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SUMMARY WITH CRITICAL APPRAISAL

Transcatheter Mitral Valve Repair Device for the Treatment of Tricuspid or Tricuspid and Mitral Regurgitation: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

CRD	University of York Centre for Reviews and Dissemination
HF	heart failure
NYHA	New York Heart Association functional classification
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MR	mitral regurgitation
MV	mitral valve
NT-proBNP	N-Terminal Pro-B-Type natriuretic peptide
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	quality of life
TR	tricuspid regurgitation
TTVR	tricuspid edge-to-edge repair
TV	tricuspid valve
6MWT	six-minute walk test
6MWD	six-minute walk distance

Context and Policy Issues

Tricuspid valve regurgitation is a heart condition in which the valve between the right ventricle and right atrium does not close properly.[1] The malfunctioning valve allows blood to flow back into the heart's right atrium.[1] Tricuspid regurgitation (TR) can be the result of congenital heart disease (e.g., Ebstein's anomaly) or valve abnormalities caused by other conditions, such as infective endocarditis, radiation therapy, or mitral regurgitation.[1,2] Noticeable signs and symptoms of tricuspid regurgitation may include: fatigue, declining exercise capacity, peripheral edema, and abnormal heart rhythms.[1] Long term consequences of untreated TR may include heart failure and atrial fibrillation.[1] TR severity is graded as mild, moderate, severe, or massive (grade I to IV, respectively).[3] In the United States in 2005, the prevalence of moderate and severe TR was estimated to be around 1,600,000, and the estimated number of surgically treated patients was 8,000.[4] In a Canadian hospital in 2014, the prevalence of severe TR was 1.2% in patients referred for echocardiography.[5] With limited effective treatment options, surgery to repair or replace the tricuspid valve (TV) is the current standard of care but has operative mortality of 13 to 18% and ten-year survival rate of 49 to 66%.[2,6] In patients with untreated TR, prognosis remains poor.[2]

MitraClip, also known as transcatheter mitral valve repair device, is a technology designed for catheter-based mitral valve (MV, also known as bicuspid valve) repair on the left side of the heart.[2] It is a less invasive treatment that is performed in the cardiac catheterization laboratory.[7] Although designed for mitral valve repair, MitraClip has recently been considered as an alternative treatment option for the treatment of patients with significant TR who are deemed high-risk for open-heart surgery.[2] The use of MitraClip for the TV, with the transcatheter tricuspid edge-to-edge repair (TTVR) technique, is currently off-label.[8]

The purpose of this report is to summarize the clinical effectiveness and cost-effectiveness of the transcatheter mitral valve repair device for TR with or without mitral regurgitation.

Research Questions

1. What is the clinical effectiveness of the transcatheter mitral valve repair device for the treatment of tricuspid regurgitation alone or both tricuspid and mitral regurgitation?
2. What is the cost-effectiveness of the transcatheter mitral valve repair device for the treatment of tricuspid regurgitation alone or both tricuspid and mitral regurgitation?

Key Findings

This report included one single-arm study regarding the clinical effectiveness of the transcatheter mitral valve repair device (MitraClip) for the treatment of tricuspid regurgitation, and four single-arm studies regarding the effectiveness of the device for tricuspid or both tricuspid and mitral regurgitation. No evidence regarding the cost-effectiveness of the transcatheter mitral valve repair device for this indication was identified.

Overall, compared to pre-procedure, patients MitraClip for the treatment of tricuspid regurgitation or both tricuspid and mitral regurgitation had significantly improved tricuspid regurgitation grade, New York Heart Association functional class, edema, and ascites at follow-up. Across four studies that reported on procedural success, the percentage of patients with procedural success ranged from 92% to 97%. There was no statistically significant difference in quality of life between baseline and follow-up in the three studies that measured this outcome. Four of the studies showed statistically significant improvement in the six-minute walking distance at one month or six months, in patients who received tricuspid valve (TV) repair or both TV and mitral valve (MV) repair. One study observed a numerical (but not significant) improvement in the six-minute walking distance from baseline to one-year follow up. For heart failure severity when comparing baseline and follow up, two studies found significant improvement; two studies found no statistically significant difference; and one study demonstrated a statistically significant improvement in patients who received TV-only repair but no significant difference in patients who received both TV and MV repair. The mortality incidence after the procedure was 4.7% to 7% across the included studies.

The findings summarized in this report have a high degree of uncertainty due to the limitations of the included studies (e.g., a total of 209 patients in single-arm studies, longest follow-up duration of one year).

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were transcatheter mitral valve repair devices and tricuspid regurgitation with or without mitral regurgitation. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and April 30, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18 years or older) with tricuspid regurgitation, with or without mitral regurgitation
Intervention	Transcatheter tricuspid valve repair using the transcatheter mitral valve repair device (i.e., MitraClip), or transcatheter tricuspid and mitral valve repair using the MitraClip device
Comparator	Medical management (volume control, compression stockings, antihypertensive medications, medications for pulmonary arterial hypertension), no treatment, surgery
Outcomes	Q1: Clinical effectiveness (e.g., tricuspid regurgitation grade, quality of life, complications, all-cause mortality, New York Heart Association Functional Class, ankle swelling, shortness of breath, hospitalizations) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2015.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the Downs and Black checklist[9] for randomized and non-randomized studies tool as a guide. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 324 citations were identified in the literature search. Following the screening of titles and abstracts, 315 citations were excluded, and nine potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, four publications were excluded for various reasons, and five non-randomized studies[3,10-13] met the inclusion criteria and were included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The five included non-randomized studies[3,10-13] were single-arm uncontrolled before-and-after observational studies.

Country of Origin

All of the included non-randomized studies[3,10-13] were by authors in Germany. The non-randomized study by Nickenig et al.[11] recruited patients from ten international centres, for which the details of country location and the names of centres were not reported.

Given all the included studies[3,10-13] were by authors in Germany with overlapping patient recruitment periods and study centres, there may be some (or complete) overlap in the included patient populations. There were not enough details in the publications to discern whether this is the case; therefore, we considered the included publications as independent studies.

Patient Population

The non-randomized study by Rommel et al.[3] included 29 consecutive patients treated successfully with TTVR using MitraClip for isolated TR between July 2016 and April 2018. The included patients were referred with symptoms of right hearted heart failure (HF) and were in New York Heart Association (NYHA) functional classes II to IV despite guideline-directed medical therapy.[3] The mean age was 78 years.[3]

Four of the included studies[10-13] included patients with TR only and patients with both TR and mitral regurgitation (MR). The non-randomized study by Braun et al.[10] included 24 consecutive patients from March until September 2016, with predominantly TR secondary to pulmonary hypertension or volume overload[15] or both TR and MR. The mean age was 79 years.[10] The Lurz et al. study[11] included 42 consecutive patients with NYHA functional class II or higher despite optimal medical therapy and at high surgical risk, who had TR with or without concomitant MR from June 2016 to April 2017. The Orban et al. study[13] included 50 consecutive patients who were treated for symptomatic severe TR or both TR and MR from March to November 2016. The mean age was 77 years.[13] The non-randomized study by Nickenig et al.[12] included 64 consecutive patients with symptomatic moderate to massive TR on optimal medical treatment with the mean age of 77 years, who were considered unsuitable for surgery, and to whom the intervention with MitraClip was offered as compassionate use for TR only or TR and MR.

Interventions and Comparators

In all five included studies,[3,10-13] the interventions were TTVR with MitraClip for the tricuspid valve (or both the tricuspid and mitral valves) compared to before the intervention. In one study,[3] all patients had TTVR with MitraClip for the TV alone. In the other four[10-13] the included studies, the intervention was the MitraClip for the TV or for both the TV and MV using two MitraClip devices. In Lurz et al.,[11] more than one clip was used if a satisfactory reduction of TR was not achieved after implantation of the first clip. In the studies by Lurz et al.[11] and Orban et al.,[13] results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV; in the studies by Braun et al.[10] and Nickenig et al.,[12] results were reported for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). For the purpose of this report, valve repair using the transcatheter valve repair device will be referred to throughout the report as “TV or MV repair”.

Outcomes

The five included studies[3,10-13] reported on a number of outcomes that were relevant to the current report, including procedural success, TR grade, NYHA functional classes, six-minute walk distance, edema, ascites, heart failure measured by N-Terminal Pro-B-Type natriuretic peptide, quality of life measured by the Minnesota Living with Heart Failure Questionnaire score, and safety measured by mortality and major adverse events. A brief explanation of the measurements used to assess TR symptom severity is provided below.

1. TR grade: a four-grade tricuspid regurgitation severity scale of mild (grade I), moderate (grade II), severe (grade III), and massive or torrential (grade IV)[3]
2. NYHA functional class: a four-class heart failure severity scale of class I (no limitation of physical activity), class II (slight limitation of physical activity), class III (marked limitation of physical activity), class IV (unable to perform any physical activity without discomfort).[16]
3. Six-minute walk test (6MWT): an exercise test that measures the distance a patient walks over a span of 6 minutes.[17] The result of the test, the six-minute walk distance (6MWD), provides a measure of cardiopulmonary and musculoskeletal functions involved in exercise.[17]
4. N-terminal pro–B-type natriuretic peptide (NT-proBNP): a standardized biomarker for heart failure in the plasma. The level increases when heart failure develops or worsens, and the level decreases when heart failure is stable.[18]
5. Minnesota Living with Heart Failure Questionnaire (MLHFQ): a 21-item quality of life (QoL) assessment on four dimensions: physical signs and symptoms, common physical or social functions, psychosocial and cognitive function, and overall adverse impact on QoL.[19] A higher MLHFQ score indicates worse health status.[19]

Summary of Critical Appraisal

The five included non-randomized studies[3,10-13] were critically appraised with the Downs and Black checklist.[9] The studies[3,10-13] had the common strengths: clearly described objectives, interventions, main outcomes, methodology on patient recruitment, and patient characteristics; estimates of random variability (e.g., standard deviations), and probability values (P values). The major findings of the studies[3,10-13] were presented in tabular form and clearly described. Study participants, care providers, and settings appeared to be representative of the population and care setting of interest.[3,10-13] Compliance with the treatment was reliable.[3,10-13]

The studies[3,10-13] also had common limitations: lack of power calculations and sample sizes that ranged from 24 to 64 patients The studies[3,10-13] were conducted in Germany; hence the generalizability to Canadian settings is unknown. Lurz et al.[11] and Orban et al.[13] had 31% and 6% of patients lost to follow up, respectively. Rommel et al.[3] only included patients who had successful MitraClip treatment, which may have biased findings in favour of the intervention due to the lack of information on outcomes from potential patients with attempted (but failed) intervention.

Rommel et al.[3] and Lurz et al.[11] did not report the source of study funding. Braun et al.[10] reported receiving research grant from Abbott Vascular not related to this study. Orban et al.[13] reported funding support from the Klinikum der Universität München and the Heart

Centre Leipzig. Nickenig et al.[12] reported receiving no source of funding. Braun et al.,[10] Lurz et al.,[11] and Orban et al.[13] reported receiving speaker fees from Abbott Vascular, the manufacturer of MitraClip, as a conflict of interest. Rommel et al.[3] did not report any conflicts of interest. Nickenig et al.[12] reported that one author had an unrestricted research grant from Abbott Vascular, and another author was a consultant for Abbott Vascular.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings and the authors' conclusions.

Clinical Effectiveness of the Transcatheter Mitral Valve Repair Device

Procedural Success

While Rommel et al.[3] included only patients who had successful TV-only repair, the remaining four studies[3,10-13] reported the percentage of patients with procedural success for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). In the Braun et al. study,[10] the acute procedural success (TR grade less than or equal to two) was 96%. In the Nickenig et al. study,[12] the procedural success rate (safe clip implantation without partial leaflet detachment or device migration and reduction of TR of one or more grades without creating a tricuspid stenosis) was 97%. In Lurz et al.[11] and Orban et al.,[13] procedural success, defined as successful TV clip implantation with an immediate reduction of at least one grade in TR grade, was 97%[11] and 92%,[13] respectively.

TR Grade

All five included non-randomized studies[3,10-13] examined the effect of the transcatheter mitral valve repair device on TR grade. For patients with isolated TR (severe or massive grade at baseline), Rommel et al.[3] found that TR grade was reduced to at least moderate in all but one patient (out of 29 patients) at one-month follow-up.

The four remaining studies[3,10-13] included patients with transcatheter TV repair alone or both TV and MV repair. Two[10,12] of these studies reported TR grade for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). In the Braun et al.[10] study, the percentage of patients with TR grade less than or equal to two (mild and moderate) significantly increased from baseline to one-year follow up.[10] Nickenig et al.[12] observed a statistically significant reduction in the percentage of patients with TR grade three and higher (severe and massive) from pre-MitraClip procedure to follow-up at six months.

In the remaining two studies,[11,13] TR grade results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. When comparing pre-intervention and one-month post-intervention, Lurz et al.[11] reported a statistically significant reduction in the percentage of patients with TR grade three (severe) and an increase in the percentage of patients with TR grade one (mild) in both patients with TV-only repair and both TV and MV repair from pre-intervention to one-month follow up. There was also a statistically significant reduction in the percentage of patients with TR grade two (moderate) in the TV-only repair group from pre-intervention to one-month follow up, while no statistically significant difference was found in those who had both TV and MV repair.[11] Orban et al.[13] reported that 35 out of 39 patients had a persistent reduction of one

or more TR grades from pre-MitraClip procedure to one-month follow up. There was no significant difference in TR grade between those who received TV repair alone and those who received both TV and MV repair before the intervention or at six-month follow-up.[13]

NYHA Functional Class

The five included non-randomized studies[3,10-13] reported the effect of the transcatheter mitral valve repair device on NYHA functional class. For patients with isolated TR, Rommel et al.[3] found that there was a numerical increase in the percentage of patients in NYHA functional class I and II from 20% at baseline to 72% and 80% at one month and six months, respectively (not compared statistically).[3]

The four remaining studies[3,10-13] included patients with transcatheter TV repair alone or both TV and MV repair using the transcatheter valve repair device. Two[10,12] of these studies reported the NYHA functional class for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). Braun et al.[10] found a statistically significant increase in the percentage of patients with NYHA functional class II or lower at 1 year compared to pre-intervention in all patients, with no statistically significant difference between patients who received TV-only repair or both TV and MV repair.[10] The study published by Nickenig et al.[12] observed that the percentage of all patients (including patients who received TV-only repair or both TV and MV repair) in NYHA classes III and IV numerically decreased from 93% before the intervention to 63% after the intervention (not compared statistically).

In two studies,[11,13] NYHA functional class results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. When comparing pre-intervention and one-month post-intervention, Lurz et al.[11] demonstrated statistically significant improvement in NYHA class in patients with TV-only repair or both TV- and MV-repair. The study by Orban et al.[13] found a numerical improvement of one or more NYHA classes in 79% of all patients, 64% of patients who received TV-only repair, and 86% of patients who received both TV and MV repair, from pre-intervention to follow-up at six months (not compared statistically); there was with no significant difference between the two groups.

Six-Minute Walk Distance

All five included non-randomized studies examined the effect of the transcatheter mitral valve repair device for patients with TR on the six-minute walk distance.[3,10-13] For patients with isolated TR, findings from Rommel et al.[3] found that there was a statistically significant increase in 6MWD from baseline by 20% and 22% at one month and six months.[3]

Braun et al.[10] and Nickenig et al.[12] reported 6MWD for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). Braun et al.[10] found no statistically significant change in 6MWT at one year compared to baseline. Nickenig et al.[12] observed a statistically significant improvement in 6MWD from baseline to one month follow-up.

In two other studies,[11,13] NYHA functional class results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. When comparing pre-intervention and one-month post-intervention, Lurz et al.[11] demonstrated statistically significant improvement in 6MWD in patients with TV-only repair and both TV and MV repair. Orban et al.[13] found a statistically significant improvement of 6MWD from baseline to six months for patients with TV-only repair or both TV and MV repair.

Heart Failure Severity

All five included non-randomized studies[3,10-13] examined the effect of the transcatheter mitral valve repair device for patients with TR on heart failure disease severity as measured by the NT-proBNP value. The findings from Rommel et al.[3] found no statistically significant difference between the NT-proBNP level in patients who received TV-only repair from baseline to one month or six months.

Braun et al.[10] and Nickenig et al.[12] reported heart failure severity for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). Braun et al.[10] found that there was a statistically significant decrease in NT-proBNP level from baseline to one-year follow-up. Nickenig et al.[12] found that there was no statistically significant change in the plasma NT-proBNP level from baseline to the time of hospital discharge after MitraClip placement.

In two other studies,[11,13] heart failure severity results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. Lurz et al.[11] demonstrated a statistically significant decrease in NT-proBNP level from pre-intervention in the TV-only repair group but no statistically significant difference those who received both TV and MV repair. Orban et al.[13] found a statistically significant decrease in NT-proBNP level from baseline to six months after the procedure for patients with TV-only repair or both TV and MV repair.

Quality of Life

Three included non-randomized studies[10,11,13] examined the effect of the transcatheter mitral valve repair device on NYHA functional class for patients with transcatheter TV repair alone or both TV and MV repair. Two[10,13] of these studies reported quality of life for all patients together, while one study[12] reported the outcome separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. Overall, there was no significant difference in quality of life from pre-treatment to one-month,[11] six months,[13] or one year[10] of follow-up.

Mortality and Severe Adverse Events

All five included non-randomized studies[3,10-13] examined mortality or severe adverse events. Two patients (7%) who received TV-only repair died in the study published by Rommel et al.[3]: one from stroke and one from suspected endocarditis. Ten patients (35%) in the same study had clinical events during the six months after TV-only repair; and eight patients (28%) were admitted to the hospital for decompensated heart failure.[3]

Two studies[10,12] reported mortality or adverse events for all patients together (irrespective of whether MitraClip was used for the TV alone or both the TV and MV). In the study by Braun et al.[10] there were 9 deaths (37.5%) at one-year follow-up, due to end-stage heart failure in four patients, myocardial infarction in two patients, sepsis in two patients, and unknown causes in two patients. There were no procedure-related adverse events.[10] The in-hospital mortality rate was 5% in the study by Nickenig et al.[12] There were no intraprocedural deaths, intraprocedural conversions to surgery, stroke, MI, device migration, or pericardial effusion.[12]

In two other studies,[11,13] mortality or adverse event results were reported separately for those had MitraClip for the TV only and those who had MitraClip for both the TV and MV. Lurz et al[11] reported two deaths (4.7%) at one month after the procedure, both of which

were in patients who received the both TV and MV repair.[11] The hospitalization rate was 28% after the procedure.[11] In the study by Orban et al.,[13] the event-free survival rate over six months (free from death, transcatheter reintervention or TV surgery) was 78% of all patients (for those with TV-only or both TV and MV repair).

Edema and Ascites

Two[3,11] of the included non-randomized studies examined the effect of the transcatheter mitral valve repair device on ascites and peripheral edema, which are symptoms of TR. Rommel et al.[3] concluded that there was a statistically significant decrease in the incidence of patient-reported peripheral edema as well as the incidence of ascites from baseline to one month and six months after TV-only repair.

In the study by Lurz et al.,[11] there was a statistically significant reduction in the incidence of edema and ascites from pre-intervention to three months in both patients who received TV-only repair or both TV and MV repair, but there was no statistically significant difference between baseline and one month after the procedure.

Cost-Effectiveness of the Transcatheter Mitral Valve Repair Device

No relevant evidence regarding the cost-effectiveness of the transcatheter mitral valve repair device for the treatment of tricuspid regurgitation or both tricuspid and mitral regurgitation was identified; therefore, no summary can be provided.

Limitations

Given all the included studies[3,10-13] were conducted in Germany with overlapping patient recruitment periods and study centres, it is possible that there was some (or complete overlap) in the study samples. There were not enough details in each publication to discern whether this was the case; therefore, we considered the included publications as independent studies. Caution in interpreting the data is warranted, since the same patients may have been represented in more than one study.

While one included study[10] had a relatively long follow-up duration of one year, most of the included studies[3,11-13] did not observe patients beyond six months post-procedure. The long-term effectiveness of transcatheter mitral valve repair devices for the treatment tricuspid regurgitation or both tricuspid and mitral regurgitation is uncertain.

All five of the included studies[3,10-13] were conducted in Germany with sample sizes that ranged from 24 to 64 patients; therefore, the quantity of relevant data was limited and generalizability to the Canadian context is unclear. There were no relevant studies that compared the transcatheter mitral valve repair device with surgery. No evidence regarding the cost-effectiveness of the transcatheter mitral valve repair device for the treatment of TR or both TR and MR was identified.

Conclusions and Implications for Decision or Policy Making

This review was comprised of five non-randomized studies[3,10-13] regarding the clinical effectiveness of the transcatheter mitral valve repair device for the treatment of TR alone[3] or both TR and MR.[10-13] No relevant evidence was identified regarding the cost-effectiveness of the transcatheter mitral valve repair device in this population.

The identified literature revealed relatively consistent conclusions regarding the clinical effectiveness of transcatheter mitral valve repair for TR alone or both TR and MR. Across four studies[10-13] in which procedural success was reported, the percentage of all patients with procedural success ranged from 92% to 97%. In all of the included studies,[3,10-13] the TR severity was numerically[3,13] or statistically significantly reduced[10-12] from baseline to post-procedure follow-up for TV-only repair[3,10-13] or combined TV and MV repair.[10-13] Edema and ascites improved significantly from pre-intervention to one month,[3] and six months[3] for TV-only repair, and from pre-intervention to three months[11] follow-up for TV-only repair or both TV and MV repair. The NYHA functional class was improved in all included studies[3,10-13] from pre- to post-intervention, either numerically[10,11] or statistically.[3,12,13] There was no significant change in QoL from baseline to follow-up in the three studies in which QoL was measured.[10,11,13] While four of the studies showed statistically significant improvement in the 6MWD, Braun et al.[10] observed no statistically significant difference in 6MWD despite showing a numerical improvement. For heart failure severity when comparing baseline and follow up, two studies[10,13] found significant improvement; two studies[3,12] found no statistically significant difference; and one study[11] demonstrated a statistically significant improvement in patients who received TV-only repair but no significant difference in patients who received both TV and MV repair. Across studies, transcatheter mitral valve repair for tricuspid regurgitation was found to have post-procedure mortality incidence of 4.7 to 7%.[3,10-12]

There remains a high degree of uncertainty in the effectiveness of transcatheter mitral valve repair for tricuspid regurgitation due to the limitations of the available literature. The limitations included small sample sizes with potential overlap in participants between studies. There is uncertain generalizability to Canadian context since all studies were conducted in Germany. Special considerations for implementation into the Canadian health care system may include the Canadian TR patient population characteristics, accessibility to a cardiac catheterization laboratory in urban and rural settings, and the specialized training required for performing the intervention for currently off-label use. Further research investigating the clinical effectiveness of transcatheter mitral valve repair for tricuspid regurgitation, especially with large randomized-controlled clinical trials that report long-term outcome data, would help reduce this uncertainty.

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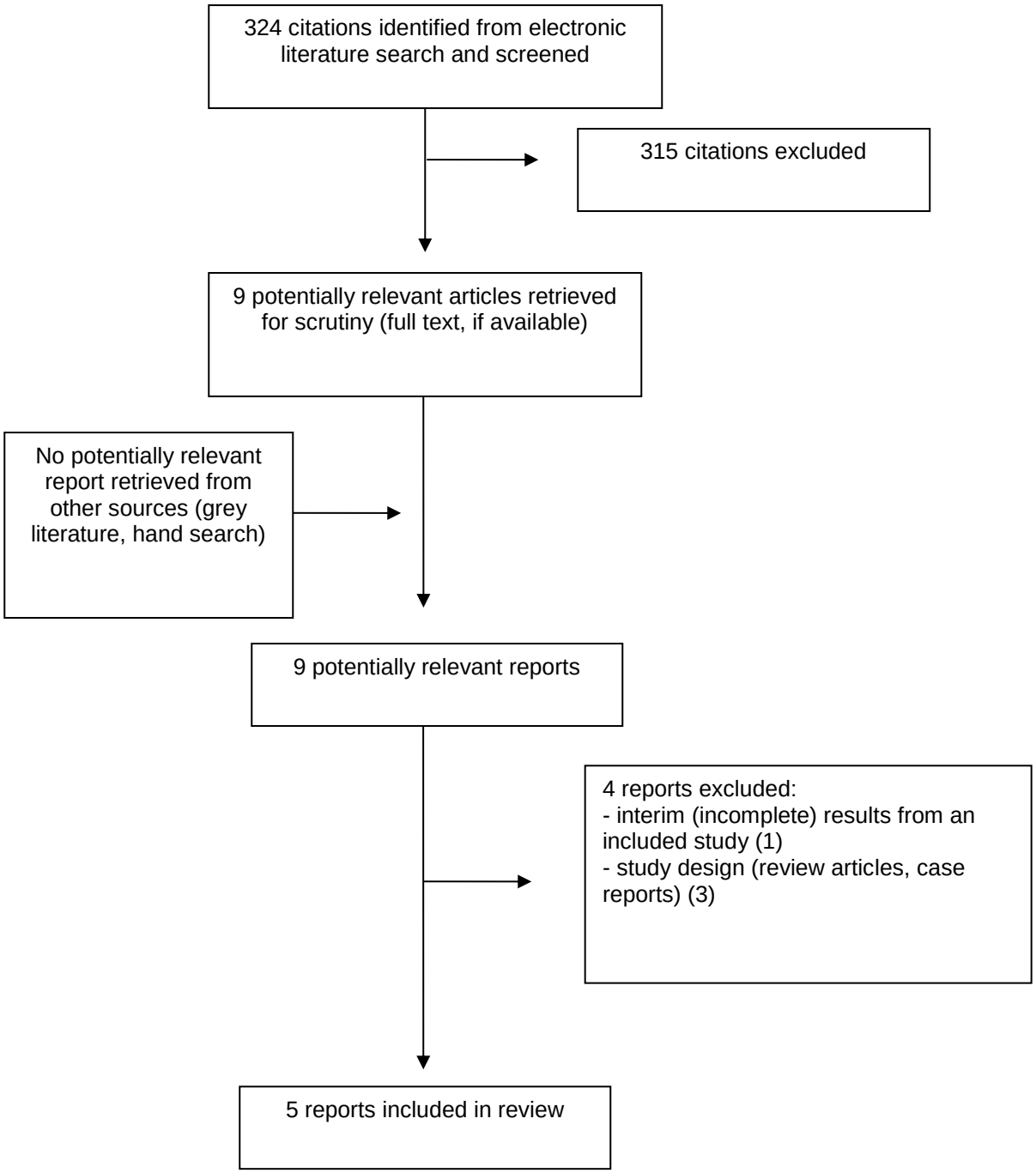
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Non-randomized studies				
Rommel et al. (2019)[3] Germany **Funding source:** NR	**Study design:** Single-centre uncontrolled before-and-after study **Setting:** patients were recruited from Heart Center Leipzig at the University of Leipzig, Germany	**Inclusion criteria:** consecutive patients treated successfully with TTVR for isolated TR between July 2016 and April 2018 were included. All patients were referred with symptoms of right-sided HF and were in NYHA functional classes II to IV despite guideline-directed medical therapy. **Excluded:** NR **Number of participants:** 29 patients **Mean age ± SD:** 78 ± 4 years	**Intervention:** TTVR with MitraClip **Comparator:** baseline (before treatment)	**Clinical outcomes:** • 6MWD • Heart failure severity measured by NT-proBNP • TR grade • NYHA functional class • Edema • Ascites • Mortality • Clinical events • Hospitalization **Follow-up:** 6 months
Braun et al. (2018)[10] Germany **Funding source:** research grant from Abbott Vascular, not related to this study	**Study design:** Single-centre uncontrolled before-and-after study **Setting:** University Hospital of the Ludwig-Maximilians-Universität Munich	**Inclusion criteria:** Consecutive patients treated with TTVR (MitraClip) with predominantly secondary TR from March until September 2016 **Excluded:** NR **Number of participants:** 24 patients 8 patients received MitraClip for TV alone 16 patients received MitraClip for both TV and MV **Mean age ± SD**: 79 ± 7 years	**Intervention:** TTVR with MitraClip **Comparator:** baseline (before treatment)	**Clinical outcomes:** • Procedural success • TR grade: • Mortality • NYHA functional class • 6MWD • Heart failure severity measured by NT-proBNP • QoL measured by MLHFQ **Follow-up:**1 year
Lurz et al. (2018)[11] Germany	**Study design:** Single-centre uncontrolled before-and-after study **Setting:** Heart Center, Leipzig University	**Inclusion criteria:** consecutive patients with NYHA functional Class ≥ II despite optimal medical therapy, relevant TR and at high surgical risk with	**Intervention:** TTVR with MitraClip **Comparator:** baseline (before treatment)	**Clinical outcomes:** • Procedural success • TR grade: • Mortality

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding source: NR		or without concomitant relevant MR from June 2016 to April 2017 **Excluded:** Patients with any degree of mitral or TV stenosis, patients with severe aortic stenosis and patients with tricuspid anatomy deemed unsuitable for edge-to-edge repair **Number of participants:** 42 patients 11 patients received MitraClip for TV alone 31 patients received MitraClip for both TV and MV		• NYHA functional class • 6MWD • Heart failure severity measured by NT-proBNP • QoL measured by MLHFQ • Edema • Ascites **Follow-up:** 3 months
Orban et al. (2018)[13] Germany **Funding source:** supported by the Klinikum der Universität München and the Heart Center Leipzig.	**Study design:** dual-centre uncontrolled before-and-after study **Setting:** University hospital of the Ludwig–Maximilians University, Munich, and at the Heart Center Leipzig, University of Leipzig, both in Germany	**Inclusion criteria:** consecutive, eligible patients were treated for symptomatic severe TR from March to November 2016 **Excluded:** only moderate TR and tricuspid annulus <40mm in screening transoesophageal echocardiography; tricuspid anatomy deemed unsuitable for edge-to-edge repair with extremely large coaptation gaps impossible to bridge with the device; any degree of mitral or tricuspid valve stenosis; poor echocardiographic visibility during screening TOE; patients recommended by an interdisciplinary heart team to undergo a surgical procedure; any transtricuspid RV lead hindering leaflet adaption and thus the predominant	**Intervention:** TTVR with MitraClip **Comparator:** baseline (before treatment)	**Clinical outcomes:** • Procedural success • TR grade: • Mortality • NYHA functional class • 6MWD • Heart failure severity measured by NT-proBNP • QoL measured by MLHFQ • Hospitalization • Event-free survival rate **Follow-up:** 6 months

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		reason for TR; severe aortic stenosis or patients undergoing a transcatheter aortic valve replacement procedure for this reason; patients undergoing heart transplantation **Number of participants:** N = 50 n = 14 received MitraClip for TV alone n = 36 received MitraClip for both TV and MV **Mean age ± SD:** 77 ± 8 years		
Nickenig et al. (2017)[12] Germany **Funding source:** None	**Study design:** multi-centre single-arm observational study **Setting:** 10 international centers (countries and centre names NR)	**Inclusion criteria:** consecutive patients with symptomatic moderate to massive TR on optimal medical treatment, who were considered unsuitable for surgery, and the interventional with MitraClip was offered as compassionate use **Excluded:** Patients with a systolic pulmonary arterial pressure >60 mmHg, severe coaptation defect (>2 cm) of the tricuspid leaflets, patients who refused the interventional procedure **Number of participants:** N = 64 n = 22 received MitraClip for both TV and MV **Mean age ± SD:** 76.6 ± 9.6 years	**Intervention:** TTVR with MitraClip **Comparator:** baseline (before treatment)	**Clinical outcomes:** • Procedural success • TR grade: • NYHA functional class • 6MWD • Serious adverse events • Heart failure severity measured by NT-proBNP • QoL measured by MLHFQ **Follow-up:** 1 month

HF = heart failure; NYHA = New York Heart Association functional classification; NR = not reported; NT-proBNP = N-Terminal Pro-B-Type natriuretic peptide; QoL = quality of life; MLHFQ = Minnesota Living with Heart Failure Questionnaire, SD = standard deviation; TR = tricuspid regurgitation; TTVR = transcatheter tricuspid edge-to-edge repair; 6MWD = six-minute walking distance.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[9]

Strengths	Limitations
Rommel et al. (2019)[3]	
• The objectives, interventions, and main outcomes were clearly described • Methodology regarding patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics were clearly described • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the treatment was reliable with the in-hospital procedure	• No power calculation was performed. The sample size was 29 patients. • The study only included patients who had successful MitraClip treatment. This is a key source of bias due to the lack of information on outcomes from potential patients with attempted (but failed) MitraClip intervention. • The study was conducted in Germany; the generalizability to Canadian settings is unknown • The authors did not report the source of funding or conflicts of interest.
Braun et al. (2018)[10]	
• The objectives, interventions, and main outcomes were clearly described • Methodology regarding patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics were clearly described • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the treatment was reliable with the in-hospital procedure	• No power calculation was performed. The sample size was 24 patients • The study was conducted in Germany; the generalizability to Canadian settings is unknown • The authors reported a research grant by Abbott Vascular as the source of funding. • Three of the authors reported receiving speaker honoraria from Abbott Vascular.
Lurz et al. (2018)[11]	
• The objectives, interventions, and main outcomes were clearly described • Methodology regarding patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics were clearly described • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the treatment was reliable with the in-hospital procedure	• 7 out of the 42 participants were lost to follow-up at one month and 13 out of 42 patients lost to follow up at three months • No power calculation was performed • The study was conducted in Germany; the generalizability to Canadian settings is unknown • The authors did not report on the source of funding. • Four of the authors reported a conflict of interest: receipt of speaker fees from Abbott.

Strengths	Limitations
Orban et al. (2018)[13]	
• The objectives, interventions, and main outcomes were clearly described • Methodology regarding patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics were clearly described • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the treatment was reliable with the in-hospital procedure • The authors reported the source of funding and was interpreted as unlikely to have had an effect on the findings of the study. • The authors reported no conflicts of interest.	• No power calculation was performed. The sample size was 18 patients. • One participant was lost to follow-up at 6-month follow-up • The study was conducted in Germany; the generalizability to Canadian settings is unknown
Nickenig et al. (2017)[12]	
• The objectives, interventions, and main outcomes were clearly described • Methodology regarding patient recruitment and assessment of inclusion/exclusion criteria was provided • Participant characteristics were clearly described • Estimates of random variability (e.g., standard deviations) and actual probability values (P values) were reported • The major findings of the study were presented in tabular form and clearly described • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Compliance with the treatment was reliable with the in-hospital procedure • The authors reported no source of funding. • The authors reported no conflicts of interest.	• The 10 international centres where patients were recruited from were not reported in detail (e.g., countries, numbers of patients from each site). • No power calculation was performed • The study was conducted in Germany; the generalizability to Canadian settings is unknown

Appendix 4: Main Study Findings and Authors' Conclusions

Table 3: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Rommel et al. (2019)[3]	
6MWD (m): increased by 20% at 1 month compared to baseline, specific values NR increased by 22% at 6 months compared to baseline, specific values NR P < 0.01 from baseline to 6 months **Heart failure measured by median NT-pro-BNP (ng/l):** No statistically significant change P = 0.41 from baseline to 6 months P = 0.20 from baseline to 1 month **Disease severity measured by NYHA functional class:** No statistical testing reported Baseline: 80% of patients in NYHA functional classes III and IV At 1 month: NYHA class improved in all but 5 out of # patients (who stayed in class III) 72% of patients in functional class I and II At 6 months: subjective dyspnea improved in 7 and deteriorated in 5 out of 18 patients overall 80% of patients in NYHA functional classes I and II **Disease severity measured by peripheral edema:** decreased from 76% at baseline to 57% at 1 month and 44% at 6 months; P < 0.01 **Disease severity measured by ascites:** decreased from 31% at baseline to 18% at 1 month and 16% at 6 months; P = 0.04 **Disease severity measured by TR grade:** No statistical testing reported At baseline: 90% of patients at TR grade 3 (severe) 10% of patents at TR grade 4 (massive of torrential) At 1 month: 32% of patients at TR grade 1 (mild) 64% of patients at TR grade 2 (moderate) 4% of patients at TR grade 3 (severe) At 6 months: 32% of patients at TR grade 1 (mild) 57% of patients at TR grade 2 (moderate) 11% of patients at TR grade 3 (severe) TR grade reduced to at least moderate in all but 1 patient. **Mortality**: 2 patients (7%), no statistical testing reported **Clinical events:** 10 (35%) patients during the 6 months after TTVR, no statistical testing reported	"[T]he limited number of patients prohibits any conclusions and potential differing implications of TTVR in patients with and without pulmonary hypertension, which need assessment in larger trials." (p. 1433) [3] "TTVR, for the first time, provides a pure model with which to study the effects of chronic RV volume overload in patients with severe TR. A biventricular assessment should enhance our present limited understanding of RV performance under unfavorable loading condition, inform on how to judge procedural success and suggest that focusing on effective SV rather than EF permits better interpretation of the physiology." (p. 1433) [3]

Main study findings	Authors' conclusion
Hospital admission for decompensated HF: 8 (28%), no statistical testing reported	
Braun et al. (2018)[10]	
Acute procedural success (TR grade ≤ 2): 23 out of 24 patients (96%) **Patients with TR ≤2:** • 1/24 (4%) at baseline • 13/15 (87%) off the surviving patients at 1 year • P < 0.001 • 12/12 (100%) in all patients treated simultaneously for severe TR and MR at 1 year **Procedure-related adverse events:** None **Mortality at 1 year:** 9 deaths (37.5%) **Clinical benefit measured by NYHA functional class:** Patients with NYHA ≤ II: • 0/24 (0%) at baseline • 10/15 (67%) of the surviving patients at 1 year • P < 0.001 Clinical benefit in surviving patients treated for isolated TR was not statistically significantly different to that in patients treated for TR and MR (P > 0.99) **6MWD (mean ± SD):** • 205 ± 136 m at baseline • 268 ± 134 m at one-year follow-up • P = 0.28 **Heart failure measured by level of NT-proBNP (mean ± SD):** • 18,573 ± 39,889 pg/ml at baseline • 6,483 ± 8,811 pg/ml at 1 year • P = 0.03 **QoL measured by MLHFQ score** (reduction in MLHFQ score means an improvement in QoL) **(mean ± SD):** • 35 ± 18 at baseline • 27 ± 16 at 1 year • P = 0.12	"The preliminary echocardiographic and clinical results reported here encourage further studies on the use of percutaneous edge-to-edge repair in inoperable patients with severe TR." (p. 415)[10]
Lurz et al. (2018)[11]	
Overall procedural success (successful TV clip implantation with an immediate reduction of at least one grade in TR grade): 97% **Mortality:** 2 deaths in total (4.7% in all patients) at 1 month, both of which were in patients who received both TV and MV repair, representing 6.45% of this group **NYHA functional class:** TV only group: Significant improvement in NYHA functional class: P < 0.02 for comparing 1-month follow-up to baseline 8 out of 11 patients in the TV-only group did not show any improvement at 1 month	"The results of the present retrospective analysis indicate that TV edge-to-edge repair using the MitraClip system in patients with symptomatic TR and at high surgical risk is feasible and safe with an overall success rate of 83%. Although TR is significantly reduced by TV edge-to-edge repair, residual TR remains in

Main study findings	Authors' conclusion
Combined TV and MV group Significant improvement in NYHA functional class: P < 0.001 comparing 1-month follow-up to baseline 8 out of 25 patients in combined TV and MV group did not show any improvement at 1 month **TR grade:** TR grade I, n (%): 0 (0%) at baseline and 12 (48%) at 1 month for TV and MV group 0 (0%) at baseline and 5 (50%) at 1 month for TV only group TR grade II, n (%): 4 (16%) at baseline and 8 (32%) at 1 month for TV and MV group 0 (0%) at baseline and 4 (40%) at 1 month for TV only group TR grade III, n (%): 18 (72%) at baseline and 5 (20%) at 1 month for TV and MV group 9 (90%) at baseline and 1 (10%) at 1 month for TV only group TR grade IV, n (%): 3 (12%) at baseline and 0 (0%) at 1 month for TV and MV group 1 (10%) at baseline and 0 (0%) at 1 month for TV only group **6MWD (mean):** P = 0.02 for comparison of baseline to 1 month for TV only group P = 0.03 for comparison of baseline to 1 month for TV and MV group **NT-proBNP levels:** At 1 month, decreased from baseline in both groups numerically with statistical significance in the TV only group P = 0.0046 for TV only group P = 0.17 for TV and MV group **QoL measured by MLHFQ score (mean ± SD):** In patients with combined MV and TV repair: • No statistically significant change in MLHFQ score • 36.9 ± 14.3 at baseline • 28.4 ± 15.9 at 1 month • P = 0.071 In patients with isolated TV repair: • No statistically significant change in MLHFQ score • 27.4 ± 10.4 at baseline • 31.6 ± 18.2 at 1 month • P = 0.351 **Edema and ascites:** statistically significantly reduced from baseline to three months of follow-up in both groups Peripheral oedema, n (%): 30 (71%) at baseline 19 (50%) at 1 month, P = 0.051 12 (41%) at 3 months, P = 0.032 Ascites, n (%): 12 (29%) at baseline 7 (18%) at 1 month, P = 0.063	most patients, highlighting the need for further technical and procedural refinement. Nevertheless, TR reduction was maintained during three months of follow-up and translated into stable improvements in NYHA functional class and six-minute walking distance." (p. 295)[11]

Main study findings	Authors' conclusion
4 (14%) at 3 months, P = 0.041	
Orban et al. (2018)[13]	

Procedural success (successful TV clip implantation with an immediate reduction of at least one grade in TR grade): 46 patients out of 50 patients (92%)
 	
Hospitalization, n (%):
14 (28% of total) hospitalized for worsening of HF with right heart decompensation
• 5 (36%) in the isolated TV group
• 9 (25%) in combined TV and MV repair group
• P = 0.49
 	
Severity measured by TR grade:
at 6 months:
35 out of 39 patients had a persistent reduction of ≥ 1 TR grade
 	
Reduction of ≥ 1 TR grade:
• 1% in the isolated TV group
• 93% in combined TV and MV repair group
• P = 0.561
 	
TR grade ≤ 2+ at 6 months:
• 63% in the isolated TV group
• 82% in combined TV and MV repair group
• P = 0.238
 	
NYHA functional class:
Improvement ≥ 1 NYHA class compared to baseline:
• 79% of all patients
• 64% in the isolated TV group
• 86% in combined TV and MV repair group
• P = 0.188
 	
NYHA class ≥ III:
• 100% at baseline
• 36% at 6 months
• No statistically significant differences were found between patients treated for isolated TR or combined TR and MR.
  ○ 45% in the isolated TV group
  ○ 32% in combined TV and MV repair group
  ○ P = 0.478
 	
Heart failure measured by NT-proBNP:
• 3,625 (IQR, 2,229 to 6,931) pg/mL to 2,526 (IQR, 1,261 to 5,303) pg/mL in the overall group (P =0.002)
• data from 36 patients available
 	
6MWD (mean ± SD):
• 191 ± 124 m at baseline
• 275 ± 142 m at 6 months
• P < 0.001
• data from 32 patients available
 	
QoL measured by MLHFQ score (mean ± SD):
	"This dual-centre study suggests that percutaneous edge-to-edge TV repair is feasible and safe. Furthermore, the reduction of TR in patients with severe right-sided HF appears to be associated with a durable improvement in HF symptoms up to 6 months. This improvement was observed in patients treated with isolated TV repair and concomitant mitral and tricuspid valve repair. Based on these results, further randomized studies comparing percutaneous TV repair with optimal medical therapy are warranted to confirm the preliminary clinical impact of this new strategy in HF patients." (p. 1061) [13]

Main study findings	Authors' conclusion
• 37 ± 16 points at baseline • 31 ± 21 points at 6 months • P = 0.056 • data from 36 patients available **Survival:** At 6 months: • Event-free survival from death, transcatheter reintervention and subsequent TV surgery: 78%	
Nickenig et al. (2017)[12]	
Procedural success (safe clip implantation without partial leaflet detachment or device migration and reduction of TR of ≥1 grade without creating a tricuspid stenosis): 97% **Mortality:** No intraprocedural deaths or emergent conversions to open-heart surgery In-hospital mortality: 5% **TR grade:** Severe/massive TR: • Baseline: 88% • At 6 months: 13% • P = 0.01 **Serious adverse events:** No stroke, myocardial infarction, or pericardial effusion, or device migration occurred. **NYHA functional class:** 93% in NYHA classes III and IV before the intervention 63% of the patients remained in NYHA class III, and 0% were in NYHA class IV after the intervention **6MWD (meter ± SD):** • Baseline: 177.4 ± 103.0 • 30 days after the procedure: 193.5 ± 115.9 • P = 0.007 • data from 21 patients completing both before and after procedure test **Heart failure measured by NT-proBNP:** • No statistically significant change occurred in the plasma NT-proBNP level • P = 0.9	"Treatment of TR with the MitraClip device seems feasible and safe in this preselected high-risk patient cohort. A reduction of TR may potentially translate into better clinical symptoms and performance. Because anatomic and echocardiographic feasibility criteria are not well defined, further research is needed to determine which patients may benefit most from interventional TR repair." (p. 1813) [11]

HF = heart failure; IQR = interquartile range; NYHA = New York Heart Association functional classification; NR = not reported; NT-proBNP = N-Terminal Pro-B-Type natriuretic peptide; QoL = quality of life; MLHFQ = Minnesota Living with Heart Failure Questionnaire, SD = standard deviation; TR = tricuspid regurgitation; TTVR = transcatheter tricuspid edge-to-edge repair; 6MWD = six-minute walking distance.