients with symptomatic severe tricuspid regurgitation (TR) who are at high risk of or ineligible for surgery.[1]

Zielpopulation: Patient*innen mit schwerwiegender Trikuspidalinsuffizienz (TI)

The tricuspid valve in the heart is situated between the right atrium and right ventricle. It is the largest of the four cardiac valves [1, 2]. The valve generally consists of three flaps or leaflets (anterior, posterior and septal) attached to a fibrous ring (tricuspid annulus). The leaflets are connected to the papillary muscles of the ventricle, or directly to the myocardial wall, by inelastic fibrous cords (chordae tendinae), which prevent the valve prolapsing into the atrium [2, 3]. The tricuspid valve opens and closes during heart contractions to allow the one-way flow of blood from the right atrium into the right ventricle. Tricuspid regurgitation or insufficiency occurs when the valve does not close properly, allowing blood to flow backward into the right atrium when the right ventricle contracts and reducing the amount of blood that flows to the rest of the body.[2] TR is a heterogeneous condition that can be caused by primary abnormalities of the valve apparatus (congenital or acquired), secondary disease affecting the surrounding supporting structures, or both [4].

TI: Blutrückfluss aus rechter Herzkammer in rechten Vorhof durch unvollständige Schließung der Trikuspidalklappe

Primary (organic) TR can be either congenital (e.g., Ebstein anomaly) or acquired. The most common causes of primary acquired TR are infective endocarditis (especially among intravenous drug users) and rheumatic heart disease [5, 6]. Other causes include carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, thoracic trauma and iatrogenic damage due to implanted pacemaker or defibrillator leads (results in progressive TR in 20% to 30% of patients following implantation) [5, 7].

primäre TI: angeboren oder erworben (z. B. infektiöse Endokarditis, rheumatische Herzerkrankungen, etc.)

In secondary (functional) TR, which constitutes 90% of cases in adults, the structurally normal valve leaflets are unable to close properly (coapt) [1, 3]. In most cases this is due to severe right ventricular dilation caused by dilated cardiomyopathy or pulmonary hypertension (usually resulting from left-sided heart disease, pulmonary embolism, chronic obstructive pulmonary disease or stenosis of the pulmonary valve or artery) [8]. Secondary TR may also occur after left-sided heart valve surgery [6, 9]. Although left-sided heart disease and pulmonary hypertension are the most common aetiologies of secondary TR (≥60% of cases) [10], around 8% of patients have isolated TR due to enlargement of the right atrium and tricuspid annulus, usually because of chronic atrial fibrillation (in the absence of pulmonary hypertension or left ventricular dysfunction) [6-8]. Up to 63% of patients with TR have other valve disorders, most commonly mitral regurgitation (29%) [11], and around 25% of patients with severe aortic stenosis develop at least moderate TR; significant TR is present in 20% to 30% of patients with heart failure [5]. The relevant International Classification of Diseases (ICD)-11 codes for the various aetiologies of TR are listed in Table 1-1.

sekundäre TI: 90 % aller Fälle; verursacht durch z. B. Dilatation des rechten Ventrikels aufgrund von pulmonaler Hypertonie oder nach linksseitigen Herzklappenoperation

[1] **A0007** – What is the target population in this assessment?

[2] **A0002** – What is the disease or health condition in the scope of this assessment?

Table 1-1: Relevant ICD-11 codes for TR

Category	ICD-11 code
Congenital anomaly of tricuspid valve	LA87.0
Traumatic injury to tricuspid valve	NB31.4Y
Mitral and tricuspid regurgitation	BC00
Active or acute tricuspid endocarditis	1B41.1Y
Postprocedural tricuspid valve insufficiency	BE12.5
Acute or subacute tricuspid nonrheumatic endocarditis	BB4Z
Tricuspid valve disease	
Tricuspid valve insufficiency	BB81
Tricuspid valvular abscess	BB83
Tricuspid valve rupture	BB84
Other specified tricuspid valve disease	BB8Y
Tricuspid valve disease, unspecified	BB8Z

Source: International Classification of Diseases 11th Revision [12]

langsame Vergrößerung des rechten Vorhofs und Herzkammer, oftmals asymptomatisch

In chronic TR, the right atrium and ventricle gradually enlarge to maintain cardiac output and the forward flow of blood. During this stage patients are often asymptomatic, but over time the ventricle wall weakens and dilates under the extra workload. The additional ventricular dilatation separates the valve leaflets further, leading to more regurgitation. As the disease progresses, the enlarged atrium may develop arrhythmia, further reducing the heart's ability to pump blood efficiently and increasing the risk of blood clots [3, 13]. The longstanding volume overload caused by this positive feedback loop eventually results in symptoms and potentially irreversible right ventricular dysfunction, which sometimes occurs while the patient is still asymptomatic (up to 62% of patients with severe TR) [3, 13, 14].

1.1.1 Categorisation of severity and stage of TR

TI Einteilung in 5 Schweregrade: mild, moderat, schwerwiegend, massiv, torrential

Risikofaktoren: Alter ≥60, weibliches Geschlecht, Vorhofflimmern, pulmonare Hypertonie, etc.

The severity of TR is categorised as mild, moderate, severe, massive, or torrential based on the criteria listed in Table 1-2. Mild TR is usually detected with a transthoracic echocardiography that has been ordered for other reasons [10]. Risk factors for progression of untreated TR include age (≥60 years), female sex, tricuspid annulus dilation of more than 40 mm, reduced RV function, heart failure, pulmonary artery hypertension (≥36 mm Hg), atrial fibrillation, and a pacemaker or a cardioverter-defibrillator lead that runs across the valve, and left-sided valve surgery without concomitant tricuspid surgery [15-17]. At the population level, the main risk factors for TR are aging, atrial arrythmias, pulmonary hypertension, right ventricle dysfunction and the presence of a device lead in the right ventricle [8, 16].[3]

[3] **A0003** – What are the known risk factors for the disease or health condition?

Table 1-2: Severity grading of TR

Measure	Mild	Moderate	Severe	Massive	Torrential
Vena contracta (biplane), mm	<3	3-6.9	7-13	14-20	>21
Effective regurgitant orifice area (PISA), mm^2	<20	20-39	40-59	60-79	≥80
3-dimensional vena contracta area, mm^2	-	-	75-94	95-114	≥115

Abbreviations: PISA – proximal isovelocity surface area
Source: Hahn et al. 2017 [18]

Symptome bei moderater bis schwerwiegender TI: Halsvenenstauung, Erschöpfung, Atemschwierigkeiten beim Liegen, Brustschmerzen, etc.

The stages of TR are classified as listed in Table 1-3. Signs and symptoms of moderate to severe TR include jugular vein distention, active pulsing in the neck veins, generalised weakness and fatigue due to decreased cardiac output, difficulty breathing when lying down, swollen ankles and feet, chest pain, shortness of breath with exercise, abdominal bloating, ascites (fluid build up in the abdomen) and enlarged liver and leg oedema [15, 19]. Clinical features of the underlying condition causing TR may also be present. For example, patients with infective endocarditis may have febrile episodes in addition to symptoms of TR [9]. If left untreated, longstanding TR can lead to heart failure and premature death [19].

Table 1-3: Clinical stages of TR

Stage	Definition	Haemodynamic consequences	Signs and symptoms
B	Progressive TR	None	None
C	Asymptomatic severe TR	Dilated RV and RA Elevated RA with "c-V" wave	Elevated venous pressure No symptoms
D	Symptomatic severe TR	Dilated RV and RA Elevated RA with "c-V" wave	Elevated venous pressure Dyspnoea on exertion, fatigue, ascites, oedema

Abbreviations: RA – right atrium; RV – right ventricle; TR – tricuspid regurgitation.
Source: Otto et al. 2021 [7].

1.1.2 Natural history

niedrigeres Überleben bei schneller Krankheitsprogression

Up to 25% of patients with moderate or severe TR will experience disease progression within 14 months, and a further 25% will progress within 5 years [17]. Patients with rapid TR progression have lower rates of survival than those with slower TR development [17]. Isolated TR is associated with a lower survival at 10 years, regardless of whether other cardiovascular comorbidities are present [5]. The five-year mortality rate in patients with isolated primary TR can be at least 48% [15].[4]

Lebenserwartung schwerwiegende TI: Ø 4.4 Jahre nach Diagnose, Ø 2.3 Jahre nach Einsetzen der Symptome

The long-term prognosis for patients with severe TR is poor. Patients with moderate or severe TR have a two-fold higher mortality rate than those with no or mild TR, regardless of pulmonary artery pressure and or the presence of right ventricular failure [20]. Patients with severe TR can expect to live a mean 4.4 years after diagnosis and 2.3 years from the onset of symptoms [21]. The all-cause mortality rates at two and four years after diagnosis of severe TR are 50% and 69%, respectively [22].[4]

[4] **A0004** – What is the natural course of the disease or health condition?

1.1.3 Epidemiology[5]

moderate bis schwerwiegende TI in 0.55 % der allgemeinen Population

Some degree of TR is relatively common. Between 50% and 60% of asymptomatic young adults have mild TR and up to 15% have moderate TR [4]. Moderate or severe TR is present in 0.55% of the general population, increasing in prevalence with age. TR affects approximately 4% of people older than 75 years, more commonly women [8, 23].

ca. 1/3 Patient*innen mit Herzinsuffizienz mit gleichzeitiger TI

A recent study of patients in Vienna with heart failure (n=13,469) found that 11% had moderate secondary TR and 25% had severe disease [24]. Severe TR was more common in women (15%) than in men (10%). Other chronic conditions were also present in this population, including coronary artery disease (49%), hypertension (62%) and type II diabetes (26%). Therefore, roughly a third of people with heart failure (1% to 2% in Europe [25]) are likely to have concomitant moderate or severe TR.

1.1.4 Burden of disease

hohes Mortalitätsrisiko bei symptomatischer, schwerwiegender TI

Symptomatic patients with severe TR have an increased risk of death, morbidity, hospitalisation and rehospitalisation, and quality of life is inversely related to TR severity [8, 14, 21]. In a Viennese population with heart failure, 44% of patients with severe TR and 24% with no or mild TR died over a four-year period, compared with 2% in an age- and sex-matched sample from the general population [24]. After eight years, 61% of patients with severe TR had died, compared with 38% for no or mild TR and 15% in the general population. The rate of hospitalisation also increases proportionally with severity of TR: 1.0%, 2.2%, 5.7% and 23.1% for absent, mild, moderate and severe TR, respectively. Patients with moderate or severe TR are also more likely to be hospitalised for heart failure, regardless of the degree of pulmonary hypertension present [14].[6]

aufgrund häufiger Komorbiditäten nur Schätzungen zur tatsächlichen Krankheitslast verfügbar

Since TR is usually present in conjunction with other chronic conditions, there are little data on the burden of TR in isolation. However, one analysis of 92,994 adults with TR in the USA indicated that those with no heart failure or clinically significant TR had 0.20 annualised all-cause hospitalisations (one inpatient hospitalisation every five years), 1.07 hospital days and USD17,478 in expenditures [26]. In contrast, patients with clinically significant TR in the absence of heart failure had 0.41 annualised all-cause hospitalisations, 3.13 hospital days and USD29,985 in expenditures. For patients with both heart failure and clinically significant TR, the annualised all-cause hospitalisations were 0.59, with 4.31 hospital days and USD42,255 in expenditures [26].[7]

[5] **A0023** – How many people belong to the target population?

[6] **A0005** – What is the burden of disease for the patients with the disease or health condition?

[7] **A0006** – What are the consequences of the disease or health condition for the society?

1.2 Current clinical practice[8]

3 Therapieoptionen bei TI: chirurgische Herzklappenersatz am offenen Herzen, transkatheter Interventionen oder medikamentöse Behandlung

Transthoracic echocardiography with Doppler is the key diagnostic test for diagnosing and assessing the severity of TR, and for evaluating valve morphology, disease aetiology and the size of various anatomical features to determine eligibility for treatment [27].[9] The three possible therapeutic options for TR are surgical valve repair or replacement with open heart surgery, transcatheter intervention and medical therapy [19]. The recommended treatment for significant valvular disease is surgical repair with a prosthetic ring (annuloplasty). Replacement with a prosthetic valve should only be considered when annuloplasty is not feasible, such as when the tricuspid valve leaflets are tethered and the annulus is severely dilated [6, 7]. Ideally, tricuspid valve surgery should be performed at the same time as left-sided valve surgery, rather than as an isolated procedure [6].

transkathether TI Interventionen bei Patient*innen mit hohem Operationsrisiko

Transcatheter TR intervention has recently emerged as a less invasive alternative for patients with high surgical risk. The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) state that transcatheter interventions may be considered in patients with symptomatic secondary severe TR who are ineligible for surgery when the service is provided at a centre with expertise in the treatment of tricuspid valve disease (class IIb recommendation; usefulness or efficacy of the intervention is less well established by evidence or opinion) [6].[10]

Erstlinientherapie: medikamentöse Behandlung

Medical therapy is the recommended first-line treatment for patients with TR and right-sided heart failure; asymptomatic patients with severe primary TR and no right ventricle dilation; and symptomatic patients with severe secondary TR and severe right ventricular dysfunction or irreversible pulmonary hypertension in whom surgery or less invasive techniques are likely to be futile [6, 7].

durch späte Diagnose aufgrund anderer Komorbiditäten: chirurgische Eingriffe bei weniger als 10 % mit schwerwiegender TI

Factors that define a high-risk surgical patient include old age, the presence of comorbidities, advanced heart failure and the surgery specific estimate of risk [28, 29]. Since the signs and symptoms of TR are often ascribed to other medical conditions or advanced age. As a result, patients are usually diagnosed at a late stage of disease when they are older, have already undergone left-sided valve surgery and have multiple comorbidities, particularly atrial fibrillation, severe kidney and liver deficiency, pulmonary hypertension and right heart failure [10, 13]. The severity of clinical presentation before surgery has a greater impact on patient outcome than TR mechanism or aetiology [30]. Consequently, fewer than 10% of patients with severe TR receive a surgical intervention [22]. A recent study of 13,469 patients in Vienna with heart failure found that only 3% of those with moderate or severe TR received surgical treatment: valve repair in 2.6%, valve replacement in 0.2% and a transcatheter tricuspid valve intervention in 0.2% [24].

[8] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

[9] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

[10] **B0002 –** What is the claimed benefit of the technology in relation to the comparators?

1.3 Features of the intervention and comparators[11]

1.3.1 Features of the comparators

Transcatheter interventions[12]

Komparatoren: andere transkatheter Trikuspidinterventionen

Transcatheter tricuspid valve interventions can be categorised as annuloplasty devices, leaflet coaptation devices, or valve replacement devices [6, 7, 31]. A list of various tricuspid valve devices is provided in Table 1-4, all of which aim to re-establish the integrity of the native tricuspid valve. Transcatheter techniques involve inserting a catheter into a blood vessel in the groin or chest under local or general anaesthetic. The catheter is steered to the tricuspid valve under fluoroscopic or transoesophageal echocardiographic guidance. Once in position, a prosthesis is passed down the catheter and fixed into place, after which the delivery system is removed [32].[13]

andere TI-Produkte mit CE-Zertifizierung: Cardioband Tricuspid System, EVOQUE valve und TriClip™

Most tricuspid valve devices are still in the early stages of development.[14] The only devices with a CE Mark for functional TR are the Cardioband Tricuspid System, EVOQUE valve and TriClip™ Transcatheter Tricuspid Valve Repair System. The transcatheter approach for TR has various challenges, such as achieving proper sizing and sealing of devices when in place, difficulties with obtaining adequate imaging during the procedure and minimising damage to adjacent sensitive structures such as the right coronary artery, aortic valve, atrioventricular node and His bundle [33] Identifying the best candidates for transcatheter tricuspid interventions can be painstaking because not all valves are suitable [30, 31].

Table 1-4: List of various transcatheter tricuspid valve devices[14,15]

Device namea/ manufacturer	Design	CE Mark/ indicationb	US FDA Approval/ indicationb	Class/ GMDN code
Annuloplasty devices				
Cardioband Tricuspid System Edwards Lifesciences (California, USA)	Adjustable band that mimics ring annuloplasty	Yes (2018) Functional TR	No	Class III Code 66339
MIA-T Micro Interventional Devices, Inc. (Pennsylvania, USA)	Implanted in the native annulus in a stretched state; shortens after release to mimic ring annuloplasty	No	Breakthrough device designation (2021) Moderate to severe TR	Class III Code 66339
Millipede IRIS System Boston Scientific (Massachusetts, USA) (formerly manufactured by Millipede Inc. (California, USA))	Adjustable semirigid ring that mimics ring annuloplasty	No	No	Class III Code 66339
Trialign System Mitralign Inc. (Massachusetts, USA)	Suture device that mimics direct suture annuloplasty	No	Investigational device exemption (2020) TR	Class III Unclassified

[11] **B0001** – What is the technology and the comparator(s)?

[12] **A0018 –** What are the other typical or common alternatives to the current technology?

[13] **B0009 –** What supplies are needed to use the technology and the comparator(s)?

[14] **B0003** – What is the phase of development and implementation of the technology and the comparator(s)?

[15] **A0020** – For which indications has the technology received marketing authorisation or CE marking?

Device namea/ manufacturer	Design	CE Mark/ indicationb	US FDA Approval/ indicationb	Class/ GMDN code
TriCinch™ Tricuspid Valve Repair System 4Tech Cardio Ireland Ltd (Galway, Ireland)	Suture device that cinches the annulus to mimic suture annuloplasty	No	No	Class III Unclassified
Leaflet coaptation devices				
FORMA™ Tricuspid Valve Therapy System Edwards Lifesciences (California, USA)	Foam filled spacer that expands to occlude the regurgitant orifice	No	No	Class III Unclassified
Mistral System Mitralix Ltd (Israel)	Reduces valvular coaptation by grasping the chordae tendineae	No	No	Class III Unclassified
TriClip™ Transcatheter Tricuspid Valve Repair System Abbott Vascular (California, USA)	Clips together a portion of the valve leaflets	Yes (2020) Functional TR	Investigational device exemption (2019)	Class III Code 57790
PASCAL system Edwards Lifesciences (California, USA)	Woven nitinol spacer that occludes the regurgitant orifice Combines features from the TriClip and FORMA devices	No	No	Class III Code 57790
Valve replacement devices				
EVOQUE valve Edwards Lifesciences (California, USA)	Self-expanding bioprosthetic valve	Yes (2023) TR	Yes (2024) Symptomatic severe TR despite optimal medical therapy when valve replacement is deemed appropriate by a heart team	Class III Code 65121
LuX-Valve Jenscare Scientific Co. (Ningbo, China)	Self-expanding bioprosthetic valve	No	Breakthrough device designation (2023) TR	Class III Code 65121
GATE Bioprosthesis NaviGate Cardiac Structures Inc. (California, USA)	Self-expanding bioprosthetic valve	No	No	Class III Code 65121

Abbreviations: FDA – United States Food and Drug Administration; GMDN – Global Medical Device Nomenclature; TR – tricuspid regurgitation.

Comments:

[a] *This list is not exhaustive.*

[b] *Some devices are approved for other indications, such as mitral valve regurgitation, but only approvals related to TR are listed.*

Source: Ascione et al. 2020 [10], Campelo-Parada et al. 2017 [34], Ho et al. 2019 [35], Mesnier et al. 2021 [31].

Medical therapy[12]

keine spezifische medikamentöse Therapie für TI, deshalb oftmals nur Dosiseskalation zur Symptomenreduzierung

There are no specific pharmaceutical options for treating TR itself, so medical therapy often consists of escalating doses of medications that reduce congestion, volume overload and heart failure symptoms [19]. For example, diuretics and angiotensin-converting enzyme inhibitors are used to ameliorate chronic congestive heart failure and fluid overload associated with TR; when kidney function is preserved, an aldosterone antagonist such as spironolactone or eplerenone may also be added. Patients with primary pulmonary hypertension are often prescribed calcium channel antagonists, endothelin receptor antagonists, phosphodiesterase type five inhibitors, guanylate cyclase stimulators, prostacyclin analogues and prostacyclin receptor agonists. Patients with right heart dilatation due to pulmonary embolism usually receive anticoagulation with either a direct-acting anticoagulant or warfarin. If atrial fibrillation is present, anticoagulants and other pharmacologic therapy may be used to restore normal sinus rhythm [15, 36].

jedoch keine Unterbindung der Progression durch medikamentöse Therapie

However, the effectiveness of medical therapy is limited in many patients with TR because of the presence of comorbidities, such as impaired kidney function, which limit the type and dose of medications that can be administered [36]. In addition, while medical therapy may improve TR symptoms, it does not prevent or reverse the progressive right ventricle dysfunction that eventually leads to end-stage liver or kidney failure.

1.3.2 Features of the intervention

neuer Ansatz bei transkatheter Interventionen "CAVI": Platzierung einer Herzklappenprothese in die Vena cava inferior (und superior)

Another type of transcatheter intervention for TR is caval valve implantation, in which a prosthetic valve is placed in the inferior vena cava alone (caval implantation) or in combination with a second valve in the superior vena cava (bicaval implantation). This heterotopic valve placement is different to the conventional method of placing the prosthesis within the tricuspid valve itself (orthotopic valve intervention). CAVI minimises the backflow of blood into the inferior vena cava (and superior vena cava), thereby reducing hepatic and renal vein congestion [1, 37].[16] The devices currently used for CAVI are listed in Table 1-5.

Table 1-5: List of various CAVI devices[14,17]

Device namea/ manufacturer	Design	CE Mark/ indicationb	US FDA approval/ indicationb	Class/ GMDN code
Caval devices				
DirectFlow Direct Flow Medical, Inc. (California, USA)	Balloon-expandable bioprosthetic valve Requires deployment of a stent in the IVC prior to valve placement because the IVC diameter is usually too large for the valve Sizes available: 25 and 27 mm	No	No	Class III Unclassified
SAPIEN 3 (predecessor SAPIEN XT) Edwards Lifesciences (California, USA)	Balloon-expandable bioprosthetic valve Requires deployment of a stent in the IVC prior to valve placement because the IVC diameter is usually too large for the valve Sizes available: 20, 23, 26 and 29 mm	No	No	Class III Unclassified
Bicaval devices				
TRICENTO New Valve Technology GmbH (Hechingen, Germany)	Self-expandable bioprosthetic valve implanted in the SVC and IVC Sizes available: custom made up to 48 mm	No	No	Class III Code 64127
TricValve P+F Products + Features (Vienna, Austria)	Two self-expanding bioprosthetic valves implanted in the SVC and IVC Sizes available: 25 and 29 mm for the SVC valve; 31 and 35 mm for the IVC	Yes	Breakthrough device designation (2021) Haemodynamically relevant tricuspid insufficiency	Class III Code 64127
Trillium™ Innoventric Ltd (Ness Ziona, Israel)	Self-expandable bioprosthetic valve implanted in the SVC and IVC	No	No	Class III Code 64127

Abbreviations: FDA – United States Food and Drug Administration; GMDN – Global Medical Device Nomenclature; IVC – inferior vena cava; SVC – superior vena cava; TR – tricuspid regurgitation.

Comments:

[a] *This list is not exhaustive.*

[b] *Some devices are approved for other indications, such as mitral valve regurgitation, but only approvals related to TR are listed.*

Sources: Abdul-Jawad Altisent et al. 2021 [32], Goldberg et al. 2021 [38], Russo et al. 2022 [39].

[16] **A0009 –** What aspects of the consequences/burden of disease are targeted by the technology?

[17] **A0020** – For which indications has the technology received marketing authorisation or CE marking?

CAVI valves, at present, comprise either nondedicated balloon expandable stents commonly used for transcatheter aortic or mitral valve replacement (e.g., the SAPIEN and DirectFlow valves), which have been used off label for TR, or dedicated self-expandable devices made specifically for placement in the venae cavae (e.g., TricValve and TRICENTO) [1, 33].[14]

CAVI Produkte: TricValve und TRICENTO; Off-Label: SAPIEN und DirectFlow

CAVI is a palliative procedure designed to mitigate systemic venous congestion in patients with severe TR who are ineligible for open heart surgery. Concerns about CAVI include the long-term impact of persistent right atrial volume overload, which could lead to right atrium enlargement, and the possibility of continued tricuspid annuls dilation [33]. In addition, implanting valves in the venae cavae can be challenging. The diameter of the vessels can exceed 45 mm, increasing the risk of device embolisation or migration, and the anatomic variability of the superior vena cava and presence of pacemaker or implantable cardioverter defibrillator leads can make bicaval implantation technically demanding or infeasible [1, 34, 40].

mögliche CAVI Langzeitfolgen: weitere Vergrößerung des rechten Vorhofs, Dilatation der Trikuspidalklappe, Embolisation oder Migration des Produkts

Administration, investments, personnel and tools required to use the technology and the comparators

Transcatheter cardiac interventions are performed in a tertiary hospital that has a catheterisation lab, angiography suite or hybrid operating suite (that has both catheterisation and surgical capabilities) with fixed x-ray imaging. The facility must also have anaesthesia and intensive care facilities, and access to specialised imaging equipment such as transthoracic echocardiography, transoesophageal echocardiography, vascular ultrasound, magnetic resonance angiography, peripheral angiography and computed tomography [41, 42].[18] The service requires a multidisciplinary team comprising a cardiac surgeon, interventional cardiologist, imaging specialist, echocardiologist, cardiac anaesthetist, intensive care specialist, geriatrician or internist and catheter lab or operating room nurses. A surgeon and cardiologist are required to perform the procedure [41, 42].[19]

CAVI Intervention in spezialisierten Zentren

Regulatory & reimbursement status

According to the submission materials, the expected annual utilisation of CAVI based on the previous years' experience is between 6 and 20 interventions per year in Austria.[20] Currently, CAVI is not included in the hospital catalogue of benefits (LKF, leistungsorientierte Krankenanstaltenfinanzierung) and, hence, is not a fully reimbursable service in the Austrian healthcare system.[21]

6-20 Interventionen jährlich in Ö.; derzeit nicht im LKF abgebildet

[18] **B0008** – What kind of special premises are needed to use the technology and the comparators?

[19] **B0004** – Who administers CAVI and the comparators and in what context and level of care are they provided?

[20] **A0011** – How much are the technologies utilised?

[21] **A0021** – What is the reimbursement status of the CAVI?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is CAVI in comparison with standard care more effective or safe with respect to mortality, health-related quality of life, functional status, exercise capacity and adverse event in patients with symptomatic severe TR who are at high risk of or ineligible for surgery?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Patients of any age with severe symptomatic tricuspid regurgitation who are at a high risk of or ineligible for surgery. ***ICD-11 Codes:*** LA87.0 Congenital anomaly of tricuspid valve; NB31.4Y Traumatic injury to tricuspid valve; BC00 Mitral and tricuspid regurgitation; 1B41.1Y Active or acute tricuspid endocarditis; BE12.5 Postprocedural tricuspid valve insufficiency; BB4Z Acute or subacute tricuspid nonrheumatic endocarditis; BB81 Tricuspid valve insufficiency; BB83 Tricuspid valvular abscess; BB84 Tricuspid valve rupture; BB8Y Other specified tricuspid valve disease; BB8Z Tricuspid valve disease, unspecified [12]. ***MeSH and Emtree Terms:*** ■ MesH: Tricuspid Valve, Tricuspid Valve Insufficiency, Venae Cavae ■ Emtree: Tricuspid valve, Tricuspid valve regurgitation, Cava vein **Rationale** Informed by information provided by the requestor and clinical practice guidelines [6, 7].
Intervention	**Transcutaneous heterotopic caval valve implantation** Transcutaneous placement of a valve into the inferior vena cava alone or with a second valve in the superior vena cava to reduce the backflow of blood in a patient with tricuspid valve regurgitation ***Product names:*** Various implantable stent valves, including, but not limited to: ■ *Directflow* ■ *SAPIEN XT/3* ■ *TricValve* ■ *Trillium* ■ *TRICENTO* ***MeSH and Emtree Terms:*** ■ Medline: Blood Vessel Prosthesis Implantation, Heart Valve Prosthesis Implantation ■ Emtree: Caval valve implant, Caval valve implantation, Implantation **Excluded** Transcutaneous orthotopic tricuspid valve implantation **Rationale** Informed by information provided by the requester and a scoping search of the literature.

Comparator	■ Optimised medical treatment (e.g. diuretics, anti-arrhythmic drugs, angiotensin-converting enzyme inhibitors or anticoagulants) ■ Transcatheter annuloplasty (e.g. Cardioband, Trialign or TriCinch) ■ Transcatheter orthotopic tricuspid valve replacement (e.g., EVOQUE, Lux-Valve or GATE Bioprosthesis) ■ Transcatheter tricuspid valve repair (e.g., TriClip, PASCAL or FORMA) ***MeSH and Emtree Terms:*** These were not used in the search strategy as they resulted in overly narrow search results. **Rationale** Informed by information provided by the requester and a scoping search of the literature.
Outcomes	
Efficacy	■ All-cause mortality ■ Cardiovascular mortality ■ Changes in functional status ■ Changes in exercise capacity ■ Changes in health-related quality of life **Excluded** Studies that did not report any of the listed efficacy or safety outcomes **Rationale** Informed by consensus-based reporting standards and a scoping search of the literature [43, 44].
Safety	■ Adverse events (e.g., pain at access site) ■ Serious adverse events (e.g. procedure-related mortality, thrombus, embolisation, infection, device migration, re-intervention, major bleeding, cardiac tamponade, etc.)
Study design	
Efficacy Safety	■ Systematic reviews ■ RCTs ■ Non-randomised comparative studies ■ Case series studies with ≥10 patients A best evidence approach to study selection was used, with recent, well-conducted systematic reviews selected over individual primary studies. Any eligible systematic reviews identified were updated, where necessary, with primary studies published after the review's search end date. **Excluded** Non-peer reviewed studies, narrative reviews, letters to the editor and author responses, case reports, conference abstracts

Abbreviations: ICD-11 – International Classification of Diseases-11; MeSH – medical subject heading; RCTs – randomised controlled trials

3 Methods

3.1 Research questions

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [45].

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on 12 December 2023 in the following databases:

- Medline via Ovid
- Embase via Ovid
- The Cochrane Library
- The International Health Technology Assessment Database (International Network of Agencies for Health Technology Assessment)

The systematic search was limited to articles published in English or German.

insgesamt 490 Treffer identifiziert

After deduplication, 485 citations were included. The specific search strategies employed can be found in the Appendix. Handsearching identified an additional five citations, resulting in a total of 490 hits. Manufacturers of dedicated CAVI devices (Direct Flow Medical, Inc. and P+F Products + Features) were contacted for information, but no new citations were identified.

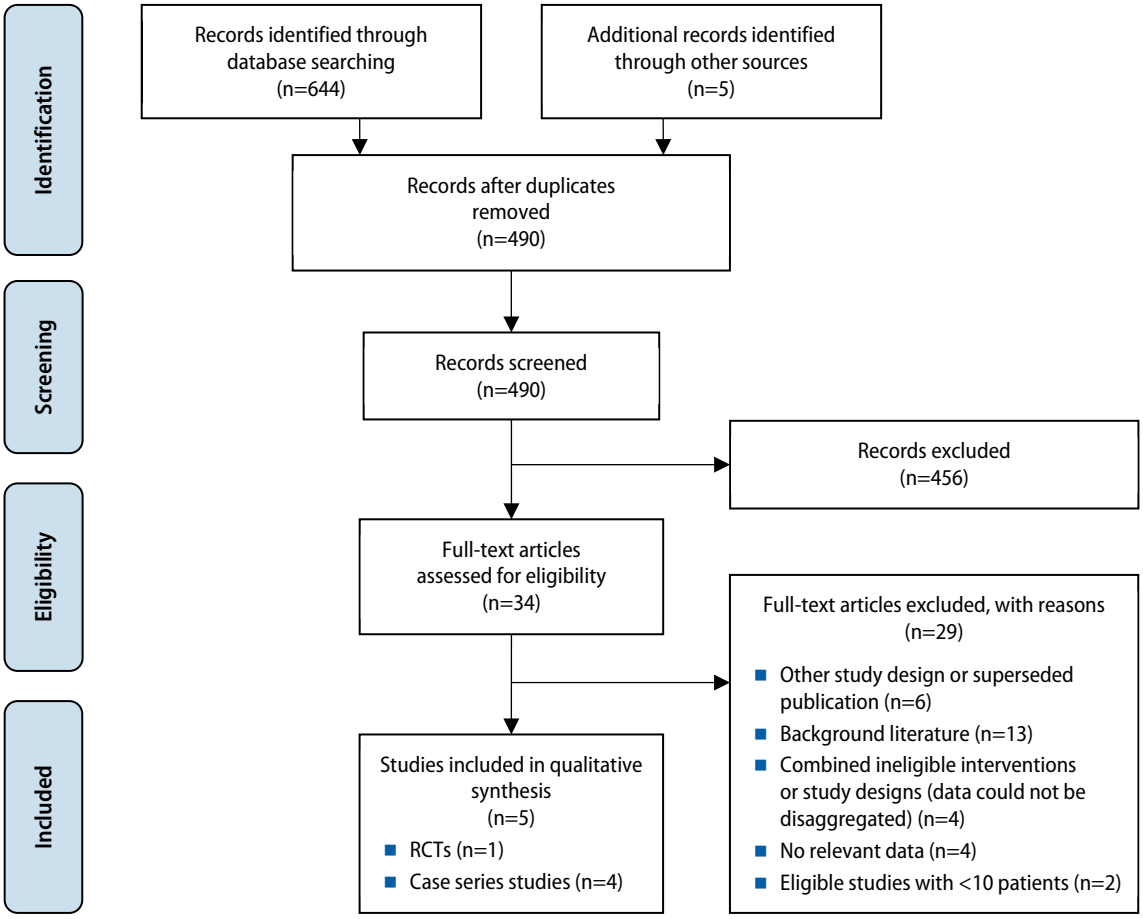
Suche nach laufenden Studien (18 Treffer)

Three clinical trials registries (ClinicalTrials.gov, WHO-ICTRP and EU Clinical Trials) were searched on 10 January 2023 to identify ongoing and unpublished studies, which resulted in 18 potentially relevant hits. The five relevant studies are summarised in the Appendix (Table A-1 and Table A-2).

3.2.2 Flow chart of study selection

Overall, 490 unique citations were identified from the literature searches. These references were screened by two researchers (AS, JK) independently. Any disagreements were resolved by consensus. The selection process is displayed in Figure 3-1.

Literaturauswahl:
5 Studien eingeschlossen



Abbreviations: RCTs – randomised controlled trials

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Risk of Bias: Cochrane RoB 2 und IHE-20 Checkliste

Relevant data from the included studies were extracted by one reviewer (AS) into tables that were designed and tested a priori. The data extraction tables were checked for accuracy by a second reviewer (JK). One reviewer (AS) assessed the studies for internal validity and risk of bias using the Cochrane Risk of Bias 2 tool [46] (for RCTs) and the IHE-20 checklist [47] (for case series studies) and the quality of the data using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) schema [48] (see Table A-3 and Table A-4 in the Appendix). A second reviewer (JK) validated these assessments for accuracy. Any disagreements with respect to the data extraction or quality analyses were resolved by consensus.

3.2.4 Synthesis

qualitative Synthese der Evidenz mithilfe von GRADE

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix (Table A-5 and Table A-6). Results are summarised in the Appendix (Table A-1 and Table A-2).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

Critical outcomes

Selection of critical outcomes was based on the patient-centred outcomes recommended for heart valve disease trials [44]. The following outcomes were defined as *critical* to derive a recommendation.

wesentliche Endpunkte: allgemeine Mortalität, kardiovaskuläre Mortalität, funktioneller Status, Leistungsfähigkeit, Lebensqualität, …

- ***All-cause mortality:*** This is an important endpoint since patients with TR may die of cardio-renal and liver complications [43].
- ***Cardiovascular mortality:*** This is an important endpoint given that one-year mortality for severe TR may be as high as 20 to 30% [43].
- ***Functional status:*** This is typically assessed using the New York Heart Association functional class, which classifies patients according to their physical activity limitations as follows: I – no symptoms of heart failure; II – symptoms of heart failure with moderate exertion; III – symptoms of heart failure with minimal exertion; and IV – symptoms of heart failure at rest [49].
- ***Exercise capacity:*** This is an accepted endpoint commonly used by regulatory agencies in cardiac intervention trials. It is usually assessed with the six-minute walk test, which measures the distance a patient can walk in six minutes [50].
- ***Health-related quality of life:*** This is usually assessed with heart failure specific questionnaires such as the Minnesota Living with Heart Failure or the Kansas City Cardiomyopathy Questionnaire, which has been endorsed by the FDA for use in cardiovascular device trials [43, 51].

All the methods outlined above were used by the included studies to measure these endpoints.

4.1.2 Outcomes safety

Selection of critical outcomes was based on the patient-centred outcomes recommended for heart valve disease trials [44]. The following outcomes were defined as *critical* to derive a recommendation.

… schwerwiegende unerwünschte Ereignisse

- ***Serious adverse events*** are any events, related or unrelated to the medical device, that result in death, are life-threatening, require hospitalisation (either initial or prolonged), result in persistent or significant disability, incapacity or chronic disease or require intervention to prevent impairment or damage [52, 53].
- Other important adverse events.

For the purposes of this review, procedure-related adverse events are defined as adverse events related to the use of a medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation or any malfunction of the investigational medical device as well as any event that is a result of a use error or intentional misuse [52].

und Komplikationen im Zusammenhang mit der Intervention

4.2 Included studies

Evidenz:
1 RCT, 4 Fallserien

One RCT and four case series studies (two prospective and two retrospective) assessing the effectiveness and safety of CAVI met the predefined inclusion criteria [40, 54-57]. Study characteristics and results of the included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-5 and Table A-6 in the Appendix.

4.2.1 RCTs

vorzeitige Beendigung des RCTs aufgrund von Sicherheitsbedenken

The single centre open label RCT from Germany examined the use of CAVI with the SAPIEN XT valve in 14 patients (mean age 77 years) with severe TR who were ineligible for conventional valve surgery despite optimised medical therapy [40]. Patient recruitment for this RCT was stopped prematurely due to safety concerns.

CAVI vs. OMT

28 Patient*innen

Ø Alter 77 Jahre

Großteil mit torrentialer TI

primärer Endpunkt: Leistungsfähigkeit nach 3 Monaten

Finanzierung: SAPIEN XT Hersteller

Fourteen patients (mean age 77 years) receiving guideline recommended medical treatment for heart failure formed the comparator group. The majority of patients in both groups were in New York Heart Association (NYHA) functional class III, had torrential regurgitation and a mean EuroSCORE of 14%.[22] Although a statistical comparison of baseline parameters between the two groups was not reported, there were no apparent differences with respect to exercise and aerobic capacity, heart failure classification or quality of life. Comorbidities were not reported. The primary outcome of the study was exercise capacity measured by treadmill spiroergometry three months after device implantation. Other safety and effectiveness outcomes were recorded at 1, 3, 6 and 12 months after implantation. Over the study period no losses to follow up occurred in the intervention group, whereas four patients in the comparator group withdrew their consent. The study was sponsored by the manufacturer of the SAPIEN XT valve, and conflicts of interest were declared by nine of the 13 authors (69%).

4.2.2 Case series studies

4 Fallserien:
105 Patient*innen

Durchschnittsalter zwischen 74 und 80 Jahre

Großteil mit schwerwiegender TI

50-76 % mit Herzchirurgie vor CAVI

The four multicentre case series studies included 105 patients undergoing caval (n=43) or bicaval (n=62) stent implantation [54-57]. Caval implantation was accomplished with the SAPEIN XT or 3 (n=40), a single TricValve in the inferior vena cava (n=2) or the DirectFlow (n=1) valve. Bicaval implantation was achieved with the dedicated TricValve (n=40) or TRICENTO system (n=21), or with two SAPEIN XT valves (n=1). The mean age of patients ranged from 74 to 80 years, nearly all of whom had severe or higher grade TR (one study included five patients with moderate TR [56]). Most patients had a NYHA class of III or higher (2/105 in NTHA class II) and a mean or median left ventricular ejection fraction of between 51 and 59%, which is in the normal range. In the three studies in which it was reported, the mean EuroSCORE ranged from 6 to 18%.[22] Between 50 and 76% of patients had undergone cardiac surgery or percutaneous intervention before CAVI and pacemakers or other implantable devices were present in 19 to 46% of pa-

[22] EuroSCORE quantifies risk of death after heart surgery as follows:
score 1-2% –low risk; score 3-5% – medium risk; score ≥6% – high risk [58].

tients. The most common comorbidities reported were diabetes (20-67%), kidney dysfunction (44-83%) and chronic obstructive pulmonary disease (6-32%).

The primary outcomes stated in two studies were change in NYHA functional class and quality of life [54] and technical success [57]. The other two studies did not identify the primary endpoints [55, 56]. Follow up ranged from a median of 61 to 332 days after implantation in three studies [54, 56, 57]; the fourth study reported outcomes over a mean of 316 days [55]. Only one study had losses to follow up (6%) [54]. The source of funding was not reported in three studies; the fourth study did not receive specific funding support [57]. Some authors in each of the four studies had connections with the device manufacturers, including receiving speaker and consultancy fees and research support. Only one study formally stated that these relationships were not relevant to the study [54].

Follow-Up (FU): 61-332 Tage nach Implantation

Loss to FU: 0-6 %

4.3 Results

4.3.1 RCT evidence (CAVI versus optimised medical treatment)

Effectiveness outcomes

One RCT reported outcomes for CAVI (n=14) and optimised medical treatment (OMT) (n=14) [40].

Evidenz aus randomisiert kontrollierten Studien (RCT):

Cardiovascular and all-cause mortality

The rate of all-cause mortality was 57% in the CAVI group and 29% in patients receiving OMT at the twelve-month follow up (p=0.16).[23] The rate of cardiovascular mortality was not reported.[24]

Mortalität: 57 % in CAVI vs. 29 % in OMT, jedoch keine statistische Signifikanz

Functional status

Improvement by one functional class on the NHYA scale occurred in 63% (n=8) of patients after CAVI and in 45% (n=11) receiving OMT, compared to baseline. Although the change was statistically significant relative to baseline values in the CAVI group (p=0.025), there was no discernible between group difference at either three or twelve months after implantation.[25]

Echocardiographic examinations showed no improvement in TR severity with respect to baseline in the 14 patients who received CAVI.[26]

Verbesserung des funktionellen Status in CAVI-Gruppe zum Anfangswert signifikant, jedoch kein Gruppenunterschied; keine Verbesserung des TI Schweregrads

[23] **D0003** – What is the effect of the technology on the mortality due to causes other than the target disease?

[24] **D0001** – What is the expected beneficial effect of the technology on mortality?

[25] **D0005** – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

[26] **D0006** – How does the technology affect progression (or recurrence) of the disease or health condition?

Exercise capacity

Three months after implantation, there was no statistically significant difference between CAVI (n=8) and OMT (n=10) with respect to mean maximum rate of oxygen consumption or six-minute walk test distance.[27]

Leistungsfähigkeit: kein stat. signifikanter Gruppenunterschied nach 3 Monaten

Health-related quality of life

Health-related quality of life scores on the Minnesota Living with Heart Failure Questionnaire had improved at three months after implantation by a mean 20 points over baseline scores among patients receiving CAVI (n=8; p=0.004), compared with eight points among the OMT group (n=10). However, the change between groups was not statistically significant at the three- or twelve-month follow up.[28]

Lebensqualität: kein stat. signifikanter Gruppenunterschied nach 3 Monaten

Safety outcomes[29]

Procedure-related adverse events

Four of the 14 patients receiving CAVI required conversion to surgery due to stent migration (n=2) and valve dislocation (n=2). Three of these patients died in hospital due to haemorrhagic shock. These unexpected complications led to the premature termination of the study.

offene Operation nach CAVI bei 4/14 Patient*innen notwendig

No vascular complications occurred following CAVI implantation.

Adverse events

Four patients (29%) in each group required hospitalisation for heart failure over the twelve-month follow-up period.

Hospitalisation aufgrund von Herzinsuffizienz in bei 4/14 vs. 4/14 Patient*innen

4.3.2 Case series evidence

Effectiveness outcomes

All-cause mortality

The rate of all-cause mortality ranged from 9% (3/33; 6-month follow up) to 24% (5/21; 12-month follow up) in the two bicaval implantation studies [54, 57]. The rates were higher in the two caval implantation studies, ranging from 58% (14/24; median 332-day follow up) to 63% (14/22; 12-month follow up) [55, 56].[23]

Evidenz aus Beobachtungsstudien: Mortalität in 4 Fallserien: 9-24 %

Cardiovascular mortality

Three studies reported cardiovascular mortality rates. No patient had died by the six- or twelve-month follow up in two studies (n=55) [54, 55], The third study reported two cardiovascular related deaths (n=21) over a twelve-month follow-up period [57].[24]

Mortalität in 3 Fallserien: 2 kardiovaskuläre Tode bei 12 Monaten Follow-Up

[27] **D0011** – What is the effect of the technology on patients' body functions?

[28] **D0013** – What is the effect of the technology on disease-specific quality of life?

[29] **C0008** – How safe is the technology in comparison to the comparator(s)?

Functional status

NYHA functional class generally improved across all studies. One study found statistically significant improvement in functional class up to six months after bicaval implantation (p=0.0006), with 79% of patients (n=29) having transitioned to class I or II after six months (there were none in these classes at baseline) and no patients in class IV [54].[27]

Leistungsfähigkeit: stat. signifikante Verbesserung in 1/4 Studien

TR was classified as severe or higher in 86% of patients (n=30) at the end of the study, compared with 100% (n=35) at baseline (p=0.02). A similar result was reported by the other study on bicaval implantation, with 65% (n=20) in NYHA functional class I or II a median 107 days after the procedure (p=0.001) [57]. However, only two of 17 patients were classified as having moderate TR at the end of the follow-up period.[25]

TI-Schweregrad: stat. signifikante Verbesserung in 2/4 Studien

The other two studies in which most patients underwent caval implantation indicated an improvement of at least one NYHA class in 84% of patients (n=19) at hospital discharge [55] and in 73% (n=11) after a mean follow up of 31 days [56]. The latter study reported that 33% of patients (n=18) had moderate or lower severity TR a median 332 days after implantation, compared with 21% (n=24) at baseline [56].[27]

funkionelle Klasse: Verbesserung um min. 1 NYHA-Klasse in 2 Studien

Exercise capacity

One study measured changes in six-minute walk test distance [54]. Six months after bicaval implantation, the mean six-minute walk distance had not changed significantly from the baseline value (n=27).[27]

Leistungsfähigkeit in 1 Fallserie: keine stat. signifikante Verbesserung im 6-Minuten Gehtest

Health-related quality of life

One study reported on change in quality of life using the 12-item Kansas City Cardiomyopathy Questionnaire. Six months after bicaval implantation, the mean score had improved significantly from 42.0 (n=35) at baseline to 59.7 (n=27; p=0.004) [54].[28]

Lebensqualität in 1 Fallserie: stat. signifikante Verbesserung der Lebensqualität nach 6 Monaten

Safety outcomes

Procedure-related adverse events

Across the four studies, conversion to surgery was required in one patient (n=105) after migration of a superior vena cava prosthesis immediately after deployment [55]. Overall, device migration occurred in 4% of patients (n=81; outcome not reported in one study) [54, 55, 57]. Only one treatment-related death was reported among the 105 patients, which was due to worsening renal failure [56]. No instances of treatment-related stroke occurred in any of the studies.

Nebenwirkungen: Konversion zu Operationen in einem Patienten, Produktmigration in 4 %, 1 Tod aufgrund der Intervention

Adverse events

Overall, 12% (n=105) of patients died in hospital after the procedure, although only one of these deaths was considered procedure related. Eleven of the 56 patients (20%) required hospitalisation for heart failure up to twelve-months after implantation in the two studies that reported this outcome [54, 57].

12 % Tode im Krankenhaus nach Intervention

Across the four studies (n=105), the rate of major bleeding complications ranged from 0% to 8% [54-57]. Other adverse events reported included kidney injury or renal failure (0% to 21%) in three studies, a cerebrovascular event (0% to 6%) in four studies and major vascular complication (0% to 2%) in two studies.

schwere Blutungskomplikationen bei 0-8 %

5 Certainty of evidence

Verzerrungspotential: Cochrane RoB 2

The risk of bias for individual studies was assessed with the Cochrane Risk of Bias 2 tool [46], and is presented in Table A-3 and Table A-4 in the Appendix. The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema for each endpoint individually [59]. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [59].

Vertrauenswürdigkeit der Evidenz nach GRADE

GRADE bestehend aus 4 Kategorien: sehr niedrig bis hoch

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

For comparative data, ranking according to the GRADE scheme for the research question can be found in the summary of findings table below (Table 5-1) and in the evidence profile in the Appendix (Table A-5).

RCT Evidenz: Verzerrungspotential größtenteils niedrig,

Bedenken bei "Verdeckte Zuordnung" und „Verblindung"

The study quality of the RCT [40] was assessed for the following critical outcomes: all-cause mortality, functional status, exercise capacity, health-related quality of life, procedure-related adverse events and in-hospital mortality. The certainty of the evidence ranged from very low to low. There were some concerns regarding allocation concealment (method not reported) and assessor blinding. For the latter aspect, although the nature of the intervention prohibited blinding while patients were in hospital, it was possible for assessors reviewing patients after hospital discharge to be blinded to the intervention received. In addition, there was an imbalance in the number of patients lost to follow up (0% in CAVI versus 29% in OMT). The trial was stopped early due to safety concerns, which led to the trial being underpowered to detect a clinically significant difference in the primary endpoint [40].

Vertrauenswürdigkeit der Evidenz bei CAVI vs. OMT sehr niedrig

Overall, the certainty of evidence for the effectiveness and safety of CAVI compared with OMT was very low. There were no studies comparing CAVI with any other transcatheter interventions.

4 Fallserien: Vertrauenswürdigkeit der Evidenz als sehr niedrig gewertet

The study quality of the four case series studies [54-57] was assessed for the following critical outcomes: all-cause and cardiovascular mortality, functional status, exercise capacity, health-related quality of life, procedure-related adverse events, in-hospital mortality and major bleeding. Although the studies were generally well conducted, they were all rated as very low certainty because they did not have a comparator group. Additional issues with this body of evidence included the lack of blinding of outcome assessors in all studies, the retrospective nature of two registry-based studies, the potential for selective recruitment in three studies, and the inadequate or uneven lengths of follow up among patients in three studies. In three studies the source of funding was not reported. These issues, in conjunction with their relatively small sample sizes, precluded any upgrading from the initial starting point of very low certainty.

Table 5-1: Summary of findings table for CAVI versus OMT in patients with TR (randomised controlled trial evidence)[30]

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with CAVI	Risk with OMT				
All-cause mortality (12 months after implantation)	57 per 100	29 per 100	RR 2.00 (0.78, 5.14)	28 (1)	⨁◯◯◯ Very low [a,b,c]	No difference between groups
Functional status (12 months after implantation)	NI	NI	Not estimable	17 (1)	⨁◯◯◯ Very low [a,b,d]	No difference between groups
Exercise capacity (3 months after implantation)	NA	NA	MD 21.70 [-121.79, 165.19] Mean change *Intervention*: 18.9 metres *Comparator*: -2.8 metres	18 (1)	⨁◯◯◯ Very low [a,b,c]	No difference between groups
Health-related quality of life (12 months after implantation)	NA	NA	Not estimable	18 (1)	⨁⨁◯◯ Low[a,b]	No difference between groups
Procedure-related adverse events	29 per 100	NA	Not estimable	28 (1)	⨁⨁◯◯ Very low[a,b,d]	Not estimable
In-hospital mortality	21 per 100	NA	Not estimable	28 (1)	⨁⨁◯◯ Low[a,b]	Not estimable
Hospitalisation for heart failure (12 months after implantation)	29 per 100	29 per 100	RR 1.00 (0.31, 3.23)	28 (1)	⨁◯◯◯ Very low [a,b,c]	No difference between groups

Abbreviations: CAVI –caval valve implantation; CI – confidence interval; MD – mean difference; NA –not applicable; NI – no information; OMT – optimised medical therapy; TR – tricuspid regurgitation.

Explanations:

[a] *No mention of method used to conceal allocation; imbalance in losses to follow up between groups; trial stopped early due to safety concerns (this was not considered sufficient to downgrade the certainty of the evidence because it would serve to underestimate the treatment effect).*

[b] *Small sample size; trial underpowered to detect a clinically significant difference in the primary endpoint [40].*

[c] *Point estimate has wide confidence interval.*

[d] *Blinding of operators not possible due to the nature of the interventions, but potentially possible to blind assessors conducting post-discharge measurements to treatment allocation.*

[30] **D0017** – Was the use of the technology worthwhile?

Overall, the certainty of evidence for the effectiveness and safety of CAVI provided by case series studies was very low.

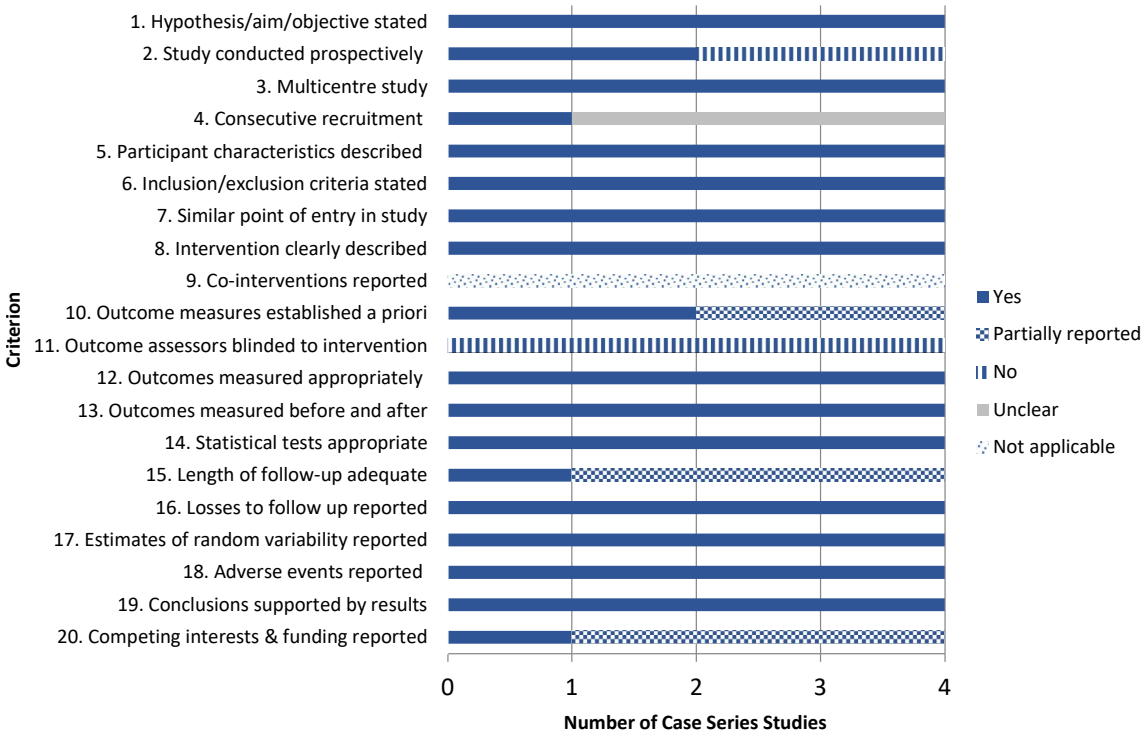


Figure 5-1: Quality appraisal results for included case series studies using the IHE case series checklist [47]

6 Discussion

6.1 Summary of findings

Zusammenfassung der Ergebnisse: 1 RCT und 4 Fallserien

Limited evidence from one small RCT [40] suggested that CAVI was no more effective than OMT in terms of improving exercise capacity, quality of life or functional status three months after implantation (very low to low certainty evidence). Although quality of life and functional status improved relative to baseline values after three months in the CAVI group, this was no longer the case after twelve months, and there was no difference between CAVI and OMT in these parameters over the entire follow-up period (very low to low certainty evidence). The rates of all-cause mortality did not differ between the two treatment groups 12 months after implantation (very low certainty evidence).[30]

RCT: keine stat. signifikanten Unterschiede zwischen CAVI und optimaler medikamentöser Therapie

4 Fallserien: Verbesserungen in Leistungsfähigkeit und Lebensqualität, aber kein direkter Vergleich verfügbar

Evidence from four case series studies [54-57] (very low certainty evidence) indicated that CAVI improved functional status (four studies), exercise capacity (one study) and quality of life (one study) up to six months after the procedure. However, it is unclear how these effects compare with OMT, or whether the degree of improvement would be clinically meaningful to patients. The rate of all-cause mortality ranged from 9% to 63% up to twelve months following the procedure, whereas the rate of cardiovascular mortality was low (2.5%).[30]

Vorzeitiger Abbruch des RCTs aufgrund von Ventilverschiebung in 4/14 Patient*innen

The small RCT [40] was terminated prematurely due to the relative high rates of valve dislocation and migration (4 of the 14 patients), which necessitated surgical intervention in all cases (very low certainty evidence). However, the rate of hospitalisation for heart failure was identical for both groups over the twelve-month follow-up period (very low certainty evidence). In contrast, the rate of device migration was much lower in the case series studies (4%) (very low certainty evidence for all safety outcomes) and only one in-hospital death was considered procedure-related. Major bleeding complications occurred in 6% of patients up to 12 months after CAVI, 20% of patients required hospitalisation for heart failure and 9% experienced kidney injury or renal failure.

Einbettung in bestehendes Wissen: 1 SR in 2023: möglicher Link zwischen hoher Mortalität und Off-Label Produkten

The results of this report align with the only other published systematic review on CAVI from 2023, which included all the studies in this report as well some smaller case series studies and case reports [60]. The review authors similarly noted the potential link between high mortality rates and the use of non-dedicated CAVI devices.

6.2 Internal and external validity

Limitationen der Evidenz:

The results of this review should be interpreted cautiously due to concerns with the internal validity of the studies. The main issues for the RCT were a lack of information regarding allocation concealment, the lack of blinding to treatment allocation of assessors conducting post-discharge measurements and the imbalance in losses to follow up between the treatment groups [40]. In addition, since the trial was stopped early due to safety concerns, this meant that it was underpowered to detect a clinically significant difference in the primary endpoint. The most significant problems among the case series studies were the lack of blinding of assessors measuring post-discharge outcomes, the potential for selective recruitment and the inadequate or uneven lengths of follow up among patients. In addition, the lack of a comparator group made it difficult to gauge the value of CAVI over other treatment options in patients with severe TR.

nicht genug Power durch Abbruch des RCTs zur Feststellung signifikanter Unterschiede,

zusätzlich keine Vergleiche in den Fallserien

Verbesserung der Prozedur könnten in Zukunft Einschlusskriterien verändern

In terms of external validity, the main consideration is that the study participants comprised a select group of very ill patients with severe TR who were ineligible for surgery and met stringent clinical and anatomical criteria. This reflects the type of patient who would undergo CAVI in its current form. However, further refinements of the procedure, delivery systems and prostheses may change the patient eligibility criteria in such a way that the current results no longer apply.

6.3 Evidence gaps and ongoing studies

derzeitige Ergebnisse auf Patient*innen mit schwerwiegenden TI beschränkt, potentiell höherer Nutzen in früheren Stadien

The evidence base for CAVI is currently limited to small feasibility studies where the procedure was conducted for compassionate reasons. Consequently, most of the patients had severe, often life-limiting comorbidities and were undergoing CAVI as a last resort [55, 60], which potentially confounds the results of the studies. This also means that these patient groups may not be representative of the patients who will ultimately form the target population for this intervention. CAVI addresses regurgitation of blood into the caval veins rather than TR itself, but only a subgroup of patients with severe TR and right ventricular enlargement has caval regurgitation [61]. In addition, CAVI may have more capacity to improve cardiac function and morphology in high-risk patients who are still in the early stages of valvular disease and have the potential for reverse cardiac remodelling, in contrast to patients in the current studies with advanced right heart failure [40].

weitere Entwicklung des Produktes könnten zu besseren Ergebnissen führen

Since the technique is still evolving, there are potential improvements that can be made in terms of stent sizing, design and deployment. For example, the TRICENTO valve is currently custom made and continues to undergo design changes to improve its performance [57]. There is some suggestion that better outcomes may also be obtained using a dedicated self-expanding stent for implantation in the venae cavae, rather than non-dedicated balloon expandable devices that appear to be more prone to device migration and embolisation [40]. It may eventually become apparent that, in most cases, balloon expandable stents should only be used in the inferior vena cava [55].

Other issues that need to be addressed regarding the CAVI technique include: its long-term durability, particularly its long-term impact on right atrium and ventricular function; whether caval or bicaval implantation has superior outcomes for particular patient subgroups; and how the procedure compares with transcatheter interventions that address TR directly [39, 61]. The current evidence base is too limited and the follow-up periods are too short to answer these questions. In addition, minimal clinically important differences[31] have yet to be universally adopted in cardiac surgery [64]. However, this will be an important consideration when ascertaining whether the statistically significant changes observed, particularly in the case series studies, are of meaningful benefit to patients.

offene Fragen:

Langzeitauswirkungen auf die Ventrikelfunktion; Vergleich mit transkatheter Prozeduren, die sich direkt auf die Trikuspidalklappe auswirken

6.3.1 Ongoing studies

There are four ongoing open label, multicentre studies (one RCT and four prospective case series studies) assessing the bicaval application of the TricValve in patients with severe TR (Table A-8 in the Appendix). The industry sponsored RCT will compare bicaval implantation with OMT up to 12 months following implantation. It has a target enrolment of 430 patients and a primary completion date of January 2025, although recruitment is not yet underway. The sample sizes of the four case series studies range from 10 to 450 and will provide data on patients from three to twelve months after device implantation. Two of these studies are currently recruiting patients. The primary completion dates cited for two of the studies are May and December 2025; a completion date has not been reported for the third study. The fourth open label, single centre case series study, with a primary completion date of October 2023, is assessing the bicaval implantation of the TRICENTO valve in 15 patients with carcinoid heart disease and symptomatic severe TR.

fünf laufende Studien:

1 RCT (Vergleich Implantation vs. optimale medikamentöse Therapie) und 4 Fallserien derzeit laufend

6.4 Limitations of the assessment

Due to the amount of case series evidence identified, case series with fewer than 10 participants were excluded. The latter criterion resulted in the exclusion of two case series studies [65, 66] (9 patients in total) and several case reports. Excluding this evidence may have led to rare safety events being missed. However, any unusual safety events reported in these studies are likely to reflect the early stagy of development of the procedure rather than its true safety profile. In addition, a comparison of the results from this report and a recent systematic review that included case series study and case report data suggested that limiting studies according to sample size did not lead to the exclusion of any data that would have changed the outcome of this assessment [60].

Limitationen des Berichts: Exklusion von Fallserien mit <10 Patient*innen

Although a comprehensive search of medical literature databases was conducted, an extensive grey literature search was not undertaken. In addition, some relevant articles may have been overlooked by restricting the searches to studies published in the English or German language. However, clinical

und keine Suche nach grauer Literatur

[31] The minimal clinically important difference (MCID) is defined as the smallest change in an outcome that a patient would perceive as clinically meaningful [62, 63]

trial databases were searched, the references of all retrieved studies (including systematic and narrative reviews) were hand searched and some device manufacturers were contacted for additional information, so it is unlikely that any significant studies were missed. In addition, results from a recent meta-epidemiological study suggest that excluding non-English publications from systematic reviews on clinical interventions has little effect on the overall conclusions [67].

6.5 Conclusion

Schlussfolgerung: vergleichende Wirksamkeit von CAVI vs. optimale medikamentöse Therapie derzeit unklar

The current evidence base for CAVI is limited to one small RCT that was stopped early due to safety concerns and four small case series studies with a total of 105 patients. Given the stage of development of the procedure and the fact that only two of the included studies used dedicated CAVI devices, as opposed to stents were used off label in the tricuspid valve, it is still unclear whether CAVI offers enough benefit over OMT to justify the risks.

7 Evidence-based conclusions

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based conclusions

	Strong evidence for added benefit in routine use
	Evidence indicates added benefit only in specific indications
	Less robust evidence indicating an added benefit in routine use or in specific indications
X	No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest
	Strong evidence indicates that intervention is ineffective and or harmful

Reasoning:

CAVI is a palliative procedure that does not reverse or improve the underlying cause of TR. Very low to low certainty evidence indicated that the small improvements in mortality rates and symptoms achieved after CAVI may be similar to those achieved with OMT, but with the added risk of exposing patients to potentially life-threatening procedure-related adverse events. There is some suggestion that dedicated bicaval implants may be safer than non-dedicated caval implants.

Evidenz unzureichend: CAVI derzeit nicht empfohlen

TRICAV, a large international open label, multicentre RCT comparing bicaval implantation with OMT in 430 patients with severe TR is due for completion in January 2025. Based on this, a re-evaluation is recommended not before 2026.

Re-Evaluierung 2026, bei Vorliegen von Ergebnissen von TRICAV

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: CAVI: Results from randomised controlled trials

Author, year	Dreger 2020 [40]
Country	Germany
Sponsor	Edwards Lifesciences (California, USA)
Study design	Prospective, open label, single centre
Time period	January 2015 to November 2017
Intervention (I)	Caval valved stent implantation
Device	SAPIEN XT valve (Edwards Lifesciences, California, USA)
Access	Femoral vein (guided by transthoracic echocardiography)
Anaesthesia	Local
Valve placement	Inferior vena cava
Duration of procedure (minutes), mean [SD]	Not reported
Elective procedure, n/N (%)	14/14 (100)
Cointerventions	None
Comparator (C)	Optimised medical therapy (guideline recommended treatment for heart failure)
Number of patients (I vs. C)	14 vs.14
Inclusion criteria	Severe tricuspid regurgitation; NYHA class ≥II despite optimised medical therapy; age ≥50 years; high surgical risk (logistic EuroSCORE I ≥15% or other contraindications to conventional valve surgery
Exclusion criteria	*Clinical*: Left ventricular ejection fraction <30%; severe kidney dysfunction or mitral regurgitation; life expectancy <12 months; active upper gastrointestinal bleeding or acute myocardial infarction within one month of treatment; evidence of stroke or transient ischemic attack in the previous 180 days; presence of leukopenia, anaemia, thrombocytopaenia, any blood clotting disorder or intracardiac mass, thrombus, or vegetation in the right heart; undergoing regular dialysis or a serum creatinine >3.0 mg/dL; active bacterial endocarditis within 6 months of treatment; women of childbearing age without effective contraception *Anatomic*: Inferior vena cava diameter at implantation site >32 mm (assessed by computed tomography or 3D echocardiography)
Age of patients (years), median (IQR) (I vs. C)	77 (68.2-82.0) vs. 77 (72.2-79.5)
Sex, male, n/N (%) (I vs. C)	2/14 (14) vs. 7/14 (50)
Tricuspid regurgitation severity, n/N (%)	Severe: 4/28 (14) Massive: 4/28 (14) Torrential: 20/28 (72)
Heart failure classification, n/N (%) (I vs. C)	Ejection fraction ≥50%: 12 (86) vs. 13 (93) Ejection fraction 40-49%: 2 (14) vs. 1 (7)
NYHA class, n/N (%)a (I vs. C)	I. 0 vs. 0 II. 2/14 (14) vs. 3/14 (21) III. 12/14 (86) vs. 10/14 (71) IV. 0/14 vs. 1/14 (7)

Author, year	Dreger 2020 [40]
Surgical risk (EuroSCORE I) b, mean % [SD] (I vs. C)	14.6 [11.6] vs. 14.2 [7.9]
History of heart surgery, n/N (%) (I vs. C)	3/14 (21) vs. 6/14 (43)
Pacemaker or implantable cardioverter defibrillator, n/N (%)	Not reported
VO2max (mL/kg/minute)b, mean [SD] (I vs. C)	11.7 [2.8] vs. 11.2 [3.6]
6-minute walk test (metres), mean [SD] (I vs. C)	294 [115] vs. 286 [114]
Quality of life (MLHFQ score), mean [SD] (I vs. C)	41.9 [15.1] vs. 41.8 [14.0]
Length of follow up	1, 3, 6 and 12 months after implantation
Losses to follow up, n/N (%) (I vs. C)	0 vs. 4/14 (29)
Differences in baseline demographics between groups	No apparent differences, but a statistical analysis was not reported
Outcomes	
Efficacy	
Successful device placement, n/N (%)	14/14 (100)
All-cause mortality, n (%)	**12-month FU** I [n=14]: 8 (57) C [n=14]: 4 (29) (p=0.16)
Change in NYHA class, mean [SD]	**3-month FU** **I [n=8] vs. C [n=11]:** -0.6 [0.5]* vs. -0.3 [0.9] (p=0.40) ***p=0.025 vs. baseline** Improved by one class, n/N (%): 5/8 (63) vs. 5/11 (45) Unchanged, n/N (%): 3/8 (38) vs. 5/11 (45) Worsened by two classes, n/N (%): 0/8 vs. 1/11 (10) **12-month FU** No difference between groups over entire FU period (p>0.05)
Tricuspid regurgitation severity	I [n=14]: Echocardiographic examinations showed no significant effect compared with baseline values
Change in VO2max (mL/kg/minute)c, mean [SD]	**3-month FU** **I [n=8] vs. C [n=10]:** -1.0 [1.6] vs. -0.1 [1.8] (p=0.299)
Change in 6-minute walk test (metres), mean [SD]	**3-month FU** **I [n=8] vs. C [n=10]:** 18.9 [47.0] vs. -2.8 [71.3] (p=0.49)
Change in quality of life (MLHFQ score), mean [SD] **(lower score is better)**	**3-month FU** **I [n=8] vs. C [n=10]:** -19.9 [13.1]* vs. -7.6 [16.3] (p=0.098) ***p=0.004 vs. baseline** **12-month FU** No difference between groups over entire FU period (p=0.68)
Safety	
Conversion to surgery, n/N (%)	4/14 (29)[d]
In-hospital mortality, n/N (%)	3/14 (21) (due to haemorrhagic shock after conversion to surgery)
Hospitalisation for heart failure, n (%)	I [n=14] vs. C [n=14]: 4 (29) vs. 4 (29) (p=1.00)
Vascular complications, n (%)	I [n=14]: 0

Abbreviations: FU –follow up; IQR – interquartile range; MLHFQ – Minnesota Living with Heart Failure Questionnaire; NYHA – New York Heart Association; SD – standard deviation; VO_{2max} – maximum volume of oxygen.

Comments:

[a] *NYHA I – No symptoms and no limitation in ordinary physical activity; II – Mild symptoms and slight limitation in ordinary physical activity (e.g., fatigue, palpitation, shortness of breath or chest pain); III – Marked limitation in physical activity due to symptoms. Comfortable only at rest.; IV – Symptoms of heart failure at rest; any physical activity causes further discomfort [49].*

[b] *EuroSCORE quantifies risk of death after heart surgery as follows: score 1-2% – low risk; score 3-5% – medium risk; score ≥6% – high risk [58].*

[c] *Maximum rate of oxygen consumption attainable during physical exertion.*

[d] *Cardiac tamponade due to stent migration (n=2); valve dislocation (n=2).*

Table A-2: CAVI: Results from case series studies

Author, year	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
Country	Austria, Spain	Canada, Germany	United States	Austria, Germany, Italy, Spain, Switzerland
Sponsor	Not reported	Not reported	Not reported	None
Study design	Prospective, open label, multicentre (n=12)	Prospective, open label, multicentre (n=6)	Retrospective, multicentre (n=7) registry	Retrospective, multicentre (n=12) registry
Time period	December 2019 to February 2021	March 2010 to February 2017	1 April 2013 to 31 March 2018	March 2017 to October 2019
Intervention	Bicaval valved stent implantation	Caval and bicaval valved stent implantation	Caval valved stent implantation	Bicaval valved stent implantation
Device	TricValve (P+F Products + Features GMBH, Vienna, Austria)	Edwards SAPIEN 3 or XT (n=17) valve (Edwards LIfesciences, California, USA) TricValve (n=7) (P+F Products + Features GMBH, Vienna, Austria) Directflow valve (n=1) (Direct Flow Medical, California, USA)	Edwards SAPIEN 3 (n=23) or XT (n=1) valve (Edwards LIfescences, California, USA)	TRICENTO system (Medira AG, Balingen, Germany)
Anaesthesia	Not reported	General	Not reported	General (n=20); local anaesthesia (n=1)
Access	Femoral vein	Femoral vein (n=24) or internal jugular (n=1)	Femoral vein	Femoral vein
Valve placement	Superior and inferior vena cava	Superior and inferior vena cava (n=6) Inferior vena cava only (n=19)	Inferior vena cava	Superior and inferior vena cava
Duration of procedure (minutes), mean [SD]	Not reported	Not reported	Not reported	92 [48]
Elective procedure, n/N (%)	Not reported	Not reported	21/24 (87.5)	
Cointerventions	None	None	None	None
Number of patients	35	25	24	21
Inclusion criteria	Adults with symptomatic severe tricuspid regurgitation (≥3 in a 5-grade classification within 8 weeks of treatment) despite optimal medical therapy who were ineligible for open heart surgery; symptoms and signs of right heart failure; NYHA class III or IV; left ventricular ejection fraction ≥40%; able to achieve a 6-minute walk distance ≥60 metres	Patients with severe symptomatic tricuspid regurgitation despite optimal medical treatment who were ineligible for surgery	Patients with symptomatic tricuspid regurgitation who were poor candidates for surgical valve intervention	Patients with symptomatic severe or higher grade tricuspid regurgitation who are ineligible for surgery or other transcutaneous treatment options
Exclusion criteria	Severe right ventricular dysfunction (tricuspid annular plane systolic excursion <13 mm) or severe pulmonary hypertension (systolic pulmonary pressure >65 mmHg); significant renal dysfunction (serum creatinine >3.0 mg/dL) or use of any form of dialysis within the past 4 weeks and at time of screening; significant intracardiac shunt;	*Clinical*: Life expectancy <3 months; severely depressed right ventricular function (tricuspid annular plane systolic excursion <10 mm); systolic pulmonary artery pressure >60 mmHg	Inferior vena cava diameter at the superior-most hepatic vein >29 mm (determined by computed tomography)	Inferior and superior vena cava diameter <16 mm or >35 mm; right atrial length <40 mm or >80 mm; distance from right atrium to liver veins <10 mm

Author, year	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
Exclusion criteria *(continuation)*	requires other cardiac procedures 30 days before or 90 days after the procedure; life expectancy <1 year; cerebrovascular event within the past 3 months; history of mitral or tricuspid endocarditis within the last 12 months; untreated significant left sided valvular heart disease; primary coagulopathy or platelet disorder; acute myocardial infection within 30 days of screening; liver cirrhosis; women of child bearing potential; gastrointestinal bleeding within 90 days of screening; requires antibiotic treatment with 48 hours before treatment	*Anatomic*: Inferior and superior vena cava diameter >35 mm at the relevant anatomic landmarks		
Age of patients (years)	Mean 76 (SD 6.8)	Mean 73.9 (SD 7.6)	Median 79.5 (range 49.0-91.0)	Mean 76 (SD 7)
Sex, male, n/N (%)	6/35 (17)	12/25 (48)	9/24 (38)	7/21 (33)
Tricuspid regurgitation severity, n/N (%)	Grade 3-5: 35/35 (100)	Massive: 25/25 (100)	Moderate: 5/24 (21) Severe: 16/24 (67) Torrential: 2/24 (8) Not available: 1/24 (4)	Severe: 13/21 (62) Massive: 4/21 (19) Torrential: 4/21 (19)
Degree of heart failure	Mean left ventricular ejection fraction: 59.2%	Mean left ventricular ejection fraction: 51% (SD 15; range 15-74) Ejection fraction <50%:10/25	Median left ventricular ejection fraction: 57.5% (range 30.0-70.0)	Mean left ventricular ejection fraction: 55% (SD 7) Ejection fraction ≥50%: 17/21 (81) Ejection fraction 30-49%: 4/21 (19)
NYHA class, n/N (%)a	III. 29/35 (83) IV. 6/35 (17)	III. 7/25 (28) IV. 18/25 (72)	II: 1/24 (4); III: 16/24 (67); IV: 7/24 (29)	I: 0; II: 1/21 (4); III: 18/21 (86); IV: 2/21 (10)
Surgical risk (EuroSCORE II)b, mean % [SD]	5.8 [4.2]	18.2 [12.9]	Not reported	11 [7]
History of heart surgery, n/N (%)	Valve interventions: 24/35 (68)	Open heart surgery: 19/25 (76) Percutaneous coronary intervention: 7/25 (28) (valve interventions: 5/25 (20))	Median 1 (range 0-3)	Open heart surgery: 13/21 (62) Previous transcatheter aortic valve replacement: 2/21 (10)
Pacemaker or implantable cardioverter defibrillator, n/N (%)	8/35 (23)	9/25 (36)	11/24 (46)	4/21 (19)
Comorbidities, n/N (%)	Diabetes: 7/35 (20) Renal dysfunction: 21/35 (60) COPD: 2/35 (6) Cerebrovascular event: 3 (9)	Diabetes: 11/25 (44) Hypertension: 23/25 (92) End stage renal failure requiring dialysis: 11/25 (44) COPD: 8/25 (32) Cerebrovascular event: 2 (8)	Diabetes: 12/24 (50) Hypertension: 21/24 (88) Chronic kidney disease: 20/24 (83) Cerebrovascular event: 3 (13)	Heart failure: 14/21 (67) COPD: 6/21 (29) Renal failure: 16/21 (76) Dialysis: 6/21 (29)

Author, year	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
6-minute walk test (metres), mean [SD]	244.96 [85.96]	Not reported	Not reported	Not reported
Quality of life, mean [SD]	KCCQ12 score: 42.01 [22.3]	Not reported	Not reported	Not reported
Length of follow up	Median 6 months (IQR 5.8-6.2) after implantation	Mean 316 (SD 453) days (range 14-1,540) after implantation	Median 332 (2-1,161) days after implantation	12 months after implantation (median 61 days)
Losses to follow up, n/N (%)	2/35 (6)	0/25	6/24 (25)	0/21
Outcomes				
Efficacy				
Successful device placement, n/N (%)	34/35 (97)	23/25 (92)	24/24 (100)	21/21 (100)
Cardiovascular mortality, n (%)	**6-month FU (n=33):** 0	0 (0)	Not reported	**30-day FU (n=21):** 0 **12-month FU (n=21):** 2 (10)
All-cause mortality, n (%)	**6-month FU (n=33):** 3 (9)	**30-day FU (n=25):** 3 (12)[c] **12-month FU (n=22):** 14 (63)	**30-day, (n=24), n (%):** 6 (25) **FU median 332 days (range 2-1,161) (n=24), n (%)** 14 (58)	**30-day FU (n=21):** 1 (5) (not procedure related) **12-month FU (n=21):** 5 (24)
NYHA class, n (%)	Baseline (n=35): I/II: 0; III: 29 (83); IV: 6 (17) **30-day FU (n=30):** I/II: 15 (50); III: 15 (50) **(p=0.005)** **3-month FU (n=31):** I/II: 19 (61); III: 12 (39) **(p=0.005)** **6-month FU (n=29):** I/II: 23 (79); III: 6 (21) **(p=0.0006)**	Baseline (n=19): I: 0; II: 0; III: 7 (37); IV: 12 (63) **At hospital discharge (n=19)** I: 2 (11); II: 8 (42); III: 7 (37); IV: 2 (11) Improvement by ≥1 NYHA class: 16/19 (84)	Baseline (n=11): I: 0; II: 1 (9); III/IV: 10 (91) **Mean 30.5-day FU (range 14-64) (n=11)** I: 3 (27); II: 3 (27); III/IV: 5 (46)	Baseline (n=21): I: 0; II: 1 (4); III: 18 (86); IV: 2 (10) **Median 107-day FU (IQR 50-189) (n=20)** I: 6 (30); II: 7 (35); III: 6 (30); IV: 1 (5) **p=0.001** relative to baseline
Tricuspid regurgitation severity	Grade 3-5 Baseline (n=35): 100% **6-month FU (n=30):** 86% **(p=0.02)**	Not reported	Baseline (n=24): Moderate: 5 (21); severe: 16 (67); torrential: 2 (8); not available: 1 (4) **Median 332-day FU (range 2-1,161) (n=18), n (%)** None: 1 (6) ; mild: 1 (6); moderate: 4 (22); severe: 11 (61); torrential: 1 (6)	Baseline (n=21): Severe: 13 (62); massive: 4 (19); torrential: 4 (19) **Median 93-day FU (IQR 55-134) (n=17)** Moderate: 2 (12); severe: 6 (35); massive: 7 (41); torrential: 2 (12)
Change in 6-minute walk test (metres), mean [SD]	Baseline (n=35): 244.96 [85.96] **30-day FU (n=23):** 261.65 [93.06] **3-month FU (n=23):** 262.48 [114.09] **6-month FU (n=27):** 276.13 [90.00] (p=0.46) >40 metre improvement: 24%	Not reported	Not reported	Not reported

Author, year	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
Change in quality of life, mean [SD]	KCCQ12 score (higher is better) Baseline (n=35): 42.01 [22.30] **30-day FU (n=29):** 58.59 [26.06] **3-month FU (n=31):** 56.5 [23.59] **6-month FU (n=30):** 59.7 [23.60] **(p=0.004)**	Not reported	Not reported	Not reported
Safety				
Conversion to surgery, n/N (%)	0	1/25 (4)	0 (0)	0 (0)
Device migration, n/N (%)	1/35 (3) (no clinical consequences)	2/25 (8) (both required surgery)	Not reported	0 (0)
In-hospital mortality, n/N (%)	1/35 (3)	6/25 (24)	5/24 (21) (one was procedure related)	0 (0)
Treatment-related mortality, n (%)	**6-month FU (n=33):** 0 (0)	0 (0)	1/24 (4)	0 (0)
Hospitalisation for heart failure, n/N (%)	7/35 (20)	Not reported	Not reported	**12-month FU** 4/21 (19); unrelated to procedure in one patient
Bleeding complications, n/N (%)	Major bleeding at access site: 2/35 (6) Major bleeding (other than access site): 4/35 (11)	Bleeding complications at access site: 0/25 Bleeding complications (other than access site): 3/25 (12)	2/24 (8)	Major: 0
Treatment related stroke, n (%)	**6-month FU (n=33):** 0 (0)	0 (0)	0 (0)	0 (0)
Other adverse events, n/N (%)	**6-month FU (n=33)** Cerebrovascular event: 2 (6) Myocardial infarction or cardiac tamponade: 0	Cerebrovascular event or myocardial infarction: 0/25 New onset renal failure requiring dialysis: 0/14	Cerebrovascular event: 0 Renal failure: 5/24 (21) Major vascular complication: 1/24 (4)	Cerebrovascular event or myocardial infarction: 0/21 Acute kidney injury: 4 (19) (one patient required temporary dialysis) Systemic inflammatory syndrome: 1 (5) (stabilised within 24 hours) Vascular complications: minor, 3/21 (14); major: 1/21 (5)

Abbreviations: COPD – chronic obstructive pulmonary disease; FU – follow up; IQR – interquartile range; KCCQ12 – 12-item Kansas City Cardiomyopathy Questionnaire; NYHA – New York Heart Association; SD – standard deviation; VO_{2max} – maximum volume of oxygen.

Comments:

[a] *NYHA I – No symptoms and no limitation in ordinary physical activity; II – Mild symptoms and slight limitation in ordinary physical activity (e.g., fatigue, palpitation, shortness of breath or chest pain); III – Marked limitation in physical activity due to symptoms. Comfortable only at rest.; IV – Symptoms of heart failure at rest; any physical activity causes further discomfort [49].*

[b] *EuroSCORE quantifies risk of death after heart surgery as follows: score 1-2% – low risk; score 3-5% – medium risk; score ≥6% – high risk [58].*

[c] *Multiorgan failure and septic complications.*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [2] and in the Guidelines of EUnetHTA [45].

Table A-3: Risk of bias – study level (RCTs), see [59]

Trial	Endpoints	Bias arising from randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of reported result	Overall risk of bias
Dreger 2020 [40]	All-cause and cardiovascular mortality	Some concern [a]	Low	Some concern [b]	Low	Low	**Some concern**
	Functional status	Some concern [a]	Low	Some concern [b]	Low	Low	
	Exercise capacity	Some concern [a]	Low	Some concern [b]	Low	Low	
	Health-related quality of life	Some concern [a]	Low	Some concern [b]	Low	Low	
	Adverse events	Some concern [a]	Low	Some concern [b]	Low	Low	

Comments:

[a] *Blinding of operators not possible due to the nature of the interventions, but potentially possible to blind assessors conducting post-discharge measurements to treatment allocation; no mention of method used to conceal allocation.*

[b] *Imbalance in losses to follow up between groups; trial stopped early due to safety concerns.*

Table A-4: Risk of bias – study level (case series), see [47]

Criterion	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	●	●	●	●
Study design				
2. Was the study conducted prospectively?	●	●	○	○
3. Were the cases collected in more than one centre?	●	●	●	●
4. Were patients recruited consecutively?	?	?	?	●
Study population				
5. Were the characteristics of the patients included in the study described?	●	●	●	●
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	●	●	●	●
7. Did patients enter the study at a similar point in the disease?a	●	●	●	●

Criterion	Estévez-Loureiro 2022 [54]	Lauten 2018 [55]	O'Neill 2020 [56]	Wild 2022 [57]
Intervention and co-intervention				
8. Was the intervention of interest clearly described?	●	●	●	●
9. Were additional interventions (co-interventions) clearly described?	NA	NA	NA	NA
Outcome measures				
10. Were relevant outcome measures established a priori?	●	◐	◐	●
11. Were outcome assessors blinded to the intervention that patients received?	○	○	○	○
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	●	●	●	●
13. Were the relevant outcome measured before and after the intervention?	●	●	●	●
Statistical Analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	●	●	●	●
Results and Conclusions				
15. Was follow up long enough for important events and outcomes to occur?	◐	◐[b]	◐[b]	●
16. Were losses to follow up reported?	●	●	●	●
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	●	●	●	●
18. Were the adverse events reported?	●	●	●	●
19. Were the conclusions of the study supported by results?	●	●	●	●
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	◐[c]	◐[c]	◐[c]	●

Abbreviations: Yes – ●; Partially – ◐; No – ○; Unclear – ?; Not applicable –NA.

Comments:

[a] *The point in the disease that patients entered the study was judged by their degree of tricuspid regurgitation (mild to torrential). Studies that included at least 95% of patients with severe, massive, or torrential regurgitation were scored 'yes' for this item.*

[b] *Only in some patients.*

[c] *Only competing interests reported.*

Table A-5: Evidence profile: efficacy and safety of CAVI versus OMT in patients with severe TR

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Certainty of evidence
							CAVI	OMT	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (12 months after implantation)											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Very serious[c,d]	Publication bias suspected[e]	8/14 (57%)	4/14 (29%)	RR 2.00 (0.78, 5.14)	No difference between groups (p=0.16)	⊕◯◯◯ Very low
Functional status: assessed with improvement by one NYHA class (3 months after implantation)											
1 [40]	Randomised controlled trial	Very serious[a,b]	Not serious	Not serious	Very serious[c,d]	Publication bias suspected[b]	5/8 (63%)	5/11 (45%)	RR 1.38 [0.59, 3.19]	No difference between groups (p=0.40)	⊕◯◯◯ Very low
Functional status: assessed with NYHA class (12 months after implantation)											
1 [40]	Randomised controlled trial	Very serious[a,b]	Not serious	Not serious	Serious[c]	Publication bias suspected[e]	NI	NI	No difference between groups (p>0.05)		⊕◯◯◯ Very low
Exercise capacity: assessed with 6-minute walk test distance (3 months after implantation)											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Very serious[c,d]	Publication bias suspected[e]	Mean change: 18.9 metres (n=8)	Mean change: -2.8 metres (n=10)	MD 21.70 [-121.79, 165.19]	No difference between groups (p=0.49)	⊕◯◯◯ Very low
Health-related quality of life: assessed with MLHFQ score (lower is better) (3 months after implantation)											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Very serious[c,d]	Publication bias suspected[e]	Mean change: -19.9 (n=8)	Mean change: -7.6 metres (n=10)	MD -12.30 [-45.51, 20.91]	No difference between groups (p=0.098)	⊕◯◯◯ Very low
Health-related quality of life: assessed with MLHFQ score (lower is better) (12 months after implantation)											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Serious[c]	Publication bias suspected[e]	NI	NI	No difference between groups (p=0.68)		⊕⊕◯◯ Low
Procedure-related adverse events											
1 [40]	Randomised controlled trial	Very serious[a,b]	Not serious	Not serious	Serious[c]	Publication bias suspected[e]	4/14 (29%)	NA	Not estimable		⊕◯◯◯ Very low
In-hospital mortality											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Serious[c]	Publication bias suspected[e]	3/14 (21%)	NA	Not estimable		⊕⊕◯◯ Low
In-hospital mortality											
1 [40]	Randomised controlled trial	Serious[b]	Not serious	Not serious	Very Verserious[c,d]	Publication bias suspected[e]	4/14 (29%)	4/14 (29%)	RR 1.00 [0.31, 3.23]	No difference between groups (p=1.00)	⊕◯◯◯ Very low

Abbreviations: CAVI –caval valve implantation; MD – mean difference; MLHFQ –Minnesota Living with Heart Failure Questionnaire; NA – not applicable; NI – no information; NYHA – New York Heart Association; OMT – optimised medical therapy.

Comments:

[a] *Blinding of operators not possible due to the nature of the interventions, but potentially possible to blind assessors conducting post-discharge measurements to treatment allocation.*

[b] *No mention of method used to conceal allocation; imbalance in losses to follow up between groups; trial stopped early due to safety concerns (this was not considered sufficient to downgrade the certainty of the evidence because it would serve to underestimate the treatment effect).*

[c] *Small sample size; trial underpowered to detect a clinically significant difference in the primary endpoint [40].*

[d] *Point estimate has wide confidence interval.*

[e] *Difficult to determine but suspected. This is a new area of research and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the quality of the evidence.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1).

GRADE Working Group grades of evidence [48]:

⊕⊕⊕⊕ ***High certainty:*** *We are very confident that the true effect lies close to that of the estimate of effect.*

⊕⊕⊕◯ ***Moderate certainty:*** *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

⊕⊕◯◯ ***Low certainty:*** *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*

⊕◯◯◯ ***Very low certainty:*** *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Table A-6: Evidence profile: efficacy and safety of CAVI in patients with severe TR

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect	Quality
							CAVI n/N or N	OMT n/N		
Cardiovascular mortality (up to 12 months after implantation)										
3 [54, 55, 57]	Case series	Very serious[a]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	2/81	NA	2.5% (median 0; range: 0 to 2.5)	⊕◯◯◯ Very low
All-cause mortality (6 months after implantation)										
1 [54]	Case series	Very serious[e]	Not serious	Not serious	Serious[f]	Publication bias suspected[c]	3/35	NA	9%	⊕◯◯◯ Very low
All-cause mortality (up to 12 months after implantation)										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	36/100	NA	36% (median 41; range 9 to 63)	⊕◯◯◯ Very low

Quality assessment							Summary of findings			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect	Quality
							CAVI n/N or N	OMT n/N		
Functional status: assessed with NYHA class (raw data not reported in 1 study) (up to 6 months after implantation)										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	51 [55-57]	NA	Class I/II at baseline: 4% Class I/II after intervention: 57%[g] Statistical analysis of comparison reported in two studies: p≤0.001 [54, 57]	⊕◯◯◯ Very low
Exercise capacity: assessed with 6-minute walk test distance (6 months after implantation)										
1 [54]	Case series	Very serious[e]	Not serious	Not serious	Serious[f]	Publication bias suspected[c]	27[h]	NA	No difference relative to baseline (p=0.46)	⊕◯◯◯ Very low
Health-related quality of life: assessed with KCCQ12 score (higher is better) (6 months after implantation)										
1 [54]	Case series	Very serious[e]	Not serious	Not serious	Serious[f]	Publication bias suspected[c]	27[h]	NA	Improvement relative to baseline (p=0.004)	⊕◯◯◯ Very low
Procedure-related mortality										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	1/105	NA	1% (median 0; range: 0 to 1)	⊕◯◯◯ Very low
Procedure-related adverse events										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	3/105	NA	3% (median 1.5; range: 0 to 8)	⊕◯◯◯ Very low
In-hospital mortality										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	12/105	NA	12% (median 12; range: 0 to 24)	⊕◯◯◯ Very low
Major bleeding (up to 12 months after implantation)										
4 [54-57]	Case series	Very serious[d]	Not serious	Not serious	Serious[b]	Publication bias suspected[c]	6/105	NA	6% (median 0; range: 0 to 17)	⊕◯◯◯ Very low

Abbreviations: CAVI –caval valve implantation; KCCQ12 – 12-item Kansas City Cardiomyopathy Questionnaire; NA – not applicable; NYHA – New York Heart Association; OMT – optimised medical therapy.

Comments:

[a] *Single arm open label study (k=3); retrospective (k=1); unclear if patients recruited consecutively (k=2); follow up not adequate for some patients (k=2).*

[b] *Small sample size.*

[c] *Difficult to determine but suspected. This is a new area of research and many studies are preliminary or exploratory. However, this was not considered sufficient to downgrade the certainty of the evidence.*

[d] *Single arm open label study (k=4); retrospective (k=2); unclear if patients recruited consecutively (k=3); follow up not adequate for some patients (k=3).*

[e] *Single arm open label study; unclear if patients recruited consecutively; follow up not adequate.*

[f] *Single study with small sample size.*

[g] *Baseline values for specific subset of patients not reported in one study [54].*

[h] *Baseline values for these specific patients not reported.*

Nomenclature for GRADE table:
Limitations: 0: no limitations or no serious limitations; -1: serious limitations
Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency
Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty
Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1).

GRADE Working Group grades of evidence [48]
⊕⊕⊕⊕ ***High certainty:*** *We are very confident that the true effect lies close to that of the estimate of effect.*
⊕⊕⊕◯ ***Moderate certainty:*** *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
⊕⊕◯◯ ***Low certainty:*** *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*
⊕◯◯◯ ***Very low certainty:*** *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Applicability table

Table A-7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The participants in the studies comprised a select group of patients with severe TR who were ineligible for surgery and met stringent clinical and anatomical criteria. In most cases they underwent the procedure on compassionate grounds as a last resort. Given the stage of development of CAVI, this reflects the type of patients who would undergo CAVI in the Austrian health system. However, the results pertaining to these patient groups are not necessarily applicable to individuals who have fewer comorbidities or less severe TR.
Intervention	The devices used for caval implantation are commercially available for other indications but were used off label in the tricuspid valve. This may not be feasible in the Austrian health system. Of the bicaval devices used in the studies, only one has the CE mark. Since this device is manufactured by an Austrian company, it is likely to be readily available in Austria.
Comparators	The only comparator reported in the studies was optimised medical treatment, which would be routinely used in patients with severe TR in Austria.
Outcomes	The critical outcomes of all-cause and cardiovascular mortality, exercise capacity, functional status and quality of life were reported in most of the studies over periods ranging from three to twelve months folowing device implantation. Considering that the main purpose of CAVI is to reduce symptoms of TR and increase survival, these outcomes are appropriate. However, follow-up periods of less than twelve months may not be long enough to track the durability of the procedure. The occurrence of procedure-related adverse events was reported in most studies.
Setting	The studies were conducted in the Canada, Europe and the USA. CAVI was conducted in tertiary hospitals by teams of specialist personnel with experience in transcatheter cardiac interventions. This is reflective of the likely utilisation of the device in Austria.

Abbreviations: CAVI – caval valve implantation; TR – tricuspid regurgitation; USA – United States of America.

List of ongoing trials

Table A-8: List of ongoing trials of CAVI

Identifier/ Trial name	Study design	Condition	Target enrolment	Intervention	Comparator	Primary outcome	Primary completion date/Status	Sponsor
NCT06137807 (TRICAV)	Open label RCT	Severe TR with NYHA Class II-IV or heart failure admission in the past 6 months	430	TricValve – Transcatheter Bicaval Valves System	Standard of care therapy	Mortality (1 and 12 months) Adverse events Need for surgery or re-intervention Heart failure events Need for right ventricular assist device implantation Change in quality of life (KCCQ score) Change in functional status (NYHA class) Change in exercise capacity (6MWT)	January 2025 Not yet recruiting	P+F Products + Features GmbH (Vienna, Austria)
NCT05114850 (TRICUS Registry)	Prospective open label multicentre observational cohort (patient registry)	Successful treatment with the TricValve – Transcatheter Bicavla Valves System	450	TricValve – Transcatheter Bicaval Valves System	Not applicable	Number of patients with readmission for heart failure (12 months)	December 2025 Recruiting	P+F Products + Features GmbH (Vienna, Austria)
NCT05820516 (CRITICAL)	Prospective open label multicentre observational cohort (patient registry)	Patients with severe, massive or torrential TR	100	TricValve – Transcatheter Bicaval Valves System	Not applicable	Composite of all-cause mortality and heart failure rehospitalisation (6 months)	May 2025 Not yet recruiting	Azienda Ospedaliero, Universitaria Pisana (Pisa, Italy)
NCT05064514 (TRICAR)	Prospective open label single centre observational cohort	Carcinoid heart disease with symptomatic severe TR with significant backflow in the caval and hepatic veins	15	TRICENTO valve (bicaval)	Not applicable	Number of patients with successful device implantation and a 35% reduction in V wave pressure in the inferior vena cava	October 2023 Active	Queen Mary University of London, United Kingdom
CTRI/2023/09/ 057356 (TRIO-2)	Prospective open label multicentre observational cohort (post-marketing surveillance)	Symptomatic severe TR with NYHA class III-IV	10	TricValve – Transcatheter Bicaval Valves System	Not applicable	Clinical efficacy based on two-dimensional echocardiography and questionnaire (3 months)	Completion date not available Recruiting	Relisys Medical Devices Limited (Telangana, India)

Abbreviations: 6MWT – six-minute walk test; KCCQ – Kansas City Cardiomyopathy Questionnaire; NYHA – New York Heart Association; RCT – randomised controlled trial; TR – tricuspid regurgitation.

Research questions

Table A-9: Health problem and current use

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-10: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-11: Clinical effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A -12: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?

Literature search strategies

Search strategy for Cochrane

Search Name: CAVI for tricuspid valve regurgitation	
Search date: 12.12.2023	
ID	Search
#1	MeSH descriptor: [Tricuspid Valve Insufficiency] explode all trees
#2	MeSH descriptor: [Tricuspid Valve] explode all trees
#3	(tricuspid*) (Word variations have been searched)
#4	#2 OR #3
#5	(regurgitat*) (Word variations have been searched)
#6	(leak*) (Word variations have been searched)
#7	#5 OR #6
#8	#4 AND #7
#9	#1 OR #8
10	MeSH descriptor: [Venae Cavae] explode all trees
#11	(vena* NEXT cava*) (Word variations have been searched)
#12	(caval)
#13	(bi?caval) (Word variations have been searched)
#14	(bi-caval)
#15	#10 OR #11 OR #12 OR #13 OR #14
#16	MeSH descriptor: [Blood Vessel Prosthesis Implantation] explode all trees
#17	MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees
#18	(implant*) (Word variations have been searched)
#19	#16 OR #17 OR #18
#20	(CAVI):ti,ab,kw
#21	#19 OR #20
#22	#9 AND #21
#23	(conference proceeding):pt
#24	(abstract):so
#25	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#26	#23 OR #24 OR #25
#27	#22 NOT #26
#28	English:la
#29	German:la
#30	#28 OR #29
#31	#27 AND #30
Total hits: 91	

Search strategy for Embase

Search Name: CAVI for tricuspid valve regurgitation	
Search date: 12.12.2023	
ID	Search
#1	'tricuspid valve regurgitation'/exp
#2	'tricuspid valve'/exp
#3	tricuspid*
#4	#2 OR #3
#5	regurgitat*
#6	'leak'/exp
#7	'leakage'/exp
#8	leak*
#9	#5 OR #6 OR #7 OR #8
10	#4 AND #9
#11	#1 OR #10
#12	'caval valve implant'/exp
#13	'caval valve implantation'/exp
#14	'cava vein'/exp
#15	'vena* cava*'
#16	caval
#17	bicaval
#18	'bi-caval'
#19	#14 OR #15 OR #16 OR #17 OR #18
#20	'implantation'/exp
#21	implant*
#22	#20 OR #21
#23	#19 AND #22
#24	cavi:ti,ab,kw
#25	#12 OR #13 OR #23 OR #24
#26	#11 AND #25
#27	#11 AND #25 AND ([english]/lim OR [german]/lim)
#28	#27 AND 'Conference Abstract'/it
#29	#27 NOT #28
Total hits: 378	

Search strategy for Medline via Ovid

Search Name: CAVI for tricuspid valve regurgitation	
Search date: 07.12.2023	
ID	Search
1	exp Tricuspid Valve Insufficiency/
2	exp Tricuspid Valve/
3	tricuspid*.mp.
4	2 or 3
5	regurgitat*.mp.
6	leak*.mp.
7	5 or 6
8	4 and 7
9	1 or 8
10	exp Venae Cavae/
11	vena* cava*.mp.
12	caval.mp.
13	bi?caval.mp.
14	bi-caval.mp.
15	10 or 11 or 12 or 13 or 14
16	exp Blood Vessel Prosthesis Implantation/
17	exp Heart Valve Prosthesis Implantation/
18	implant*.mp.
19	15 and 18
20	CAVI.ti,ab.
21	19 or 20
22	9 and 21
23	limit 22 to (english or german)
Total hits: 173	

Search strategy for HTA-INAHTA

Search Name: CAVI for tricuspid valve regurgitation	
Search date: 12.12.2023	
ID	Search
1	"Tricuspid Valve Insufficiency"[mhe],"4","2023-12-12T18:18:46.000000Z"
2	"Tricuspid Valve"[mhe],"5","2023-12-12T18:19:21.000000Z"
3	tricuspid*,"7","2023-12-12T18:19:43.000000Z"
4	(tricuspid*) OR ("Tricuspid Valve"[mhe]),"7","2023-12-12T18:19:53.000000Z"
5	regurgitat*,"41","2023-12-12T18:20:11.000000Z"
6	leak*,"54","2023-12-12T18:20:26.000000Z"
7	(leak*) OR (regurgitat*),"92","2023-12-12T18:20:34.000000Z"
8	((leak*) OR (regurgitat*)) AND ((tricuspid*) OR ("Tricuspid Valve"[mhe])),"3","2023-12-12T18:20:45.000000Z"
9	(((leak*) OR (regurgitat*)) AND ((tricuspid*) OR ("Tricuspid Valve"[mhe]))) OR ("Tricuspid Valve Insufficiency"[mhe]),"4","2023-12-12T18:21:29.000000Z"
10	(((leak*) OR (regurgitat*)) AND ((tricuspid*) OR ("Tricuspid Valve"[mhe]))) OR ("Tricuspid Valve Insufficiency"[mhe]),"4","2023-12-12T18:21:43.000000Z"
11	((((leak*) OR (regurgitat*)) AND ((tricuspid*) OR ("Tricuspid Valve"[mhe]))) OR ("Tricuspid Valve Insufficiency"[mhe])) AND (English OR German)[Language],"2","2023-12-12T18:22:29.000000Z
Total hits: 2	

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