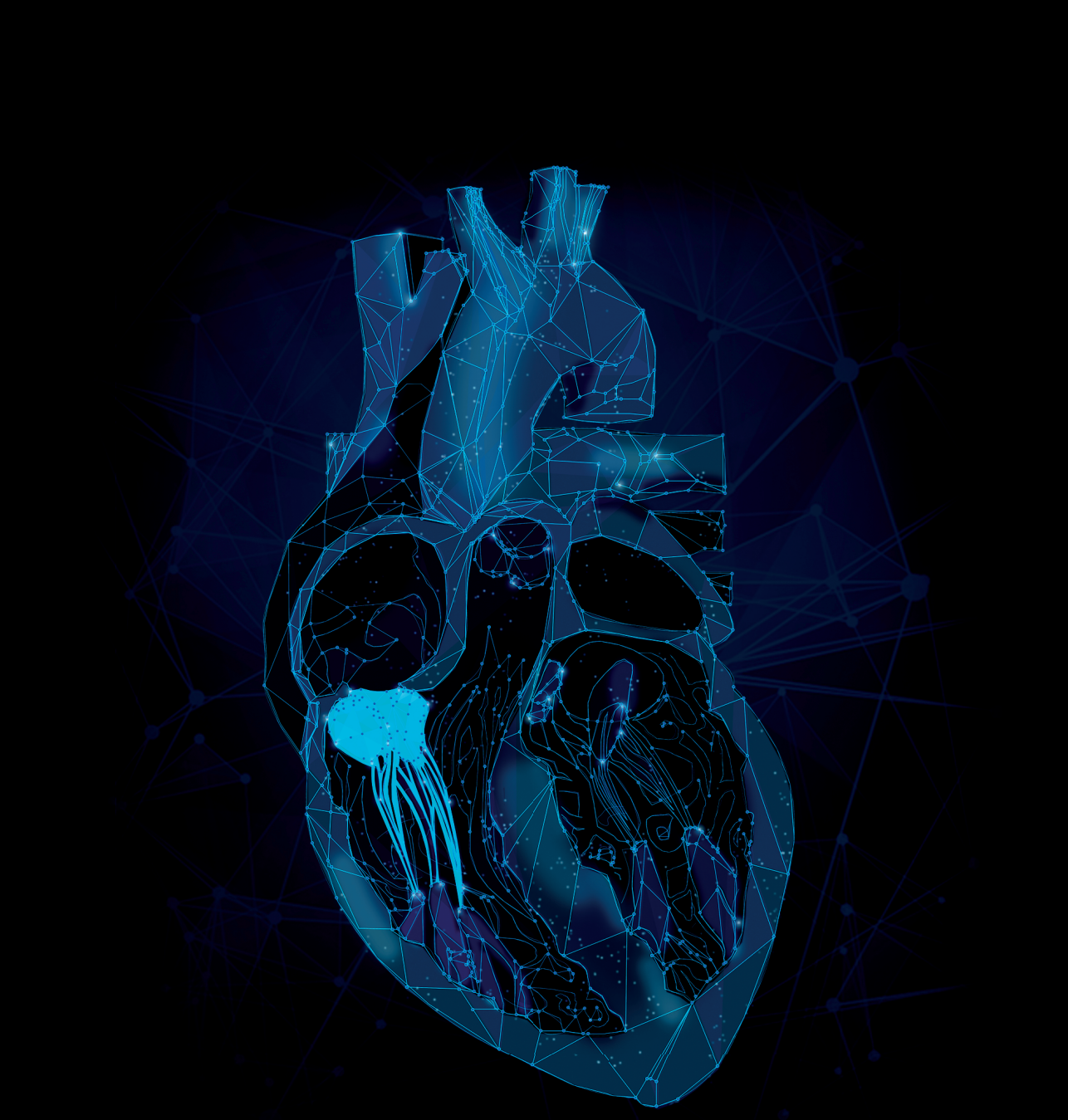

Determinants of outcome in patients with tricuspid valve disease

Kevin M. Veen

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Determinants of Outcome in Patients with Tricuspid Valve Disease

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CONTENTS

1

General introduction

INTRODUCTION

A human heart requires four valves; two in the atrio-ventricular connections and two in the ventriculo-arterial connections. On the left side of the heart the atrio-ventricular valve is called the mitral valve and the ventriculo-arterial valve is called the aortic valve. On the right side of the heart the atrio-ventricular valve is called the tricuspid valve and the ventriculo-arterial valve is called the pulmonary valve. During contraction of the heart -systole- the atrio-ventricular valves are closed and ventriculo-arterial valves are open. This is vice versa during relaxation of the heart, called diastole.

Proper function of all valves is needed to ensure that the right amount of blood flows into the right direction. Valve dysfunction, characterized by stenosis (a valve opening too small) or regurgitation (a leaking valve), disrupts this flow. Valve dysfunction can lead to an impaired quality of life or even be life threatening. Hence, in some cases treatment of valve dysfunction is necessary, usually in the form of medication, intervention or surgery. All four valves can become dysfunctional. This thesis will focus on outcomes after surgery of the tricuspid valve.

TRICUSPID VALVE DYSFUNCTION

Tricuspid valve dysfunction occurs when the tricuspid valve does not work correctly due to stenosis or regurgitation, or a combination of the two. Tricuspid valve stenosis occurs when the opening of the tricuspid valve becomes too small, limiting blood flow through the valve. Tricuspid valve regurgitation occurs when there is still an opening in the tricuspid valve when it should be closed, resulting in blood flow back to the right atrium during systole.

Different etiologies can underlie tricuspid valve dysfunction. In case of tricuspid valve stenosis the most common causes are rheumatic heart disease or endocarditis, or less common a congenital defect or carcinoid heart valve disease. Since rheumatic heart disease is almost eradicated in the developed world, tricuspid valve stenosis has become an uncommon disorder (1). In case of tricuspid valve regurgitation one can distinguish structural (primary) and functional (secondary) tricuspid valve regurgitation. In structural tricuspid valve regurgitation the tricuspid valve itself is damaged, for example by endocarditis, degeneration or even pacemaker leads (2). In functional tricuspid valve regurgitation the valve itself is undamaged, however, a geometric distortion of normal spatial relations has developed. It is usually a result of left sided valve disease, subsequently leading to pulmonary hypertension, causing right ventricular dysfunction. The right ventricle responds, according to the law of Laplace, by dilating. This results in an orifice that is too large to be covered by the leaflets, subsequently resulting in malcoaptation and regurgitation.

Patients with tricuspid valve dysfunction and right ventricular dysfunction will often develop symptoms of right heart failure, characterized by lower functional status, fatigue, leg edema

and liver and kidney dysfunction (3). Furthermore, longstanding tricuspid valve dysfunction is associated with impaired survival (4). Hence, in some patients it treatment of the tricuspid valve disease becomes necessary.

TREATMENT MODALITIES OF TRICUSPID VALVE DISEASE

One of the treatment modalities of tricuspid valve disease is optimal medical treatment. Diuretics are the cornerstone of the cardiologists to treat the symptoms of regurgitant tricuspid valve disease, and offer relief from systemic congestion. Also, in selective cases pulmonary vasodilators and adequate treatment of atrial fibrillation is recommended. Nevertheless, medical intervention is quality of life specific and does not offer survival benefit (2).

Another treatment modality is surgical intervention of the tricuspid valve. Two main techniques within the surgical landscape exist: tricuspid valve repair and replacement. The most frequently used tricuspid valve repair technique is reducing the orifice of the tricuspid valve by decreasing the annulus size, also called annuloplasty (5). Current guidelines advise to perform annuloplasty of the tricuspid valve during left sided valve surgery in case of moderate-to-severe tricuspid regurgitation or annular dilation above 40 mm (6). Moreover, the valve leaflets (valvoplasty) and subvavular apparatus can be repaired. In some cases a repair is not feasible and a tricuspid valve replacement becomes necessary. The tricuspid valve can be replaced with either a mechanical valve or a biological valve. Mechanical valves are exceptionally durable in design, however require life-long anticoagulation with increased risk of bleeding and valve thrombosis. Biological valves do not require lifelong anticoagulation, however are prone to degeneration in which a re-operation becomes necessary.

A third treatment modality is emerging with the development of transcatheter tricuspid valve interventions (7).

MONITORING VALVE (DYS)FUNCTION OVER TIME

Tricuspid valve regurgitation is a very dynamic disease, which can increase and decrease over time. Following tricuspid valve function over time is commonly done with repeated echocardiograms. It is not advisable to use time-to-event analysis in the setting of tricuspid regurgitation, due to the dynamic nature of tricuspid valve regurgitation, also depending upon loading conditions which can vary over time. Furthermore, one needs to account for the correlation *within* a patients' measurements and the correlation *between* a patient's measurements. Not accounting for these correlations can lead to spurious conclusions (8).

Next to the novel repeated measurements and joint modelling other advanced statistical tools are used in this thesis to give an optimal overview of outcomes. Systematic reviews with

meta-analysis are powerful methods to accumulate and pool results of the literature, enabling us to make robust estimates of outcomes. Furthermore, utilizing novel methodology it is possible to reconstruct individual patient data and develop pooled Kaplan Meier curves (9).

With the use of large databases with missing variables multiple imputation can be used to impute missing variables (10). Moreover, not accounting for competing risks can result in overestimation of event rates in large datasets. These outcomes should be addressed accordingly with competing risk analyses (11).

THESIS AIM

The main aim of this thesis is to gain an improved insight in tricuspid valve surgery outcomes and its determinants. The secondary aim is to illustrate how novel statistical tools can assist in monitoring and predicting outcomes after heart valve surgery.

To achieve this goal several research questions are addressed:

- What are the outcomes after surgery for functional tricuspid regurgitation in the setting of left sided valve disease, left ventricular assist device implantation (LVAD) and heart transplantation (**Chapter 1**-**3, 8**-**12**).
- Do patients with functional tricuspid valve regurgitation require concomitant tricuspid valve surgery during LVAD implantation (**Chapter 8**-**10**)
- What are the outcomes and determinants of outcome after surgery for structural tricuspid valve disease (**Chapter 5**-**7**).
- How can advanced statistical methodology be used to assist reporting of outcome after tricuspid valve surgery (**Chapter 5**, **6**, **9**, **10**, **12).**

OUTLINE

Functional tricuspid valve regurgitation is in about 85% the underlying etiology of tricuspid valve regurgitation (**Chapter 2**)(12). **Chapter 3** discusses outcomes after surgery for functional tricuspid valve regurgitation, with the use of novel methodology to reconstruct individual patient data. Male-female differences in surgery for tricuspid valve disease are discussed in **Chapter 4**.

Structural tricuspid valve regurgitation is in about 15% the underlying etiology of tricuspid valve regurgitation (12), and in most cases a replacement is necessary. This is also the case in carcinoid tricuspid valve disease, in which a tumor secretes vaso-active peptides, damaging the tricuspid valve (13). In **Chapter 5** outcomes after surgery for this select subset of patients are discussed, with special attention for prosthesis choice. In some congenital anomalies, such as Ebstein anomaly, the tricuspid valve can be repaired, as is presented in **Chapter 6**. How the

indications for tricuspid valve replacement have shifted over the years is discussed in **Chapter 7**.

Nowadays, the implantation of a left ventricular assist device is becoming increasingly more common (14) and a new patient population arises; patients with functional tricuspid valve regurgitation and a left ventricular assist device. In **Chapter 8**-**10** the natural history and outcomes after tricuspid valve surgery in this population is discussed. Furthermore, tricuspid valve regurgitation can occur in the setting of heart transplantation which is discussed in **Chapter 11** and **12.** Advanced methodology is used to analyze tricuspid valve function over time (**Chapter 5, 6, 9, 10, 12**). Furthermore, to assess the impact of this changing tricuspid regurgitation over time, the mixed-model can be inserted in a survival model, under the joint modelling framework (**Chapter 12**).

While this research focusses on surgical interventions of the tricuspid valve new transcatheter interventions are on the horizon. In **Chapter 13** the current evidence regarding these devices is summarized and a future roadmap for further tricuspid regurgitation therapy is presented. In **Chapter 14** a general overview and the implications of this research is discussed.

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2

Tricuspid Valve Disease: Surgical Outcome

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ABSTRACT

Outcomes after tricuspid valve surgery were initially extremely poor but have improved over time thanks to innovations in diagnostics, guidelines for treatment, emerging surgical experience and technical advances. This chapter provides a contemporary overview of patient and procedural characteristics of tricuspid valve repair and replacement and early and late outcomes in different settings, such as functional tricuspid regurgitation, rheumatic, congenital, carcinoid tricuspid valve disease, iatrogenic tricuspid valve damage, and finally endocarditis of the tricuspid valve. For this purpose a systematic literature review and meta-analysis was conducted including 132 studies published after 2005 and reporting on outcome after tricuspid valve surgery. This thorough review of reported experience with tricuspid valve repair and replacement reveals a strong variation in patient presentation and outcome among the various indications and highlights that tricuspid valve replacement is still associated with high early and late mortality. Innovations in the treatment of tricuspid valve disease are direly needed to improve outcome in this complicated patient population.

INTRODUCTION

The first valve ever to be operated on was the aortic valve in 1912, when Theodore Tuffnier attempted to dilate a stenotic aortic valve with his finger [1]. Next in line was the mitral valve; in 1923 Elliot Cutler performed the first successful mitral valve repair on a 12-year old girl. Right sided valves were only given attention much later. The first pulmonary valve stenosis was repaired in 1947 [4] and in the 1950s the first tricuspid valvotomy was performed by Dr. Bailey [5]. Subsequently, additional techniques were developed for tricuspid valve repair. Nowadays, most suture annuloplasty techniques are a variation on the Kay technique [2] or the DeVega technique [3]. Rings and bands have also become available for tricuspid valve repair. With the introduction of cardiopulmonary bypass, replacement of the tricuspid valve became an option.

Outcomes after tricuspid valve surgery were initially extremely poor. However, outcomes have improved over time thanks to innovations in diagnostics, guidelines for treatment, emerging surgical experience and technical advances. Nevertheless, nowadays tricuspid valve surgery is still associated with considerable early and late mortality, in particular when valve replacement is needed.

This chapter aims to provide an overview of contemporary outcomes after tricuspid valve surgery in different settings. Given the heterogeneity in the indications for tricuspid valve surgery and their interrelationship with surgical approach (replacement versus repair), first characteristics and outcomes of tricuspid valve repair and tricuspid valve replacement will be discussed separately. Next, reported outcomes after tricuspid valve surgery will be discussed for the following surgical indications: functional tricuspid regurgitation, rheumatic tricuspid valve disease, congenital tricuspid valve disease, carcinoid tricuspid valve disease, iatrogenic tricuspid valve damage, and finally endocarditis of the tricuspid valve.

In order to provide a contemporary overview of outcomes after tricuspid valve surgery we conducted a systematic review and meta-analysis of studies published after 2005. Several databases were searched for publications on outcome after tricuspid valve surgery. The search yielded 6026 abstracts and eventually 132 publications were included. Outcomes were pooled in a random-effects model.

TRICUSPID VALVE REPAIR AND REPLACEMENT

One-hunderd thirty two publications encompassing a total of 20,559 patients with 82,103 patient-years were included in the meta-analysis [6–137]. Among all patients undergoing tricuspid valve surgery, mean age at the time of surgery is 56.8 years and 60.4% of patients are female. Pooled early mortality (<30 days or in-hospital) is 7.3% (95% CI [6.4–8.3%]). Meta regression shows that prior heart surgery is significantly associated with a higher early mortality, odds ratio of 3.4 (95% CI [1.8–6.1]), $p < 0.001$.

However, this early mortality is lower than the early mortality in the Society of Thoracic Surgeons (STS) database. The STS database, which describes 34,469 operations since 1993 involving the tricuspid valve, reports an early mortality of 10.0% for isolated tricuspid valve surgery and as high as 14.0% for patients undergoing triple valve surgery involving the tricuspid valve [138]. The difference between the STS database and our systematic review of published literature may be due in part to publication bias.

TRICUSPID VALVE REPAIR

Tricuspid valve repair is the procedure of choice for surgical treatment of tricuspid valve disease. There are two approaches to repair the tricuspid valve: valvoplasty, where the valve leaflets and chordae are repaired and annuloplasty, where the annulus diameter is reduced and stabilised by either sutures (DeVega and Kay) or a rigid/ flexible ring. Since the most prevalent tricuspid valve disease by far is functional tricuspid valve regurgitation [139], in which the valve leaflets and chordae are generally unaffected, annuloplasty is performed more frequently than valvoplasty.

There were 75 publications on tricuspid valve repair [6, 10, 13, 14, 17–26, 28, 29, 32, 33, 36, 37, 39, 41, 42, 46, 47, 49, 52, 54, 56, 58, 59, 64, 66, 70, 72–77, 80– 82, 84, 86, 87, 89–91, 95, 97, 98, 100, 101, 105, 107, 109, 110, 112, 115, 117, 118, 121–123, 127, 129, 130, 133, 135, 137, 140–145].

Patient Presentation and Intraoperative Details

Patient characteristics and etiology are presented in Table 1. The most prevalent etiology is functional tricuspid disease. In 98.6% of cases, patients present with isolated tricuspid valve regurgitation, in 0.5% of cases with isolated stenosis and in 0.9% with combined stenosis and regurgitation. Four out of 10 patients have a history of hypertension and 6 out of 10 patients have preoperative atrial fibrillation. Mean preoperative systolic pulmonary artery pressure is 50.1 ± 15.4 mm Hg. Isolated annuloplasty is performed in 96% of patients, isolated valvoplasty in 2% and a further 2% of patients undergo combined annuloplasty and valvoplasty. Of all patients undergoing annuloplasty, suture annuloplasty is performed in 3 out of 10 patients and ring annuloplasty in 7 out 10 patients. Nearly all patients (97%) undergo concomitant procedures. Mitral valve procedures were performed in 88%, aortic in 19% and pulmonary valve procedures in 0.1%. CABG and maze procedures were performed in 16% and 20%, respectively.

Table 1. Preoperative characteristics and etiology of replacement and repair of the tricuspid valve

Characteristic	Replacement	Repair
Number of patients	3,662	13,299
Follow up (years)	4.2 ± 4.3	4.7 ± 4.0
Age (years)	51.0 ± 13.8	58.9 ± 12.4
Male	34%	42%
Previous heart surgery	54%	31%
NYHA I–II	16%	32%
NYHA III–IV	84%	68%
Etiology		
Functional (%)	15.4%	84.9%
Primary disease (%)	84.3%	14.3%
– Congenital[a]	31.3%	51.9%
– Endocarditis[a]	7.3%	4.4%
– Degeneration[a]	7.4%	3.3%
– Rheumatic[a]	34.6%	29.7%
– Carcinoid[a]	13.4%	0.0%
– Iatrogen[a]	1.3%	1.3%
– Degenerated prosthesis[a]	3.9%	0.2%
Unknown (%)	0.3%	0.9%

Presented as "percentage" or "mean ± standard deviation"

[a]Percentage of primary disease

Outcomes

Pooled early morality is 4.4% (95% CI [3.6—5.3%]). Late outcomes are shown in Table 3. Late mortality is substantial and nearly half of all deaths are cardiac.

Low cardiac output syndrome occurs in 9.3% (95% CI[6.6%–13.2%]) of cases and the risk of early (<30 days) pacemaker implantation is 3.4% (95% CI[2.4– 4.8%]). An early reintervention is necessary in 1 out of 100 patients.

Late pacemaker implantation rate is 0.8%/year (95% CI[0.5%/–1.2%/year]). Late reintervention rate is relatively low (0.6%/year). Pooled estimate shows that late endocarditis of the repaired tricuspid valve is rare (0.2%/year).

TRICUSPID VALVE REPLACEMENT

Tricuspid valve replacement is generally reserved for cases in which tricuspid valve repair is not technically feasible or when a tricuspid repair fails. The systematic review included 37 publications, 12 on mechanical and 15 on bioprosthetic valve replacement and 13 mixed. [9, 13, 16,

27, 30, 35, 40, 42, 48, 50, 55, 60–62, 67, 69, 79, 81, 88, 92, 94, 96–98, 100, 102, 103, 108, 111, 119, 128, 131, 132, 134, 135, 146–148].

Table 2. Late outcomes of tricuspid valve repair

Outcome	LOR	95% CI
Late mortality	2.6%/year	2.1–3.4
Late cardiac mortality	1.1%/year	0.8–1.7
Late valve-related mortality	0.6%/year	0.4–1.0
Reintervention	0.6%/year	0.2–0.4

LOR linearized occurrence rate, CI confidence interval

Patient Presentation and Intraoperative Details

Patient characteristics and etiology are shown in Table 1. Notably, more than half of the patients has undergone previous heart surgery. Primary tricuspid valve disease is the most common etiology. Isolated tricuspid valve regurgitation is present in 85.7%, isolated stenosis in 4.5% of patients, and 9.8% of patients present with combined stenosis and regurgitation. Ascites prior surgery is present in almost a quarter of patients at the time of surgery. Atrial fibrillation is present in approximately half of the patients. Mean pooled systolic pulmonary artery pressure is 47.1 ± 14.4 mm Hg. Approximately half of patients undergo at least one concomitant procedure, mostly mitral valve (36%), aortic valve (23%) and/or pulmonary valve (13%) procedures.

A bioprosthesis is implanted in 72% of patients and a mechanical prosthesis in 28%. None of the patients received an allograft. Patients receiving a bioprosthesis are generally younger (41.6 ± 16.2 years) compared with patients receiving a mechanical prosthesis (49.6 ± 13.1 years). This can be explained by the fact that patients receiving a bioprosthesis are diagnosed with congenital tricuspid disease more frequently than those receiving a mechanical prosthesis (72.5% vs. 22.2%). In the bioprostheses group 59.3% were female versus 76.7% in the mechanical group. Patients receiving a mechanical prosthesis underwent prior heart surgery more frequently compared with patients receiving a bioprosthesis (72.9 vs. 35.3%).

Outcome

Pooled early mortality risk is 14.5% (95% CI [11.9–17.3%]). This risk is markedly higher than in mitral and aortic valve replacement [149, 150]. The high early mortality may be explained in part by the poor preoperative state of patients, characterized by a high prevalence of ascites and poor functional status (NYHA class III-IV). Early mortality has declined significantly in more recent years of surgery (odds ratio/10 years [0.73 (95% CI: 0.57–0.93]).

Low cardiac output syndrome occurred in 22.2% (95% CI [15.7–31.3%]) of patients. Early pacemaker implantation risk is 11.0% (95% CI [7.7–15.6%]) and late pacemaker implantation rate is 1.2%/year (95% CI [0.5–2.9%]). This can partly be explained by the close proximity of the

atrioventricular conduction system to the tricuspid valve annulus. As a result, tricuspid valve replacement can cause a total atrioventricular block.

Late outcomes are presented in Table 3. Late mortality is substantial and the majority is cardiac. However, valve-related death is relatively low. Reintervention rate is 1.1%/year. Endocarditis of the tricuspid valve is also occurs rarely.

Table 3. Late outcomes after tricuspid valve replacement stratified by prosthesis type

Outcome	LOR Overall (95% CI)	LOR Bioprosthesis (95% CI)	LOR Mechanical prosthesis (95% CI)
Number of publications	37	15	13
Late mortality	3.9%/year (3.1–4.8)	2.8%/year (1.7–4.7)	3.1%/year (1.9–5.1)
Cardiac death	1.7%/year (1.3–2.4)	1.1%/year (0.5–2.3)	1.0%/year (0.5–2.3)
Valve-related mortality	0.3%/year (0.2–0.6)	0.3%/year (0.1–0.9)	0.2%/year (0.0–0.9)
Reintervention	1.1%/year (0.8–1.5)	1.2%/year (0.7–2.0)	0.9%/year (0.5–1.6)
Thromboembolism	0.4%/year (0.2–0.7)	0.3%/year (0.1–0.7)	0.6%/year (0.2–1.6)
Bleeding	1.2%/year (0.8–1.7)	0.6%/year (0.4–1.1)	2.2%/year (1.2–4.2)
SVD	0.9%/year (0.6–1.3)	1.1%/year (0.6–2.0)	0.2%/year (0.1–0.6)
NSVD	0.2%/year (0.1–0.4)	0.2%/year (0.1–0.4)	0.3%/year (0.1–1.0)
Valve thrombosis	0.9%/year (0.6–1.3)	0.2%/year (0.1–0.7)	1.8%/year (1.1–3.0)
Endocarditis	0.2%/year (0.1–0.4)	0.2%/year (0.1–0.5)	0.4%/year (0.1–1.2)

LOR linearized occurence rate, CI confidence interval, SVD structural valve deterioration, NSVD non-structural valve deterioration

Outcomes of Bioprosthesis vs. Mechanical Prosthesis

Pooled early mortality for bioprosthesis is 14.0% (95% CI [9.2–21.4%]) and 14.1% (95% CI [9.0–21.0%]) for mechanical prosthesis. However, the substantial preoperative differences between patients receiving a bioprosthesis and those receiving a mechanical prosthesis preclude direct comparison of outcome between these prostheses.

Late outcomes are presented in Table 3. Bioprostheses are characterized by a high rate of SVD and subsequent reintervention and low, but not absent, rates of NSVD and valve thrombosis. On the contrary, mechanical prostheses are exceptionally durable in design, but require lifelong anticoagulation due to their thrombogenicity. This is reflected in the high rates of bleeding and valve thrombosis, but low rates of SVD. In conclusion, anticoagulation-related events remain an important limitation of mechanical valves. Most importantly, the lower risk of SVD compared to bioprostheses does not translate to a considerably lower risk of reintervention. This is due to the higher incidence of other indications for reintervention, in particular valve thrombosis. Thus, although valve thrombosis may often be successfully treated with thrombolytics, as evidenced by the low reintervention and valve-related mortality rates relative to the higher valve thrombosis rate, valve thrombosis still gives rise to a substantial reintervention

risk in patients with a mechanical valve, which largely negates the advantage of the increased durability compared to bioprostheses.

FUNCTIONAL TRICUSPID REGURGITATION

Secondary tricuspid regurgitation, more commonly known as functional tricuspid regurgitation, is the most prevalent form of tricuspid valve disease [139]. Functional tricuspid regurgitation is defined as regurgitation with apparently normal leaflets and chords due to annular dilation of the tricuspid valve, mostly due to left sided valve disease [151]. Sometimes tethering is also present [152]. Functional tricuspid regurgitation (functional TR) has been found to be an independent risk factor for long term mortality [153]. Therefore, it has become common practice to repair the tricuspid valve during mitral valve surgery when deemed necessary. Among 46.500 mitral valve operations in the USA between 2011 and 2014, 4% of patients with no or mild TR underwent concomitant tricuspid valve repair, 35% of patients with moderate TR and 79% of patients with severe TR [154]. The systematic review for functional tricuspid disease encompassed 52 publications [7, 8, 10, 14, 18, 19, 22, 23, 28, 33, 34, 39, 45, 52, 54, 56, 63, 64, 66, 70–77, 80, 82, 84, 86, 90, 91, 93, 95, 105, 107, 112, 114, 115, 117, 121–123, 127, 129, 155–158].

Patient Presentation and Intraoperative Details

Characteristics are shown in Table 4. Notably, 6 out of 10 patients present with atrial fibrillation, probably due to the large proportion of patients with concomitant mitral valve disease. Only 79% of patients actually present with moderate or greater tricuspid regurgitation. This is due to the fact that current guidelines recommend tricuspid valve surgery if there is tricuspid annular dilatation of >40 mm, even when there is less than moderate tricuspid regurgitation, because this can help in prevent progressive regurgitation [159]. None of the patients presents with tricuspid stenosis. Intraoperative characteristics are presented in Table 5. The tricuspid valve is repaired in the vast majority of patients (99%), whereas replacement is performed rarely. Nearly all patients undergo concomitant surgery, usually a mitral valve operation. Some patients undergo multiple concomitant procedures, with a mean of 1.6 procedures per patient. Pulmonary valve procedures and tricuspid valve surgery for functional disease are rarely performed concomitantly.

Table 4. Pooled characteristics of functional TR, rheumatic tricuspid valve disease and congenital tricuspid valve disease

Characteristic	Functional	Rheumatic	Congenital
Number of patients	10,558	1,808	1,555
Follow up (years)	3.7 ± 2,4	10.4 ± 7.4	5.8 ± 5.0
Age (years)	62.8 ± 11.8	45.3 ± 12.1	21.6 ± 15.8
Male	46%	23%	51%
Previous heart surgery	29%	23%	25%
NYHA I–II	35%	15%	37%
NYHA III-IV	65%	85%	63%

NYHA New York heart association

Table 5. Pooled intraoperative characteristics of functional TR, rheumatic tricuspid valve disease and congenital tricuspid valve disease

Intraoperative	Functional	Rheumatic	Congenital
Repair (%)	99%	88%	70%
Replacement (%)	1%	12%	30%
Concomitant procedure (%)[a]	98%	98%	88%
–MV procedure[b]	91.3%	97.3%	1.5%
–AV procedures[b]	18.4%	74.8%	0.0%
–PV procedures[b]	0.4%	0.0%	4.4%
–Maze[b]	22.3%	0.0%	10.1%
–CABG[b]	19.3%	0.5%	0.8%
–ASD/VSD closure[b]	1.7%	0.0%	69.8%

[a]Percentage of patients that underwent at least 1 concomitant procedure

[b]Percetage of patients that underwent that specific concomitant procedure (non-exclusive groups due multiple concomitant procedures in some patients). MV mitral valve, AV aortic valve, PV pulmonary valve, CABG coronary artery bypass graft, ASD atrial septal defect, VSD ventricular septal defect

Table 6. Late outcome after surgery for functional tricuspid valve disease

Outcome	LOR	95% CI
Late mortality	2.7%/year	2.1–3.4
Late cardiac mortality	1.1%/year	0.8–1.7
Late valve-related mortality	0.6%/year	0.4–1.0
Reintervention	0.3%/year	0.2–0.4

LOR linearized occurence rate, CI confidence interval

Outcome

Early mortality is 3.6% (95% CI [2.9– 4.5%]). The STS database describes a cohort of 21,056 double mitral and tricuspid valve procedures. For tricuspid valve repair concomitant with mitral valve replacement and repair, respectively, they report an operative mortality of 10.3% and

8.0%. The discrepancy between present meta-analysis and this study may be explained in part by the large proportion of nonelective surgeries in the STS cohort (31% and 29%), whereas only 5.8% of surgeries in this meta-analysis were non-elective [160]. Also, the STS database includes all etiologies. Late outcomes are presented in Table 6. Tricuspid valve surgery for functional disease is associated with high late mortality, with a vast majority being cardiac.

Pacemaker implantation is a common complication after tricuspid valve surgery for functional tricuspid regurgitation, as evidenced by the pooled estimate of early pacemaker implantation risk in the systematic review of 3.6% (95% CI [2.5–5.3%]) and a late pacemaker implantation hazard rate of 0.7%/year (95% CI [0.3–1.3%]).

Reintervention rate is low, only 0.3%/year. The reintervention rate alone suggests that surgery for functional tricuspid disease is associated with exceptional durability. However, taking hemodynamic dysfunction into account besides reintervention, paints a different picture. Overall hazard of valve dysfunction, defined as recurrent tricuspid regurgitation graded as moderate or severe or the necessity for an reintervention is 2.2%/year, which indicates a suboptimal result after tricuspid valve surgery for functional disease.

Little is known about outcomes related to replacement of the tricuspid valve for functional TR, but Huang et al. described patients who received a tricuspid valve replacement for functional TR and reported a valve thrombosis rate of 0.2%/year and structural valve deterioration (SVD) and non-structural valve deterioration (NSVD) each occurred at a rate of 0.2%/year [19].

In summary, surgery for functional tricuspid regurgitation is associated with acceptable early mortality and late outcomes are characterized by a considerable occurence of valve dysfunction, with a low rate of subsequent reintervention.

RHEUMATIC TRICUSPID VALVE DISEASE

The prevalence of rheumatic heart disease has declined rapidly in industrialized and developed countries [161]. However, in third world countries the prevalence of rheumatic heart disease and subsequently the prevalence of rheumatic tricuspid valve disease remains high [162]. The systematic search of the literature resulted in seven publications [27, 31, 49, 99, 104, 144, 146], most of which originate from developing countries.

Patient Presentation and Intraoperative Details

Patient characteristics are presented in Table 4. In the included studies 77% is female. This is remarkable because no distinct gender difference in the incidence of rheumatic valve disease has been described in prior epidemiologic studies [162, 163]. Patients present in 84.6% of cases with isolated regurgitation, 8.6% with isolated stenosis and 6.8% with combined stenosis and regurgitation. Intraoperative details are presented in Table 5. When the valve is replaced, bioprostheses are used (60%) more frequently than mechanical prostheses (40%). Nearly all

patients undergo concomitant surgery. Both mitral valve surgery and aortic valve surgery are performed frequently. Hence, most patients undergo triple valve surgery. The pulmonary valve is not operated on in this group of patients.

Outcomes

Pooled early mortality of rheumatic tricuspid valve disease is 7.4% (95% CI [5.5– 10.1%]). Late outcomes are presented in Table 7. Late mortality is excessive, with most patients dying from cardiac causes. Almost a third of cardiac deaths are valve-related.

Of the patients that undergo valve replacement, 40% received a mechanical prosthesis, which requires lifelong anticoagulation. Additionally, a proportion of patients in which the tricuspid valve is repaired, may have undergone concomitant mechanical mitral and/or aortic valve replacement, which may explain the high rate of bleeding in these patients.

In summary, surgery for rheumatic tricuspid valve disease is associated with high early and late mortality and late complications is characterized by bleeding.

Table 7. Late outcomes after surgery for rheumatic tricuspid valve disease

Outcome	LOR	95% CI
Late mortality	3.2%/year	2.4–4.1
Late cardiac mortality	2.5%/year	2.0–3.4
Late valve-related mortality	0.9%/year	0.6–1.5
Reintervention	0.8%/year	0.6–1.2
Bleeding	1.2%/year	0.8–1.5
Replacement		
SVD[a]	0.4%/year	0.2–0.6
NSVD[a]	0.2%/year	0.1–0.5
Valve thrombosis[a]	0.2%/year	0.1–0.5

LOR linearized occurence rate, CI confidence interval.
[a]Outcomes only relate to valve replacement

CONGENITAL TRICUSPID VALVE DISEASE

Congenital defects of the tricuspid valve are rare when compared to other congenital heart disease [164]. Generally, three entities of congenital tricuspid valve disease are recognized: Ebstein's anomaly, tricuspid valve dysplasia, hypoplasia or cleft and double orifice tricuspid valve [154]. The latter two are extremely rare and only a few cases have been reported to date [165, 166]. Ebstein's anomaly is more prevalent with an incidence of 1 in 20,000 live births in the general population [167]. The systematic search of the literature resulted in 23 publications [12, 20, 21, 24, 29, 32, 41, 46, 50, 51, 83, 87, 101, 102, 110, 116, 118, 130, 133, 136, 137, 143, 168].

Patient Presentation and Intraoperative Details

Patient characteristics are presented in Table 4. Of all patients, 99.4% of patients is diagnosed with Ebstein's anomaly. Patients are generally younger at the time of surgery than those with other etiologies of tricuspid valve disease. Approximately half of the patients is female, which is in line with the general belief that Ebstein's anomaly has no predilection for either gender. 99.9% of patients present with isolated regurgitation and 0.1% of patients present with isolated stenosis. No patients present with combined stenosis and regurgitation. The intraoperative characteristics are presented in Table 5. The tricuspid valve is repaired in 7 out of 10 patients and replaced in 3 out of 10 patients. Of replacements in 85% a bioprosthesis is used and in 15% a mechanical prosthesis is used. Atrial and ventricular septal defect closure and other concomitant procedures are frequently performed in patients with Ebstein's anomaly, with a mean of 2.2 procedures per patient.

Outcome

Pooled early mortality of congenital tricuspid disease is 4.0% (95% CI[2.6–6.2%]). Late mortality is low and deaths are mostly cardiac, a substantial proportion of which are valve-related. Late outcomes are presented in Table 8.

Early reintervention (<30 days) is relatively frequent in these patients (2.8%), mostly due to early failure of the repair.

Late morbidity is characterized by high rates of SVD after valve replacement, which may be due in part to the frequent use of bioprostheses in this younger population and it has been previously described that younger age is associated with higher rates of SVD [169]. Furthermore, these younger patients with relatively favorable long-term survival are more likely to outlive the implanted prosthesis. Additionally, some repairs of tricuspid valve tend to fail over time. Subsequently, reintervention is frequent in these patients.

In summary, congenital tricuspid valve disease is associated with low late mortality, however some patients will eventually face a reoperation.

Table 8. Late outcomes of congenital tricuspid valve disease

Outcome	LOR	95% CI
Late mortality	0.8%/year	0.5–1.4
Late cardiac mortality	0.6%/year	0.4–1.1
Late valve-related mortality	0.4%/year	0.2–0.7
Reintervention	1.4%/year	0.9–2.2
Replacement		
SVD[a]	1.0%/year	0.4–3.0
NSVD[a]	0.2%/year	0.0–1.1
Valve thrombosis[a]	0.4%/year	0.1–1.9

LOR linearized occurence rate, CI confidence interval.

[a]Outcomes only relate to valve replacement.

CARCINOID DISEASE OF THE TRICUSPID VALVE

Carcinoid heart disease may develop in patients with carcinoid syndrome, which is caused by the secretion of a range of vasoactive peptides by hepatic metastases of gastrointestinal carcinoid tumors. Symptoms of carcinoid heart syndrome are diarrhoea, flushing and bronchoconstriction [170].

Bhattachryya and colleagues reported on a series of 22 patients with carcinoid heart disease operated between 2006 and 2010. All tricuspid valves are replaced. In this series, 4 of 22 (18%) patients died within 30 days postoperative and actuarial 2-year survival is 44% ± 11.7%. During the follow up, one patient developed SVD (LOR 0.5 %/year) of the tricuspid valve but no patient required reintervention. NYHA class improvement with more than one grade is seen in 67% [111].

Another paper presented 195 patients operated between 1985 and 2012. All tricuspid valves are replaced. In this series overall 30-day mortality risk is 10%. After 2000 the 30-day mortality risk declines to 6% (8 deaths of 124 patients). Actuarial 10-year survival is 24%. During follow up, nine reinterventions on the tricuspid valve took place (during the initial intervention eight received a bioprosthesis and one received a mechanical prosthesis). NHYA class improvement is noted in 75% of patients that were in NYHA class III or IV preoperatively [132].

In conclusion, if patients undergo surgery for carcinoid tricuspid valve disease, a valve replacement is generally inevitable and long term prognosis is poor. However, with rapidly improving cancer treatment this may change in the near future.

IATROGENIC DAMAGE OF THE TRICUSPID VALVE

The tricuspid valve may be damaged radiation or leads from a pacemaker or cardioverter- defibrillator (ICD). Lin et al. reported on 41 patients with tricuspid valves damaged by pacemaker or ICD leads. In only 5 of 41 (12%) malfunction of the tricuspid valve is diagnosed pre-operatively by echocardiography. The tricuspid valve is replaced in 22 patients. One patient died in the early postoperative period (2.4%). During follow-up (mean 8.2 years) five patients died. Functional status according to the NYHA classification improved in all surviving patients [171].

ENDOCARDITIS OF THE TRICUSPID VALVE

The incidence of community acquired endocarditis ranges from 1.7 to 6.2 cases per 100,000 person years [172] and approximately 5–10% of overall endocarditis is right sided [173]. Endocarditis vegetations on the tricuspid valve often dislodge and cause pulmonary embolism.

Therefore, in tricuspid valve endocarditis the presenting symptoms are more frequently pulmonary in nature rather than those of congestive heart failure. The majority of patients with right sided endocarditis are intravenous drug users, in whom *Staphylococcus aureus* is the most prevalent pathogen [174]. Among articles in our systematic literature review reporting on mixed etiology cohorts, endocarditis is diagnosed in 7.0% of patients. However, throughout literature only a few studies report on outcomes after tricuspid valve surgery for endocarditis specifically.

The STS database contains 910 tricuspid valve operations for tricuspid valve endocarditis between 2002 and 2009 (median age: 40 years, 50.6% male). Active infective endocarditis (IE) is present in 68.5% of patients. The tricuspid valve is replaced in 54% and repaired in 39% and a valvectomy is performed in 7%. Early mortality is 7.3% with no significant differences between the various surgical techniques employed [175].

Baraki et al. published a series of 33 patients (mean age 49 ± 21, 68% male) operated on for tricuspid valve IE. Fourteen patients were intravenous drug abusers (of which ten were infected with *Staphylococcus aureus*). Three patients (9%) died within the first 30 days postoperative. During the mean follow-up of 6.0 ± 4.1 years seven patients died (LOR 3.1%/year) of which three died of cardiac causes (LOR 1.1%/year). Actuarial freedom from reoperation at 10 years is 88%.

TAKE HOME MESSAGE

This chapter provides a contemporary overview of tricuspid valve surgery in the form of a systematic review and meta-analysis.

Reviewing the outcomes after tricuspid valve surgery it becomes clear that early mortality after tricuspid valve replacement is still poor. Nevertheless, some progress has been made over the years. Bioprosthetic and mechanical tricuspid valve replacement are associated with comparable reintervention rates. Moreover, mechanical prostheses require anticoagulation, which imparts a risk of anticoagulation-related events. Thus, outcomes for bioprostheses appear to be more favorable.

Outcomes after tricuspid valve repair, which is performed predominantly for functional tricuspid regurgitation, are more favorable than after tricuspid valve replacment, which is usually performed for primary tricuspid valve disease in patients in poorer preoperative clinical condition. These differences in indication preclude direct comparison between repair and replacement.

For functional tricuspid disease the valve is almost exclusively repaired and early and late outcomes are acceptable.

In patients diagnosed with rheumatic tricuspid valve disease, the mitral and aortic valve are often affected simultaneously, often resulting in triple valve surgery. Rheumatic valve disease is associated with high late mortality, of which the majority is cardiac.

Almost all patients suffering from congenital tricuspid disease are diagnosed with Ebstein's anomaly. A valve replacement is performed in 3 out of 10 patients. Congenital tricuspid disease is associated with relatively low late mortality, but a substantial reintervention rate.

Future surgical developments have the potential to change tricuspid valve surgery drastically. Percutaneous interventions may provide a promising solution in reducing operative mortality in patients in need of a tricuspid valve intervention. These techniques may prove particularly beneficial in patients requiring reintervention, since operative mortality is substantially higher in these patients [141].

Tissue engineering is another promising development, with the prospect of a durable living heart valve with growth potential, which may be especially useful in young patients with congenital tricuspid valve disease since reinterventions are frequent in these patients, partly due to the patients outgrowing their initial valve prosthesis.

REVIEW QUESTIONS

74. What is early mortality for tricuspid valve replacement
(a) Comparable to aortic valve replacement
(b) Comparable to mitral valve replacement
(c) Less than 5%
(d) More than 10%

75. In tricuspid valve replacement, what are the advantages and drawbacks of a bioprosthesis compared with a mechanical valve?
(a) Less thrombosis, less bleeding and more reinterventions
(b) More thrombosis, less bleeding, more reinterventions
(c) Less thrombosis, less bleeding, comparable reintervention rates

76. What is the most widely employed technique for the surgical treatment of carcinoid tricuspid valve disease (in current literature)?
(a) Tricuspid valvotomy
(b) Tricuspid valvoplasty
(c) Tricuspid replacement

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3

Outcomes after surgery for functional tricuspid regurgitation: a systematic review and meta-analysis

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Aims

This study aims to provide a contemporary overview of outcomes after tricuspid valve (TV) surgery for functional tricuspid regurgitation (TR).

Methods and results

The literature was systematically searched for papers published between January 2005 and December 2017 reporting on clinical/echocardiographic outcomes after TV surgery for functional TR. A random effects meta-analysis was conducted for outcome variables, and late outcomes are visualized by pooled Kaplan–Meier curves. Subgroup analyses were performed for studies with a within-study comparison of suture vs. ring repair and flexible vs. rigid ring repair. Eighty-seven publications were included, encompassing 13 184 patients (mean age: 62.1 ± 11.8 years, 55% females). A mitral valve procedure was performed in 92% of patients. Pooled mean follow-up was 4.0 ± 2.8 years. Pooled early mortality was 3.9% (95% CI: 3.2–4.6), and late mortality rate was 2.7%/year (95% CI: 2.0–3.5), of which approximately half was cardiac-related 1.2%/year (95% CI: 0.8–1.9). Pooled risk of early moderate-to-severe TR at discharge was 9.4% (95% CI: 7.0–12.1). Late moderate-to-severe TR rate after discharge was 1.9%/year (95% CI: 1.0–3.5). Late reintervention rate was 0.3%/year (95% CI: 0.2–0.4). Mortality and overall (early and late) TR rate were comparable between suture vs. ring annuloplasty (14 studies), whereas overall TR rate was higher after flexible ring vs. rigid ring annuloplasty (6 studies) (7.5%/year vs. 3.9%/year, $P = 0.002$).

Conclusion

This study shows that patients undergoing surgery for functional tricuspid regurgitation (FTR) have an acceptable early and late mortality. However, TR remains prevalent after surgery. The results of this study can be used to inform patients and clinicians about the expected outcome after surgery for FTR and can results serve as a benchmark for the performance of emerging transcatheter TV interventions.

INTRODUCTION

Functional tricuspid regurgitation (FTR) is the most common form of tricuspid valve (TV) disease. Functional tricuspid regurgitation is the result of changes in the tricuspid annular geometry caused by dilatation of the right ventricle in the absence of structural valve abnormalities. In most, FTR is caused by left-sided heart disease and subsequent pulmonary hypertension.[1] Historically, FTR was believed to be benign and to resolve after the left-sided heart disease was corrected.[2] However, recent research shows that FTR is an ongoing process, which can even worsen if left untreated[3–5] and that the presence of TV regurgitation is associated with impaired long-term survival.[6] Therefore, latest guidelines recommend TV surgery in patients undergoing left-sided valve surgery if severe FTR is present and/or when annulus dilatation exceeds 40mm.[7,8] Whenever feasible, the TV is repaired with either a suture or ring annuloplasty. Optimal patient selection with current techniques remains controversial. Additionally, new transcatheter technologies for treating FTR are already on the horizon.[9] In this light a comprehensive overview of both clinical and echocardiographic outcomes is warranted, which is currently lacking in the literature. This systematic review of the literature and meta-analysis aims to provide a contemporary overview of outcomes after surgery for FTR. Furthermore, we analysed studies specifically addressing ring vs. suture annuloplasty and flexible vs. rigid ring annuloplasty.

METHODS

Search strategy

To establish an overview of reported outcome, we conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] On 13 December 2017, Embase, Medline, Web of science, Cochrane, and Google scholar were searched by a biomedical information specialist (search terms are available in Supplementary material online, Text S1). The search was limited to studies that were published after 1 January 2005. Two researchers (K.M.V. and J.R.G.E.) independently reviewed abstracts and full texts. We included observational studies and randomized controlled trials that reported on outcome after surgery for FTR in humans with a sample size ≥20 patients and were published in English. Studies solely reporting on primary TV disease or studies with a mix of patients with FTR and primary TV disease without extractable data on patients with FTR were excluded. In case of multiple publications on overlapping study populations, the publication with the greatest total follow-up in patient-years and/or overall completeness of data was included for each outcome of interest separately. In case of disagreement, an agreement was negotiated.

Data extraction

Microsoft Office Excel 2011 (Microsoft Corp., Redmond,WA, USA) was used for data extraction. If total follow-up in patient-years was not reported, it was calculated by multiplying the number of patients with the mean follow-up (or median follow-up, if the mean was not provided). Outcomes were recorded according to the guidelines described by Akins et al.[11] Early mortality was defined as either hospital mortality or 30-day mortality. A sensitivity analyses were performed for studies reporting 30-day mortality. Extracted baseline characteristics and outcomes are provided in Supplementary material online, Table S1. Early tricuspid regurgitation (TR) was defined as moderate-to-severe TR at discharge echocardiogram. Late TR was defined as number of patients that progressed from none-to-mild at discharge to moderate-to-severe at last follow-up. Overall TR was defined as moderate-to-severe TR at last follow-up (early TR plus late TR).

Statistical analyses

Sample sized weighted pooled baseline patient and procedural characteristics were calculated. Event risks (early) and rates (late) were pooled using inverse variance weighting. Outcomes were pooled on a logarithmic scale, because the Shapiro–Wilk test revealed a skewed distribution among the majority of outcomes. Outcomes were pooled in a random effects model using the Der Simonian and Laird method to estimate the between-study variance.[12] In case, a particular event was reported not to occur, we assumed that 0.5 patient experienced the event for pooling purposes (continuity correction). Subgroup analyses were conducted of studies comparing ring vs. suture annuloplasty and flexible vs. rigid ring annuloplasty, in which risk ratios (RRs) and mean differences (MDs) were calculated for baseline characteristics and outcomes, a random model was used to pool outcomes and a fixed model was used to pool baseline characteristics.[12] We did not use continuity correction in subgroup analyses and if only two studies reported the variable of interest or had zero events, no pooling of RR/MD was performed. The Cochrane Q statistic and I^2 were used to assess heterogeneity. Potential causes of heterogeneity in early/late mortality and early TR were explored by investigating the association of all baseline patient characteristics and operative details listed in Supplementary material online, Table S3 by means of univariable random effects meta-regression. The influence of potential publication bias on pooled outcome was investigated by conducting sensitivity analyses by temporarily excluding the smallest quartile (by sample size). Microsoft Office Excel 2011 was used to conduct the random effects meta-analyses and R (Version 3.3.3, Vienna, Austria, using the Open Meta Analyses interface) for the univariable meta-regression analyses. Comprehensive meta-analysis (Biostat, Englewood, USA) was used to pool RRs and MDs from studies included in the subgroup analyses. A *P*-value of <0.05 was considered significant.

We visualized the survival and freedom from late TR in pooled KM curves derived from the original published KM curves using the method described by Guyot et al.[13] Published Kaplan–Meier curves were digitized and an estimate of the individual patient time-to-event data was then extrapolated from the digitized curve co-ordinates, assuming a constant rate of

censorship between each time point at which the number of patients at risk was specified.[12] We used Engauge Digitizer 9.7 to create a list of co-ordinates of the KM curve and employed an in-house developed algorithm written in R language (Version 3.3.3) to reconstruct the original patient data. The mortality of the general population was obtained for the pooled median year of intervention among included studies (2006) and for the regions that the majority of the included study population originated from (North America, 41% of patients; Europe, 23% of patients; and Japan 16% of patients).

RESULTS

The literature search resulted in 11 707 publications. After applying inclusion and exclusion criteria 87 studies were included for analysis, of which 14 publications compared ring vs. suture annuloplasty and six compared flexible vs. rigid ring annuloplasty (Figure 1) (Supplementary material online, References S1–S87). In 18 of the 87 included publications only a subgroup or part of the outcomes could be extracted in order to prevent overlapping study populations (Supplementary material online, Table S2).

Study and patient characteristics

Individual study characteristics are presented in Supplementary material online, Table S2. In total, 13 184 patients with a mean age of 62.1 ± 11.8 years (55% females) were included, encompassing 41 874 patient-years of total follow-up. In total, 10 418 patients had late follow-up, resulting in a mean pooled follow-up of 4.0 ± 2.8 years. Pooled patient and procedural characteristics are presented in Table 1. Al least one concomitant procedure was performed in 98.7% of patients, usually a mitral valve procedure (92.6%).

Clinical outcomes

Early and late outcomes are presented in Table 2. Heterogeneity was high in all outcome measures, except for late valve-related mortality, late pacemaker implantation, and reintervention (Table 2). Unvariable meta-regression identified several potential sources of heterogeneity. These were older mean age and higher proportion concomitant coronary artery bypass graft (CABG) associated with higher early mortality risk; older mean age, higher proportion concomitant CABG, higher CPB, and aortic cross clamp (ACC) time associated with higher late mortality rate (Supplementary material online, Table S3). Sensitivity analysis did not reveal major changes in pooled outcomes when studies with a sample size lower than 25th percentile were temporarily excluded, nor did 30-mortality differ from early mortality (3.9% vs. 3.9%; Supplementary material online, Table S4). Twenty-five studies reported a Kaplan–Meier curve encompassing 7531 patients in total (Supplementary material online, References S1–S25), which could be pooled (Figure 2). Survival at 1, 3, and 8 years was 87.7%, 80.9%, and 64.5%, respectively.

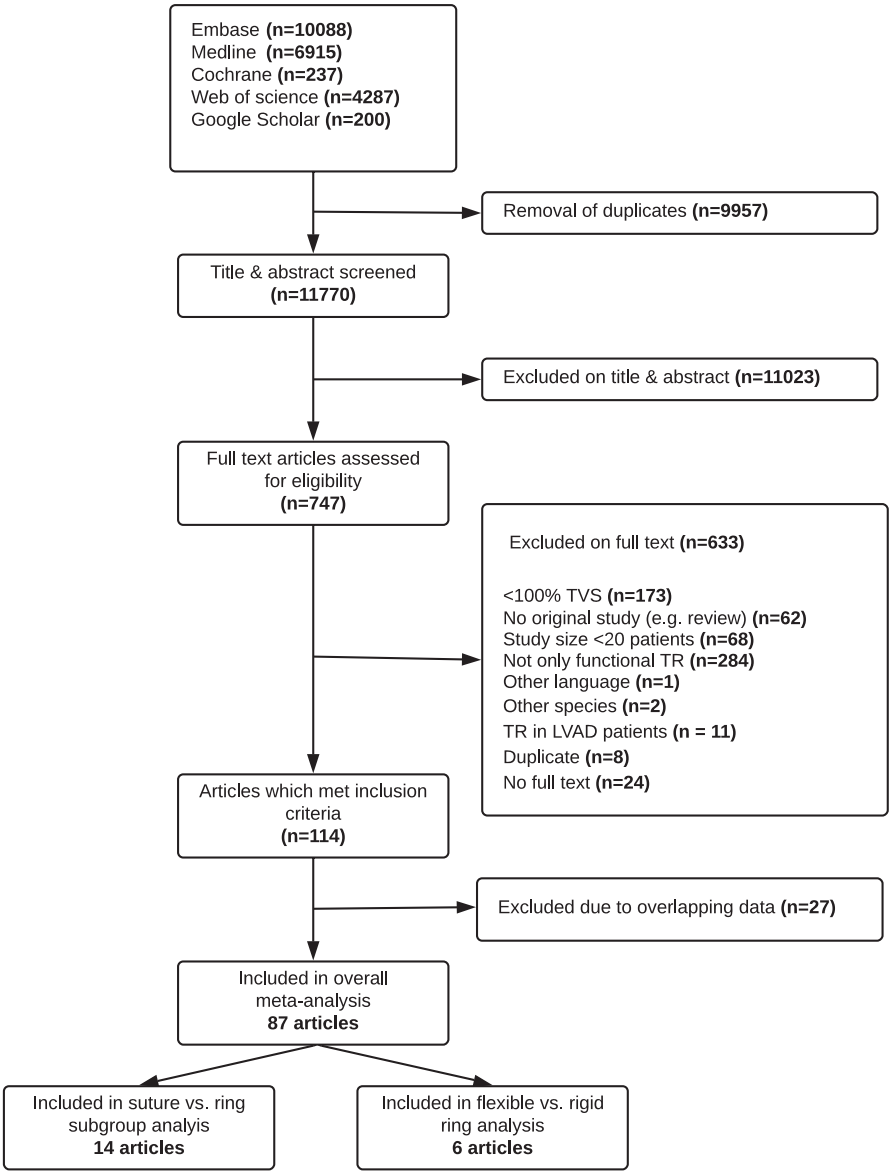

Figure 1. A flow chart of included studies.

Tricuspid regurgitation

Pooled risk of early moderate-to-severe TR is 9.4% (Table 2). Possible sources of heterogeneity in early TR risk were higher proportion of moderate-to-severe TR at baseline and higher proportion of patients with diabetes (Supplementary material online, Table S3). Twenty-four studies reported both early and late moderate-to-severe TR, of which two had to be excluded

due to large discrepancy in number of patients with a discharge echocardiogram compared to a follow-up echocardiogram. Pooled estimate of late TR is 1.9%/year and overall TR rate (early and late combined) was 3.5%/year (Table 2).

In total, 18 studies presented a KM curve reporting freedom from moderate-to-severe TR, encompassing 4138 patients in total (Figure 3A). Overall freedom from TR at 1, 3, and 5 years was 92.9%, 89.4%, and 84.9%. Seventeen studies reported a KM curve in which it was distinguishable whether patients underwent suture or ring annuloplasty, encompassing 4046 patients in total (Figure 3B). Eight studies reported on a KM on flexible/rigid rings encompassing 1727 patients

(Figure 3C).

Table 1. Pooled baseline characteristics

Characteristics	Pooled proportion (*n* = 13 184)	Range	N studies reported
Age (years)	62.1 ± 11.8	25.1–72.5	75
Female (%)	55.5	17.6–90	72
NYHA III–IV (%)	58.5	16.1–100	47
AF (%)	60.7	20.0–100	58
≥ Moderate TR (%)	78.5	0.0–100	57
LVEF (%)	51.8 ± 13.5	28.5–65.0	57
PAPs (mmHg)	48.6 ± 14.2	35.3–76.9	42
TV repair[1] (%)	98.6	0.0–100	75
Suture repair[2]	22.6	0.0–100	72
Ring repair[2]	77.4	0.0–100	72
TV replacement[1] (%)	1.4	0.0–100	75
MV procedure (%)	92.6	16.9–100	75
MV repair[3]	40.9	0.0–100	58
MV replacement[3]	59.1	0.0–100	59
AV procedure (%)	20.9	0.0–64.9	66
CABG (%)	16.6	0.0–58.8	66
CPB time (min)	148 ± 61	45–256	52
ACC time (min)	101 ± 39	35–168	47

ACC, aortic cross-clamp; AF, atrial fibrillation; AV, aortic valve; CABG, coronary artery bypass graft; CPB, cardio pulmonary bypass; LVEF, left ventricular ejection fraction; MV, mitral valve; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; TR, tricuspid regurgitation; TV, tricuspid valve.

[1]Percentage of patients with reported technique.

[2]Percentage of patient with reported TV repair.

[3]Percentage of patient with reported MV procedure.

Table 2. Pooled outcomes

Outcomes	Pooled estimate (95% CI)	Heterogeneity (I^2)	*N* studies reported
Early outcome (%)			
Early mortality	3.9 (3.2–4.6)	62.6	73
Early pacemaker implantation	3.2 (2.1–5.0)	83.0	27
AKI	4.8 (3.6–6.5)	86.0	26
LCOS	7.4 (5.5–9.9)	71.8	19
Early re-exploration	5.5 (4.4–6.9)	87.1	34
Early moderate-to-severe TR	9.4 (7.0–12.3)	90.5	35
Late outcome (%/year)			
All-cause mortality	2.7 (2.0–3.5)	92.9	46
Cardiac mortality	1.2 (0.8–1.9)	88.9	32
Valve-related mortality	0.7 (0.5–0.9)	21.0	26
Late pacemaker implantation	0.8 (0.5–1.3)	27.5	7
Late admission HF	2.1 (0.8–5.4)	94.8	9
Late reintervention[a]	0.3 (0.2–0.4)	14.1	34
Overall moderate-to-severe TR[b]	3.5 (2.1–6.0)	96.5	24
Late moderate-to-severe TR	1.9 (1.0–3.5)	95.1	22

AKI, acute kidney injury; HF, heart failure; LCOS, low cardiac output syndrome; TR, tricuspid regurgitation.
[a]Only containing tricuspid valve reinterventions.
[b]Combining late and early TR.

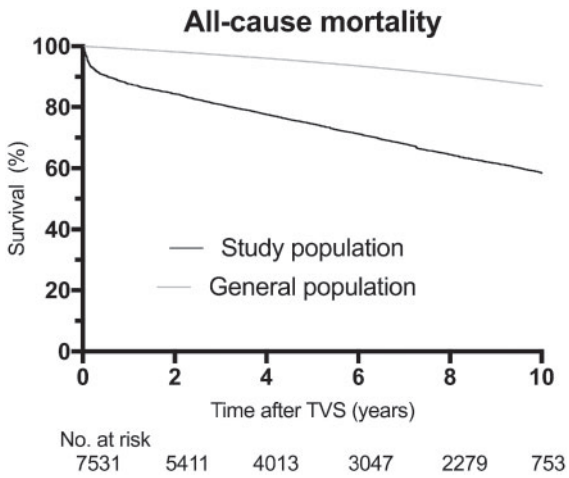

Figure 2. Pooled Kaplan–Meier curve of overall survival (both early and late).

Suture repair vs. ring repair

In total, 14 studies focused on ring repair vs. suture repair (Supplementary material online, References S7, S10, S12, S20, S32, S36–S44) encompassing 1425 patients (ring) and 586 pa-

tients (suture). Pooled baseline characteristics were comparable between patients; except for age and pulmonary systolic artery pressure which was both higher in the ring group (Table 3). Cardiopulmonary bypass (CPB) time of patients undergoing suture annuloplasty was on average 9.2 min shorter compared to patients undergoing ring annuloplasty (Table 4). Early mortality risk and late mortality rate were comparable (Table 3). Furthermore, early TR, overall TR, and late reintervention were comparable (Table 3). Only two studies reported both early and TR at last follow-up, hence pooled late TR could not be computed. Forest plots of all outcomes are presented in Supplementary material online, Figures S1–S7.

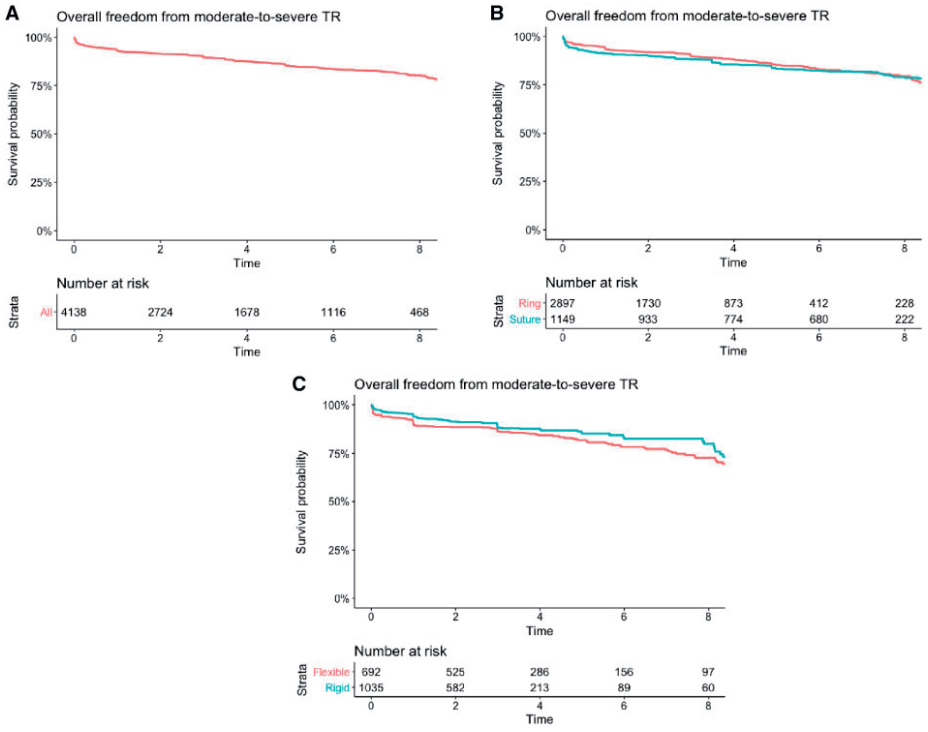

Figure 3. Pooled Kaplan–Meier curve overall freedom from moderate-to-severe tricuspid regurgitation (both early and late) (A) and with either a suture or a ring repair (B) and a flexible ring or a rigid ring (C). TR: Tricuspid regurgitation.

Flexible vs. rigid ring repair

In total, six studies focused on flexible vs. ring repair encompassing 749 (flexible) and 745 (rigid) patients (Supplementary material online, References S13, S18, S28, S30, S35, and S36). On average, patients receiving a rigid ring were older, had less atrial fibrillation, and were more frequently in New York Heart Association Class III–IV (Table 4). cardiopulmonary bypass times and early/late mortality and late mortality were comparable between groups (Table 4).One

study reported early pacemaker implant, which was comparable (3% vs. 2%).[14] Three studies reported early TR, which was comparable in all studies.[15–17] Overall TR rate was significantly higher in the flexible group (7.5%/year) vs. the rigid group (3.9%/year, *P*=0.002) (Table 4). Late TV re-intervention was comparable; however, only in two studies patients underwent late TV reintervention.[14,15] In two other studies, no TV interventions were performed.[16,17] Four studies reported ring dehiscence: one study found higher incidence of ring dehiscence in the rigid ring group,[15] whereas the three other studies no ring dehiscence was noted in both groups.[17–19] Forest plots of all outcomes are presented in Supplementary material online, Figures S8–S11.

Table 3. Pooled baseline characteristics and outcomes of studies with a within-study comparison of ring vs. suture repair

	Ring (*n* = 1425)	**95% CI**	**Suture (*n* = 586)**	**95% CI**	**RR/MD**	**95% CI**	***P*-value**
Baseline characteristics							
Age (years)	57.8	57.1–58.8	55.9	55.3–56.5	-1.2	-2.1 to -0.3	0.010
Female	56.6	53.5–59.4	56.9	54.2–59.6	1.02	0.96–1.09	0.564
NYHA III–IV	66.0	62.9–69.0	65.2	62.4–67.9	1.04	0.99–1.08	0.127
AF	62.9	59.8–66.0	61.5	58.4–64.5	0.99	0.94–1.03	0.631
LVEF (%)	50.3	49.8–50.8	46.7	46.3–47.2	0.31	-0.40 to 1.01	0.396
PAPs (mmHG)	49.5	49.0–49.9	48.3	47.8–48.7	1.00	0.34–1.67	0.003
≥ Moderate TR	76.5	73.1–79.6	77.2	73.7–80.3	1.01	0.99–1.3	0.517
MV procedure	89.5	87.0–91.6	90.3	88.2–92.7	1.00	0.98–1.02	0.803
AV procedure	22.2	19.6–25.0	22.3	19.8–24.9	1.03	0.87–1.21	0.757
Outcomes							
CPB time (min)	145	113–177	134	106–162	9.2	4.5–14.0	>0.001
Early mortality	2.5	2.3–4.6	2.5	1.6–3.9	1.21	0.75–1.96	0.427
Late mortality[a]	1.7	0.9–3.3	2.6	0.2–3.4	0.67	0.33–1.35	0.264
Late reintervention[a]	0.2	0.1–0.4	0.3	0.2–0.5	1.25	0.53–2.94	0.604
Early TR	10.2	4.3–22.8	6.8	2.8–15.3	0.82	0.61–1.01	0.179
Overall TR[a]	4.3	2.1–8.3	6.3	1.2–28.1	0.98	0.72–1.33	0.889

AV, aortic valve; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; MD, mean difference; MV, mitral valve; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; RR, risk ratio; TR, tricuspid regurgitation.
[a]Rate ratios instead of risk ratios.

Table 4. Pooled baseline characteristics and outcomes of studies with a within-study comparison of flexible ring vs. rigid ring repair

	Flexible ring (*n* = 749)	95% CI	Rigid ring (*n* = 745)	95% CI	RR/MD	95% CI	*P*-value
Baseline characteristics							
Age	64.8	64.1–65.5	66.2	65.6–66.7	-1.02	-1.95 to -0.09	0.032
Female	55.3	51.7–55.8	54.2	50.6–57.7	1.03	0.94–1.13	0.527
NYHA III–IV	61.6	54.2–68.4	71.6	63.0–79.2	0.89	0.80–1.0	0.045
AF	56.1	52.0–60.0	54.0	50.1–57.8	1.13	1.04–2.81	0.005
LVEF	54.1	53.5–54.8	54.9	54.0–55.8	-0.77	-1.87 to 0.32	0.167
≥ Moderate TR	63.2	55.7–70.1	71.1	65.0–77.5	1.02	0.98–1.07	0.304
MV procedure	88.0	83.1–91.6	90.7	86.5–93.8	0.99	0.96–1.03	0.707
AV procedure	31.6	25.2–38.7	26.4	21.0–32.6	1.13	0.82–1.55	0.456
Outcomes							
CPB time	136	100–173	145	107–184	-5.5	-11.4 to 0.3	0.063
Early mortality	6.4	3.2–12.5	6.0	3.6–10.1	1.21	0.65–2.24	0.543
Late mortality[a]	4.4	0.5–28.2	3.8	1.2–11.2	1.74	0.91–3.33	0.093
Late reintervention[a]	0.3	0.1–0.8	0.3	0.1–0.7	—[b]	—[b]	—[b]
Early TR	3.6	1.9–6.6	2.5	0.4–12.5	—[b]	—[b]	—[b]
Overall TR[a]	7.5	2.7–19.1	3.9	1.4–10.5	1.83	1.24–2.74	0.002
Ring dehiscence	0.0	0.0–0.0	0.9	0.5–1.7	—[b]	—[b]	—[b]

AV, aortic valve; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; MD, mean difference; MV, mitral valve; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; RR, risk ratio; TR, tricuspid regurgitation.

[a]Rate ratios instead of risk ratios.

[b]No pooling attempt was made, since only two studies reported non-zero events.

DISCUSSION

In this study, we provide a comprehensive overview of outcomes after TV surgery for FTR in the light of emerging transcatheter TV interventions. To the best of our knowledge, this is the first comprehensive review and meta-analysis of outcomes after surgery for FTR. We noted acceptable early and late mortality, nevertheless early and late TR remain prevalent. Subgroup analyses revealed a significantly higher rate of overall TR of flexible rings compared to rigid rings. The results of this study can be used to inform patient and clinicians about the expected outcome after surgery for FTR. Furthermore, these data can be used for microsimulation models.[20] In addition, these results can be used as benchmark for the performance of emerging transcatheter TV interventions.

Patient and study characteristics

Patient characteristics varied considerably among studies. Interestingly, some studies included exclusively patients without moderate-to-severe FTR at baseline.[21,22] These studies investigated the 'prophylactic' approach of surgery for FTR in which only annular dilation is present, originally presented by Dreyfus et al.,[3] who proposed a cut-off of 70 mm intraoperatively, which was later converted to 40 mm on echocardiography. Nevertheless, this concept has been debated, especially since no specific evidence exist for 70–40 mm conversion, or the initial 70 mm cut-off.[3,23] Nearly all patients underwent a concomitant procedure, usually a mitral valve procedure. This indicated that the main cause of FTR in the included studies is left-sided heart disease. In only four studies patients underwent TV replacement for FTR, reflecting the preference for TV repair in this population. Notwithstanding, the current consensus is that TV replacement is preferred in case of very severe functional TR, with severe tethering.[24]

Early outcomes

Early mortality is acceptable in this patient population (3.9%) and studies with higher mean age and proportion of concomitant CABG reported higher mortality risks. Prior research has shown that TV surgery during left-sided valve surgery does not increase perioperative risk and even seems to protect against cardiac-related mortality compared to patients that did not undergo concomitant TV surgery.[25] Early pacemaker implantation (3.2%) is comparable with other large cohorts.[26,27] This may indicate that TV surgery does not add extra risk for pacemaker implant. Notwithstanding, other studies identified TV surgery as risk factor for post-operative pacemaker implant or noted high incidence of pacemaker implantation after TV surgery.[28–30] Jouan et al.[28] mentioned the close proximity of TV annular septal segment to the atrioventricular node may increase the risk of damage to the latter during TV interventions.

Late outcome

Our Kaplan–Meier analysis illustrates that mortality hazard is higher in the early post-operative period and becomes relatively stable thereafter. Compared to the general population, the survival in the study population is impaired. This is mainly due to the early morality, but late mortality is also higher compared to the general population. Studies with higher mean age, higher CPB/ACC time, and higher proportion of CABG reported higher rates of late mortality. Approximately half of the observed mortality can be attributed to cardiac causes, which is roughly two times higher compared to the general USA population.[31] Late re-intervention rate of the TV is low (0.3%/year) and little heterogeneity is present, indicating re-intervention is low uniformly among studies.

Tricuspid regurgitation

The incidence of early moderate-to-severe TR is relatively high (9.3%) and studies with a higher proportion moderate-to-severe TR at baseline reported higher risks of early moderate-to-

severe TR, explaining partly the heterogeneity in this outcome. Interestingly, the type of repair (suture vs. ring) was not associated with risk of early TR upon univariable meta-regression. After the hospital period some patients develop late TR (1.9%/year), indicating a suboptimal durability. This rate does not correspond to the reintervention rate, meaning that only a part of the patients with early/late TR are reoperated. This can partly be explained by the fact that mortality risk after re-intervention of the TV is high, especially after late referral if right ventricular failure has already developed.[24,32,33]

Subgroup analyses

On average there were statistically significant differences between the suture group and the ring group [age, systolic pulmonary artery pressure (PAPs)]. Nevertheless, these differences are small (age: 1.2 years, PAPs: 1.0 mmHg) and may not be clinically relevant. Mortality and postoperative TR rates were comparable between ring vs. suture repair. In regard to early mortality and TR rate, this is in disagreement with a prior meta-analysis by Parolari et al.[34] focusing solely on the comparison ring vs. suture. Several factors may have contributed to this disagreement. Firstly, the prior meta-analysis did not exclude studies with primary TR. Secondly, the prior metaanalysis also compared studies without a within-study comparison of suture vs. ring, and variations in study populations between studies may have contributed to the observed differences in TR rates. Thirdly, two studies included in our TR rate analyses utilized the modified De Vega technique, with multiple pledgets, which is associated with better outcome than classical De Vega with two pledgets on the ends (Supplementary material online, References S12, S38, and S40). This technique was not used in the studies included in the prior systematic review.

In studies, comparing flexible rings vs. rigid rings a higher TR rate in the flexible ring group was noted. This is in agreement with a prior systematic review only including studies comparing flexible rings vs. rigid rings, regardless of TV disease aetiology.[35]

Future perspectives

The threshold to perform concomitant TV surgery has become increasingly lower.[1] Indeed, untreated TR does seem to be associated with impaired mortality.[6] Nevertheless, prediction of progression of TR after left-sided valve surgery remains difficult. In order to adequately address FTR multiple approaches are possible. Firstly, one can become even more liberal in performing concomitant TV surgery or optimize selection criteria for concomitant TV surgery by investigating longitudinal evolution of TR after left-sided valve surgery. Another approach emerges with the rise of transcatheter TV devices. One may be more conservative during the initial left-sided valve surgery and treat late TR using transcatheter tricuspid valve devices. Nevertheless, these devices are still in development and no evidence exists whether late percutaneous intervention of TR is beneficial. Future studies have to elucidate whether late transcatheter intervention is equivalent to earlier concomitant surgical intervention.

Limitations

This is a systematic review and meta-analysis of mainly retrospective observational studies. Therefore, inherent limitations of pooling such studies apply to this study.[36] Secondly, publication bias may be present which can potentially lead to underestimation of the estimates. We did not assess publication bias using funnel plots, as funnel plots do not allow for meaningful interpretation in case of absolute risk outcomes because of substantial methodological limitations, which may in itself give rise to funnel plot asymmetry.[37] Furthermore, heterogeneity was present in most outcomes which may lead to inaccurate results. Nevertheless, we conducted a thorough examination of heterogeneity by meta-regression. Linearized occurrence rates assume a constant hazard over time, while in fact most of the distribution of events may be time related.[38] Therefore, a pooled KM analyses was performed, illustrating the distribution of time-to-event. Inconsistencies in the reporting of TR and loss to echocardiographic follow-up among the included studies may have introduced uncertainty. Unfortunately, important variables, such as TV tethering, were not frequently reported in the primary studies.

CONCLUSION

This comprehensive systematic review with meta-analysis provides an overview of outcomes after surgery for FTR, which is in most cases performed concomitantly to left-sided valve surgery. It illustrates an acceptable early and late mortality, while early and late TR risk and rate are still suboptimal. These results can be used as benchmark for the performance of emerging transcatheter TV interventions.

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SUPPLEMENTARY MATERIAL

Contents

SUPPLEMENTARY TEXT 1: SEARCH TERMS

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('tricuspid valve'/de OR 'Ebstein anomaly'/exp OR 'tricuspid valve disease'/exp OR 'tricuspid valve prosthesis'/de OR 'tricuspid valve repair'/de OR 'tricuspid valve replacement'/de OR (tricuspid* OR ((right-atrioventricul*) NEAR/3 valv*) OR Ebstein*):ab,ti) AND ('surgery'/de OR surgery:lnk OR 'cardiovascular surgery'/de OR 'heart surgery'/exp OR 'tricuspid valve prosthesis'/de OR 'tricuspid valve repair'/de OR 'tricuspid valve replacement'/de OR 'surgical technique'/de OR 'surgical mortality'/de OR 'postoperative period'/de OR (surger* OR surgic* OR operati* OR prosthe* OR bioprosthe* OR graft* OR homograft* OR allograft* OR transplant* OR homotransplant* OR allotransplant* OR repair* OR replace* OR implant* OR correct* OR valvotom* OR valvuloplast*):ab,ti) AND ('observational study'/exp OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'health survey'/de OR 'health care survey'/de OR 'epidemiological data'/de OR 'case control study'/de OR 'cross-sectional study'/de OR 'correlational study'/de OR 'population research'/de OR 'family study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'comparative study'/de OR 'follow up'/de OR 'clinical study'/de OR 'clinical article'/de OR 'clinical trial'/exp OR 'controlled study'/de OR 'randomization'/exp OR 'intervention study'/de OR 'open study'/de OR 'community trial'/de OR 'review'/exp OR 'systematic review'/exp OR 'meta analysis'/de OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/3 (stud* OR survey)) OR (health* NEAR/3 survey*) OR ((case OR cases OR match*) NEAR/3 control*) OR (cross NEXT/1 section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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("Tricuspid Valve"/ OR "Ebstein Anomaly"/ OR "Tricuspid Valve Stenosis"/ OR "Tricuspid Valve Prolapse"/ OR "Tricuspid Valve Insufficiency"/ OR (tricuspid* OR ((right-atrioventricul*) ADJ3 valv*) OR Ebstein*).ab,ti.) AND ("Surgical Procedures, Operative"/ OR surgery.xs. OR "Cardiovascular Surgical Procedures"/ OR exp "Cardiac Surgical Procedures"/ OR "postoperative period"/ OR (surger* OR surgic* OR operati* OR prosthe* OR bioprosthe* OR graft* OR homograft* OR allograft* OR transplant* OR homotransplant* OR allotransplant* OR repair* OR replace* OR implant* OR correct* OR valvotom* OR valvuloplast*).ab,ti.) AND ("observational study"/ OR exp "Cohort Studies"/ OR "Health Surveys"/ OR "Epidemiologic Studies"/ OR "Case-Control Studies"/ OR "Cross-Sectional Studies"/ OR "multicenter study"/ OR "comparative study"/ OR "clinical study"/ OR exp "clinical trial"/ OR "Controlled Before-After Studies"/ OR "Random Allocation"/ OR "review"/ OR "meta-analysis"/ OR (((observation* OR epidemiolog*

OR famil* OR comparativ* OR communit*) ADJ6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* ADJ3 (stud* OR survey)) OR (health* ADJ3 survey*) OR ((case OR cases OR match*) ADJ3 control*) OR (cross ADJ section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

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((tricuspid* OR ((right-atrioventricul*) NEAR/3 valv*) OR Ebstein*):ab,ti) AND ((surger* OR surgic* OR operati* OR prosthe* OR bioprosthe* OR graft* OR homograft* OR allograft* OR transplant* OR homotransplant* OR allotransplant* OR repair* OR replace* OR implant* OR correct* OR valvotom* OR valvuloplast*):ab,ti)

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TS=(((tricuspid* OR (("right atrioventricul*") NEAR/2 valv*) OR Ebstein*)) AND ((surger* OR surgic* OR operati* OR prosthe* OR bioprosthe* OR graft* OR homograft* OR allograft* OR transplant* OR homotransplant* OR allotransplant* OR repair* OR replace* OR implant* OR correct* OR valvotom* OR valvuloplast*)) AND ((((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/5 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/2 (stud* OR survey)) OR (health* NEAR/2 survey*) OR ((case OR cases OR match*) NEAR/2 control*) OR (cross NEAR/1 section*) OR correlation* OR multicenter* OR multi-center* OR follow-up* OR followup* OR clinical* OR trial OR random* OR review* OR meta-analy*))) AND DT=(article) AND LA=(english)

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Tricuspid surgery|surgical|operative|prosthetic|bioprosthesis|repair|replacement observational|cohort|longitudinal|prospective|trial

Supplementary Table 1: Extracted outcome and baseline variables

Baseline variables	Outcomes
Age	Cardio-pulmonary bypass time
Sex	Aortic clamp time
NYHA class	Early mortality
Left ventricle ventricular function	Early pacemaker implantation
Systolic pulmonary artery pressure	Early low cardiac output syndrome
TR grade at baseline	Acute kidney failure
Atrial fibrillation	Early reopening
Diabetes mellitus	Residual moderate-to-severe TR (= TR at discharge)
TV repair	Late mortality
- Ring	Cardiac mortality
o Flexible ring	Valve related mortality
o Rigid ring	Late pacemaker implantation
- Suture repair	Late admission for heart failure
o De Vega	Late reintervention
o Kay	Overall TR (TR at last echocardiogram)
TV replacement	
- Biological prostheses	
- Mechanical prostheses	
MV procedure	
- MV replacement	
- MV repair	
AV procedure	
Concomitant coronary artery bypass grafting	

NYHA: New York heart association, TR: tricuspid regurgitation, TV: tricuspid valve, MV: mitral valve, AV: aortic valve.

Supplementary Table 2: Baseline characteristics of individual studies

Author (year)	N	Follow-Up (years)	Age	Female (n,%)	≥moderate TR (n,%)	AF (n,%)	NYHA III-IV (n,%)	TV repair	TV ring repair	MV procedure
Abdelgawad (2017)[1]	20	1,0	38,9	9 (45)	20 (100)	9 (45)	15 (75)	20 (100)	20 (100)	20 (100)
Ada (2017)	43	-	56,2	27 (63)	43 (100)	24 (56)	20 (47)	43 (100)	43 (100)	35 (81)
Ariyoshi (2013)	47	4,6	66,1	32 (68)	-	44 (94)	30 (64)	47 (100)	25 (53)	47 (100)
Aykut (2011)	62	-	48,1	36 (58)	-	37 (60)	-	62 (100)	-	62 (100)
Basel (2010)	129	2,2	38,8	81 (63)	130 (100)	41 (32)	-	129 (100)	67 (52)	129 (100)
Benedetto (2012)	22	1,0	64,0	9 (41)	6 (27)	9 (41)	17 (77)	22 (100)	22 (100)	22 (100)
Bertrand (2014)[4]	-	-	-	-	32 (71)	-	-	-	-	-
Calafiore (2009)	51	5,5	63,9	9 (18)	51 (100)	20 (39)	-	51 (100)	0 (0)	51 (100)
Calafiore (2011)[4]	-	-	-	-	-	-	-	-	-	-
Cao (2014)	135	-	42,2	75 (56)	-	-	-	135 (100)	135 (100)	135 (100)
Chan (2009)	125	6,8	64,3	93 (74)	-	76 (61)	80 (64)	125 (100)	85 (68)	125 (100)
Chang (2008)	334	3,5	52,7	87 (26)	295 (88)	298 (89)	299 (90)	334 (100)	0 (0)	334 (100)
Chen (2016)	137	2,1	61,0	96 (70)	137 (100)	113 (82)	55 (40)	137 (100)	-	132 (96)
Chikwe (2015)	419	3,7	59,2	143 (34)	72 (17)	95 (23)	-	419 (100)	419 (100)	419 (100)
Choi (2017)	72	6,5	54,5	46 (64)	0 (0)	57 (79)	27 (38)	72 (100)	72 (100)	72 (100)
Choi (2016)[4]	-	-	-	-	40 (100)	-	-	-	-	-
De Bonis (2012)	140	1,8	63,8	60 (43)	134 (96)	73 (52)	71 (51)	140 (100)	140 (100)	138 (99)
De Meester (2015)	37	5,0	70,0	27 (73)	-	25 (68)	-	37 (100)	16 (43)	37 (100)
Di Mauro (2017)	541	-	54,1	303 (56)	-	-	-	-	-	541 (100)
Dreyfus (2005)	148	4,8	58,5	60 (41)	18 (12)	47,952 (32)	-	148 (100)	144 (97)	148 (100)
Filsoufi (2006)[5]	-	-	-	-	-	-	-	-	-	-
Fujita (2013)	67	-	62,7	36 (54)	52 (78)	53 (79)	19 (28)	67 (100)	67 (100)	58 (87)
Fukuda (2007)	136	3,5	65,0	83 (61)	123 (90)	36 (26)	-	136 (100)	136 (100)	61 (45)
Fukunaga (2015)	220	4,4	65,4	-	124 (56)	147 (67)	61 (28)	220 (100)	220 (100)	220 (100)

Supplementary Table 2: Baseline characteristics of individual studies (continued)

Author (year)	N	Follow-Up (years)	Age	Female (n,%)	≥moderate TR (n,%)	AF (n,%)	NYHA III-IV (n,%)	TV repair	TV ring repair	MV procedure
Gatti (2016)	527	5,2	69,6	279 (53)	325 (68)	169 (32)	337 (64)	527 (100)	449 (85)	488 (93)
Gatti (2016) [6]	-	-	-	-	-	-	-	-	-	-
Ghanta (2007)	237	3,0	67,0	126 (53)	227 (96)	-	125 (53)	237 (100)	80 (34)	195 (82)
Giamberti (2011)	65	5,3	46,0	24 (37)	65 (100)	-	42 (65)	62 (95)	14 (23)	11 (17)
Goncu (2015) [4]	-	-	-	-	64 (100)	-	-	-	-	-
Gosev (2015)	60	4,5	67,4	31 (52)	60 (100)	-	12 (20)	-	-	45 (75)
Hata (2017)	684	2,3	65,6	404 (59)	492 (72)	524 (77)	420 (61)	684 (100)	372 (54)	609 (89)
He (2012)	39	-	49,8	28 (72)	39 (100)	-	9 (23)	39 (100)	0 (0)	39 (100)
Hou (2017)	85	2,7	52,1	38 (45)	-	18 (21)	-	85 (100)	40 (47)	85 (100)
Huang (2013)	237	6,5	61,3	85 (36)	177 (75)	86 (36)	185 (78)	237 (100)	0 (0)	212 (89)
Huang (2014) [1]	232	7,4	64,2	-	227 (98)	208 (90)	208 (90)	232 (100)	232 (100)	232 (100)
Hwang (2014) [2]	67	6,9	57,0	48 (72)	-	62 (93)	22 (33)	0 (0)	-	14 (21)
Isomura (2015)	76	3,9	68,0	46 (61)	73 (96)	53 (70)	49 (64)	76 (100)	76 (100)	64 (84)
Ito (2017)	98	3,4		52 (53)	41 (42)	76 (78)	42 (43)	98 (100)	98 (100)	87 (89)
Izutani (2010)	117	2,0	72,5	71 (61)	111 (95)	89 (76)	-	117 (100)	117 (100)	102 (87)
Jeong (2010) [10]	-	-	-	-	-	-	35 (34)	-	-	84 (82)
Jeong (2017)	123	7,3	53,7	75 (61)	-	95 (77)	-	123 (100)	74 (60)	-
Jouan (2016)	88	3,0	60,7	41 (47)	28 (32)	35,991 (41)	-	88 (100)	88 (100)	88 (100)
Jung (2010)	219	3,0	54,2	154 (70)	216 (99)	180 (82)	108 (49)	219 (100)	219 (100)	198 (90)
Kara (2013)	93	2,1	54,3	50 (54)	-	55 (59)	81 (87)	93 (100)	34 (37)	93 (100)
Kawaura (2015) [1]	56	-	67,6	28 (50)	56 (100)	40 (71)	9 (16)	56 (100)	56 (100)	56 (100)
Khallaf (2016) [3]	62	1,0	33,0	39 (63)	-	-	-	62 (100)	0 (0)	62 (100)
Koppers (2013)	89	1,3	69,0	47 (53)	-	-	-	89 (100)	89 (100)	89 (100)
Kunova (2015)	43	4,6	-	26 (60)	34 (79)	36 (84)	31 (72)	43 (100)	0 (0)	36 (84)

Supplementary Table 2: Baseline characteristics of individual studies (continued)

Author (year)	N	Follow-Up (years)	Age	Female (n,%)	≥moderate TR (n,%)	AF (n,%)	NYHA III-IV (n,%)	TV repair	TV ring repair	MV procedure
Lee (2016)	91	7,6	49,0	51 (56)	-	72 (79)	23 (25)	91 (100)	60 (66)	-
Lin (2012)	45	6,8	49,0	33 (73)	45 (100)	40 (89)	45 (100)	11 (24)	0 (0)	-
Lin (2014)	399	3,3	46,4	211 (53)	391 (98)	184 (46)	254 (64)	399 (100)	157 (39)	394 (99)
Maghami (2016)	216	2,8	69,0	150 (69)	216 (100)	104 (48)	93 (43)	216 (100)	216 (100)	198 (92)
Masherbauer (2013)	46	5,2	-	-	-	-	-	-	-	193 (420)
Meng (2015)	69	1,7	51,7	-	45 (65)	69 (100)	-	69 (100)	40 (58)	-
Muller (2011)	25	-	-	-	-	-	-	25 (100)	-	25 (100)
Murashita (2014) [3]	42	9,1	64,0	24 (57)	25 (60)	36 (86)	29 (69)	42 (100)	0 (0)	42 (100)
Naqshband (2010)	83	5,1	27,0	43 (52)	83 (100)	52 (63)	23 (28)	83 (100)	0 (0)	83 (100)
Navia (2012) [9]	91	3,0	69,0	51 (56)	91 (100)	34 (37)	32 (35)	91 (100)	64 (70)	84 (92)
Navia (2010) [7]	2277	-	68,0	1376 (60)	2116 (96)	1549 (68)	1133 (50)	2277 (100)	1856 (82)	2097 (92)
Patel (2016)	25	1,0	40,0	11 (44)	10 (40)	12 (48)	20 (80)	25 (100)	25 (100)	25 (100)
Pettinari (2016)	260	2,1	68,0	119 (46)	-	97 (37)	133 (51)	-	-	235 (90)
pfanmuller (2013)	441	3,4	68,7	257 (58)	-	287 (65)	-	441 (100)	419 (95)	441 (100)
Pfannmüller (2012) [6]	-	-	-	-	-	-	-	-	-	-
Pradhan (2011) [8]	23	0,3	25,1	14 (61)	-	11 (48)	21 (91)	23 (100)	0 (0)	23 (100)
Ratschiller (2015)	415	2,0	70,1	195 (47)	400 (96)	285 (69)	318 (77)	415 (100)	415 (100)	319 (77)
Ren (2015)	74	2,8	48,4	63 (85)	52 (70)	-	71 (96)	74 (100)	40 (54)	74 (100)
Rhashwan (2017)	50	2,2	42,6	38 (76)	48 (96)	23 (46)	24 (48)	50 (100)	50 (100)	50 (100)
Risteski (2016)	37	4,8	67,0	9 (24)	25 (68)	12 (32)	-	37 (100)	-	37 (100)
Ro (2013)	431	5,4	53,3	279 (65)	281 (65)	303 (70)	-	431 (100)	-	431 (100)
Roshanali (2010)	210	-	55,4	133 (63)	-	151 (72)	-	210 (100)	105 (50)	185 (88)
Sharma (2016) [7]	117	-	-	-	-	-	-	117 (100)	-	117 (100)
Shi (2012)	70	6,6	61,2	15 (21)	12 (17)	27 (39)	-	70 (100)	0 (0)	70 (100)

Supplementary Table 2: Baseline characteristics of individual studies (continued)

Author (year)	N	Follow-Up (years)	Age	Female (n,%)	≥moderate TR (n,%)	AF (n,%)	NYHA III-IV (n,%)	TV repair	TV ring repair	MV procedure
Shinn (2016)	296	7,4	71,0	188 (64)	-	174 (59)	224 (76)	296 (100)	148 (50)	296 (100)
Šmíd (2010)	45	0,3	71,3	27 (60)	-	-	-	45 (100)	45 (100)	45 (100)
Song (2016)	50	2,0	46,6	25 (50)	0 (0)	-	41 (82)	50 (100)	-	50 (100)
Sorabella (2015)	272	3,1	70,3	165 (61)	-	172 (63)	-	272 (100)	250 (92)	236 (87)
Takano (2016)	52	11,7	61,9	33 (63)	25 (48)	30 (58)	-	52 (100)	52 (100)	52 (100)
Teman (2014)	63	2,3	65,4	45 (71)	-	-	-	57 (90)	57 (100)	63 (100)
Toporcer (2017)	54	-	58,9	24 (44)	-	-	-	54 (100)	-	54 (100)
Utsunomiya (2017)	97	-	66,0	56 (58)	97 (100)	-	-	97 (100)	97 (100)	65 (67)
Verdonk (2017)	165	-	61,0	105 (64)	86 (52)	89 (54)	132 (80)	165 (100)	165 (100)	165 (100)
Wang (2016)	106	2,9	57,1	56 (53)	106 (100)	-	91 (86)	106 (100)	106 (100)	106 (100)
Wang (2013)	60	2,6	45,3	31 (52)	55 (92)	-	48 (80)	60 (100)	0 (0)	53 (88)
Yeates (2014)	22	3,9	65,2	15 (68)	22 (100)	-	10 (45)	22 (100)	-	22 (100)
Yilmaz (2006)	25	1,5	36,3	-	25 (100)	20 (80)	-	25 (100)	0 (0)	-
Yoda (2011)	136	1,5	64,7	56 (41)	101 (74)	-	-	136 (100)	136 (100)	115 (85)
Zientara (2015)	22	-	67,0	12 (55)	22 (100)	15 (68)	-	22 (100)	22 (100)	22 (100)

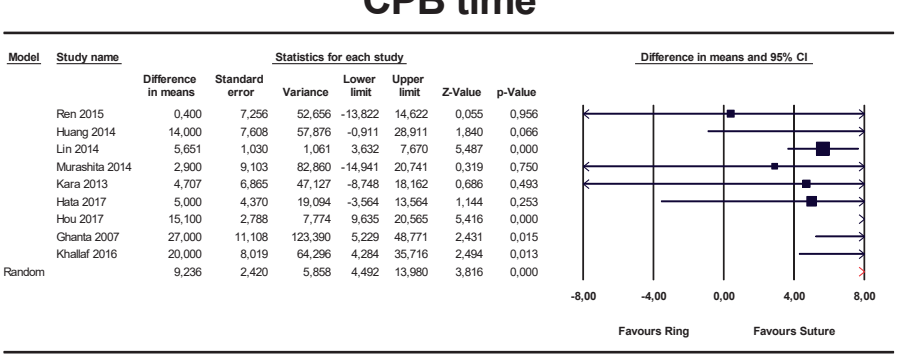
1 Only ring cohort extracted
2 Only replacement cohort extracted
3 Only suture subgroup extracted
4 Only echocardiographic data extracted
5 Only KM curve extracted
6 Only included in flexibe vs rigid ring subgroup analyses
7 Only hospital mort extraxted
8 Other outcomes than hosp mort extracted
9 Other outcomes than hosp mort extracted and late outcomes extracted
10 Only outcomes not in Jeong (2017)

Supplementary Table 3: Meta-regression estimates

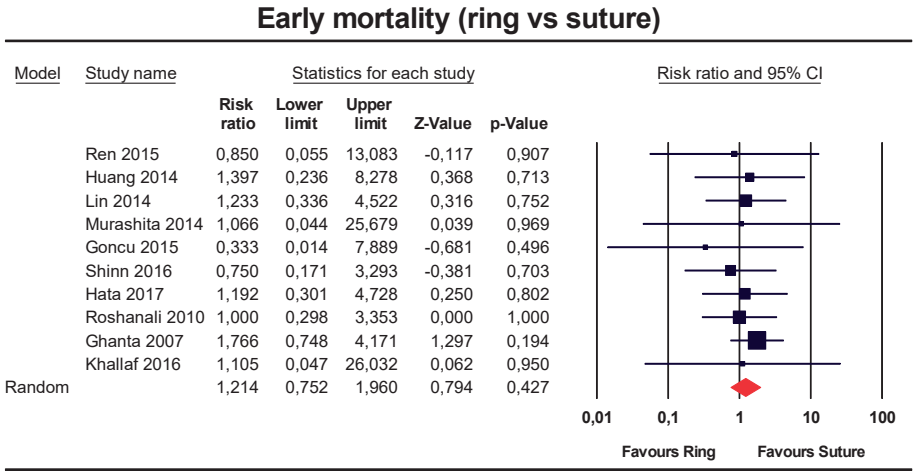
Covariate	Outcome measure		
	Early mortality (OR [95% CI], p value)	Overall late mortality (HR [95% CI], p value)	TR at discharge
Age	1.01 (1 to 1.01) p <0.001	1.62 (1.25 to 2.12) p<0.001	0.9 (0.7 to 1.14) p= 0.376
Female	1 (0.85 to 1.19) p= 0.962	1.08 (0.87 to 1.35) p= 0.48	1.21 (0.9 to 1.62) p= 0.214
NYHA III-IV	0.95 (0.84 to 1.07) p= 0.446	1.06 (0.9 to 1.25) p= 0.512	0.99 (0.83 to 1.19) p= 0.916
Mean cohort	1.01 (1 to 1.02) p= 0.172	1.42 (0.67 to 3) p= 0.360	0.99 (0.99 to 1) p= 0.095
Mean CPB	1.05 (1 to 1.12) p= 0.053	1.11 (1.01 to 1.2) p= 0.024	0.97 (0.9 to 1.06) p= 0.54
Mean ACC	1.06 (0.99 to 1.15) p= 0.083	1.17 (1.04 to 1.31) p= 0.01	0.96 (0.86 to 1.07) p= 0.476
Mean LVEF	0.99 (0.72 to 1.35) p= 0.942	0.70 (0.49 to 1.01) p= 0.058	1.17 (0.82 to 1.67) p= 0.386
Prior cardiac surgery	1.07 (0.97 to 1.19) p= 0.195	1.15 (0.76 to 1.75) p= 0.511	0.9 (0.7 to 1.15) p= 0.387
AF	0.94 (0.84 to 1.06) p= 0.362	0.88 (0.73 to 1.05) p= 0.154	1 (0.84 to 1.2) p= 0.969
Diabetes	1.34 (0.91 to 1.97) p= 0.136	0.76 (0.38 to 1.49) p= 0.418	2.69 (1.16 to 6.23) p= 0.02
MV procedure	0.94 (0.82 to 1.07) p= 0.345	1.12 (0.84 to 1.48) p= 0.438	1.01 (0.81 to 1.25) p= 0.953
AV procedure	1.16 (1.04 to 1.3) p= 0.006	1.15 (0.95 to 1.38) p= 0.158	0.92 (0.73 to 1.15) p= 0.479
CABG	1.26 (1.09 to 1.43) p<0.001	1.54 (1.23 to 1.92) p< 0.001	0.97 (0.79 to 1.19) p= 0.777
%moderate/severe TR at baseline	1.01 (0.92 to 1.11) p= 0.835	1.02 (0.89 to 1.17) p= 0.776	1.28 (1.15 to 1.43) p= <0.001
TV repair (vs replacement)	0.98 (0.91 to 1.05) p= 0.555	0.94 (0.84 to 1.05) p= 0.254	1.02 (0.9 to 1.16) p= 0.717
TV ring repair (vs suture)	1.03 (0.98 to 1.08) p= 0.209	1.00 (0.93 to 1.08) p= 0.912	0.99 (0.91 to 1.06) p= 0.756

Supplementary Table 4: Outcomes after Sensitivity analyses in which studies with sample size below 25th quantile are excluded

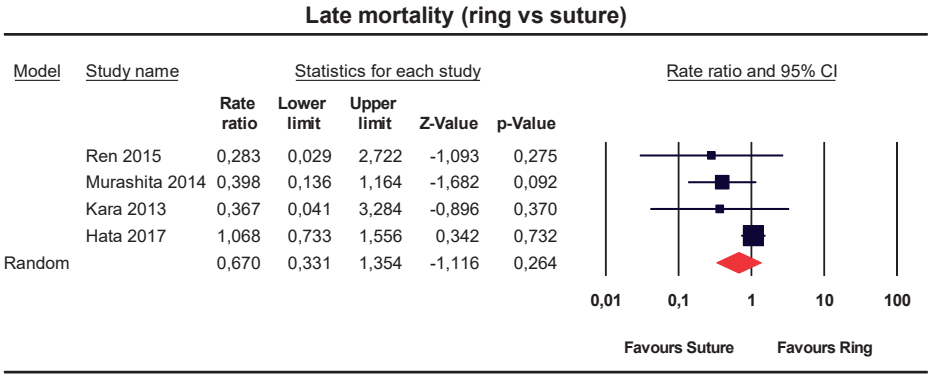
Outcomes	Pooled estimate (95% CI)	Heterogeneity	N studies reported
	Early outcome (%)		
Early mortality	3.8 (3.1 to 4.6)	I^2 = 68.9	62
30-day mortality*	3.9 (3.0 to 5.2)	I^2 = 73.2	33
Early pacemaker implantation	3.3 (2.1 to 5.2)	I^2 = 86.3	21
AKI	4.8 (3.5 to 6.6)	I^2 = 88.4	21
LCOS	6.9 (5.0 to 9.6)	I^2 = 77.4	14
Early reopening	5.4 (4.3 to 7.0)	I^2 = 89.7	27
Early moderate-to-severe TR	7.5 (5.5 to 10.3)	I^2 =90.5	26
	Late outcome (%/y)		
All-cause mortality	2.4 (1.7 to 3.3)	I^2 = 94.4	34
Cardiac mortality	1.1 (0.7 to 1.8)	I^2 = 91.4	24
Valve related mortality	0.6 (0.4 to 0.8)	I^2 = 27.7	20
Late pacemaker implantation	0.8 (0.5 to 1.5)	I^2 = 39.6	5
Late admission HF	1.7 (0.8 to 3.7)	I^2 = 89.0	8
Late reintervention[1]	0.3 (0.2 to 0.4)	I^2 = 30.3	26
Overall TR**	2.8 (1.9 to 4.0)	I^2 = 90.8	20
Late TR	1.6 (1.0 to 2.5)	I^2 = 89.7	15



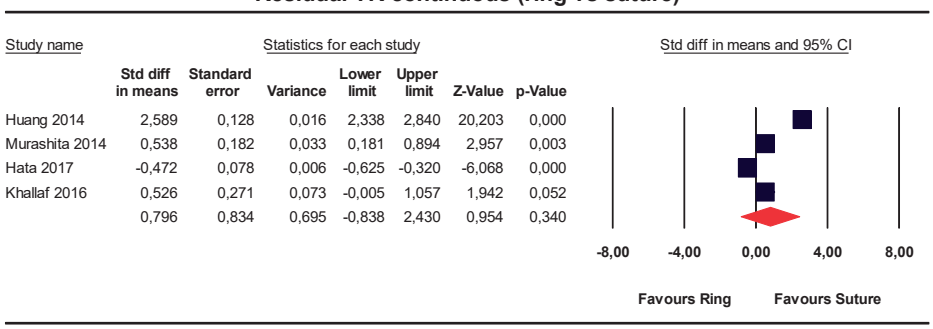
Supplementary figure 1: Cardiopulmonary bypass time suture vs ring repair



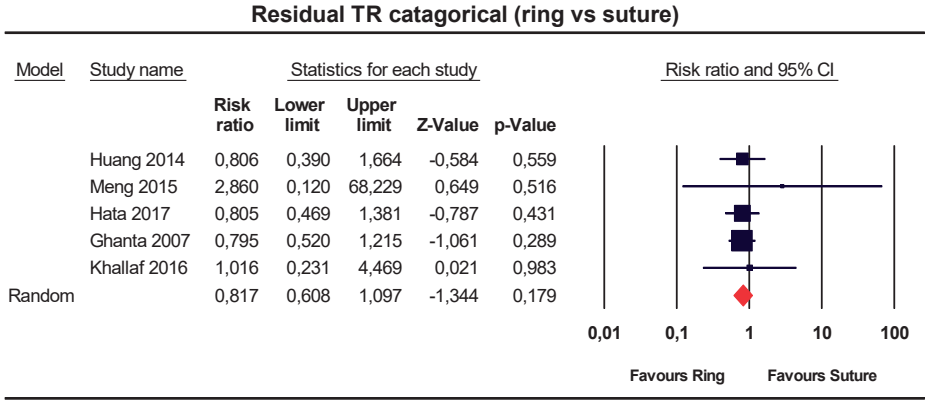
Supplementary figure 2: Early mortality, suture vs ring repair



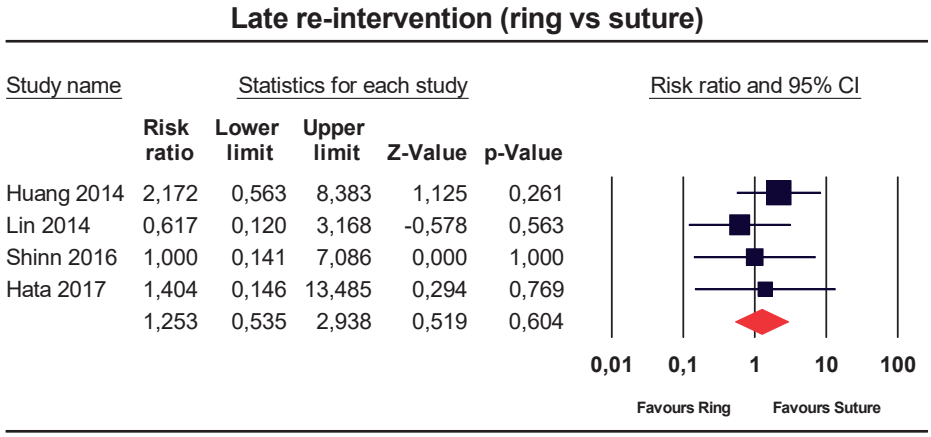
Supplementary figure 3: Late mortality, suture vs ring



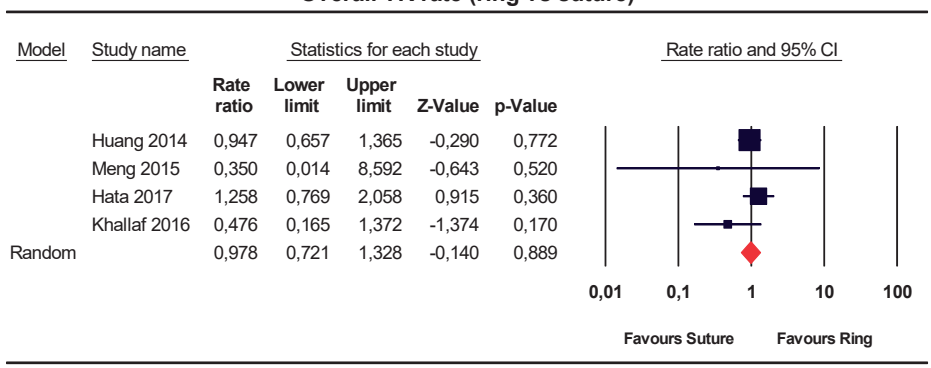
Supplementary figure 4: Residual TR (as continuous variable) suture vs ring



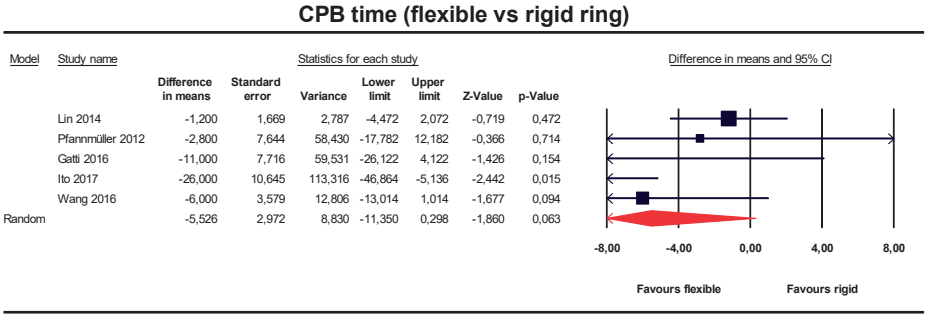
Supplementary figure 5: Residual TR moderate-to-severe (as categorical variable), suture vs ring



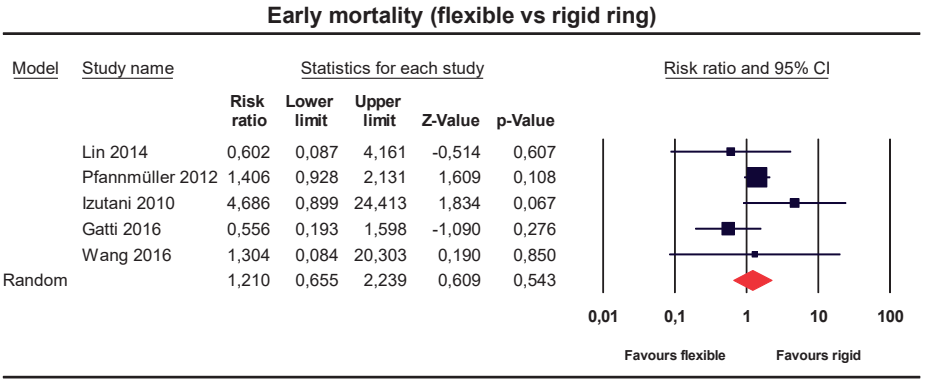
Supplementary figure 6: Late reintervention rate, suture vs ring



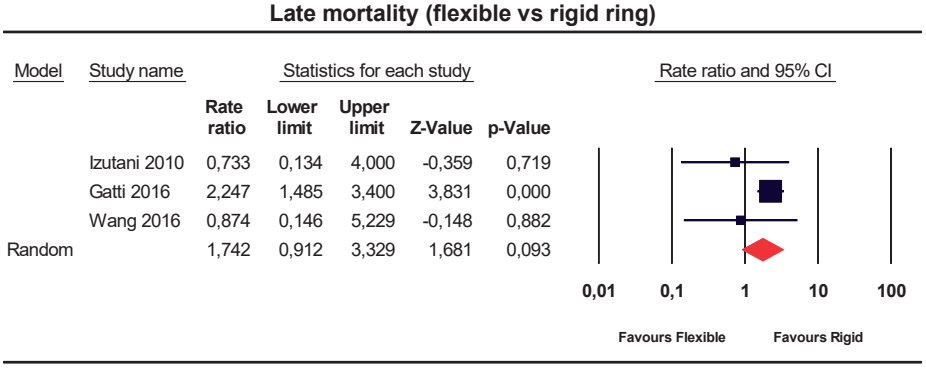
Supplementary figure 7: Overall TR rate, suture vs ring



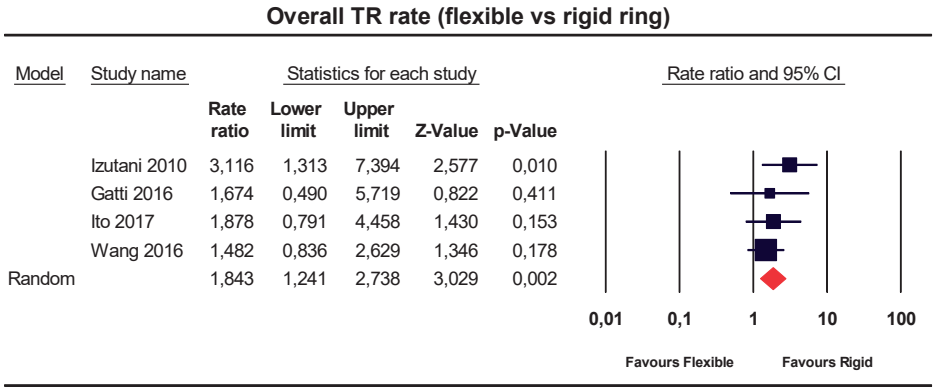
Supplementary figure 8: Cardiopulmonary bypass time, flexible vs rigid



Supplementary figure 9: Early mortality, flexible vs rigid ring



Supplementary figure 10: Late mortality, flexible vs rigid ring



Supplementary figure 11: Overall TR rate, flexible vs rigid ring

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4

Male–female differences in characteristics and early outcomes of patients undergoing tricuspid valve surgery: a national cohort study in the Netherlands

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ABSTRACT

Objectives

This study aims to explore male–female differences in baseline and procedural characteristics, and outcomes of patients undergoing isolated or concomitant tricuspid valve (TV) surgery.

Methods

All TV procedures registered between 2007 and 2016 in the database of the Netherlands Association for Cardio-Thoracic Surgery were analysed. Logistic regression analyses with interaction terms were used to determine whether sex was associated with hospital mortality.

Results

Five thousand five hundred and eighty-two patients underwent TV surgery [isolated: *N* = 685 (49% male), TV_{repair}: *N* = 5286 (50% male) and $TV_{replacement}$: *N* = 250 (46% male)]. In the TV_{repair} group, females were significantly older, had less prior percutaneous/surgical coronary interventions, less extracardiac arteriopathies, a lower prevalence of renal impairment, less endocarditis, a lower prevalence of preoperative critical condition, less recent myocardial infarction, less concomitant coronary artery bypass grafting (CABG) and, in case of concomitant mitral valve surgery, less concomitant mitral valve repair compared to males. In the $TV_{replacement}$ group, females more often had a history of prior valve surgery and less prior CABG. Hospital mortality for males and females was 7.0% (*N* = 183) and 6.1% (*N* = 163), *P* = 0.241 in the TV_{repair} group and 2.6% (*N* = 3) and 8.8% (*N* = 12), *P* = 0.074 in the $TV_{replacement}$ group. Sex was not associated with hospital mortality (odds ratio (OR) 1.14, 95% confidence interval (CI) 0.88–1.48; *P* = 0.322). Sex demonstrated a significant interaction with the parameter 'critical preoperative condition' (OR 0.44, 95% CI 0.22–0.90; *P* = 0.026).

Conclusions

Substantial differences in patient and procedural characteristics existed between male and female patients undergoing TV surgery, although sex was not a derterminant for hospital mortality. Nevertheless, sex interacted with a critical preoperative condition, indicating the usefulness of separate risk factor models for males and females requiring TV surgery.

Keywords

Tricuspid valve surgery • Sex differences

INTRODUCTION

Male–female differences in cardiac diseases are being increasingly recognized and incorporated in risk models [1]. Outcomes for female patients have been reported to be less favourable than those for male patients, especially regarding in-hospital mortality [2–4]. Most reported series have focused on male–female specific outcomes after coronary artery bypass grafting (CABG) or mitral valve surgery [2, 3, 5] and data on male–female specific outcomes after tricuspid valve (TV) surgery remain scarce. TV regurgitation is reported to be more prevalent in women [6] and, overall, TV surgery, especially TV replacement is predominantly performed in females [7, 8]. Elucidating sex differences and identifying sexspecific risk factors in patients undergoing TV surgery could lead to better insight in disease presentation, treatment differences and outcomes. Hence, we aimed to study male–female differences in baseline and procedural characteristics, and outcomes after TV surgery using data from a Dutch nationwide prospective database. Given the relationship between aetiology and choice of surgery (repair versus replacement), both groups were analysed separately. In addition, patients undergoing isolated TV surgery were analysed separately. The performance of logistic EuroSCORE I was tested in all the subgroups. It was investigated whether sex-specific risk models are necessary. Furthermore, it was investigated whether sex is associated with the probability of undergoing TV repair versus TV replacement, and undergoing isolated TV surgery versus multiple valve surgery.

METHODS

Data source

The national database of the Netherlands Association for Cardio- Thoracic Surgery is a prospective database that contains anonymized patient data on baseline a procedural characteristics, risk factors and outcomes. Risk factors were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE I) model [9]. Specifically, a critical preoperative condition was defined as: ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/h) [9]. A detailed description of the database has been published previously [10]. Approval from the data registry committee of Netherlands Association for Cardio-Thoracic Surgery was obtained to analyse this dataset.

In total, 15 466 procedures involving a heart valve were registered in the Netherlands from 1 January 2007 to 31 December 2016, of which 5582 were isolated or concomitant TV repair or replacement. The type of TV surgery was not known in 46 patients, who were omitted in the analyses of the TV repair and replacement subgroups.

Missing values

The national database of the Netherlands Association for Cardio- Thoracic Surgery has an exceptionally high degree of completeness in regards to most variables. However, missing data were not clustered and the exclusion of incomplete cases would significantly reduce the dataset. Therefore, multiple imputation by chained equations was performed to impute missing values. Five imputed datasets were generated using this method using 5 iterations each. All baseline variables were imputed, except for atrium septum defect and left ventricular function, since >30% of the data was missing. Imputation was done based on the other baseline variables. The imputations were visually checked by strip plots and density plots. The imputed datasets were used for the logistic regression models and to test the performance of EuroSCORE I.

Statistical analyses

Variables were presented as mean ± standard deviation (Gaussian) and as median [interquartile range (IQR)] (non- Gaussian). Categorical data was presented as percentages. Normality was tested using the Shapiro–Wilk test. Comparisons were made with the Student's t-test or Mann–Whitney test, as appropriate. Categorical data were compared with the χ^2 test or Fisher's exact test, as appropriate. A *P*-value of <0.05 was considered statistically significant. Both univariable and multivariable logistic regressions were used to explore determinants of hospital mortality, TV replacement (versus repair) and isolated TV surgery (versus multiple valve surgery). Included variables are shown in Supplementary Material, Table S1. Two modelling strategies were applied for hospital mortality. Firstly, a risk factor modelling approach was applied, forcing all variables in a multivariable model, regardless of significance. Interaction terms of sex and other variables were explored and significant interaction terms were incorporated in the multivariable model. Secondly, modelling hospital mortality in the males and females separately, an approach using forwards and backwards elimination was applied (Supplementary Material, Fig. S1), in order to obtain most important determinants in these populations. The latter was also applied for TV replacement and isolated TV surgery. In addition, in the final multivariable models of TV replacement and isolated TV surgery, it was tested whether sex interacted with the remaining covariates. In case of highly correlated variables, variables with most clinical relevance were entered the multivariable model. Correlation was tested with the Pearson or the Spearman method, as appropriate. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Linearity of continuous variables in the logit was checked using fractional polynomials. Model discrimination was assessed with area under the curve and model calibration was tested using the Hosmer–Lemeshow test (10 categories). Performance of EuroSCORE I was tested in the same manner. Statistical analyses were done in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.3.3) with the use of the 'glm', 'MICE' and 'mfp' package.

RESULTS

Isolated tricuspid valve surgery

In total, 685 patients underwent isolated TV surgery. Table 1 presents baseline characteristics of patients undergoing isolated TV surgery. The type of TV surgery was comparable between males and females (replacement: 21.6% in females and 18.9% in males, *P* = 0.434). In case of a valve replacement, valve type was comparable between males and females (biological valve: 54.8% in females vs 47.6% in males, *P* = 0.507). Male patients underwent concomitant CABG more frequently (21.8%, *N* = 74) compared to female patients (11.8%, *N* = 41, *P* < 0.001).

Hospital mortality was 5.8% (*N* = 20) in females and 7.1% (*N* = 24) in males (*P* = 0.591). Hospital stay was longer in males compared to females (10.5 days, IQR 7.00–24.75 vs 8 days, IQR 6.00–16.00; *P* = 0.011).

Tricuspid valve repair

TV repair was performed in the majority of patients (*N* = 5286), of whom 50.3% were female and 49.7% male (*P* = 0.66). Baseline characteristics are presented in Table 1 and procedural characteristics in Table 2.

Hospital mortality in males and females was 7.0% (*N* = 183) and 6.1% (*N* = 163) *P* = 0.241, respectively. In approximately half the population, hospital stay was reported, which did not differ between males and females (median 8 days, IQR 6–14 vs median 8 days, IQR 6–13; *P* = 0.367). Comparable hospital mortality was found in the different age groups (Fig. 1), which was also true for the subgroups TV repair and replacement.

Tricuspid valve replacement

TV replacement was performed in the minority of patients (*N* = 250), of whom 45.6% were male and 54.4% female. Female patients underwent more prior valve surgery of one or more heart valves (Table 1). Data specifying which valve had been previously operated on were not collected uniformly (222 missing of 250 patients). No differences in procedural characteristics were found, except for CABG, which was performed more frequently in males (Table 2). Valve type (biological versus mechanical) was comparable between sexes (*P* = 0.513).

Hospital mortality in males and females was 2.6% (*N* = 3) and 8.8% (*N* = 12) (*P* = 0.074). Median hospital stay was comparable (females 10, IQR 7–19 days vs males 12.5, IQR 7–21 days; *P* = 0.329).

Table 1: Patient characteristics of males and females undergoing tricuspid valve repair or replacement

		Isolated TVS			TV repair			TV replacement		
Characteristics	**Entire cohort**	**Male**	**Female**	***P*-value**	**Male**	**Female**	**P-value**	**Male**	**Female**	***P*-value**
N	5582	339	346		2627	2659		114	136	
Age (years), median (IQR)	70 (61–75)	62 (49–71)	63 (49–71)	0.675	69 (61–75)	71 (63–76)	<0.001	59.5 (46–68)	59.5 (48–69.25)	0.85
Prior PCI, *n* (%)	287 (6.9)	27 (11.1)	7 (3.3)	0.003	177 (9.0)	100 (5.0)	<0.001	2 (2.3)	5 (5.3)	0.446
Prior CABG, *n* (%)	275 (5.4)	31 (10.2)	13 (4.5)	0.012	163 (6.7)	100 (4.2)	<0.001	7 (6.9)	3 (2.5)	0.192
Prior valve surgery, *n* (%)	576 (11.3)	49 (16.1)	57 (19.5)	0.319	237 (9.8)	263 (10.9)	0.208	24 (23.5)	48 (39.7)	0.015
Prior aortic surgery, *n* (%)	42 (0.9)	3 (1.0)	3 (1.1)	1.000	23 (1.0)	16 (0.7)	0.342	1 (1.0)	2 (1.7)	0.999
ASD, *n* (%)	162 (5.4)	28 (13.4)	42 (21.3)	0.048	59 (4.1)	90 (6.5)	0.007	4 (5.3)	6 (6.8)	0.754
Chronic lung disease, *n* (%)	833 (15.0)	33 (9.8)	35 (10.2)	0.949	418 (15.9)	387 (14.6)	0.18	9 (7.9)	14 (10.4)	0.651
Extracardiac arteriopathy, *n* (%)	395 (7.1)	19 (5.6)	12 (3.5)	0.252	233 (8.9)	148 (5.6)	<0.001	7 (6.1)	4 (3.0)	0.354
Neurological dysfunction, *n* (%)	168 (3.0)	6 (1.8)	7 (2.0)	1.000	72 (2.7)	91 (3.4)	0.177	1 (0.9)	4 (3.0)	0.379
Renal impairment, *n* (%)	169 (3.1)	18 (5.4)	6 (1.8)	0.019	108 (4.2)	49 (1.9)	<0.001	4 (3.5)	4 (3.0)	0.999
Endocarditis, *n* (%)	227 (4.1)	35 (10.4)	17 (5.0)	0.012	122 (4.7)	72 (2.7)	<0.001	16 (14)	10 (7.4)	0.135
Critical preoperative condition *n* (%)	268 (4.8)	45 (13.3)	21 (6.1)	0.002	159 (6.1)	93 (3.5)	<0.001	5 (4.4)	8 (5.9)	0.796
Unstable AP, *n* (%)	34 (0.6)	4 (1.2)	7 (2.0)	0.560	18 (0.7)	13 (0.5)	0.45	0 (0.0)	1 (0.7)	0.999
Recent MI, *n* (%)	187 (3.4)	20 (5.9)	12 (3.5)	0.190	114 (4.3)	65 (2.5)	<0.001	1 (0.9)	1 (0.7)	0.999
Pulmonary hypertension, *n* (%)	721 (13.0)	25 (7.4)	17 (5.0)	0.244	334 (12.8)	364 (13.8)	0.299	7 (6.1)	12 (8.9)	0.479
Emergency operation, *n* (%)	109 (2.0)	14 (4.1)	18 (5.2)	0.617	46 (1.8)	48 (1.8)	0.966	5 (4.4)	4 (3.0)	0.736

Percentages excluded missing cases.

AP: angina pectoris; ASD: atrium septum defect; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention; TVS: tricuspid valve surgery.

Table 2: Procedural characteristics of males and females undergoing tricuspid valve repair or replacement

		TV repair			TV replacement		
Characteristics	**Entire cohort, *n* (%)**	**Male, *n* (%)**	**Female, *n* (%)**	***P*-value**	**Male, *n* (%)**	**Female, *n* (%)**	**P-value**
N	5582	2627	2659		114	136	
CABG	1399 (25.1)	851 (32.4)	514 (19.3)	<0.001	12 (10.5)	5 (3.7)	0.043
Arterial graft/venous graft	652 (46.7)	436 (51.3)	204 (39.8)	<0.001	3 (25.0)	2 (40.0)	0.783
Arterial graft	373 (26.6)	213 (23.6)	155 (30.2)		7 (58.3)	2 (40.0)	
Venous graft	371 (26.7)	201 (25.1)	154 (30.0)		2 (16.7)	1 (20.0)	
Aortic valve surgery	112 (19.9)	514 (19.6)	557 (21.0)	0.219	11 (9.6)	19 (14.0)	0.394
Repair	57 (5.1)	21 (4.1)	33 (5.9)	0.220	2 (18.2)	1 (5.3)	0.537
Replacement	1056 (94.9)	494 (95.9)	524 (94.1)		9 (81.8)	18 (94.7)	
Bio	745 (70.5)	368 (74.4)	361 (68.9)	0.147	3 (33.3)	10 (55.6)	0.420
Mechanical	307 (29.1)	124 (25.2)	161 (30.7)		6 (66.7)	8 (44.4)	
Homograft	4 (0.4)	2 (0.4)	2 (0.4)		0 (0.0)	0	
Mitral valve surgery	4473 (80.1)	2200 (83.7)	2178 (81.9)	0.083	31 (27.2)	33 (24.3)	0.702
Repair	3273 (73.3)	1770 (80.6)	1463 (67.2)	<0.001	14 (45.2)	11 (33.3)	0.476
Replacement	1193 (26.7)	426 (19.4)	713 (32.8)		17 (54.8)	22 (66.7)	
Bio	469 (38.8)	158 (36.2	286 (39.8)	0.241	9 (52.9)	13 (59.1)	0.754
Mechanical	731 (61.2)	273 (63.8)	268 (60.2)		8 (47.1)	9 (40.9)	
Homograft	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pulmonary valve surgery	88 (1.6)	25 (1.0)	31 (1.2)	0.529	13 (11.4)	18 (13.2)	0.806
Repair	7 (4.8)	6 (16.0)	1 (0.0)	0.086	0 (0.0)	0 (0.0)	1
Replacement	80 (95.2)	21 (84.0)	29 (100)		12 (100)	18 (100)	
Bio	20 (25.3)	5 (23.8)	6 (20.7)	0.258	6 (50.0)	3 (17.6)	0.106
Mechanical	22 (27.8)	2 (9.5)	1 (3.4)		6 (50.0)	13 (76.5)	
Homograft	37 (46.8)	14 (66.7)	22 (75.9)		0 (0)	1 (5.9)	

Table 2: Procedural characteristics of males and females undergoing tricuspid valve repair or replacement (continued)

		TV repair			TV replacement		
Tricuspid valve replacement	250 (4.5)	0 (0.0)	0 (0.0)		114 (100)	136 (100)	
Bio	134 (54.0)				58 (51.3)	76 (56.3)	0.513
Mechanical	114 (46.0)				55 (48.7)	59 (43.7)	
Isolated tricuspid valve surgery	12.2 (685)	270 (10.2)	268 (10.1)	0.180	63 (55.2)	74 (54.4)	0.999
Aortic surgery	176 (3.2)	95 (3.6)	75 (2.8)	0.120	0 (0.0)	3 (2.2)	0.253
Rhythm surgery	1464 (26.2)	713 (27.1)	730 (27.1)	0.810	7 (6.1)	7 (6.1)	0.787

Percentages excluded missing cases.

CABG: coronary artery bypass grafting; TV, tricuspid valve.

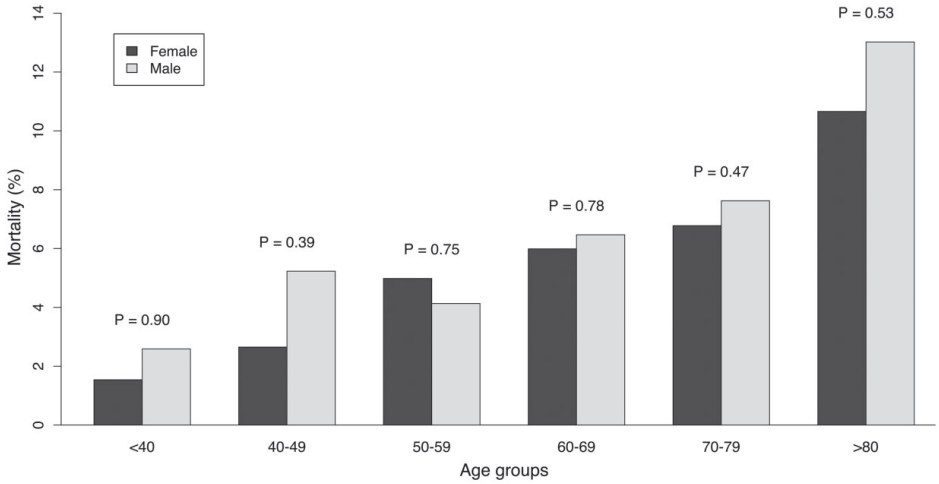

Figure 1: Hospital mortality in males and females of the entire cohort, stratified by age.

Performance of EuroSCORE I

Performance of EuroSCORE I is presented in Table 3. Observed/expected ratio was less than 1 in all groups (Supplementary Material, Tables S2–S7).

Determinants of hospital mortality

Determinants of hospital mortality were only explored in the TV repair subpopulation, because of limited number of events in the TV replacement and isolated TV subgroup (Supplementary Material, Table S8). Sex was not significantly associated with hospital mortality, even when adjusted for possible confounders (OR 1.15, 95% CI 0.88–1.49; *P* = 0.31). However, sex demonstrated a significant interaction with a critical preoperative condition (OR 0.44, 95% CI 0.22–0.90; *P* = 0.026) (Supplementary Material, Table S8). Table 4 presents determinants associated with hospital mortality for male and female patients separately. Age was associated with hospital mortality after TV repair in a linear fashion for females, but not for males. The determinant 'critical preoperative condition' weighted ~2.8 times heavier in females compared to males.

Table 3: Calibration and discrimination of EuroScore I in dif-ferent subgroups

Group	*N*	*P*-value Hosmer–Lemeshow test	AUC (95% CI)
Entire cohort	1517	<0.0001	0.73 (0.67–0.79)
Male	780	0.0001	0.72 (0.64–0.81)
Female	737	<0.0001	0.73 (0.65–0.82)
TV repair	1420	<0.0001	0.73 (0.67–0.79)
Male	736	0.0005	0.72 (0.64–0.81)
Female	684	<0.0001	0.74 (0.62–0.83)

AUC: area under the curve; CI: confidence interval; TV, tricuspid valve.

Table 4: Multivariable models of hospital mortality in the tricuspid valve repair group, stratified by sex

Characteristics	Multivariable male		Multivariable female	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age(FP for males)	1.00 (1.00–1.00)*	<0.001	1.05 (1.03–1.07)	<0.001
Prior CABG	2.08 (1.30–3.35)	0.003		
Chronic lung disease	1.90 (1.31–2.72)	0.001		
Creatinine > 200	3.90 (2.34–6.49)	<0.001	2.32 (1.02–5.26)	0.046
Critical preoperative condition	3.32 (2.10–5.31)	<0.001	9.30 (5.37–16.12)	<0.001
Concomitant CABG	1.90 (1.38–2.64)	<0.001	2.56 (1.79–3.67)	<0.001
AV repair			4.81 (1.67–13.87)	0.004
AV replacement	2.23 (1.60–3.13)	<0.001	2.75 (1.93–3.94)	<0.001
MV replacement	2.29 (1.60–3.29)	<0.001		
Endocarditis			2.94 (1.40–6.23)	0.005
Pulmonary hypertension			1.82 (1.21–2.75)	0.004
Area under curve	0.77 (0.74–0.81)		0.80 (0.76–0.83)	
P-value Hosmer–Lemeshow test	0.08		0.88	

FP male = $(age)^3$. *Due to the FP the estimates are small, resulting in a rounded hazard of 1.00.
AV: aortic valve; CABG: coronary artery bypass grafting; CI: confidence interval; FP, fractional polynomial; MV: mitral valve; OR: odds ratio.

Determinants of tricuspid valve replacement versus tricuspid valve repair

Sex was not a derterminant for the probability of undergoing TV replacement versus TV repair in univariable analyses (OR 0.86, 95% CI 0.67–1.11; *P* = 0.246). Determinants of the probability of undergoing TV replacement are presented in Table 5. The odds of requiring TV replacement increased from young age to midlife and decreased thereafter, with 2 fractional polynomials best describing this relationship. Sex did not interact significantly with the included variables. However, a trend was noted for the interaction between the term 'prior valve surgery' and sex (OR 0.53, 95% CI 0.28–1.01; *P* = 0.062) (Supplementary Material, Table S9).

Determinants of isolated tricuspid valve surgery versus multiple valve surgery

Sex was not a determinant for the probability of undergoing isolated TV surgery (OR 1.00, 95% CI 0.85–1.70; *P* = 0.996). Table 5 presents determinants of undergoing isolated TV surgery. Sex had a significant interaction with the term 'critical preoperative condition' (OR 2.44, 95% CI 1.21–4.90; *P* = 0.012), making it a stronger predictor in males (Supplementary Material, Table S10).

Table 5: Multivariable determinants of the probability of undergoing tricuspid valve replacement versus tricuspid valve repair and isolated tricuspid valve surgery versus multiple valve surgery

Characteristics	OR (95% CI)	*P*-value
Tricuspid valve replacement versus repair		
$Age_{(FP1)}$	0.88 (0.83–0.93)	<0.001
$Age_{(FP2)}$	0.02 (0.01–0.09)	<0.001
Prior valve surgery	2.11 (1.53–2.92)	<0.001
AV replacement	0.38 (0.25–0.6)	<0.001
MV repair	0.06 (0.04–0.09)	<0.001
MV replacement	0.17 (0.12–0.25)	<0.001
PV surgery	2.39 (1.41–4.05)	0.001
Rhythm surgery	0.29 (0.17–0.51)	<0.001
Aortic surgery	0.27 (0.08–0.9)	0.034
Other cardiac surgery	1.78 (1.21–2.62)	0.007
Endocarditis	1.83 (1.13–2.96)	0.014
AUC	0.88 (0.85–0.90)	
P-value Hosmer–Lemeshow	0.86	
Isolated tricuspid valve surgery versus multiple valve surgery		
Age	0.96 (0.95–0.96)	<0.001
TV replacement	7.39 (5.53–9.78)	<0.001
Rhythm surgery	0.57 (0.45–0.73)	<0.001
Critical preoperative condition	1.86 (1.32–2.59)	<0.001
Unstable angina pectoris	3.16 (1.38–7.32)	0.007
Pulmonary hypertension	0.41 (0.29–0.57)	<0.001
Postinfarct VSR	10.91 (3.78–31.5)	<0.002
AUC	0.74 (0.73–0.77)	
P-value Hosmer–Lemeshow	0.66	

$FP1 = \frac{1}{\left(\frac{age}{100}\right)^2}$, $FP2 = age/100$.

AUC: area under curve; AV: aortic valve; CI: confidence interval; MV: mitral valve; OR: odds ratio; PV: pulmonary valve; TV: tricuspid valve; VSR: ventricular septal rupture.

DISCUSSION

Significant male–female differences were found in both patient and procedural characteristics in patients undergoing TV surgery. Early mortality did not differ between males and females, even across the different age groups. Sex was not found to be a predictor of hospital mortality during TV repair. This is contrary to previous studies exploring male–female differences in other procedures [2, 11]. Nevertheless, these results are in agreement with previous studies focusing on isolated TV surgery [12, 13]. In addition, different determinants associated with hospital mortality in males and females were found. Sex interacted with determinants associated with TV replacement versus repair and isolated valve surgery versus multiple valve surgery.

Tricuspid valve repair

In TV repair surgery in the Netherlands, female patients presented at an older age, while male patients presented with more comorbidities. In case of concomitant mitral valve surgery, females received mitral valve replacement more often. This is in line with our previous study on isolated mitral valve surgery [5]. Unfortunately, the registry did not contain data on the aetiology of the valve disease. However, concomitant mitral and aortic valve surgery was performed frequently in this cohort and a recent systematic review found that in 85% of TV repair cases, the underlying aetiology was functional regurgitation [8]. In this respect, 2 other observations are interesting: in the general population, TV regurgitation is more prevalent in females [6] and female patients more frequently undergo TV interventions during mitral valve surgery [7]. These data raise 2 interesting questions: is it possible that female patients are more prone to TV regurgitation and does this occur earlier in the natural history of the disease compared to males? It has been reported that tricuspid annular circumference corrected for heart weight is larger in females compared to males and that the tricuspid annulus of females had a lesser degree of annular cellularity, which may lead to TR faster [14]. Furthermore, if females are more prone to TR, uncorrected TV regurgitation during left-sided valve surgery may be more progressive in females. Controversy exists as to whether sex is an independent predictor for progressive tricuspid regurgitation after left-sided valve surgery. Several studies found it to be predictive [15, 16], while others did not [17, 18]. Another explanation might be that confounding factors associated with TR, such as atrium septum defect with enlarged right atrium or atrial fibrillation [19], are more prevalent in females. This also seems to be partly the case in the cohort described by Vassileva et al. [7] analysing Medicare data, in which females underwent concomitant TV surgery more frequently, but also had a higher prevalence of atrial fibrillation. Further research on this topic is warranted, because if functional TR has a sex-dependent component, this may have major implications on the choice of whether or not to perform concomitant TV surgery.

Tricuspid valve replacement

TV replacement is performed rarely in the Netherlands. Contrary to the previous literature, TV replacement is approximately equally divided between males and females (46% males vs 54% females) [8]. Females undergoing TV replacement more frequently had prior heart valve surgery. These results match prior reported series in which the majority of patients undergoing TV operation after previous left-sided or TV surgery were females [20, 21]. Leviner et al. [22] noted that females undergoing TV replacement tended to have more previous surgery (P = 0.08) and were older (P = 0.04). Additionally, sex was not a predictor of late mortality in their cohort.

Isolated tricuspid valve surgery

Not surprisingly, length of hospital stay was longer in male patients because they were in a worse preoperative condition and underwent more concomitant CABG. Chandrashekar et al. [13] did not observe differences in length of stay between males and females when analysing the National Inpatient Sample database of the USA. However, they excluded patients with concomitant non-CABG surgery or endocarditis, which have been shown to be associated with longer hospital stay [23]. In this cohort, male patients had endocarditis more frequently (P = 0.012).

Determinants of hospital mortality after tricuspid valve repair

Sex was not a predictor of hospital mortality after TV repair, but mortality was, among others, associated with renal impairment, concomitant CABG and aortic valve replacement and a critical preoperative condition. Interestingly, while using the same modelling strategy, modelling of determinants of hospital mortality for males and females separately resulted in different models. This may indicate that some determinants were more predictive in either males or females. In this regard, sex-specific predictive models may be needed. Discrimination of EuroSCORE I was comparable between males and females and EuroSCORE I uniformly overpredicted mortality in this population. However, calibration was relatively better in males. Our group has previously shown that EuroSCORE I predicted hospital mortality relatively better in male patients undergoing isolated mitral valve surgery, both in terms of accuracy and calibration [5]. Furthermore, Massoudy et al. [24] showed that sex-specific weighting was needed to improve the predictability of EuroSCORE I in females. These findings support the need for sexspecific risk prediction models since some determinants have a more considerable impact on patient outcome based on sex.

Determinants of tricuspid valve replacement and isolated tricuspid valve surgery

The predictors associated with a higher chance of undergoing TV replacement rather than repair were endocarditis, other cardiac surgery and prior valve surgery, indicating that TV replacement was performed in case of structural valve damage or prior valve surgery. Additionally, pulmonary valve surgery was associated with TV replacement. In this case, the underlying aetiology may be carcinoid heart valve disease, because both pulmonary and TV are often affected simultaneously in patients with carcinoid heart valve disease [25]. Factors associated with a lower chance of undergoing TV replacement were concomitant mitral valve surgery, aortic valve surgery and aortic surgery, indicating that, in these patients, TV disease was secondary to left-sided valve disease and, therefore, functional in nature, for which a replacement of the valve was not necessary. Interestingly, a trend was found of sex interacting with prior valve surgery. Specifically, in females, prior valve surgery was more associated with TV replacement than in males, matching the observations by Leviner et al. [22]. In line with the reasoning above, this

may indicate that females are more prone for recurrent tricuspid regurgitation. However, since it was not known which valve had been previously operated on, this could not be confirmed.

A critical preoperative condition and TV replacement were associated with a higher probability of undergoing isolated TV surgery, suggesting that isolated TV surgery was only performed when absolutely necessary and in the case that the underlying cause may be either primary TV disease or progression/recurrence of tricuspid regurgitation after prior valve surgery. Sex had a significant interaction with a preoperative critical condition, and was associated with a higher chance of undergoing isolated TV surgery in males.

Strengths and limitations

A major strength of this study is that we were able to use a nationwide database of adult cardiac surgery procedures, with exceptionally high degree of completeness. Nevertheless, TV replacement is performed rarely, which prohibits extensive modelling in this subpopulation. Another limitation was that this database does not record valve disease aetiology. Our modelling strategy may have caused some overfitting due to the 2 selection steps. Therefore, we expect that this model would not perform as well with external data. However, our aim was to explore which covariates were important in males compared to females, and whether this resulted in the same models, rather than to develop a prediction model in this subpopulation of mostly concomitant TV surgery. Furthermore, a prediction model will be mainly driven by initial indication, which is in most cases left-sided valve surgery. Due to multiple testing, especially of the baseline variables, it is possible that some differences were found by chance.

CONCLUSION

In TV surgery, substantial differences in patient and procedural characteristics exist between males and females. Sex is not a risk factor for hospital mortality or undergoing TV replacement versus TV repair. However, differences in the models for hospital death after TV repair were observed for females and males, characterized by a stronger effect of a preoperative critical condition in females. These observations indicate the need for separate risk factor models for males and females. Furthermore, sex interacted with preoperative critical condition, which in term was associated with undergoing isolated TV surgery versus multiple valve surgery (with a stronger effect in males), suggesting that the decision to perform isolated TV surgery may be sex-dependent.

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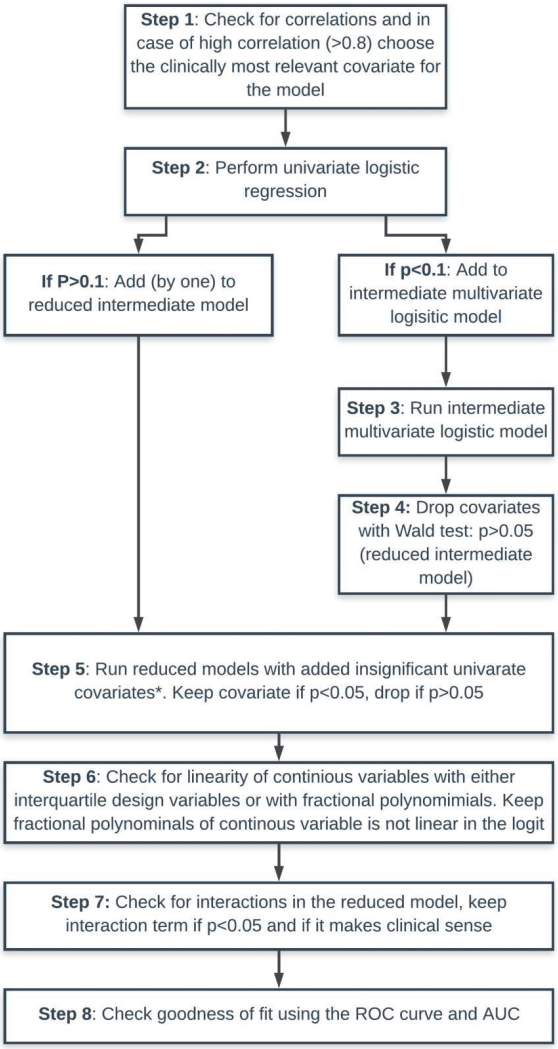
SUPPLEMENTARY MATERIAL

CONTENTS

Supplementary figure 1: Flow chart of modeling technique



Supplementary Table 1: Percentage missing per variables and variables used in analyses. *: indicates this variable was tested in univariable analyses. TVR: tricuspid valve replacement, TVS: tricuspid valve surgery

Characteristic	Percentage missing (%)	Univariable analyses mortality	Univariable analyses determinants TVR	Univariable analyses determinant isolated TVS
Age	0.00	*	*	*
Sex	0.00	*	*	*
Prior PCI	25.13	*	*	*
Prior CABG	8.81	*	*	*
Prior valve surgery	8.81	*	*	*
Prior aortic sugery	15.03	*	*	*
Concomitant CABG	0.02	*	*	*
Arterial graft	0.00			
Venous graft	0.00			
Aortic valve surgery	0.04			
Aortic valve procedure	0.56	*	*	
Aortic valve implant	0.56			
Mitral valve surgery	0.00			
Mitral valve procedure	0.32	*	*	
Mitral valve implant	0.23			
Pulmonary vavle surgery	0.04			
Pulmonary valve procedure	0.70	*	*	
Pulmonary valve implant	0.70			
Tricuspid valve surgery	0.00			
Tricuspid valve procedure	0.82		Dependent	*
Tricuspid valve implant	0.09			
Aortic surgery	0.04	*	*	*
Rythm surgery	0.04	*	*	*
ASD	46.01			
Chronic lung disease	0.21	*	*	*
Extracardiac ateriopathy	0.21	*	*	*
Neurlogical dysfunction	0.21	*	*	*
Creatinine >200	0.97	*	*	*
Endocarditis	0.23	*	*	*
Critical preoperative condition	0.21	*	*	*
Instable angina pectors	0.21	*	*	*
Recent MI	0.23	*	*	*
Pulmonary hypertension	0.91	*	*	*
Emergency surgery	0.21	*	*	*
Postinfarct VSR	0.20	*	*	*
Left ventricular function	72.0			
Isolated TVR	0.0			Dependent

Supplementary Table 2: Observed and expected frequencies in entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	155.6	153.504	1	3,096	0,32
Quantile 2	148	144.659	1	4,341	0,23
Quantile 3	147	145.142	4	5,858	0,68
Quantile 4	164.8	159.572	3	8,228	0,36
Quantile 5	130.6	127.161	4,6	8,039	0,57
Quantile 6	144.2	139.943	6,4	10,657	0,60
Quantile 7	148	138.745	4	13,255	0,30
Quantile 8	142.4	134.513	9,6	17,487	0,55
Quantile 9	137.6	125.927	13,4	25,073	0,53
Quantile 10	133.8	99.571	18	52,229	0,34

Supplementary Table 3: Observed and expected frequencies in male subpopulation of the entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	105	103.971	1	2	0,44
Quantile 2	50.2	49.859	1	1,341	0,75
Quantile 3	81.6	80.662	2	2,938	0,68
Quantile 4	70.6	68.524	1	3,076	0,33
Quantile 5	91.4	88.308	2	5,092	0,39
Quantile 6	63.6	62.166	3	4,434	0,68
Quantile 7	71.6	67.631	2	5,969	0,34
Quantile 8	73.4	69.698	5	8,702	0,57
Quantile 9	68.6	64.622	9	12,978	0,69
Quantile 10	69	49.379	9	28,621	0,31

Supplementary Table 4: Observed and expected frequencies in female subpopulation of the entire cohort. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	67,6	66,087	0	1.513	0,00
Quantile 2	80	78,303	1	2,697	0,37
Quantile 3	71,4	69,198	1	3,202	0,31
Quantile 4	82	78,404	1	4,596	0,22
Quantile 5	64,8	64,359	4	4,441	0,90
Quantile 6	67,8	64,409	2	5,391	0,37
Quantile 7	73,2	68,224	2	6,976	0,29
Quantile 8	66,6	63,08	5	8,52	0,59
Quantile 9	69,2	61,472	4,4	12,128	0,36
Quantile 10	64,4	50,383	9,6	23,617	0,41

Supplementary Table 5: Observed and expected frequencies in tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	141	139,19	1	2,81	0,36
Quantile 2	145	141,699	1	4,301	0,23
Quantile 3	141	139,288	4	5,712	0,70
Quantile 4	144	138,802	2	7,198	0,28
Quantile 5	126	123,176	5	7,824	0,64
Quantile 6	138	132,77	5	10,23	0,49
Quantile 7	137	128,591	4	12,409	0,32
Quantile 8	133	126,472	10	16,528	0,61
Quantile 9	129	117,508	12	23,492	0,51
Quantile 10	126	93,537	16	48,463	0,33

Supplementary Table 6: Observed and expected frequencies in the male subpopulation of the tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	96	95,14	1	1,86	0,54
Quantile 2	53	52,57	1	1,43	0,70
Quantile 3	73	72,331	2	2,669	0,75
Quantile 4	68	66,037	1	2,963	0,34
Quantile 5	81	78,48	2	4,52	0,44
Quantile 6	61	59,741	3	4,259	0,70
Quantile 7	71	67,915	3	6,085	0,49
Quantile 8	69	64,735	4	8,265	0,48
Quantile 9	64	60,803	9	12,197	0,74
Quantile 10	65	47,171	9	26,829	0,34

Supplementary Table 7: Observed and expected frequencies in the female subpopulation of the tricuspid valve repair group. (Five imputed datasets are analyzed and number of patients per quantile could differ per dataset, since different chances can arise with different imputed covariates. Therefore, in some cases the observed columns have decimals)

Quantiles	Observed alive	Expected alive	Observed death	Expected death	O/E ratio mortality
Quantile 1	59	57,682	0	1,318	0,00
Quantile 2	82	80,173	1	2,827	0,35
Quantile 3	73	69,64	0	3,36	0,00
Quantile 4	62	59,462	1	3,538	0,28
Quantile 5	61	59,862	3	4,138	0,72
Quantile 6	66	62,75	2	5,25	0,38
Quantile 7	68	63,515	2	6,485	0,31
Quantile 8	63	59,953	5	8,047	0,62
Quantile 9	63	55,906	4	11,094	0,36
Quantile 10	62	47,17	7	21,83	0,32

Supplementary table 8: Univariate and multivariable determinants of hospital mortality in patients undergoing tricuspid valve repair. PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, ASD: Atrium septum defect, AP: angina pectoris, MI: myocardial infarction. AV: aortic valve, MV: mitral valve, TV: tricuspid valve. VSR: Ventricular septum rupture. OR: odds ratio, CI: confidence interval.

Characteristics	Univariate		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age(per 1 year)	1.03 (1.02 – 1.04)	<0.001	1.04 (1.03 – 1.05)	<0.001
Sex (Female vs Male)	1.15 (0.92 – 1.43)	0.220	1.15 (0.88 – 1.49)	0.302
Prior PCI	1.65 (1.15 – 2.36)	0.007	1.03 (0.67 – 1.59)	0.900
Prior CABG	2.56 (1.80 – 3.63)	<0.001	2.24 (1.74 – 2.88)	<0.001
Prior valve surgery	1.77 (1.31 – 2.39)	<0.001	1.95 (1.3 – 2.94)	0.001
Prior aortic surgery	1.38 (0.52 – 3.63)	0.533	1.15 (0.78 – 1.69)	0.480
Prior other cardiac surgery	1.13 (0.70 – 1.84)	0.616	1.24 (0.40 – 3.85)	0.705
CABG	2.41 (1.93 – 30)	<0.001	1.41 (0.80 – 2.48)	0.238
AV repair	2.41 (1.02 – 5.7)	0.046	2.68 (1.07 – 6.70)	0.036
AV replacement	2.83 (2.25 – 3.56)	<0.001	2.20 (1.69 – 2.85)	<0.001
MV repair	0.61 (0.45 – 0.82)	0.001	0.76 (0.55 – 1.06)	0.103
MV replacement	1.38 (1.01 – 1.86)	0.046	1.66 (1.17 – 2.35)	0.005
PV surgery	0.53 (0.13 – 2.16)	0.373	1.85 (0.40 – 8.54)	0.431
Aortic surgery	2.08 (1.30 – 3.32)	0.002	1.51 (0.88 – 2.58)	0.134
Rhytm surgery	0.61 (0.46 – 0.8)	<0.001	0.90 (0.67 – 1.21)	0.482
Chronic lung disease	1.88 (1.45 – 2.44)	<0.001	1.56 (1.17 – 2.06)	0.002
Extracardiac ateriopathy	1.77 (1.25 – 2.48)	0.001	1.17 (0.80 – 1.72)	0.404
Neurlogical dysfunction	1.35 (0.77 – 2.36)	0.288	1.00 (0.54 – 1.86)	0.994
Renal impairment	4.95 (3.39 – 7.24)	<0.001	3.22 (2.06 – 5.04)	<0.001
Endocarditis	3.00 (2.01 – 4.48)	<0.001	1.67 (1.03 – 2.72)	0.039
Critical preoperative condition	5.70 (4.18 – 7.77)	<0.001	6.80 (3.79 – 12.21)	<0.001
Unstable AP	5.81 (2.66 – 12.68)	<0.001	2.13 (0.79 – 5.72)	0.134
Recent MI	2.89 (1.92 – 4.39)	<0.001	1.43 (0.63 – 3.24)	0.395
Pulmonary hypertension	1.82 (1.39 – 2.39)	<0.001	1.28 (0.95 – 1.74)	0.104
Emergency operation	5.81 (3.63 – 9.21)	<0.001	1.12 (0.58 – 2.16)	0.736
Postinfarct VSR	5.58 (1.97 – 15.64)	0.001	2.51 (0.42 – 14.89)	0.309
Interaction terms with seks				
Critical preoperative condition	0.49 (0.26 – 0.92)	0.026	0.44 (0.22 – 0.90)	0.026
Recent MI	0.40 (0.17 – 0.91)	0.031	0.69 (0.25 – 1.93)	0.481
Postinfarct VSR	0.09 (0.01 – 1.15)	0.065	0.18 (0.01 – 3.33)	0.248

Supplementary Table 9: Tricuspid valve replacement vs repair with interaction term between sex and prior valve surgery. AV: aortic valve, MV: mitral valve, PV: Pulmonary valve. * denotes the product between variables (interaction term)

Characteristic	OR (95% CI)	P value
	Tricuspid valve replacement vs repair	
MV repair	0,06 (0,04 to 0,09)	0
MV replacement	0,17 (0,12 to 0,25)	0
AV replacement	0,38 (0,25 to 0,59)	0
Rythm surgery	0,3 (0,17 to 0,52)	0
Prior valve surgery	2,75 (1,8 to 4,14)	0
Sex	1,06 (0,76 to 1,48)	0,737
PV surgery	2,36 (1,39 to 4,01)	0,001
$Age_{(FP1)}$	0,88 (0,83 to 0,93)	0
$Age_{(FP2)}$	0,02 (0,01 to 0,09)	0
Aortic surgery	0,26 (0,08 to 0,87)	0,029
Endocarditis	1,9 (1,17 to 3,06)	0,01
Sex* Prior valve surgery	0,53 (0,28 to 1,01)	0,062

Supplementary Table 10: Isolated tricuspid valve surgery vs multiple valve surgery with interaction term between sex and peropeative critical condition. AP: angina pectoris, TV: tricuspid valve, VSR: Ventricle septum rupture. * denotes the product between variables (interaction term)

Characteristic	OR (95% CI)	P value
	Isolated tricuspid valve surgery vs multiple valve surgery	
Age	0,96 (0,95 to 0,96)	<0,001
TV replacement	7,39 (5,58 to 9,87)	<0,001
Rythm surgery	0,57 (0,45 to 0,73)	<0,001
Critical preop condition	1,06 (0,59 to 1,9)	0,843
Unstable AP	3,35 (1,45 to 7,77)	0,005
Pulmonary hypertension	0,41 (0,29 to 0,57)	<0,001
Postinfarct VSR	12,3 (4,18 to 36,6)	<0,001
Sex	0,9 (0,75 to 1,07)	0,247
Sex* Critical preop condition	2,44 (1,21 to 4,9)	0,012

5

Outcomes after Tricuspid Valve Replacement for Carcinoid Heart Disease: A Multicenter Study

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ABSTRACT

Background

This study evaluates clinical and echocardiographic outcomes in patients who underwent tricuspid valve replacement (TVR) for carcinoid heart disease (CaHD) stratified to prosthesis type (biological vs mechanical).

Methods

All patients undergoing TVR for CaHD between 1991 and 2017 were analyzed retrospectively in four tertiary centers. Cox-proportional hazard models were used to analyze survival data and mixed-models for repeated measurements of echo and laboratory data.

Results

In total, 49 patients (median age: 59 [51–66], 45% male) underwent biological (n = 20, 41%) or mechanical (n = 29, 59%) TVR. Three (6%) patients died in-hospital and 3-year actuarial survival was 73.3 ± 8.7% (biological) and 56.1 ± 10.0% (mechanical) (P = 0.69). During a median follow-up of 17 months, two patients with a biological prosthesis required reoperation for structural valve deterioration, while one patient with mechanical prostheses had a reoperation due to valve thrombosis. No significant differences in bleeding, thrombosis, thromboembolism and heart failure admissions were noted between prosthesis types. Postoperative valve regurgitation increased more in patients with a biological prosthesis (p = 0.022). Maximum tricuspid inflow gradient was higher in patients with biological prostheses (p = 0.02); however, course over time was comparable between prosthesis types (p = 0.136).

Conclusion

Tricuspid valve surgery for CaHD can be performed with acceptable hospital mortality risk. This data shows no apparent benefit of biological valves over mechanical prosthesis or vice versa. Valve choice should be made in a multi-disciplinary team taking into account expected lifespan, planned treatment for the carcinoid syndrome and neuroendocrine tumor and patient preferences.

INTRODUCTION

Bronchopulmonary and gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are rare malignancies, with an annual incidence of 2–5 persons per 100,000.[1,2] NETs secrete a range of vaso-active peptideswhich can lead to damage to the tricuspid and pulmonary valves and the endocardium of the right ventricle, known as carcinoid heart disease (CaHD) or Hedinger syndrome. CaHD develops in approximately 20% to 50% of the patients with NETs.[3,4] While treatment for NETs continues to improve cardiac involvement remains a major cause of mortality and morbidity, especially when right heart failure develops.[5] Surgical intervention is the only effective treatment for CaHD. However, most surgical series are small single-center studies. Therefore, this study aimed to evaluate clinical, echocardiographic, and laboratory outcomes in patients who underwent tricuspid valve (TV) replacement for CaHD in four tertiary centers in the Netherlands. Since prosthetic valve choice in these patients is still controversial due to limited data[6], patients receiving mechanical prostheses and biological prostheses are analyzed separately.

MATERIALS AND METHODS

All patients who underwent tricuspid valve replacement (TVR) for CaHD between 1991 and September 2017 were included in this retrospective cohort study. Follow-up closed in December 2018. Four academic centers participated in this study resulting in 49 patients eligible for analyses. Included patients and inclusion years per center are presented in Supplementary Table 1. Approval was obtained from the medical ethical committee of the Erasmus MC to conduct this study (MEC-2017-135) and in the other centers approval was obtained from the local ethical committee.

Operation

In all centers, the operation was performed on extracorporeal circulation with moderate hypothermia and under cardioplegic arrest. Intravenous octreotide was administered peri-operatively to avoid possibly a life-threatening carcinoid crisis.[7] One center exclusively implanted mechanical prostheses, two centers exclusively biological prostheses and in one center both biological and mechanical prostheses were implanted. In case a pacemaker is indicated after tricuspid valve prosthesis implantation the pacemaker leads are placed epicardially, either by resternotomy or by minimally invasive surgery.

Data collection

Patient records were reviewed. Clinical outcomes were recorded according to the guidelines of Akins et al.[8] Clinical data, laboratory data and echocardiograms were collected longitudinally.

Anticoagulation protocol

Patients receiving biological prostheses were prescribed coumadin until 3 months after surgery unless there was another indication necessitating continuation of anticoagulation. Patients receiving mechanical prostheses were prescribed lifelong coumadin. Target internationalized normal ratio (INR) for mechanical valves was 2.5–3.5.

Statistical analyses

Continuous data are presented as mean±standard deviation (Gaussian distribution) or as median with interquartile range (IQR) (non-Gaussian distribution) and were compared using T-test or Kruskal-Wallis test, as appropriate. Categorical data are presented as percentages and were compared with the chi-squared test or fisher-exact test, as appropriate. Survival data are presented as Kaplan-Meier estimates with a standard error or in Kaplan–Meier curves. The log-rank test was used to compare strata, and Schoenfeld individual test was used to assess the proportional hazard assumption. Patients are followed till the end of follow-up, death, or reoperation. Univariable Cox-proportional hazard models were used to find potential determinants associated with mortality. Mixed-models were used for repeated measurements and visualized with effect plots. An elaborate explanation of the mixed-model usage is provided in Supplementary Text 1.

RESULTS

During the inclusion period, 49 patients underwent TVR for CaHD. Median follow-up was 1.4 years (range 0–24.3 years; IQR:0.3 to 3.7 years; total follow-up 168 patient-years [123 for patients with mechanical prostheses vs 45 for biological prostheses).

Baseline characteristics

Baseline characteristics are presented in Table 1. Median time from diagnosis of NET and cardiac operation was 1.9 years, with no differences in patients receiving biological and mechanical prostheses (1.9 vs 1.8 years, $p = 0.891$). No patients were on digoxin or inotropes prior to surgery. The two patients who had prior cardiac surgery both underwent coronary artery bypass grafting at their prior surgery. In patients who received loop diuretics, the median dose of furosemide was 40 mg [IQR: 20 to 70] daily. Preoperative echocardiographic measurements were comparable between patients receiving mechanical and biological prostheses (Table 2), except for TV peak inflow gradient, which was significantly higher in patients receiving biological prostheses (12 mmHg vs. 6 mmHg, $p = 0.015$).

Table 1. Baseline characteristics. BMI: body mass index, 5-HIAA: 5-hydroxyindoleacetic acid, ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase, MCV: Mean corpuscular volume, LDH: lactate dehydrogenase, INR: International normalized ratio. *Noted during physical examination.

Characteristic	Overall group	Biological prostheses	Mechanical prostheses	P-value
N	49	20	29	-
Age (median [IQR])	59.34 [51.83–66.43]	61.42[52.21–66.54]	59.34[51.83–65.72]	0.935
Female sex	27(55.1)	11(55.0)	16(55.2)	1.000
BMI (median [IQR])	23.00 [20.91–26.65]	24.00 [21.00–26.25]	21.86 [20.80–26.74]	0.551
Primary tumor(%)				0.914
Small intestine	28(57.1)	12(60.0)	16(55.2)	
Appendix	1(2.0)	0(0.0)	1(3.4)	
Colon	5(10.2)	2(10.0)	3(10.3)	
Other	4(8.2)	2(10.0)	2(6.9)	
Unknown	11(22.4)	4(20.0)	7(24.1)	
Liver metastasis(%)	46(93.9)	17(85.0)	29(100.0)	0.122
Bone metastasis(%)	8(16.3)	3(15.0)	5(17.2)	1.000
Other metastasis(%)	20(40.8)	7(35.0)	13(44.8)	0.695
NYHA (%)				0.301
I	0(0.0)	0(0.0)	0(0.0)	
II	10(27.8)	2(22.2)	8(29.6)	
III	20(55.6)	4(44.4)	16(59.3)	
IV	6(16.7)	3(33.3)	3(11.1)	
Hypertension (%)	15(30.6)	9(45.0)	6(20.7)	0.134
Diabetes (non-insulin)(%)	4(8.2)	2(10.0)	2(6.9)	1.000
Smoking (%)	5(10.2)	3(15.0)	2(6.9)	0.659
Ascitis*(%)	7(14.3)	2(10.0)	5(17.2)	0.767
Leg edema*(%)	25(51.0)	8(40.0)	17(58.6)	0.322
Palpable liver*(%)	19(38.8)	4(20.0)	15(51.7)	0.052
Anticogulants(%)	6(12.2)	3(15.0)	3(10.3)	0.964
Diuretics(%)	42(85.7)	16(80.0)	26(89.7)	0.593
Somatostatin analog(%)	42(85.7)	16(80.0)	26(89.7)	0.593
Atrial fibrilation(%)	2(4.1)	0(0.0)	2(6.9)	0.642
Pacemaker(%)	1(2.0)	1(5.0)	0(0.0)	0.850
Laboratory measurements				
5-HIAA(median[IQR])	721.50 [416.52–1347.00]	1281.00 [846.50–1485.10]	703.00 [410.70–1237.50]	0.495
Creatinin (median[IQR])	95.50 [84.50–113.25]	95.00 [87.50–111.00]	99.00 [83.00–114.00]	0.866

Table 1. Baseline characteristics. BMI: body mass index, 5-HIAA: 5-hydroxyindoleacetic acid, ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase, MCV: Mean corpuscular volume, LDH: lactate dehydrogenase, INR: International normalized ratio. *Noted during physical examination. (continued)

Characteristic	Overall group	Biological prostheses	Mechanical prostheses	P-value
ALAT (median[IQR])	21.50 [14.50–29.75]	29.00 [19.50–32.00]	19.50 [13.00–26.00]	0.024
Albumin (median[IQR])	721.50 [416.52–1347.00]	40.00 [38.00–42.00]	41.00 [36.00–44.00]	0.946
ASAT (median[IQR])	29.00 [24.50–35.75]	28.00 [22.75–34.75]	29.00 [26.00–35.75]	0.398
Alkaline Phosphatase (median[IQR])	191.50 [135.25–63.75]	167.00 [130.50–240.50]	216.00 [173.50–266.00]	0.487
Hemoglobin (mean(sd))	7.96 (1.39)	8.61 (1.06)	7.54 (1.44)	0.008
Hematocrit (mean(sd))	0.39 (0.07)	0.42 (0.05)	0.38 (0.07)	0.014
MCV (mean(sd))	91.12 (9.33)	89.67 (5.77)	91.64 (10.37)	0.594
RDW (median[IQR])	15.20 [14.55–15.95]	14.20 [14.20–14.20]	15.30 [14.70–16.00]	0.278
LDH (median[IQR])	236.00 [177.00–51.00]	236.00 [177.50–248.00]	227.50 [178.50,-252.50]	0.707
INR (median[IQR])	1.15 [1.04–1.25]	1.11 [1.02–1.19]	1.15 [1.05–1.24]	0.673

Table 2. Preoperative echocardiographic parameters. TV: Tricuspid valve, TR: tricuspid regurgitation, PV: pulmonary valve, AV: aortic valve, LVED: left ventricular end diastolic volume, LVES: left ventricular end systolic volume, RVF: right ventricle function, MV: mitral valve.

Characteristic	Overall group	Biological prostheses	Mechanical prostheses	P-value
N	49	20	29	-
TV regurgitation(%)				NA
Severe	49(100.0)	20(100.0)	29(100.0)	
TR gradient (mmHg) (mean(sd))	24.55(12.96)	27.69(13.74)	22.61(12.40)	0.273
TV inflow gradient (mmHg) (median[IQR])	7.00 [4.50–11.50]	12.00 [7.75–25.75]	6.00 [3.50–8.50]	0.015
PV gradient (mmHg) (mean(sd))	17.32(9.89)	17.25(12.42)	17.35(9.18)	0.981
AV gradient (mmHg) (median[IQR])	5.00 [3.00–7.00]	6.00 [4.00–9.00]	4.00 [3.00–6.00]	0.192
LVF (n,%)				0.666
Normal	23(62.2)	9(69.2)	14(58.3)	
Mild impairment	13(35.1)	4(30.8)	9(37.5)	
Moderate impairment	1(2.7)	0(0.0)	1(4.2)	
Severe impairment	0(0.0)	0(0.0)	0(0.0)	

Table 2. Preoperative echocardiographic parameters. TV: Tricuspid valve, TR: tricuspid regurgitation, PV: pulmonary valve, AV: aortic valve, LVED: left ventricular end diastolic volume, LVES: left ventricular end systolic volume, RVF: right ventricle function, MV: mitral valve. (continued)

Characteristic	Overall group	Biological prostheses	Mechanical prostheses	P-value
LVED (mm) (mean(sd))	41.59(6.10)	42.00(4.99)	41.36(6.72)	0.776
LVES (mm) (median[IQR])	27.00 [22.50–29.00]	27.00 [24.00–29.00]	27.00 [22.00–29.00]	0.663
RVF(%)				0.118
Normal	22(66.7)	13 (81.2)	9 (52.9)	
Mild impairment	7(21.2)	1 (6.2)	6 (35.3)	
Moderate impairment	4(12.1)	2 (12.5)	2 (11.8)	
Severe impairment	0(0.0)	0 (0.0)	0 (0.0)	
PV regurgitation (n,%)				0.558
None	4(10.5)	3(20.0)	1(4.3)	
Trivial	3(7.9)	1(6.7)	1(4.3)	
Mild	12(31.6)	5(33.3)	7(30.4)	
Moderate	17(44.7)	5(33.3)	12(52.2)	
Severe	4(10.5)	1(6.7)	2(8.7)	
AV regurgitation(n,%)				0.487
None	14(42.4)	3(20.0)	1(5.6)	
Trivial	4(12.1)	4(26.7)	10(55.6)	
Mild	9(27.3)	5(33.3)	4(22.2)	
Moderate	4(12.1)	2(13.3)	2(11.1)	
Severe	2(6.1)	1(6.7)	1(5.6)	
MV regurgitation(n,%)				0.304
None	8(19.5)	6(33.3)	9(39.1)	
Trivial	15(36.6)	5(27.8)	3(13.0)	
Mild	9(22.0)	2(11.1)	7(30.4)	
Moderate	8(19.5)	5(27.8)	3(13.0)	
Severe	1(2.4)	0(0.0)	1(4.3)	

Operative characteristics

Operative characteristics are shown in Table 3. In total, 20 (41%) patients received a biological prosthesis and 29 (59%) patients received a mechanical prosthesis. Concomitant pulmonary valve replacement was comparable between patients with mechanical and biological prostheses (55% vs 79%, p = 0.134). In the case of pulmonary valve replacement, a transannular

enlargement patch was used more often in patients receiving a mechanical prosthesis (18% vs 83%, $p < 0.001$).

Table 3. Operative characteristics. PVR: Pulmonary valve replacement, MVR: mitral valve replacement, AVR: aortic valve replacement, CABG: coronary artery bypass grafting, CPB: Cardio-pulmonary bypass, ACC: aortic cross-clamp ASD: Atrium septum defect, OFO: open foramen ovale. **Other manufacturers: Medtronic (2) and LivaNova (2). *P value after corrected for body surface index: $P = 0.02$.

Characteristic	Overall group	Biological prostheses	Mechnical prostheses	P-value
N	49	20	29	-
PVR	34(69.4)	11(55.0)	23(79.3)	0.134
With annular enlargement patch	21(42.9	2(18.2)	19(82.6)	<0.001
MVR	2(4.1)	1(5.0)	1(3.4)	0.999
AVR	3(6.1)	1(5.0)	2(6.9)	0.999
CABG	4(8.2)	2(10.0)	2(6.9)	0.999
ASD/OFO closure	28 (57.1)	4(20.0)	3(10.3)	0.369
CPB time (min) (median[IQR])	132.00 [101.00–181.50]	153.00 [78.50–183.50]	129.00 [105.75–180.25]	0.404
ACC time (min) (median[IQR])	97.50 [65.00–139.25]	82.00 [60.00–138.25]	99.50 [66.75–135.75]	0.485
Size prosthesis (median[IQR])*	29.00 [27.00–31.00]	31.00 [29.00–33.00]	29.00 [27.00–31.00]	0.002
Manufacturer(%)				<0.001
St. Jude Medical	33(68.8)	5(25.0)	29(100.0)	
Carpentier-Edwards	11(22.9)	11(55.0)	0(0.0)	
Other**	4(8.3)	4(20.0)	0(0.0)	
Hospital outcomes				
Hospital mortality	3(6.1)	1(5.0)	2(6.9)	0.999
ICU stay (days) (median[IQR])	1.00 [1.00–3.00]	1.00 [1.00–3.00]	1.00 [1.00–2.50]	0.794
Hospital stay (days) (median[IQR])	10.50 [9.00–13.00]	10.00 [9.00–12.00]	10.00 [9.00–12.00]	0.473
Resternotomies	10(20.4)	3(15.0)	7(24.1)	0.675

Hospital outcomes

In total, 3(6%) patients died in hospital [mechanical 2(7%) vs biological 1(5%)] (Table 3). One patient died due to a carcinoid crisis despite treatment with octreotide. One patient died due to sepsis and right ventricular failure and in the third patient electro-mechanical dissociation was observed. In total 10 re-explorations were performed (20%), of which 7 for bleeding and 3 for suspected tamponade. ICU stay and hospital stay were comparable between patients receiving biological prostheses and mechanical prostheses (Table 3). Significant hospital morbidity in the

patients with mechanical prostheses occurred in 6 patients and consisted of infection in 5 patients (1 urinary tract, 2 septic line infection, 2 pneumonia) and low output with renal failure in 1 patient, treated with intra-aortic balloon pump and continuous veno-venous hemofiltration. In the biological prostheses group hospital morbidity occurred in 4 patients and consisted of infection in 2 patients (1 pneumonia and 1 urinary tract), 1 pacemaker implant for third degree AV-block and 1 patient with a neurological event (pyramidal syndrome and dysphasia, without apparent thromoembolism or intracranial bleeding).

Late mortality

In total, 4 patients died [mechanical 2 (7%) vs biological 2 (10%)] within 30 days and 24 patients during late follow-up [mechanical 16 vs biological 8]. Causes of late death were valve-related in 1, cardiac-related in 2 (combined with infection), non-cardiac in 5 (all progression of carcinoid disease) and unknown in 16 patients. Overall survival stratified to valve type was comparable (p = 0.69) (Figure 1a). Kaplan-Meier survival estimates at 1 and 3 years were 70.3 ± 11.3% and 62.4 ± 12.4% for biological prostheses and 73.3 ± 8.7% and 56.1 ± 10.0% for mechanical prostheses, respectively.

Determinants of late mortality

In 44 variables the potential association with late mortality was assessed (Supplementary Table 2). Older age, preoperative intravenous diuretics, the presence of preoperative leg edema, higher aortic valve gradient, and lower preoperative hematocrit/hemoglobin were significantly associated with higher late mortality (Table 4). Notably, preoperative 5-hydroxyindoleacetic acid (5-HIAA) was not associated with late mortality [HR: 1.00, 95% CI (0.99–1.00), p = 0.22)], nor was concomitant pulmonary valve replacement [HR: 0.55, 95% CI (0.23–1.30), p = 0.173).

Table 4. Preoperative covariates potentially associated with late mortality upon univariable cox-regression. AV: aortic valve.

Variable	HR (95% CI)	P-value
Age	1.06 (1.02–1.11)	0.007
Diuretics intravenous	10.81 (2.07–56.52)	0.005
Leg edema	3.28 (1.43–7.53)	0.005
AV gradient$_{\text{per 1 mmHg}}$	1.2 (1.05–1.37)	0.009
Hemoglobin$_{\text{per 1 mmol/L}}$	0.73 (0.55–0.97)	0.028
Hematocrit$_{\text{per 0.01}}$	0.9 (0.85–0.96)	0.002

Late events

Two patients with a biological prosthesis developed structural valve deterioration (SVD) 1.5 and 1.4 years after the initial surgery and were subsequently re-operated. One patient with a mechanical valve developed a valve thrombosis and had to be re-operated 0.7 year after the

initial surgery. One patient with a biological valve developed endocarditis 2 months after the surgery, but was not re-operated and only treated with antibiotics. No valve thrombo-embolic events were described during follow-up. In total, 11 patients had a bleeding event [8 mechanical vs 3 biological], resulting in death in one patient with mechanical valve prostheses (Figure 1b). Notably, 2 patients receiving a biological prosthesis were still on anticoagulation when the bleeding event occurred. Three patients receiving a biological prosthesis continued to stay on anticoagulants after 3 months. Kaplan-Meier estimate of freedom from bleeding at 3 years was 83.4 ± 8.9% and 67.3 ± 12.8% for patients receiving biological and mechanical prostheses, respectively.

In total, 12 patients [6 mechanical vs 6 biological] were readmitted for heart failure (Figure 1c). Kaplan-Meier estimate of freedom from heart failure at 3 years is 62.7 ± 12.2% and 82.7 ± 8.0% for biological and mechanical prostheses, respectively. No significant differences in bleeding events (p = 0.68) and readmission for heart failure (p = 0.28) were observed in patients receiving mechanical or biological prostheses.

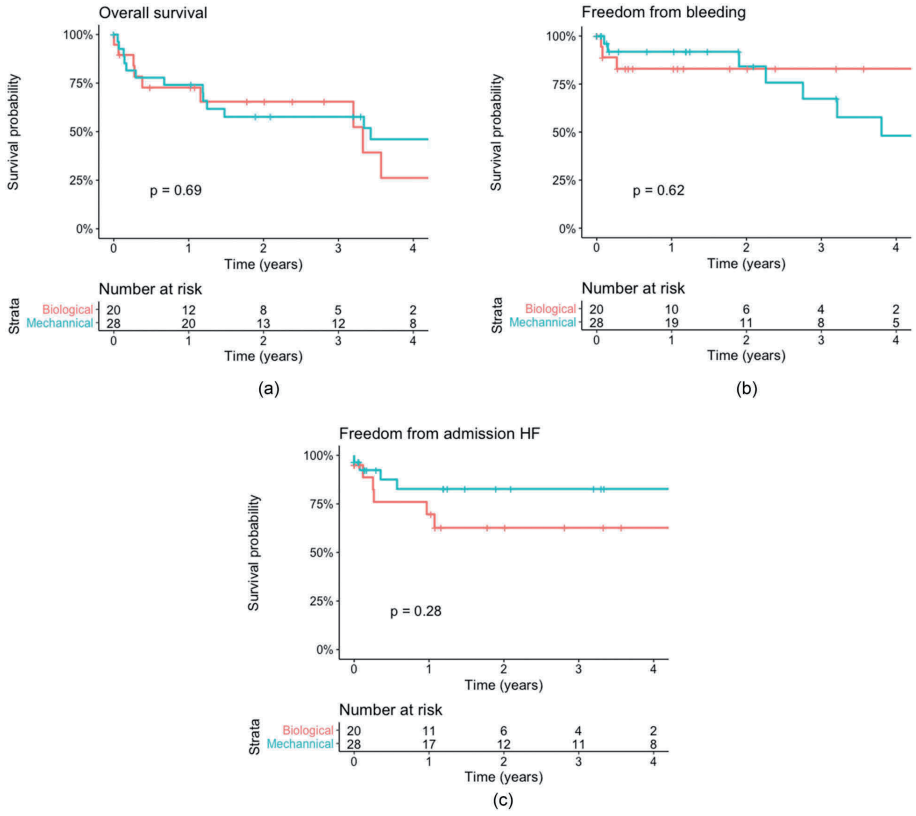

Figure 1. Kaplan–Meier curves of overall survival (a), freedom from bleeding (b) and freedom from heart failure (c). HF = heart failure. Proportional hazard assumption was not violated (p = 0.76, p = 0.13 and p = 0.94).

The odds of being in sinus rhythm over time were comparable between patients with biological and mechanical prostheses, and remained stable over time, with stable probabilities of 72% and 85% for patients with biological and mechanical prostheses, respectively (Supplementary Figure 1).

The course (p = 0.43) and starting point (p = 0.73) of diuretic use did not differ between patients receiving mechanical and biological prostheses (Supplementary Figure 2).

Functional outcome

Postoperative NYHA was recorded on 80 occasions in 27 patients (mean 2.9, range 1–10), which were too few measurements to analyze patients with biological prostheses and mechanical prostheses separately. In the overall group, the odds of being in NYHA class III-IV did not differ over time (Supplementary Figure 3), indicating that the probability of being in NYHA class III-IV remained stable over time. In patients with biological prostheses, NYHA functional class at last follow-up was II in 6, III in 2 and IV in 1 with a mean follow-up of 1.6 ± 1.8 years. In patients with mechanical prosthesis NYHA, functional class was I in 13, II in 3, III in 1 and IV in 1 with a mean follow-up of 4.4 ± 6.6 years.

Echocardiographic outcomes

During follow-up, 209 echocardiograms were collected in 46 patients (mean: 5.0, range: 1–18). Modeled postoperative TV inflow peak gradient over time and postoperative probabilities of moderate-to-severe TV regurgitation over time are presented in Figure 2a,b. TV inflow peak gradient was higher in patients with a biological prosthesis compared to mechanical prosthesis (p = 0.004) and this was constant over time during follow-up (p = 0.33) (Figure 2a). The same trends were obtained when the center effect was included in the analyses. Probability of moderate-to-severe TR was comparable immediately after surgery (p = 0.86), but increased significantly more in patients with a biological prosthesis during follow-up (p = 0.022) (Figure 3b). Severely impaired right ventricular function (RVF) was noted in 5 patients [1 mechanical, 4 biological], and was firstly noted within a week after surgery in all patients. In 3 patients the impaired RVF was transient and improvement was noted on the following echocardiogram. The other two patients died early due to heart failure (one patient) and carcinoid crises combined with heart failure (one patient) before another follow-up echo could be made.

Laboratory values

During follow-up hemoglobin and creatinine was measured 1512 and 1079 times, respectively. Effect plots of hemoglobin and creatinine are shown in Figure 3a,b. In patients with a biological prosthesis, the slope of creatinine was significantly steeper compared to patients with mechanical prostheses (p = 0.023), whereas the starting point was not (p = 0.55) (Figure 3a). Nevertheless, no cross-sectional differences were noted during the follow-up, as confidence intervals overlapped considerably (Figure 3a). Accounting for the center, the analyses did not

result in major changes in estimates or significance. The course of hemoglobin is different between patients receiving mechanical prostheses and biological prostheses. Initially, the slope is steeper in patients with a biological prosthesis (p = 0.006). However, later in follow-up differences disappear (Figure 3b). Using a simpler model without adding flexibility over time resulted in comparable observations; slope of hemoglobin is steeper in patients with a biological prosthesis (p = 0.002), meaning a relatively higher increase in hemoglobin after the operation in patients with biological prostheses (Supplementary Figure 4). Accounting for center effect, the estimates or significance did not considerably change.

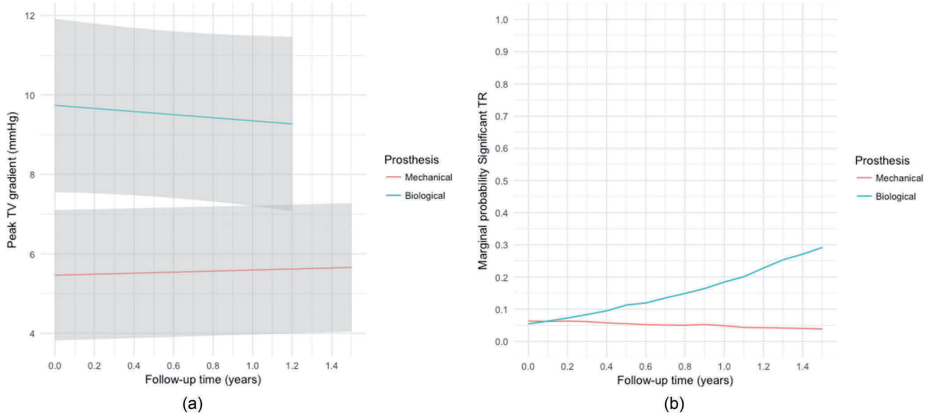

Figure 2. Temporal pattern of Tricuspid valve inflow peak gradient (a) and marginal probability of moderate-to-severe tricuspid regurgitation (b).

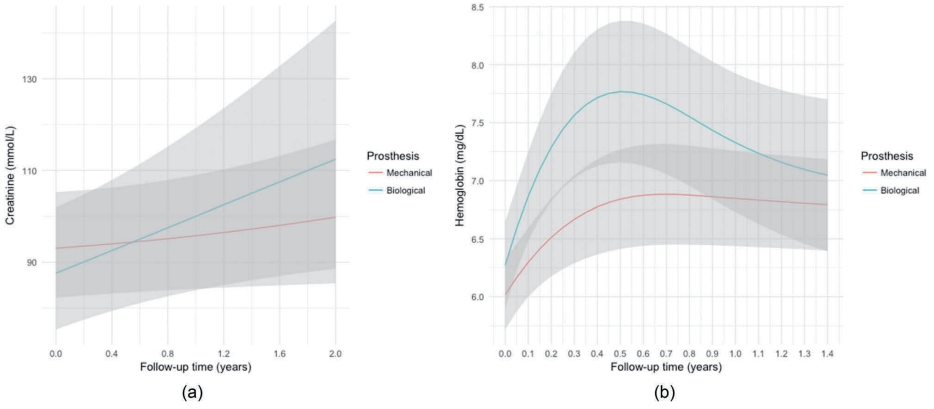

Figure 3. Temporal pattern of creatinine (a) and hemoglobin (b).

COMMENT

CaHD is associated with an impaired survival and functional class, and progressive right heart failure is the leading cause of death in patients who develop CaHD.[9,10] In most cases, surgery improves functional outcomes in patients. However, hospital mortality is reported to be higher compared to surgery for other TV valve etiology.[11] In this series hospital mortality (6%) is comparable with other contemporary series, as is late mortality[6,12–14], and does not seem higher compared to tricuspid valve replacement irrespective of etiology.[15]

One of the major controversies regarding surgery for CaHD is the valve choice (biological vs mechanical). Several authors reported accelerated structural valve deterioration (SVD) in biological valves[16-18], which was the main reason why one of the included centers in this study exclusively implanted mechanical prostheses. However, other authors argue that life expectation is limited in these patients and anticoagulation with concurrent liver metastasis should be avoided and, therefore, a biological prosthesis is justified.[6,12] This study opted to shed some light on this choice by analyzing patients receiving either a mechanical or biological prosthesis separately. No statistically significant differences in outcomes (death, bleeding, reoperation) between these groups were observed. Nevertheless, the direction of the effect reflected the properties commonly associated with the valve types, i.e. more bleeding in mechanical valves and more reoperation and valve deterioration (characterized by TR) in biological valves. Moreover, already 2 SVD cases necessitating reoperation in the biological valve group during the short follow-up period were observed. Interestingly, the relatively high reported rates of thrombosis of mechanical heart valves in the tricuspid position were not observed in this population.[15] Since the patient outcome depicts very much the standard pros and cons of biological versus mechanical prostheses, valve choice could be an item in the multidisciplinary team, taking into account expected lifespan, further carcinoid treatment and patient preferences using shared decision-making. Furthermore, valve choice can also be influenced by the prospect of transcatheter valve-in- valve replacement of dysfunctional biological prostheses, which is already performed in dysfunctional prostheses in the pulmonary valve position.[19]

The modeled value of postoperative TV inflow peak gradient of biological valves was significantly higher than mechanical valves. The difference could be intrinsic to the valves itself. Blauwet and colleagues have studied a prosthetic valve inflow gradient in the tricuspid position in well-functioning valves.[16,17] They found a higher mean gradient for a 33 mm biological valve (~4 mmHg, manufacturer: SJM and Carpentier-Edwards) compared to a 29-mm mechanical valve (~2.5 mmHg, manufacturer: SJM).[20,21] Nonetheless, differences can also be explained due to confounding factors such as different postoperative right ventricular function and pulmonary pressures. Interestingly, preoperatively TV inflow gradient was different as well; however, this did not lead to subsequently smaller biological valve prostheses; in contrast, biological prosthesis size was, in fact, larger compared to mechanical prostheses (31 vs 29 mm, $p = 0.002$). It has

to be noted that in analyses of pre-operative TV inflow gradient comparisons were not adjusted for measurement differences between centers, which can explain these findings.

Postoperative course of hemoglobin was different between patients receiving mechanical vs biological prostheses; patients receiving biological prostheses have a steeper increase in hemoglobin levels compared to patients with mechanical prostheses. Differences in blood transfusion policy between centers can explain this finding. Unfortunately, this could not be extracted reliably from the available data. Nevertheless, accounting for center differences (as a random effect) will obviate measurement differences and even treatment differences to some extent (as it accounts for the higher correlations within one center). Another plausible explanation can be hemolysis associated with mechanical heart valves, which was already noticed in the nineties.[22] Furthermore, preoperative lower hemoglobin was associated with higher late mortality, so ensuring adequate hemoglobin levels quickly may be important in this select group of patients.

Previous studies have found higher urinary 5-HIAA excretion (as the main breakdown product of serotonin), lower somatostatin analogue doses, cytotoxic chemotherapy, and tobacco use to be predictors of late mortality.[12,23] This study did not replicate these findings.

Most carcinoid heart disease patients without cardiac surgery die of progressive right-sided heart failure. An older study estimated a 2-year survival of 8% in medically treated patients compared to 40% in surgically treated patients.[23] Several studies suggest valvular intervention may be beneficial in halting right heart failure progression.[6,11,24] This series also suggests the potential benefit of the valvular intervention, as severe RVF impairment was only noted in five patients in the early postoperative period and was transient in most patients.

Strengths and limitations

Strengths of this study include a multicenter design, elaborate longitudinal follow-up and advanced statistical techniques. This study has several limitations common in retrospective studies in a small sample size, which may be underpowered to detect differences. Nevertheless, population size is reasonable for this select subgroup. Furthermore, follow-up is short in this study, which can be explained by substantial mortality rates and due to the fact that a proportion of the patients underwent surgery in more recent years. No data were available on the possible patient selection for surgical treatment, and this may very well have varied among centers. Furthermore, center and surgeon preferences for prosthesis type could lead to potential bias. Finally, this study reflects practice in the Netherlands and may not apply to other parts of Europe and the world.

Conclusion

Tricuspid valve surgery for CaHD can be performed with acceptable hospital mortality and morbidity risks. Implanting biological or mechanical prostheses resulted in comparable outcomes in terms of mortality, bleeding, valve thrombosis and reoperation, without showing a

clear benefit of one valve over another. Therefore, valve choice should be patient-tailored and carried out by a multidisciplinary team taking into account predicted lifespan, further carcinoid surgery and patient's preferences.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Centers and inclusion period

Center	Number of patients	Inclusion period
Erasmus MC, Rotterdam, The Netherlands	27	01-01-1993 to 30-12-2016
UMCU, Utrecht, The Netherlands	15	01-01-2006 to 01-01-2017
LUMC, Leiden, The Netherlands	5	01-01-1991 to 01-01-2016
AMC, Amsterdam, The Netherlands	2	01-01-2012 to 01-01-2017

Supplementary Text 1: Elaborate explanation mixed-models

Continuous repeated measurements are analyzed using mixed-models with random intercepts and time slope for patients. Dichotomous data is modelled using generalized mixed models with random intercepts for patients. In a sensitivity analyses we also added center intercept as a random effect. All the models contained time, valve prostheses and their interaction term as fixed effect. Natural splines as fixed and random effects for time were added to establish flexibility. In order not to lose interpretability of splines in random and fixed effect, the statistical models always contained the same number of knots in random as fixed effects. Model performance for different number of splines were compared using AIC and BIC, and the model with the lowest AIC and BIC was chosen. Splines were excluded if they did not improve the models. In the generalized mixed model the marginal probabilities are obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest 3000 patients are generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities is taken as estimate. The models were visualized with effect plots, depicting change of the outcome parameters over time (continuous) or probability over time (categorical). Effect plots are truncated when <10% of the data/patients remained in the study, or when remaining patients dropped below 5. QQ-plots of standardized residuals were inspected to determine if model assumptions were violated.

Supplementary Table 2: Cox-proportional hazard ratio's

Characteristic	Hazard ratio (95% confidence interval)	P-value
Aortic clamp time	1 (0.99 to 1.01)	0.543
Ascites	1.49 (0.51 to 4.4)	0.465
Atrial fibrillation	2.78 (0.36 to 21.28)	0.325
Age	1.06 (1.02 to 1.11)	0.007
Alanine Amino Transferase	1.01 (0.98 to 1.03)	0.512
Albumin	0.96 (0.91 to 1.01)	0.095
Anticoagulants	0.6 (0.14 to 2.57)	0.493
Aspartate Aminotransferase	1.02 (1 to 1.05)	0.106
Aortic valve gradient	1.2 (1.05 to 1.37)	0.009
Aortic valve regurgitation grade 1 vs none	0.17 (0.02 to 1.34)	0.092
Aortic valve regurgitation grade 2 vs none	3.63 (1.02 to 12.98)	0.047
Aortic valve regurgitation grade 3 vs none	1.9 (0.22 to 16.56)	0.562
Concomitant aortic valve replacement	2.7 (0.59 to 12.35)	0.2
Body mass index	1.08 (1 to 1.17)	0.06
Bone metastasis	0.77 (0.26 to 2.27)	0.637
Concomitant coronary artery bypass graft	4.34 (0.94 to 20.12)	0.06
Cardiopulmonary bypass time	1 (1 to 1.01)	0.341
Diuretics intravenous	10.81 (2.07 to 56.52)	0.005
Diuretics	0.82 (0.31 to 2.19)	0.695
Gender	1.35 (0.61 to 2.96)	0.461
Hemoglobin	0.73 (0.55 to 0.97)	0.028
5-Hydroxyindoleacetic acid	1 (0.99 to 1)	0.22
Hematocrit	0.9 (0.85 to 0.96)	0.002
INR	0.37 (0.03 to 4.37)	0.431
Creatinine	1.01 (1 to 1.01)	0.084
Lactate dehydrogenasis	1 (0.99 to 1.01)	0.629
Leg edema	3.28 (1.43 to 7.53)	0.005
Liver metastasis	1.15 (0.15 to 8.74)	0.889
Left ventricular end diastolic diameter	1.07 (0.99 to 1.16)	0.107
Left ventricular ejection fraction	1.28 (0.57 to 2.9)	0.552
Left ventricular end systolic diameter	0.97 (0.9 to 1.05)	0.476
Mean corpuscular volume	1 (0.95 to 1.06)	0.855
Mitral regurgitation grade 1 vs none	1.23 (0.38 to 3.94)	0.732

Supplementary Table 2: Cox-proportional hazard ratio's (continued)

Characteristic	Hazard ratio (95% confidence interval)	P-value
Mitral regurgitation grade 2 vs none	0.49 (0.12 to 1.97)	0.316
Mitral regurgitation grade 3 vs none	2.38 (0.27 to 21.28)	0.437
Concomitant mitral valve replacement	1.26 (0.17 to 9.52)	0.822
New York heart association class 3 vs 1	1.2 (0.44 to 3.25)	0.72
New York heart association class 4 vs 1	0.47 (0.11 to 1.94)	0.296
Other metastasis	1.79 (0.84 to 3.82)	0.134
Primary tumor: colon vs small intestine	2.1 (0.6 to 7.32)	0.244
Primary tumor: other vis small intestine	1.58 (0.35 to 7.16)	0.551
Primary tumor: stomach vs small intestine	1 (0.39 to 2.59)	0.997
PV gradient	1 (0.95 to 1.05)	0.862
Concomitant pulmonary valve replacement	0.55 (0.23 to 1.3)	0.173
Size prosthesis (mm)	0.95 (0.81 to 1.11)	0.518
Smoking	1.65 (0.49 to 5.59)	0.42
Somatosin analogue	0.75 (0.21 to 2.62)	0.651
Time between diagnosis neuro-endocrine tumor and diagnoses	1.05 (0.99 to 1.11)	0.114
Tricuspid regurgitation gradient	1.01 (0.97 to 1.05)	0.526
Tricuspid valve gradient (inflow)	1.01 (0.96 to 1.06)	0.749
Type prosthesis (mech vs bio)	1.17 (0.53 to 2.59)	0.693
Mild right ventricle impairment vs. normal	1.37 (0.46 to 4.05)	0.566
Moderate right ventricle impairment vs. normal	0.92 (0.20 to 4.30)	0.918

6

Reconstructive surgery for Ebstein anomaly: three decades of experience

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ABSTRACT

Objectives

Since 1988, our centre employs vertical plication repair with deattachment and reattachment of the tricuspid valve for Ebstein anomaly. This study describes the characteristics and long-term outcomes of our single-centre cohort.

Methods

Data from all patients operated on between 1988 and 2016 were retrospectively collected. Kaplan–Meier analyses were done for survival data and mixed models were used to analyse longitudinally collected clinical and echocardiography data.

Results

Thirty-six patients (mean age: 25.4 ± 15.9 years, 36% male) were operated on using the Carpentier–Chauvaud 21 (58%) or Cone repair 15 (42%). One patient (3%) died in hospital. Two late deaths were observed, yielding a survival of 97 ± 3% at 25 years. Reoperation was performed in 6 patients after a mean follow-up of 14.1 ± 10.3 years, resulting in a freedom of reoperation of 80 ± 8% at 25 years. During follow-up, predicted probability of being in New York Heart Association III/IV did not exceed 10%. Modelling longitudinal evolution of tricuspid regurgitation showed no major changes over time. Additionally, a rigid ring repair was associated with a higher probability of tricuspid regurgitation, especially after the first years after the operation. A full Cone repair was associated with less progression of tricuspid regurgitation over time.

Conclusions

Repair of Ebstein anomaly is associated with low mortality and morbidity, acceptable reoperation rate and excellent valve function over time, especially in patients with completed Cone repair. Therefore, we conclude that in our centre, repair of Ebstein abnomaly is a durable technique to treat patients.

INTRODUCTION

Ebstein's anomaly is a rare congenital heart disorder first described by Wilhelm Ebstein in 1866 and is characterized by apical displacement of the effective tricuspid valve (TV) orifice, resulting in tricuspid regurgitation (TR) and atrialization of the right ventricle (RV) [1]. The estimated prevalence of Ebstein's anomaly is 0.47 cases per 100 000 people [2]. The severity of Ebstein's anomaly varies from a mild phenotype with limited TV displacement and free moving anterior leaflet (type A) to extensive RV atrialization except for a small infundibular component (type D), as classified according to Carpentier classification [3].

Since 1988, our centre has adopted a repair technique consisting of detachment of the TV leaflets, a vertical plication of the arterialized RV and reattachment of the leaflets in the neo-annulus as described by Carpentier et al. [3] and introduced in our clinic by Chauvaud. In this study, we present our 30-year experience with this repair technique.

METHODS

Patients

All 36 patients operated on at our institution between January 1988 and November 2016 with the Carpentier–Chauvaud–Cone technique for Ebstein's anomaly were analysed retrospectively [3]. In addition, 1 patient had a tricuspid valve replacement at initial surgery, due to limited leaflet tissue, which prohibited adequate repair. Four patients received a univentricular approach directly, due to severe Ebstein and impaired right ventricle function (RVF) and 1 patient only received an atrium septum defect (ASD) closure and bidirectional cavopulmonary connection. Approval of the local Medical Ethics Committee was obtained to conduct this study (MEC-2017-384). If follow-up was done in other hospitals, patients were contacted and consent was obtained to request data of interest in these centres.

Indication for operation

The main indication for operation consisted of complaints of progressive dyspnoea, beyond the stage of mild symptoms and characterized by higher New York Heart Association (NYHA) class. Other indications were progressive exercise intolerance, repeated cerebral vascular events and exercise-induced cyanosis.

Operation technique

Carpentier et al. [3] and Quaegebeur et al. [4] described the operation technique previously in great detail. Median sternotomy was performed with cannulation in the ascending aorta and both caval veins. With mild hypothermia and cardioplegic arrest, a right atriotomy was

performed. The severity of Ebstein's anomaly was classified according to the Carpentier classification [3]. Types B, C and D were found in 11, 23 and 2 patients, respectively.

Thereafter, an incision was made in the enlarged anterior TV leaflet starting at the anteroseptal commissure, extending the incision in a clockwise fashion, if possible also into the posterior leaflet. In most cases, the septal valve leaflet was rudimentary and could not be detached. Delaminating apically, the muscular and trabecular connections between the right ventricular wall and leaflet tissue were dissected, taking care not to perforate the right ventricular free wall. Thereafter, the atrialized part of the RV was longitudinally plicated, as described by Quaegebeur et al. [4]. The detached leaflets were rotated clockwise and sutured back in the neo-annulus. Since 1988, we have tried to create a full 360-degree fit of the TV leaflets on the neo-annulus; however, in most cases, this was not possible with the available leaflet material without inducing stenosis. Hence, a subsequent residual TR was accepted. Following the reported favourable outcomes after Cone reconstruction [5], we systematically intended to create the full 360-degree fit to complete the Cone repair, suturing the posterior valve leaflet and (rudimentary) septal valve leaflet. Nowadays, we see the Cone repair as the preferred end point at Carpentier–Chauvaud repair. A ring was implanted in adult patients when considered to provide additional annular support and when the annular plication and the rotation of the leaflets resulted in a neo-annulus with a configuration that fitted with the available standard rings. The final decision as to whether or not to apply a TV ring was made upon the surgeon's discretion. A bidirectional cavopulmonary connection was performed in case of anticipated impaired right ventricular function in order to attempt to unload the RV. The risk of right ventricular impairment after surgery was more frequently deemed higher in case of a reoperation. The final decision whether or not to perform a bi-directional cavopulmonary connection was made upon the surgeon's discretion. All ASDs were closed, preferably primary.

Postoperative care

Patients received coumarins the first 3 months after operation. When patients were in sinus rhythm with adequate RVF, coumarins were stopped after 3 months. Coumarins were continued when indicated. Standard echocardiography was done at the end of operation, at discharge and at regular outpatient visits.

Follow-up

All patients were followed up in the outpatient clinic by paediatric cardiologists (patients <18 years) and congenital cardiologists (patients >18 years). Relevant events, rhythm status, functional status, echocardiograms and medication were collected longitudinally. Clinical events that were collected were implantable cardioverter defibrillator (ICD)/pacemaker implant, cardioversion, thromboembolism, bleeding, endocarditis, myocardial infarction and admission for heart failure. Vital status was checked in the civil registry. Patients were censored at tricuspid valve replacement, death, loss of follow-up and end of follow-up.

Statistical analysis

Continuous data are presented as mean ± standard deviation, if normally distributed, and as median with interquartile range (IQR), if not normally distributed. Categorical data are presented as percentages. Survival data are presented as Kaplan–Meier estimates with the accompanying standard error or in case of Kaplan–Meier plots, with 95% confidence interval (CI). TV gradient was analysed using mixed models with random intercepts for patients and random slope for time. Dichotomous data were modelled using generalized mixed models with random intercepts for patients. Natural splines for time were added to establish flexibility. All the models only contained time, one other covariate and their interaction term to prevent overfitting. In the generalized mixed model, the marginal probabilities were obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest, 3000 patients were generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities was taken as estimate.

Univariable logistic regression was performed to find determinants associated with concomitant ring implant as *post-hoc* analysis. All analyses were done in R (Version 3.3.3) using the 'glm', 'survival' and 'lme4' statistical packages.

RESULTS

Preoperative characteristics

Preoperative characteristics are presented in Table 1. In the 2 patients who underwent prior cardiac surgery, an ASD closure was performed in both patients, one of whom underwent an ASD closure twice. Seven patients had prior episodes of arrhythmias. Supraventricular tachycardia in 5 patients, of whom 1 had an ablation for re-entry tachycardia. The other 4 were treated medically. Another patient was diagnosed with Wolf–Parkinson–White syndrome unsuccessfully treated by an ablation and 1 patient had atrial fibrillation (AF) with sinusbradycardia and subsequent pacemaker implantation. In 20 patients, cor/thorax ratios on X-ray were recorded with a mean of 0.58 ± 0.06.

Procedural characteristics

Median time from diagnosis to operation is 10.3 years (IQR 5.0–12.5). Procedural characteristics are presented in Table 1. In case of a ring implant, a rigid Carpentier-Edwards ring was implanted (subtype of ring: 9 classical and 1 physio). In the 3 patients who underwent concomitant partial cavopulmonary connection, 2 also underwent ring implantation and 1 underwent a Cone reconstruction.

Hospital outcomes

One patient (3%) died 2 days after surgery due to right ventricular failure and ventricular fibrillation unresponsive to therapy. Autopsy revealed an infarction of the RV, which was not caused by the sutures. Rethoracotomy was performed in 2 patients, 1 for bleeding and 1 for suspected cardiac tamponade. Hospital morbidity consisted of episode of ventricular fibrillation in 2 patients (treated by electrical defibrillation), cardiac tamponade in 3 patients (treated by pericardiocentesis in 2) and a pacemaker implant in 1 patient. Median hospital stay is 11 days (IQR 8.5–12.5) and length of intensive care unit stay was reported in 18 patients with a median of 2 days (IQR 2–3).

Table 1: Baseline and operative characteristics

Preoperative characteristics	
n	36
Age[a] (years), mean ± SD	25.4 ± 15.9
Male gender, *n* (%)	13 (36.1)
BMI (kg/m^2), mean ± SD	20.9 ± 4.1
Carpentier classification, *n* (%)	
A	0 (0)
B	11 (31)
C	23 (64)
D	2 (6)
NYHA, *n* (%)	
I	4 (11)
II	12 (33)
III	13 (36)
IV	5 (14)
Unknown	2 (6)
Prior cardiac surgery, *n* (%)	2 (6)
Concomitant ASD,[b] *n* (%)	26 (72)
Concomitant VSD,[b] *n* (%)	2 (6)
Prior arrhythmia, *n* (%)	7 (19)
Prior CVA, *n* (%)	4 (11)
Elevated CVP,[c,d] *n* (%)	6 (17)
Ascites,[c] *n* (%)	0 (0)
Leg oedema,[c] *n* (%)	0 (0)
Hepatomegaly,[c] *n* (%)	5 (14)
Digital clubbing,[c] *n* (%)	5 (14)
Cyanosis,[c] *n* (%)	20 (56)
Diuretics, *n* (%)	1 (3)
Anticoagulation, *n* (%)	4 (11)

Table 1: Baseline and operative characteristics (continued)

Preoperative characteristics	
Digoxin, *n* (%)	2 (6)
Rhythm, *n* (%)	
Sinus	32 (89)
AF	3 (8)
Paced	1 (3)
TR grade, *n* (%)	
None/mild	0 (0)
Moderate	4 (11)
Severe	31 (86)
Unknown	1 (3)
RVF impairment, *n* (%)	
None	26 (72)
Moderate	9 (25)
Severe	1 (3)
Intraoperative characteristics	
CPB time (min), median (IQR)	117 (103–144)
ACC time (min), median (IQR)	88 (73–109)
Concomitant surgery, *n* (%)	
ASD closure	29 (81)
VSD closure	1 (3)
PCPC	3 (8)
Tricuspid ring implant	10 (28)
Cone repair	15 (42)
MAZE	1 (3)

[a]Range (2–58 years).

[b]Observed on echocardiography or during heart catheterization.

[c]Observed at physical examination during the last recorded visit prior to operation.

[d]Diagnosed by visual inspection of external jugular vein.

ACC: aortic cross-clamp; AF: atrial fibrillation; ASD: atrium septum defect; BMI: body mass index; CPB: cardio pulmonary bypass; CVA: cerebral vascular accident; CVP: central venous pressure; IQR: interquartile range; NYHA: New York Heart Association; PCPC: partial cavopulmonary connection; RVF: right ventricle function; SD: standard deviation; TR: tricuspid regurgitation; VSD: ventricular septum defect.

Late clinical outcomes

In total, 500 clinical follow-up moments were recorded during follow-up, with a mean follow-up of 14.1 ± 10.3 years (completeness = 92%). Six patients were partly followed in other centres. Late mortality occurred in 2 patients at 28.6 years and 29.0 years after surgery. Cause of death was non-cardiac in 1 patient and unknown in 1 patient. Overall, survival was 97 ± 3% at 25 years post-surgery. Thromboembolism occurred in 2 patients (1 cerebral and 1 non-cerebral) at 5.2 years and 14.2 years after surgery, yielding a freedom of thromboembolism of 100 ±

0%, 96 ± 4% and 90 ± 7% at 5, 10 and 25 years, respectively. One patient, who was prescribed anticoagulation due to AF, had 2 episodes of epistaxis, which required hospital care at 8.8 years and 9.3 years after surgery. No admissions for heart failure were recorded. Six patients had an episode of NYHA functional class III or IV. Of these 6 patients, 3 were eventually reoperated on. Longitudinal evolution of the probability of being in NYHA class 3 or 4 for an 18-year-old and a 50-year-old patient is presented in Fig. 1.

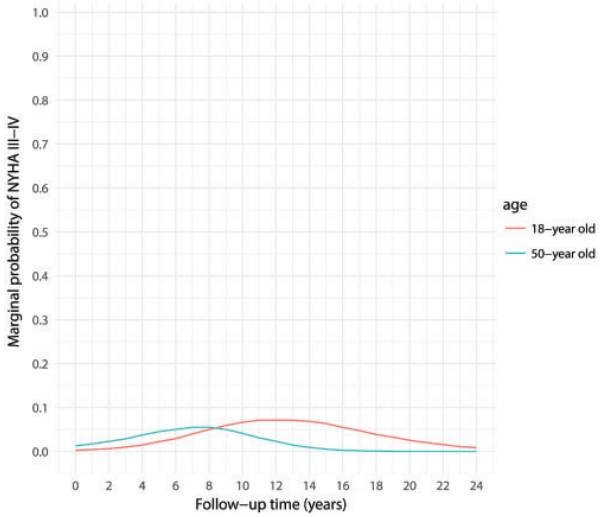

Figure 1: Marginal probability of being in functional class 3 or 4 in an 18-year-old patient and a 50-year-old patient. NYHA: New York Heart Association.

Arrhythmias

In 21 patients, 62 (mean 2.9) episodes of complaints of palpitations were recorded during follow-up, and 5 patients had a subsequent ablation. Ten patients had an electrical cardioversion for supraventricular tachycardia, including AF. In 6 patients, a pacemaker (4) or ICD (2) was implanted during follow-up. Indications for pacemaker implant were atrioventricular block in 3 patients and sinus arrest combined with atrioventricular block in 1 patient. Indications for ICD implant were non-sustained ventricular tachycardia and out-of-hospital cardiac arrest caused by ventricular tachycardia. Freedom of palpitation, cardioversion, ablation and pacemaker/ICD implants are presented in Fig. 2A–D. During follow-up, 13 patients presented with documented arrhythmias, resulting in a freedom of arrhythmia of 73 ± 8%, 64 ± 9% and 53 ± 11% at 5, 10 and 25 years, respectively. The longitudinal evolution of the probability of sinus rhythm versus no sinus rhythm (e.g. AF or paced rhythm) of an 18-year-old patient and a 50-year-old patient is presented in Fig. 3.

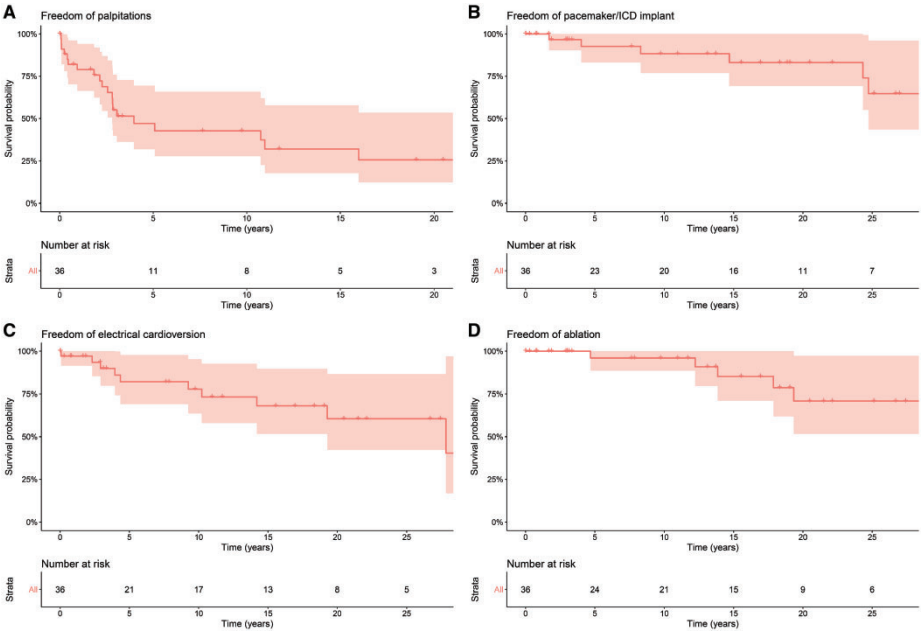

Figure 2: Kaplan–Meier plots of freedom of palpitations (A), pacemaker/ICD implant (B), electrical cardioversion (C) and ablation (D). ICD: implantable cardioverter defibrillator.

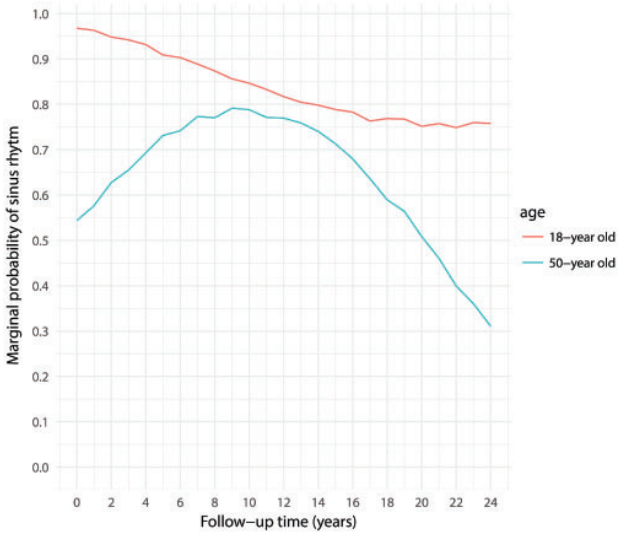

Figure 3: Marginal probability of sinus rhythm in an 18-year-old patient and a 50-year-old patient.

Reoperation

Six patients required 8 reoperations (Table 2). In patients with a tricuspid valve replacement, a St-Jude Medical mechanical valve was implanted. Freedom of reoperation was 88 ± 6%, 80 ± 8% and 80 ± 8% at 5, 10 and 25 years, respectively (Supplementary Material, Fig. S1).

Table 2: Summary of performed reoperations

Patient	First reoperation		Second reoperation	
	Interval (years)	Procedure	Interval (years)	Procedure
1	9.8	Ring implant and PCPC		
2	9.0	TV repair and PCPC		
3	1.6	Re-reconstruction plication, TV repair and ring implant		
4	0.28	TV repair and further detachment of chordal support	0.32	TVR with mechanical prosthesis
5	0.6	TV repair and PCPC	3.0	TVR with mechanical prosthesis and MAZE
6	0.02	TVR with mechanical prostheses		

PCPC: partial cavopulmonary connection; TV: tricuspid valve; TVR: tricuspid valve replacement.

Echocardiography outcomes

During mean follow-up of 14.4 ± 9.8 years, 448 echocardiograms were recorded in 34 patients (mean: 13.2 echocardiograms, range 1–32). Transoesophageal echocardiography directly after the procedure showed a significant reduction (none: 4, trivial/mild: 21, moderate: 5, severe: 3 patients) in TR compared to before surgery ($P < 0.001$). In the 6 patients who required a reoperation, TR grade was severe in 5 patients and moderate in 1 patient on last echocardiogram prior to reoperation. The longitudinal evolution of TV inflow gradient is presented in Fig. 4A, with separate lines for patients receiving a tricuspid ring repair versus repair without a ring. Having a ring repair was not significantly associated with higher overall TV gradient ($P = 0.58$), nor with different changes over time. A higher gradient was not associated with significant TR [odds ratio $(OR)_{per\ 1mmHg}$ 1.03, 95% CI 0.97–1.1; $P = 0.30$].

In Fig. 4B, the evolution of the marginal probability of significant TR is presented. Having a ring as part of the repair was associated with a significantly higher probability of clinically important TR ($P < 0.001$). The determinants associated with ring implantation were older age ($OR_{per\ 1\ year}$ 1.06, 95% CI 1.01–1.03; $P = 0.021$) and a higher systolic blood pressure ($OR_{per\ 1\ mmHg}$ 1.07, 95% CI 1.00–1.14; $P = 0.019$) and preoperative moderate RV impairment (OR 6.89, 95% CI 1.27–37.3; $P = 0.025$).

Carpentier class was not associated with higher probability of moderate-to-severe TR over time ($P = 0.85$) (Supplementary Material, Fig. S2). However, the full Cone repair showed a more

durable result, especially in the long term (Fig. 5). In 6 patients who underwent the full Cone repair, a ring was used.

Ten patients had an episode of severe RV dysfunction on echocardiography, resulting in a freedom of RV dysfunction at 5, 10 and 25 years of 83 ± 7%, 74 ± 9% and 56 ± 12%, respectively. We did not analyse the RV dysfunction longitudinally, because the missing data were highly skewed throughout the years, with more missing data in the early days (Supplementary Material, Fig. S3).

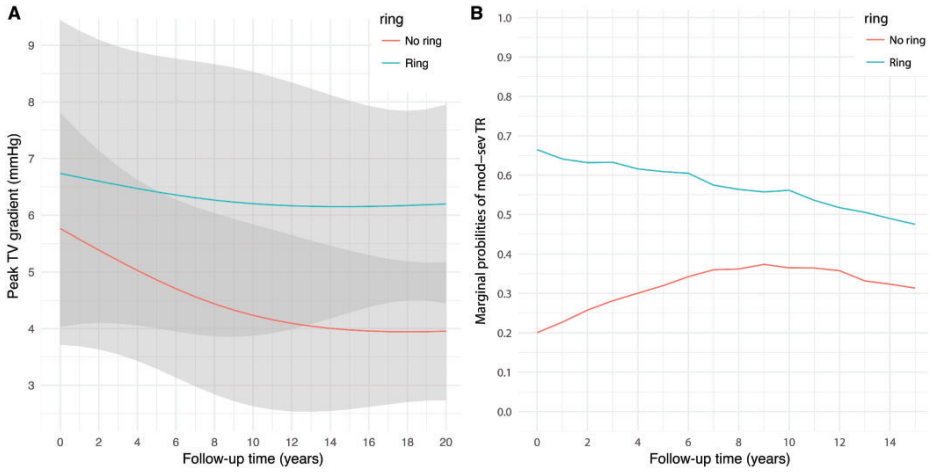

Figure 4: Longitudinal evolution over time of TV peak gradient stratified to a ring implant (A). Marginal probability of moderate-to-severe TR stratified to ring implant (B). TR: tricuspid regurgitation; TV: tricuspid valve.

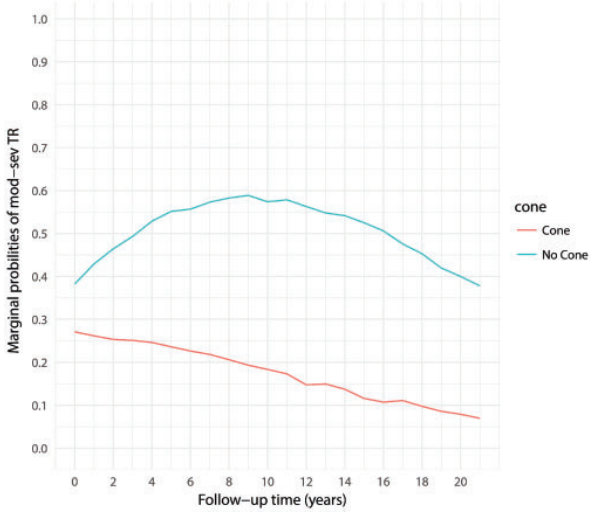

Figure 5: Marginal probability of moderate-to-severe TR stratified to cone repair. TR: tricuspid regurgitation.

Diuretic use

During follow-up, 15 patients were prescribed any form of diuretics. The longitudinal evolution of the probability of prescribed diuretics of an 18-year-old patient and a 50-year-old patient is presented in Supplementary Material, Fig. S4A and B. Seven patients were prescribed furosemide with a mean starting dose of 30 ± 10 mg/24 h (range 20–40 mg). Mean dose at last follow-up was 34.3 ± 9.8 mg/24 h (range 20–40 mg).

DISCUSSION

Ebstein's anomaly has a large variation in TV and right ventricular morphology [6]. Hence, numerous techniques to repair the TV in Ebstein's anomaly have been described [2–4, 7–9]. This study presents a detailed overview of both long-term clinical and echocardiographic outcome after the Carpentier–Chauvaud and Cone repair. As part of continuous evaluation, we have extended our previous reports in terms of the number of patients, the duration of follow-up, and in analysis with advanced statistical methods [10].

Clinical outcomes

Both hospital mortality and morbidity were low in this cohort, which is sustained during follow-up, with an overall survival estimate of 97% at 25 years. These rates are comparable to other series. Brown et al. [11] reported an actuarial survival of 80% at 20 years (337 patients), in which early deaths are excluded and Hetzer et al. [12] reported an actuarial survival of 91% at 20 years (68 patients). Furthermore, these results are very much comparable to other series (Supplementary Material, Table S1).

Functional NYHA III–IV was noted in 6 patients, indicating the overall favourable functional status. Additionally, the predicted probability of being in NYHA class III or IV remains low over time for both 18-year-old and 50-year-old patients, further establishing the low risk of being in NYHA class III/IV during follow-up.

Six patients were reoperated on in this series, yielding a freedom of reoperation of 80% at 25 years. Other studies report actuarial reoperation rates of 73% at 15 years [11]. Da Silva et al. [13] reports 4 reoperations in 52 patients after at least a 10-year follow-up. In this cohort, all patients underwent Cone reconstruction.

Echocardiographic outcome

Assessing the durability of the Carpentier–Chauvaud and Cone repair only by looking at reoperation rates would result in incorrect conclusions, since the reoperation risk may be deemed too high in some patients, and severe residual/recurrent TR or high inflow TV gradient is accepted. Therefore, we modelled the TV gradient and probability of moderate-to-severe TR in order to visualize longitudinal evolution over time.

As expected, TV gradient gradually declined over the years. This may be explained by the fact that the TV annulus dilates throughout the years, resulting in larger TV orifices, and a subsequently lower gradient. A ring implant was associated with a slightly, but not significantly, higher gradient, which was more stable over time.

TR did not increase drastically over the years, indicating a durable repair. However, surprisingly, we found that a ring implant was significantly associated with a higher probability of TR, which is contradictory to the literature [14]. Since only univariable models were used, these findings could be explained by confounding. Therefore, determinants associated with ring implant were explored using univariable logistic regression. An older age, systolic blood pressure and moderate RV impairment were found to be associated with a ring implant. The latter may explain the higher probability of TR in patients with a concomitant ring implant, as RVF impairment is associated with RV dilatation. A heavily dilated RV can result in tethering of the TV, subsequently causing TR. Additionally, confounding by indication may be present, as the choice to implant a ring may be motivated by that fact that the repair is not satisfactory and a ring is implanted to attempt to improve the repair.

When a ring was used, a Carpentier-Edwards rigid ring was applied in all patients. These rings have a predefined shape, designed for a normal TV annulus. We hypothesized that the TV annulus of patients who underwent Carpentier–Chauvaud–Cone repair does not have a normal annulus shape, even if the geometry after the repair resembles the normal annulus shape. In fact, forcing the annulus into the ring-shape might lead to deformation of the created neo-annulus, resulting in malcoaptation of the leaflets and subsequent TR. This also may explain why Dearani et al. [14] found a favourable association with concomitant ring implant, because in this cohort, only flexible rings are used.

Patients with Ebstein's anomaly have a higher risk of arrhythmias compared to the general population [15, 16]. Not surprisingly, the incidence of symptomatic palpitations in this cohort was relatively high. However, a patient may have 1 short episode of AF and undergo cardioversion and live out his remaining life in sinus rhythm [17]. Simply analysing freedom of AF could convey an inaccurate message. Therefore, we collected rhythm status serially and used mixed modelling to analyse these repeated measurements. Using these models, one can visualize the probability of being in sinus rhythm over time with effect plots, as is shown in Fig. 2. Effect plots of the longitudinal evolution of the probability of sinus rhythm of an 18-year-old patient and a 50-year-old patient showed different patterns. In the 18-year-old patient, the risk of having arrhythmia was relatively low after the surgery and this risk gradually increased over time (Fig. 3). In the 50-year-old patient, the risk of arrhythmia was relatively high after the surgery, but this risk decreased during follow-up. When patients become older, the probability of being in sinus rhythm decreases significantly. These different patterns underlie the notion that subject-specific outcome modelling is needed, especially in patients with Ebstein's anomaly, which is known to be very heterogeneous [6].

Strengths and limitations

Strengths of this study include the length of follow-up and the number of follow-up moments. We managed to obtain 500 clinical follow-up moments and 448 echocardiograms. This is mainly due to the fact that patients with congenital heart disease are closely monitored in specialized centres in the Netherlands. The abundant follow-up moments enabled us to use advanced statistical methods to visualize outcomes over time. A limitation is the relatively small single-centre sample size, which limits the use of multivariable modelling, allowing confounding factors to influence results. Other limitations include the possible recall bias in complaints of palpitations and misclassification of NYHA functional class and TR grade. However, we dichotomized these variables to create a more robust measurement, accepting the loss of information paired with dichotomization. Additionally, we did not have magnetic resonance imaging data and echocardiographic assessment of RVF was mostly missing in the early days. In these days, RVF was only reported, if impaired. This prevents longitudinal analyses since the data are not missing at random. Moreover, assessment of right ventricular function is already a semi-quantitative measure, which is expected to change over time. Lastly, the mechanism of the TR (i.e. annular dilation or tethering) was not reported.

CONCLUSIONS

Reconstructive valve surgery for Ebstein is associated with low mortality and morbidity, acceptable reoperation rates and excellent valve function of the TV beyond the first 2 postoperative decades, especially in patients with completed Cone repair. Therefore, we conclude that the Carpentier–Chauvaud (preferably extended into Cone) technique is a durable repair technique for patients with Ebstein's anomaly. When the repair included the use of a rigid ring, more TR was observed. Further studies are needed to evaluate whether this was caused by the rigid ring itself or whether confounding or selection bias was present.

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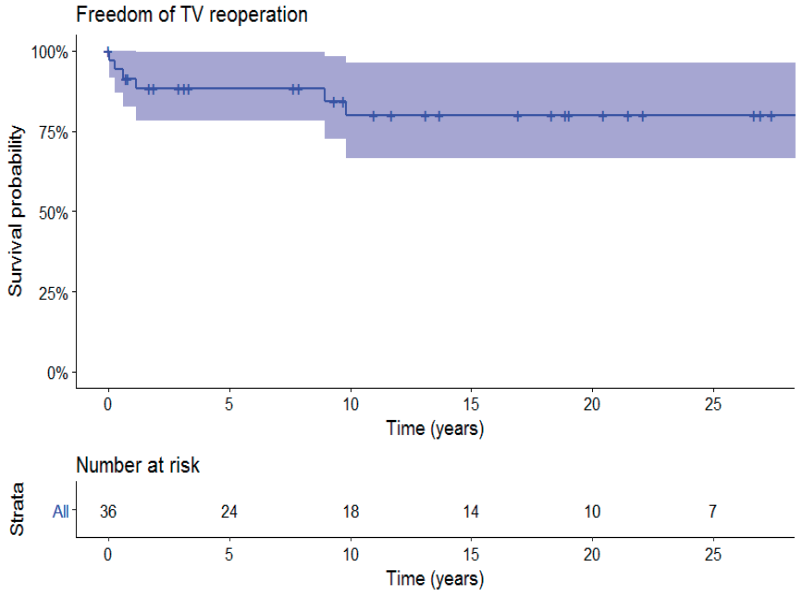
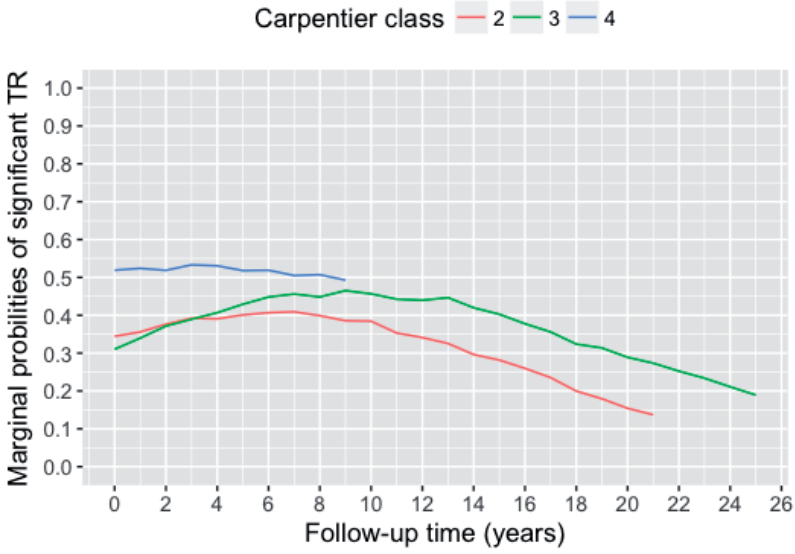
SUPPLEMENTARY MATERIAL

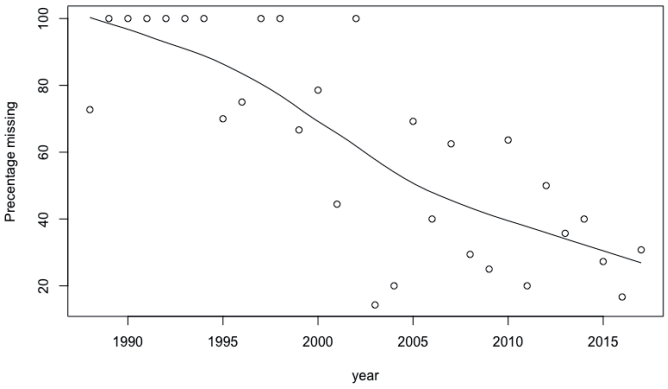
CONTENTS



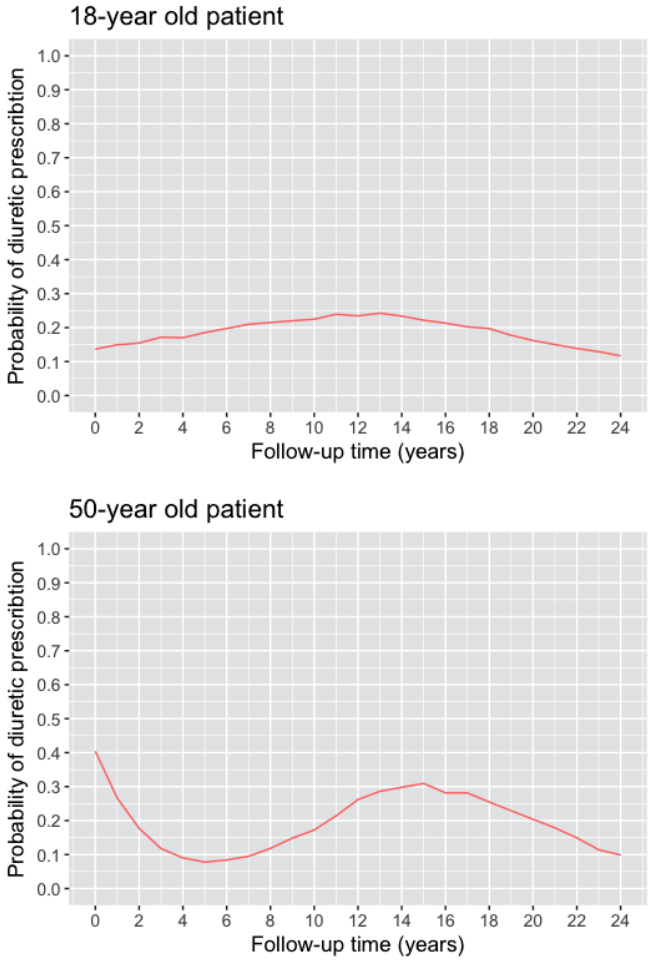
Supplementary Figure 1. Kaplan-Meier plot of freedom from reoperation



Supplementary figure 2. Marginal probability of significant TR stratified to Carpentier class



Supplementary figure 3. A plot of the percentage missing according the year of surgery, with a smoother line



Supplemetary figure 4ab. Marginal probability of diuretic use of a 18-year-old patient (A) and a 50-year-old patient (B)

Supplementary Table 1: Other reported series on reconstructive surgery for Ebstein. KM: Kaplan Meier.

Series	N patients	Mortality	Reoperation
Da Silva, 2011	52	86.2 % at six years (KM estimate)	4 patients with mean follow-up of 57 months
Wu, 2007	78	No hospital mortality	-
Li, 2016	21	None after 9.1 months follow-up	1 after 9.1 months follow-up
Liu, 2011	30	1 (hospital mortality) after 1.9 years follow-up	None after 1.9 years follow-up
Ibragim, 2015	27	None after follow-up 2.7 years	1 (for ASD) after 2.7 years of follow-up
Nguyen, 2014	52	None after follow-up of 42 months	None after follow-up of 42 months

7

Tricuspid valve replacement: an appraisal of 45 years of experience

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The first two authors contributed equally to this work.

ICVTS, February 2020

ABSTRACT

Objectives

This study provides an overview of the change over a 45-year time period in the characteristics and outcome of patients with tricuspid valve disease undergoing surgical tricuspid valve replacement (TVR).

Methods

The characteristics and outcomes of all consecutive TVRs from November 1972 to November 2017 at Erasmus MC were collected retrospectively. A logistic regression analysis was conducted to identify the significant predictors of 30-day mortality. Multivariable Cox regression analysis was used to identify the potential risk factors of patient outcome and the effect of time on these factors.

Results

Ninety-eight patients with tricuspid valve dysfunction underwent 114 consecutive TVRs at a mean age of 50.1 ± 17.2 years (68.5% female). Aetiology changed over time from predominantly functional regurgitation (42.9% in 1972-1985) to predominantly carcinoid heart disease (47.7% in 2001-2017). Early mortality declined significantly from 35% in 1972–1985 to 6.7% in 2001–2017 ($P < 0.001$). Over time, the hazard ratio of late mortality decreased for higher New York Heart Association class, lower preoperative haemoglobin, and high central venous pressure and increased for the presence of preoperative leg oedema, higher creatinine and alkaline phosphatase. The late survival was 43.8% ± 5.89% at 10 years and was comparable among eras ($P = 0.44$). The cumulative incidence of reoperation at 10 years was 14.1% (2.3–26.0) in biological valves and 4.9% (0.1–10.3) in mechanical valves ($P = 0.25$).

Conclusions: Patient characteristics, potential risk factors and patient outcome changed considerably over time in patients undergoing TVR. Notably, there was a shift in aetiology, completely altering the patient population and their characteristics.

ABBREVIATIONS

HR	**Hazard ratio**
RV	**Right ventricular**
TVR	**Tricuspid valve** replacement

INTRODUCTION

Tricuspid valve disease can be classified into functional or structural valve disease. Almost 85% of patients have functional tricuspid valve disease [1], which is related to tricuspid annular dilation and leaflet tethering in the setting of right ventricular (RV) remodelling due to pressure and/or volume overload. Since there is no structural damage, patients are usually eligible for annuloplasty [2, 3]. Tricuspid valve replacement (TVR) is consequently only reserved for advanced stages of functional tricuspid valve disease with severe tethering [2–4]. The second group, consisting of 15% of the population, with structural tricuspid valve disease repair is often not feasible [1, 3, 5]. Possible causes of structural tricuspid regurgitation (TR) are infective endocarditis, rheumatic heart disease, carcinoid syndrome, myxomatous disease, endocardial fibrosis, Ebstein's anomaly and congenitally dysplastic valves, thoracic trauma and iatrogenic valve damage [3]. Compared with aortic or mitral valve replacement surgery, the prevalence of TVR is considerably lower, compromising only 0.7– 2.0% of all valve operations [6, 7]. TVR is, therefore, a relatively rare intervention, only indicated when the repair is not feasible and for those with structural tricuspid valve disease.

Patients with tricuspid valve disease are usually asymptomatic for prolonged periods of time before RV dysfunction or failure develops [4, 5]. Patients referred for TVR are therefore usually either severely disabled by cardiac disease or have undergone previous cardiac procedures [3]. Accordingly, patients undergoing TVR tend to be at higher risk and operative outcomes have traditionally been poor [1, 4]. Operative mortality after TVR has in the past few decades declined despite worsening risk factors, reported to range from 7.7% to 37% [1, 4, 5, 8–17].

Mortality and morbidity rates after TVR have been previously reported [1]. However, a descriptive study describing how these outcomes and risk factors changed over timeis lacking. In this study, we review the change in patient presentation, outcome and risk factors for TVR in a single-centre retrospective cohort study, spanning nearly 5 decades.

METHODS

Patients

We retrospectively reviewed the hospital records for all patients who underwent TVR at our institution, Erasmus MC, between November 1972 and November 2017. Ninety-eight con-

secutive patients with tricuspid valve dysfunction undergoing TVR were identified. In total, 98 patients underwent 114 TVRs, either as an isolated procedure or in combination with another procedure. The population was divided into 3 eras: 1972–1985, 1986–2000 and 2001–2017. Approval was obtained from the institutional medical ethical committee to conduct this study (MEC-2017-135). Informed consent was waived. The final choice of prosthesis type was at the discretion of the attending surgeon. In the case of carcinoid heart disease, a mechanical prosthesis was implanted.

Outcomes

Main outcomes were early (30-day) and late mortality. Secondary outcomes were thromboembolism, bleeding events, endocarditis and reoperation, defined according to the criteria of Akins et al. [18]. Patients were followed until the end of follow-up, death or reoperation. Vital status was checked in the Dutch civil registry on 27 January 2019.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (Gaussian) and as median with interquartile range (non-Gaussian). Categorical data were presented as percentages. Normality was tested using the Shapiro–Wilk test. Comparisons were made with the analysis of variance (ANOVA) or Kruskal–Wallis test in case of a non-Gaussian distribution. Categorical data were compared with the χ^2 test or Fisher's exact test, in case of a cell frequency of <5. Potential predictors of 30-day mortality were identified using a univariable logistic regression analysis.

Both overall mortality and late mortality were calculated and presented as Kaplan–Meier estimates, and log-rank tests were used to compare groups. Unexpected bleeding, valve thrombosis and reoperation were considered a competing risk with mortality and Fine and Gray [19] competing risk models were used to calculate cumulative incidences. Gray's tests were used to quantify significant differences between biological and mechanical valve prostheses. Kaplan–Meier plots for survival were estimated by using individual patients undergoing TVR, whereas the cumulative incidence plots were estimated by using individual tricuspid valve procedures. Change in the weight of the risk factors over time for late mortality (>30 days) was assessed using a multivariable Cox regression analysis, including the risk factor, the year of surgery and the interaction term between these two. Violations of proportional hazard assumption for this Cox regression were checked by using the Schoenfeld residuals. Duration of follow-up was calculated with the inverse Kaplan–Meier method [20]. Completeness of follow-up is calculated with the modified Clarks method (*C) [21]. Statistical analysis was done in R (R Foundation for Statistical Computing, Vienna, Austria, macOS, version 1.1.463) with the use of the 'glm', 'tableone', 'survival', 'survminer' and 'cmprsk' packages.

RESULTS

Follow-up

The mean follow-up of hospital survivors was 24.7 years (range 0.06–40.5 years), with a clinical follow-up completeness of 86.0% (*C). The survival follow-up was 100% (*C) complete. The cumulative total follow-up was 694.78 patient-years.

Patient characteristics

In total, 98 patients underwent 114 consecutive TVR. Sixty-one were female patients (68.5%) with a mean age of 50.1 ± 17.2 years (range 5.4–70.1 years). Table 1 presents the baseline characteristics of these patients. The underlying diseases of these patients included functional (*n* = 20), prosthesis thrombosis (*n* = 4), valve pannus (*n* = 2), repair failure (*n* = 20), endocarditis (*n* = 3), Ebstein's anomaly (*n* = 2), carcinoid (*n* = 27), complex congenital disease (*n* = 3),

Table 1: Baseline characteristics of patients undergoing tricuspid valve replacement

Era	1972–1985	1986–2000	2001–2017	*P*-value
n	**40**	**29**	**45**	
Age (years), median (IQR)	53.23 (35.16–59.03)	53.95 (41.80–60.17)	52.54 (45.39–62.18)	0.593[a]
Female, *n* (%)	22 (59.5)	15 (68.2)	24 (61.5)	0.794[b]
BMI (kg/m^2), median (IQR)	21.09 (19.84–22.62)	22.41 (21.28–23.87)	23.62 (21.43–27.23)	0.008[a]
NYHA, *n* (%)				0.003[c]
I	0 (0.0)	0 (0.0)	2 (5.6)	
II	5 (12.5)	2 (6.9)	9 (25.0)	
III	19 (47.5)	19 (65.5)	23 (63.9)	
IV	16 (40.0)	8 (27.6)	2 (5.6)	
Hepatomegaly, *n* (%)	26 (78.8)	21 (80.8)	19 (45.2)	0.002[b]
Prior cardiac surgery, *n* (%)	25 (62.5)	22 (75.9)	21 (46.7)	0.040[b]
Prior TV related surgery, *n* (%)	7 (17.5)	17 (58.6)	17 (37.8)	0.002[b]
Concomitant surgery, *n* (%)				
Isolated TVR	4 (10.0)	8 (27.6)	15 (33.3)	0.029[c]
PVR	0 (0.0)	7 (24.1)	19 (42.2)	<0.001[c]
AVR	10 (25.0)	5 (17.2)	1 (2.2)	0.004[c]
MVR	25 (62.5)	6 (20.7)	5 (11.1)	<0.001[c]
CABG	2 (5.0)	2 (6.9)	1 (2.2)	0.626[c]
Other	7 (17.5)	14 (48.3)	24 (53.3)	0.001[b]
Aetiology: functional, *n* (%)	18 (47.4)	1 (3.6)	1 (2.3)	<0.001[c]
Urea (mmol/l), median (IQR)	9.45 (6.35–12.80)	7.25 (5.57–10.45)	6.90 (5.20–10.10)	0.276[a]
Creatinine (µmol/l), median (IQR)	85.00 (75.50–99.50)	82.00 (67.00–101.00)	92.00 (69.00–110.00)	0.495[a]

structural valve deterioration of biological prosthesis (n = 12), rheumatic (n = 13), unknown (n = 4) and others (n = 4). Distribution of aetiology changed considerably over time (Fig. 1). Functional tricuspid valve regurgitation decreased significantly over time [18 (45.0%) patients in the first era and 2 (2.7%) patients in the 2 later eras, $P < 0.001$]. Cardiopulmonary bypass time decreased significantly over time ($P = 0.011$). A total of 74 mechanical valves (74.9%) were implanted, proportionally increasing significantly over time ($P < 0.001$). All procedural characteristics are shown in Table 2.

Table 1: Baseline characteristics of patients undergoing tricuspid valve replacement (continued)

Era	1972–1985	1986–2000	2001–2017	*P*-value
Albumin (g/l), median (IQR)	43.00 (35.00–47.00)	44.00 (40.00–46.00)	41.50 (35.00–45.00)	0.242[a]
ASAT (U/l), median (IQR)	27.00 (22.00–31.00)	24.00 (16.00–29.00)	31.00 (24.75–41.00)	0.010[a]
ALAT (U/l), median (IQR)	17.00 (14.00–-25.00)	18.00 (13.00–24.00)	22.00 (17.00–36.00)	0.107[a]
ALP (U/l), median (IQR)	58.00 (43.50–83.00)	72.00 (59.00–162.00)	120.00 (85.00–201.00)	<0.001[a]
Hb (mmol/l), median (IQR)	8.05 (7.50–9.38)	7.30 (6.80–8.60)	7.90 (6.70–8.60)	0.071[a]
Ht, median (IQR)	0.40 (0.36–0.45)	0.37 (0.34–0.40)	0.38 (0.34–0.43)	0.041[a]

[a] Kruskal–Wallis.
[b] χ^2 test.
[c] Fisher's exact test.
ALAT: alanine aminotransferase; ALP: alkaline phosphatase; ASAT: aspartate aminotransferase; AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass graft; Hb: haemoglobin; Ht: haematocrit; IQR: interquartile range; MVR: mitral valve replacement; NYHA: New York Heart Association; PVR: pulmonary valve replacement; TV: tricuspid valve; TVR: tricuspid valve replacement.

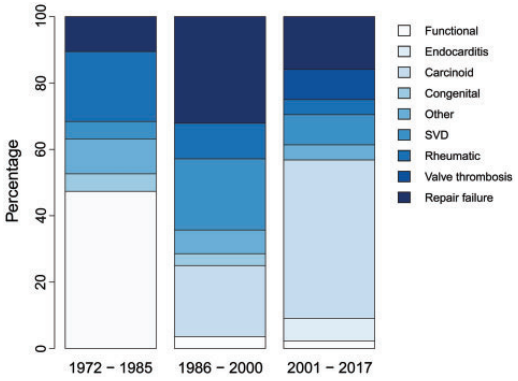

Figure 1: Stacked barplot of different valve aetiologies in 3 eras. SVD: structural valve deterioration.

Early outcomes

In total, 18 (20.2%) patients died within 30 days after TVR. Early mortality declined significantly over time [14 (35.0%) patients in the first era, 1 (3.4%) patient in the second era and 3 (6.7%) patients in the last era, $P < 0.001$]. The causes of early mortality included: heart failure ($n = 10$), thromboembolism ($n = 1$) or others ($n = 7$). The admission duration also decreased significantly from 25.0 days in 1972 to 11.5 days in 2017 ($P < 0.001$). In addition, intensive care unit stay decreased significantly from 7.5 to 2.0 days in 2017 ($P < 0.001$) (Table 2).

Using logistic regression, several determinants were significantly associated with higher 30-day mortality (Table 3). Among others, an earlier era [hazard ratio (HR) 0.29, 95% CI 0.13–0.59; $P = 0.002$] and biological prostheses (HR 0.21, 95% CI 0.07–0.58; $P = 0.004$) were associated with higher 30-day mortality.

Table 2: Procedural characteristics, postoperative outcomes and morbidity described by Akins et al. of patients undergoing tricuspid valve replacement

Era	1972–1985	1986–2000	2001–2017	*P*-value
n	**40**	**29**	**45**	
ACC (min), median (IQR)	110.00 (79.00–147.00)	71.00 (53.00–133.00)	99.00 (65.75–130.50)	0.099[a]
CPB (min), median (IQR)	185.00 (152.50–265.50)	134.00 (105.25–210.25)	140.00 (120.50–191.25)	0.011[a]
Early reopening, *n* (%)	4 (10.0)	1 (3.4)	9 (20.0)	0.108[b]
Mechanical valve prosthesis, *n* (%)	7 (17.5)	23 (79.3)	44 (97.8)	<0.001[c]
Types, *n* (%)				
SJM	1 (2.6)	21 (72.4)	43 (97.7)	<0.001[b]
Hancock	30 (76.9)	2 (6.9)	0 (0.0)	<0.001[b]
Other	8 (20.5)	6 (20.7)	1 (2.3)	0.011[b]
Early mortality (<30 days), *n* (%)	14 (35.0)	1 (3.4)	3 (6.7)	<0.001[b]
Admission duration (days), median (IQR)	25.00 (15.50–35.00)	16.00 (12.50–22.00)	11.50 (10.00–16.25)	<0.001[a]
ICU stay (days), median (IQR)	7.50 (5.75–18.50)	5.00 (4.00–9.00)	2.00 (2.00–3.00)	<0.001[a]

[a] Kruskal–Wallis.
[b] Fisher's exact test.
[c] χ^2 test.
ACC: aortic cross-clamp time; CPB: cross-pulmonary bypass time; ICU: intensive care unit; IQR: interquartile range; SJM: Saint Jude Medical.

Table 3: Univariable logistic regression for early mortality (<30 days) for patients undergoing tricuspid valve replacement

Covariate	Odds ratio (95% confidence interval)	*P*-value
Era	0.294 (0.13–0.59)	0.002
Year of surgery	0.922 (0.87–0.97)	0.026
Age	1.003 (0.97–1.04)	0.822
Female gender	0.47 (0.15–1.43)	0.182

Table 3: Univariable logistic regression for early mortality (<30 days) for patients undergoing tricuspid valve replacement (continued)

Covariate	Odds ratio (95% confidence interval)	*P*-value
Prior TV operation	0.45 (0.12–1.38)	0.193
BMI	0.963 (0.84–1.1)	0.581
Diabetes mellitus	3.5 (0.83–13.26)	0.070
NYHA	2.187 (0.99–5.25)	0.065
ACC	1.011 (1–1.02)	0.439
CPB	1.015 (1.01–1.02)	0.04
Mechanical prosthesis	0.206 (0.07–0.58)	0.004
Dose furosemide	1.011 (1–1.02)	0.014
Dose bumetanide	0.897 (0.41–1.28)	0.665
Concomitant surgery		
AVR	4.3 (1.27–13.92)	0.090
MVR	6 (2.1–18.9)	0.015
PVR	0.167 (0.01–0.88)	0.001
CABG	1.353 (0.07–9.86)	0.792
High CVD	1.236 (0.36–4.92)	0.744
Leg oedema	0.809 (0.2–2.78)	0.744
Atrial fibrillation	2.302 (0.79–7.7)	0.144
Diuretic use	0.685 (0.2– -2.7)	0.556
Aetiology: functional	5.333 (1.74–16.41)	0.003
Prosthesis type		
SJM	0.172 (0.05–0.53)	0.004
Hancock	6.46 (2.2–20.76)	0.001
Other	0.841 (0.12–3.47)	0.831
Urea (mmol/l)	1.139 (1.02–1.27)	0.018
Creatinine (µmol/l)	1.015 (1–1.03)	0.035
Albumin (g/l)	0.954 (0.88–1.03)	0.226
ASAT (U/l)	1.026 (1–1.06)	0.076
ALAT (U/l)	1.016 (1–1.04)	0.103
ALP (U/l)	0.996 (0.99–1)	0.319
Hb (mmol/l)	0.705 (0.44–1.09)	0.130
Ht	0.001 (0–8.61)	0.141

ACC: aortic cross-clamp time; ALAT: alanine aminotransferase; ALP: alkaline phosphatase; ASAT: aspartate aminotransferase; AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass graft; CPB: cross-pulmonary bypass time; CVD: central venous pressure; Hb: haemoglobin; Ht: haematocrit; MVR: mitral valve replacement; NYHA: New York Heart Association; PVR: pulmonary valve replacement; SJM: Saint Jude Medical; TV: tricuspid valve.

Late outcomes

Eighty patients died during the total follow-up period (18 early and 62 late deaths). The 1-, 5-, 10- and 15-year survival rates were 77.1% ± 4.30%, 56.5% ± 5.22%, 36.9% ± 5.23% and 22.5%

± 4.79%, respectively, and are shown in Fig. 2A. The linearized occurrence rate of late death was 8.9%/year. The 1-, 5-, 10- and 15-year survival rates excluding early mortality were 90.0% ± 3.36%, 65.6% ± 5.50%, 43.8% ± 5.89% and 26.7% ± 5.55%, respectively (Fig. 2B). Causes of late death include heart failure (*n* = 16), non-cardiac related death (*n* = 8), bleeding (*n* = 4), infection (*n* = 4), endocarditis (*n* = 1) and unknown (*n* = 20). When compared over the 3 time periods, the 1-, 5-, 10- and 15-year survival rates did not differ significantly (*P* = 0.44) (Fig. 2C).

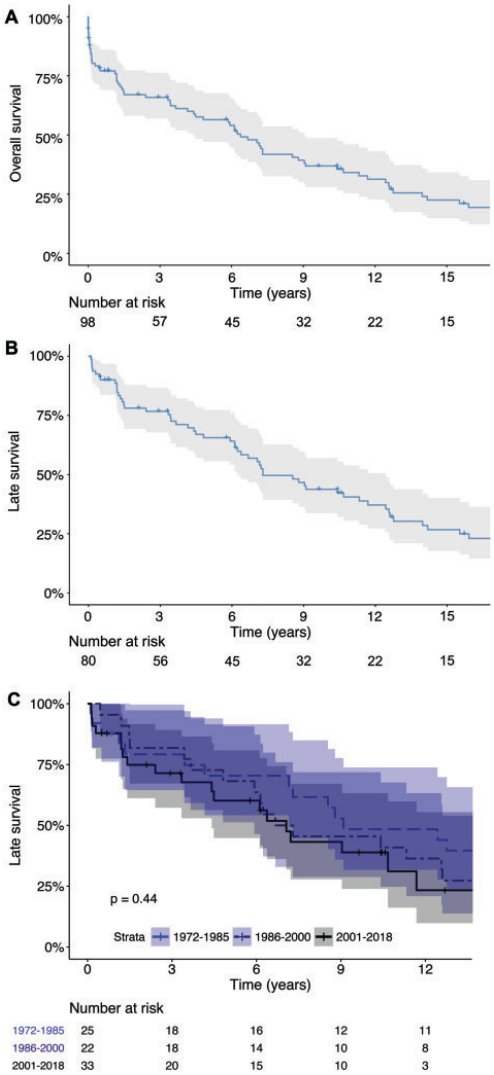

Figure 2: (A) Kaplan–Meier plot of survival (early + late) per patient after tricuspid valve replacement. (B) Kaplan–Meier plot of late survival per patient after tricuspid valve replacement. (C) Kaplan–Meier plot of late survival per patient after tricuspid valve replacement stratified to era.

Furthermore, there was no difference between the survival rate for mechanical and biological prosthesis implantations (*P* = 0.20).

There were 16 TVR reoperations in 13 different patients during the follow-up period [linearized occurrence rate (LOR): 2.4%/ year]. In 9 (36.5%) out of 16 reoperations, a patient had a biological prosthesis previously, whereas 7 (62.5%) reoperations were done in patients with a previous mechanical prosthesis. In patients with a prior mechanical prosthesis, indications for reoperation were valve thrombosis (*n* = 4), pannus (*n* = 2) and subvalular stenosis (*n* = 1). In patients with a prior biological prosthesis, indications for reoperation were structural valve deterioration (*n* = 7) and non structural valve deterioration (NSVD) (*n* = 2). Cumulative incidence of reoperation was comparable between patients receiving a mechanical- and biological valve prosthesis (*P* = 0.25) (Fig. 3). There were also no significant differences in reoperation when mechanical versus bioprosthetic valve replacement was compared over the 3 time periods (*P* = 0.71).

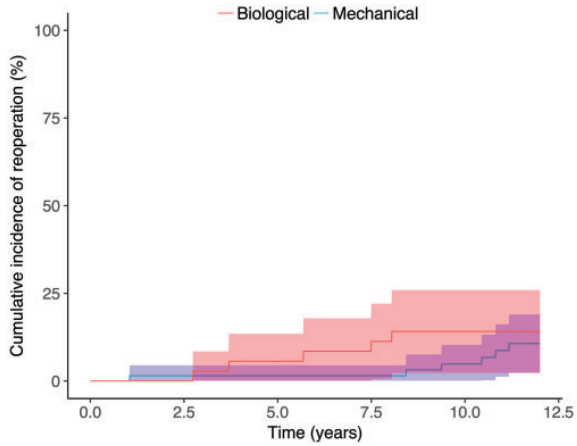

Figure 3: Cumulative incidence of freedom from reoperation after tricuspid valve replacement, mechanical compared to biological valve prosthesis (per procedure).

A bleeding event occurred in 17 patients, and 6 patients had tricuspid valve thrombosis during the follow-up period. Cumulative incidence of bleeding (*P* = 0.14) and valve thrombosis (*P* = 0.072) were comparable between patients receiving a mechanical and biological valve prosthesis (Fig. 4A and B). Four patients had endocarditis at 0.25, 4.57, 4.81 and 6.23 years after initial TVR.

Change in risk factors late mortality

Multivariable Cox regression identified multiple risk factors with either an increased or decreased HR in interaction with time. Over time the HR of late mortality decreased for New York

Heart Association, preoperative haemoglobin and high central venous pressure and increased for preoperative leg oedema, alkaline phosphatase and creatinine (Table 4).

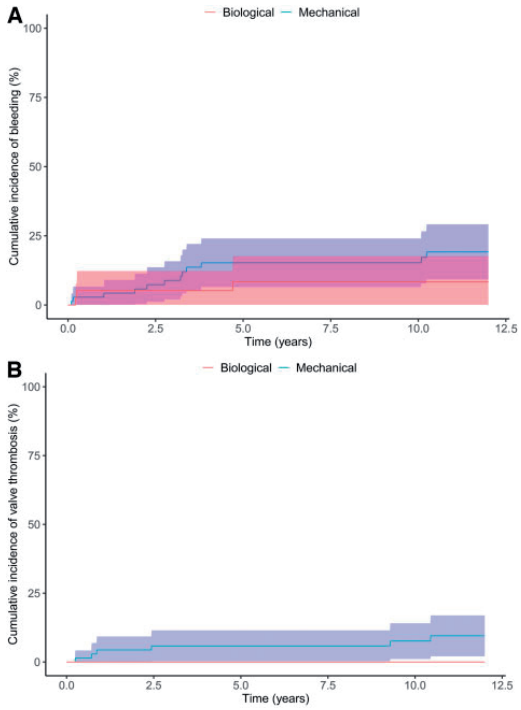

Figure 4: Cumulative incidence of (A) bleeding and (B) valve thrombosis after tricuspid valve replacement, mechanical compared to biological valve prosthesis (per procedure).

Table 4: Cox regression models of late mortality for different risk factors in patients undergoing tricuspid valve replacement

	Variables		**Year**		**Interaction term**	
	Hazard ratio (95% confidence interval)	***P*-value**	**Hazard ratio (95% confidence interval)**	***P*-value**	**Hazard ratio (95% confidence interval)**	***P*-value**
Age	1.02 (0.98–1.06)	0.418	0.93 (0.83–1.03)	0.161	1.00 (0.99–1.00)	0.120
Female gender	1.33 (0.39–4.57)	0.647	1.02 (0.97–1.06)	0.478	0.99 (0.94–1.04)	0.727
Prior TV operation	0.75 (0.17–3.30)	0.71	1.03 (1.00–1.06)	0.021	0.98 (0.93–1.04)	0.556
BMI	0.93 (0.77–1.12)	0.431	0.89 (0.76–1.05)	0.161	1.01 (1.00–1.01)	0.133
NYHA 3–4	9.96 (1.21–82.07)	0.033	1.09 (1.02–1.17)	0.013	0.92 (0.85–0.99)	0.022
Diabetes mellitus	0.02 (0–8.06)	0.206	1.00 (0.97–1.03)	0.853	1.19 (0.98–1.44)	0.078

Table 4: Cox regression models of late mortality for different risk factors in patients undergoing tricuspid valve replacement (continued)

	Variables		Year		Interaction term	
Admission duration	1.07 (1.02–1.12)	0.01	1.06 (1.00–1.12)	0.05	1.00 (0.99–1.00)	0.24
ACC	1.01 (1–1.02)	0.136	1.03 (0.98–1.09)	0.243	1.00 (0.99–1.00)	0.368
CPB	1.01 (1–1.02)	0.034	1.06 (0.98–1.15)	0.176	1.00 (0.99–1.00)	0.371
Mechanical prosthesis	0.98 (0.18–5.44)	0.981	1.01 (0.9–1.15)	0.840	1.00 (0.88–1.14)	0.979
Concomitant surgery						
AVR	1.71 (0.42–7.04)	0.456	1.02 (0.99–1.04)	0.297	1.00 (0.92–1.09)	0.990
MVR	5.14 (1.37–19.29)	0.015	1.03 (1.00–1.07)	0.056	0.94 (0.88–1.01)	0.086
PVR	0.16 (0.01–2.14)	0.165	1.00 (0.97–1.03)	0.823	1.06 (0.98–1.16)	0.139
CABG	0.91 (0.02–48.28)	0.965	1.01 (0.98–1.03)	0.582	1.04 (0.91–1.2)	0.565
High CVD	6.4 (1.4–29.22)	0.017	1.05 (1.00–1.1)	0.053	0.94 (0.89–1.00)	0.045
Leg oedema	1.06 (0.3–3.75)	0.931	0.98 (0.94–1.02)	0.236	1.06 (1.00–1.11)	0.045
Diuretic use	1.97 (0.41–9.6)	0.4	1.01 (0.95–1.08)	0.695	0.99 (0.93–1.06)	0.821
Atrial fibrillation	2.54 (0.43–14.95)	0.302	1.04 (0.98–1.1)	0.211	0.97 (0.91–1.04)	0.427
Aetiology: functional	5.04 (0.63–40.01)	0.126	1.03 (1.00–1.06)	0.086	0.94 (0.78–1.14)	0.524
Urea (mmol/l)	1.05 (0.85–1.29)	0.662	1.00 (0.92–1.08)	0.925	1.00 (0.99–1.01)	0.392
Creatinine (µmol/l)$_{per\ 50}$	1.11 (0.38–3.16)	0.846	0.94 (0.87–1.01)	0.111	1.03 (1.00–1.07)	0.043
Albumin (g/l)	0.99 (0.89–1.09)	0.796	1.07 (0.91–1.25)	0.415	1.00 (1.00–1.00)	0.564
ASAT (U/l)	1.02 (0.98–1.05)	0.407	1.00 (0.94–1.06)	0.954	1.00 (0.99–1.00)	0.652
ALAT (U/l)	1.01 (0.95–1.07)	0.796	1.00 (0.95–1.06)	0.896	1.00 (0.99–1.00)	0.892
ALP (U/l)$_{per\ 50}$	0.79 (0.54–1.15)	0.220	0.97 (0.93–1.01)	0.157	1.01 (1.00–1.02)	0.019
Hb (mmol/l)	1.56 (0.96–2.52)	0.072	1.28 (1.09–1.5)	0.003	0.97 (0.95–0.99)	0.003

Each model contained the risk factor, year of surgery and its interaction term.

ACC: aortic cross-clamp time; ALAT: alanine aminotransferase; ALP: alkaline phosphatase; ASAT: aspartate aminotransferase; AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass graft; CPB: cross-pulmonary bypass time; CVD: central venous pressure; Hb: haemoglobin; MVR: mitral valve replacement; NYHA: New York Heart Association; PVR: pulmonary valve replacement; TV: tricuspid valve.

DISCUSSION

This study presents the change in outcomes and risk factors over time for patients undergoing TVR in a single-centre retrospective cohort. We found that early mortality decreased significantly and that the prevalence and weight of risk factors changed considerably during our 45-year experience with TVR.

Early outcomes

Early outcomes after TVR have improved significantly over the past several decades [1, 9, 12–14, 22]. The 30-day mortality risk in this study of 20.2% appears to be high, nevertheless is comparable to mortality risks reported in other TVR series, ranging from 7.7% to 37% [1, 4, 5, 8–17]. However, when stratified into the era, the mortality rate during this study period declined significantly [4.1% ($P < 0.001$) after 1986], indicating that early surgical outcomes of TVR improved considerably.

This decline in early mortality and improvement in other early outcomes are probably multifactorial in nature. First, the distribution of patient aetiology changed considerably over time in this series. Prior to 1985, most patients who underwent TVR had functional tricuspid or rheumatic valve disease; thereafter, this shifted to patients having mainly carcinoid disease. The decline in the indication functional TR probably may also be attributed due to the fact that this is more aggressively treated with annuloplasty during left-sided valve surgery, following the publication of Dreyfus et al. [23]. Improved living conditions, nutrition, access to medical care and penicillin use have changed the epidemiology of rheumatic heart disease greatly [24]. The number of patients with carcinoid heart disease receiving TVR increased significantly. This may have several causes, one being that the threshold in the treatment of carcinoid heart disease with TVR has lowered, making the procedure more prevalent [25]. Another cause for the increase in patients with carcinoid heart disease receiving TVR is that Erasmus MC has profiled itself in the Netherlands as a centre of expertise for patients with carcinoid disease in need of TVR. We started implanting a mechanical prosthesis in these patients and did not change our practice following satisfactory results and following reports of accelerated structural valve deterioration in biological prostheses, even though other centres did change their practice [26, 27].

Second, the most common cause for early mortality was low cardiac output (55.6%), comparable to other studies [5]. Since the seventies, there have been made substantial advances in myocardial protection and perioperative care, which may have reduced the incidence of myocardial failure during the early postoperative period. Treatment of low cardiac output syndrome also improved considerably over time [5, 8, 9, 28, 29]. Furthermore, intervention with TVR before the development of RV failure could have reduced early death after TVR.

We noted several predictors for early mortality. The use of a mechanical prosthesis ($P = 0.004$) and the concomitant placement of a pulmonary valve replacement ($P = 0.001$) were

associated with a significant reduction in early mortality. However, these interventions were mainly performed in later eras and, therefore, it is most likely the case that the use of a mechanical prosthesis or the concomitant placement of a pulmonary valve replacement in itself is not responsible for this reduction in early death. It is presumably a confounder of the aforementioned era. Likewise, mitral valve replacement ($P = 0.015$) and aortic valve replacement ($P = 0.090$) were associated with an increase in early mortality. Similarly, these operations were mainly performed in earlier eras and could therefore probably only be partially accountable for the higher early mortality in early eras.

Late outcomes

Kaplan–Meier estimates of 10-year patient survival in our series were 43.8% and comparable to other studies, which reported 10-year survival estimates between 33% and 52% [7, 9, 12, 22]. Strikingly, we did not find any difference in late mortality when stratified to different eras. This might be due to the change in the aetiology and a shift in patient selection throughout the years, which negate the era effect. Several interaction terms were found to be significant in our Cox regression model. This could either indicate that the weight of the risk factors has changed throughout the years, or that simply distribution of these risk factors has become different over the years.

The cumulative incidence for both bleeding and valve thrombosis showed no significant difference between mechanical and biological valve prostheses. Other reports showed comparable results [7, 13, 15, 17]. In addition, our results showed no difference in freedom from reoperation between mechanical and biological valve prostheses, in agreement with other reports [5, 11, 13]. Valve choice should, therefore, be made in a multidisciplinary team taking into account expected lifespan, patient characteristics and informed patient preferences.

Strengths and limitations

Strengths of this study include the duration of follow-up and long inclusion period, which have made it possible to investigate the change in outcomes and risk factors over time. Our study has a couple of limitations mainly being a retrospective observational study in a single centre with all of the inherent limitations of such investigations. Furthermore, due to multiple testing of several variables, it is possible that some statistically observed differences were found by chance. Lastly, TVR is performed rarely, resulting in a small sample size, which prohibited extensive modelling in our patient population.

CONCLUSION

In this study a shift in aetiology over time from primarily functional valve disease to predominantly patients with carcinoid heart disease was observed, completely altering the patient population and their characteristics.

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8

Left ventricular assist device implantation with and without concomitant tricuspid valve surgery: a systematic review and meta-analysis

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ABSTRACT

Objectives

Moderate-to-severe tricuspid regurgitation is common in end-stage heart disease and is associated with an impaired survival after left ventricular assist device (LVAD) surgery. Controversy remains whether concomitant tricuspid valve surgery (TVS) during LVAD implantation is beneficial. We aimed to provide a contemporary overview of outcomes in patients who underwent LVAD surgery with or without concomitant TVS.

Methods

A systematic literature search was performed for articles published between January 2005 and March 2017. Studies comparing patients undergoing isolated LVAD implantation and LVAD + TVS were included. Early outcomes were pooled in risk ratios using random effects models, and late survival was visualized by a pooled Kaplan–Meier curve.

Results

Eight publications were included in the meta-analysis, including 562 undergoing isolated LVAD implantation and 303 patients with LVAD + TVS. Patients undergoing LVAD + TVS had a higher tricuspid regurgitation grade, central venous pressure and bilirubin levels at baseline and were more often female. We found no significant differences in early mortality and late mortality, early right ventricular failure and late right ventricular failure, acute kidney failure, early right ventricular assist device implantation or length of hospital stay. Cardiopulmonary bypass time was longer in patients undergoing additional TVS [mean difference +35 min 95% confidence interval (16–55), $P = 0.001$].

Conclusions

Adding TVS during LVAD implantation is not associated with worse outcome. Adding TVS, nevertheless, may be beneficial, as baseline characteristics of patients undergoing LVAD + TVS were suggestive of a more progressive underlying disease, but with comparable short-term outcome and long-term outcome with patients undergoing isolated LVAD.

INTRODUCTION

The favourable effects on survival of left ventricular assist devices (LVADs) as bridge-to-transplant and destination therapy for patients with end-stage heart failure are well established [1–3]. In approximately half of the patients undergoing LVAD implantation, moderate or severe tricuspid regurgitation (TR) is detected on echocardiography [2]. Usually, TR is secondary to changes in the right ventricular dimensions in response to a higher afterload due to left-sided heart disease [3].

Moderate-to-severe TR is associated with an impaired survival after LVAD surgery [2]. Significant TR has also been found to predict right ventricular failure (RVF) after LVAD implantation [2, 4], suggesting that concomitant treatment of the TR could be beneficial for these patients. However, spontaneous reduction in TR after LVAD implantation alone is also reported [5, 6]. Moreover, the sample size is small in most studies addressing this topic. Controversy remains whether TR should be surgically corrected at the time of LVAD implantation. Hence, some centres opt for an aggressive approach, whereas others are more conservative. Therefore, we conducted a systematic search of the literature to provide a comprehensive overview of outcomes in patients undergoing LVAD+ tricuspid valve surgery (TVS) when compared with patient undergoing isolated LVAD implantation using a meta-analysis.

METHODS

Search strategy

To establish an overview of reported outcome, a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted [7]. Search terms were developed in collaboration with the librarian in our centre. On 29 March 2017, Embase, MEDLINE, Web of Science, Cochrane and Google Scholar were searched for articles published after January 2005 (search terms are provided in Supplementary Material, Text S1). Inclusion and exclusion criteria were defined a priori. Randomized controlled trials and observational studies concerning adult patients undergoing LVAD implantation comparing patients with and without concomitant TVS were included. Studies with less than 20 patients or abstracts, poster and conference summaries were excluded. Reasons to exclude studies with less than 20 patients were that these studies were most likely early experiential series and do not reflect the general population and, in case of a small population, chances of zero events rise, resulting in a numerical problem in pooling the data. We did not include posters, abstracts, etc. because these formats did not undergo extensive peer reviewing. In the case of overlapping study populations, the study with the most patients-years of follow-up were selected. Exceptions were made for studies that reported on more outcomes of interest. Two researchers (M.E.A.K. and D.D.) independently reviewed abstracts and full texts in an unblinded

standardized manner. In case of disagreement to include a study, an agreement was negotiated. References in selected articles were independently cross-checked by 2 researchers (M.E.A.K. and D.D.) for other relevant studies.

Data extraction

Study design, year of surgery period and follow-up (patient-years and mean) were documented. If follow-up was not provided, patient-years were calculated by multiplying the number of patients with the mean follow-up (or median, if the mean is not provided). The following baseline characteristics were extracted: mean age at operation, gender, aetiology (ischaemic and non-ischaemic), TR grade (none, mild, moderate and severe), creatinine, central venous pressure (CVP), mean systolic pulmonary artery pressure, type of tricuspid valve repair (suture, ring), prosthesis type in case of tricuspid valve replacement and concomitant valvular procedures. In addition, the following outcomes were documented: early mortality (in-hospital or <30-day mortality), mean cardiopulmonary bypass (CPB) time, length of intensive care stay, hospital stay, early RVF, acute kidney failure, late mortality and late RVF. The individual study definitions were used to define the outcomes. Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data were independently extracted by 2 authors (M.E.A.K. and D.D.). The Newcastle–Ottawa scale was used to assess methodological quality of the studies [8], and the ROBINS-I tool was used to assess bias in the individual outcomes [9].

Statistical analyses

Log-transformed inverse variance weighted pooled baseline characteristics were calculated. Risk ratios (RRs) and mean differences (MDs) were used to compare baseline characteristics with the use of a fixed effects model, as our goal was to compute comparisons for the identified population and not to generalize to other populations and analyses of baseline characteristics similar in most cases [10]. A P-value <0.05 was considered statistically significant. Random effects models using the Der Simonian and Laird method were used to pool outcomes [11]. RRs were used for dichotomous data and MDs for continuous data. The Cochrane Q statistic and I^2 were used to assess heterogeneity. Microsoft Excel 2010 was used to calculate linearized occurrence rate and risk. Comprehensive Meta-Analysis (CMA) v2.2.064 (Biostat, Engelwood, NY, USA) was used to calculate the pooled outcomes and to generate forest and funnel plots.

Patient survival was visualized in a pooled Kaplan–Meier (KM) curve derived from the originally published KM curves using the method described by Guyot et al. [12]. The Engauge Digitizer v10.0 [13] was used to create a list of co-ordinates of the KM curve, and an algorithm written in the R language was employed (Version 3.3.3) to reconstruct the original patient data. Thereafter, GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA USA) was used to plot the pooled KM curve. The reconstructed data were used to obtain hazard ratios (HRs) of late mortality in TVS + LVAD group versus isolated LVAD implantation by univariate cox regression. Thereafter, the HRs were pooled using CMA.

RESULTS

The search of the literature resulted in 915 studies, of which 16 articles met the inclusion criteria. Eight articles had to be excluded due to overlapping data, resulting in 8 inclusions for the meta-analysis (Fig. 1). References are presented in Supplementary Material, Text S2 (References S1–S9). In 1 study, we made an exception of the general rule to include the study with the most patient-years. Piacentino et al. in 2012 (Supplementary Material, Reference S7) reported on more outcomes of interest when compared with Piacentino et al. in 2011 (Supplementary Material, Reference S8), hence we included Piacentino et al. (Supplementary Material, Reference S7). However, in the 2011 study Piacentino et al. (Supplementary Material, Reference S8) reported on the KM curves, and therefore, this study was included in the KM analyses. The meta-analysis included 562 patients in the LVAD group and 303 in the LVAD + TVS group, of which 392 patients in the LVAD group had reported late follow-up time encompassing 697 patient-years when compared with 247 in the LVAD + TVS group who had reported late follow-up time encompassing 351 patient-years. Baseline and procedural characteristics of all individual studies are shown in Table 1. All studies were observational. Most studies lost points on comparability using the Newcastle–Ottawa scale, and most outcomes are at serious risk of bias due to confounding according the ROBINS-I tool (Supplementary Material, Tables S1–S4).

Baseline characteristics

Pooled baseline and procedural characteristics are shown in Table 2. Patients who underwent LVAD + TVS were more often female, had a higher TR grade, and higher CVP and bilirubin levels. In patients who underwent TVS, the tricuspid valve was repaired in 93.2% of patients; a ring repair was performed in 87% and a suture repair in 13%. Tricuspid valve replacement—all biological prostheses—was conducted in 6.8% of patients.

Early outcomes

A forest plot containing the individual and pooled RRs for early mortality, RVF, acute kidney failure and RVAD implantation is presented in Fig. 2A–D. None of the pooled RRs were statistically significant between patients receiving LVAD + TVS and isolated LVAD. Three studies reported CPB time and length of hospital stay (Supplementary Material, References S3, S5 and S6). CPB time was longer in patients undergoing TVS [129 min, 95% confidence interval (CI) (114–126)] when compared with isolated LVAD surgery [91 min, 95% CI (81–101)] with a pooled MD of 35 min [95% CI (16–55), P =0.001] with I^2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S1). Length of hospital stay did not differ significantly between patients undergoing LVAD + TVS [35 days, 95% CI (20–49)] and isolated LVAD [41 days, 95% CI (20–61)] with a pooled MD of 4 days, 95% CI (-1 to 10), P = 0.126, with I^2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S2). Additionally, 2 other studies (Supplementary Material, References S4 and S7), which did not report data in extractable format, did not find

significant differences in hospital stay ($P < 0.05$). Funnel plots are presented in Supplementary Material, Figs S4–S9. Leave-one-out analysis did not change the significance of all outcomes.

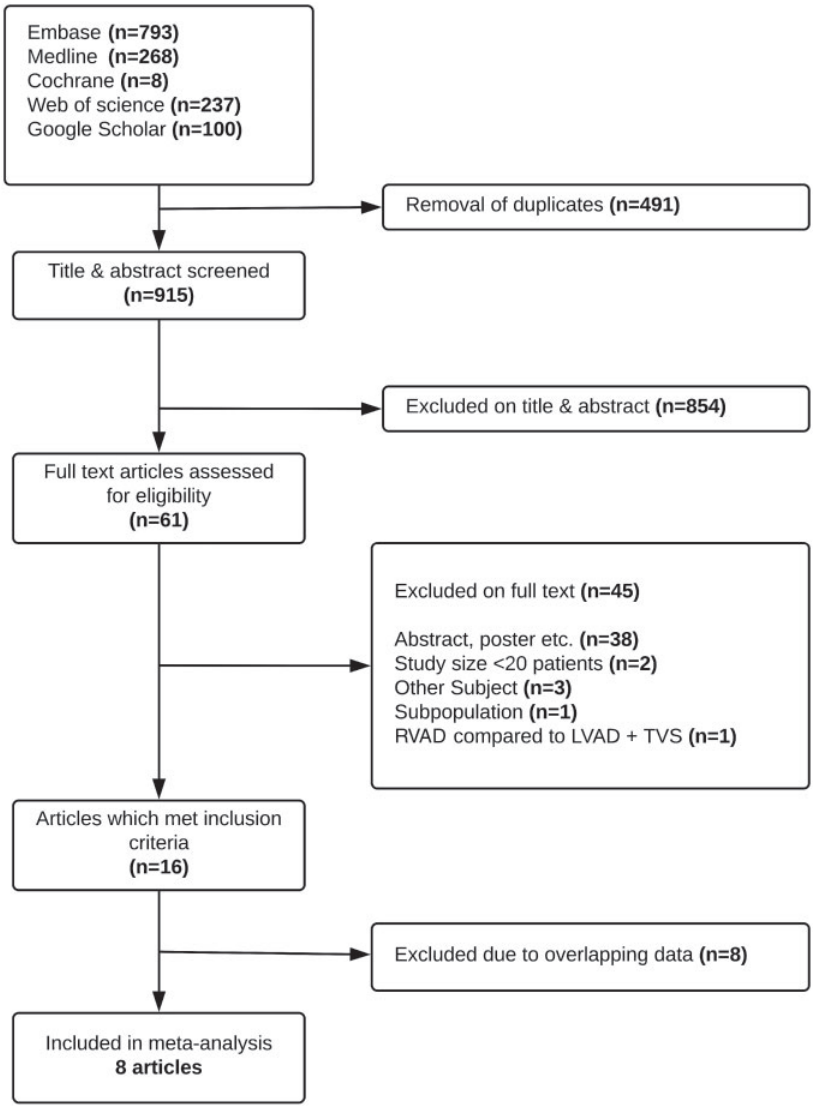

Figure 1: Flowchart of included studies in the meta-analysis. One of the 8 articles excluded due to overlapping contained a Kaplan–Meier curve which could be used in analysis, without including the article in other analysis. LVAD: left ventricular assist device; RVAD: right ventricular assist device; TVS: tricuspid valve surgery.

Table 1: Baseline characteristics of included studies

Publication	Design	Study characteristics							Newcastle–Ottawa scale		
		Group	Indication for TR surgery	*n* (% male)	Ischaemic aetiology (%)	TR severity	TV repair (%) (ring/suture)	TV replacement (%)	Selection	Comparability	Outcome
Brewer et al. (Supplementary Material, Reference S1)	Retrospective monocentre	LVAD		87 (74)	37				***	**	*
		LVAD + TVS	NR	14 (71)	14		100 (100/0)	0			
Fujita et al. Supplementary Material, Reference S2)	Retrospective monocentre	LVAD		72 (NR)	NR	Mean grade: 1.3 ± 0.8			***	–	***
		LVAD + TVS	>Moderate TR and >40 mm annulus dilatation	69 (NR)	NR	Mean grade: 2.6 ± 1.0	100 (70/30)	0			
Han et al. (Supplementary Material, Reference S3)	Retrospective monocentre	LVAD		252 (84)	43	≥Moderate 19%			***	**	***
		LVAD + TVS	≥Moderate TR	76 (76)	36	≥Moderate 99%	98 (95/3)	2			
Krishan et al. (Supplementary Material, Reference S4)	Retrospective monocentre	LVAD		14 (100)	36	≥Moderate 7%			***	–	***
		LVAD + TVS	>Moderate TR and >40 mm annulus dilatation	37 (84)	27	≥Moderate 60%	100 (100/0)	0			
Maltais et al. (Supplementary Material, Reference S5)	Retrospective multicentre	LVAD		49 (90)	52	TR VC 2.9 mm			***	*	***
		LVAD + TVS	NR	34 (71)	50	TR VC 5.6 mm	82 (12/70)	18			

Table 1: Baseline characteristics of included studies (continued)

Publication	Design	Study characteristics							Newcastle–Ottawa scale		
		Group	Indication for TR surgery	*n* (% male)	Ischaemic aetiology (%)	TR severity	TV repair (%) (ring/suture)	TV replacement (%)	Selection	Comparability	Outcome
Oezpeker et al. (Supplementary Material, Reference S6)	Retrospective monocentre	LVAD		26 (92)	58	>Moderate 100%			****	**	***
		LVAD + TVS	>Moderate TR	32 (88)	25	>Moderate 100%	100 (100/0)	0			
Piacentino et al.[b] (Supplementary Material, Reference S7)	Retrospective monocentre	LVAD		28 (54)	36	≥Moderate 100%			****	*	***
		LVAD + TVS	NR	33 (67)	56	≥Moderate 100%	88 (88/0)	12			
Piacentino et al.[a] (Supplementary Material, Reference S8)	Retrospective monocentre	LVAD		81 (79)	39	Severe 33%			****	*	***
		LVAD + TVS	NR	34 (65)	26	Severe 62%	75 (75/0)	15			
Saeed et al. (Supplementary Material, Reference S9)	Retrospective monocentre	LVAD		34 (74)	NR				***	–	**
		LVAD + TVS	>Moderate-to-severe (3) TR	8 (100)	NR		100 (37/63)	0			

*Only included in the Kaplan–Meier analysis.

**Only included in meta-analysis.

LVAD: left ventricular assist device; NR: not reported; TR: tricuspid regurgitation; TV: tricuspid valve; TVS: tricuspid valve surgery; VC: vena contracta.

Table 2: Pooled baseline and procedural characteristics

Characteristics	LVAD (*n* = 562)	95% CI	LVAD + TVS (*n* = 303)	95% CI	RR/MD	95% CI	*P*-value
Age (years)	56.0	54.8–57.2	56.9	55.1–58.7	-0.47	-2.8 to 1.9	0.693
Female (%)	24.0	20.4–28.8	40.8	34.1–48.7	0.71	0.52 to 0.94	0.020
Ischaemic heart disease (%)	44.0	39.6–48.8	41.0	34.8–48.2	1.15	0.93 to 1.4	0.195
Diabetes (%)	37.5	33.0–42.6	34.7	27.2–44.3	1.01	0.75 to 1.35	0.952
IABP (%)	41.6	36.6–47.2	47.6	41.1–55.1	0.92	0.76 to 1.20	0.407
Other valve procedure (%)	46.3	89.9–96.3	45.0	37.3–54.3	1.01	0.80 to 1.28	0.912
Moderate–severe TR (%)	93.1	89.9–96.3	97.5	95.2–99.9	0.93	0.89 to 0.97	<0.001
Severe TR (%)	17.7	11.8–26.4	57.4	49.9–66.6	0.47	0.28 to 0.80	0.006
CVP (mmHg)	10.8	10.3–11.3	12.9	12.0–13.8	-2.04	-3.08 to -0.99	<0.001
PCWP (mmHg)	23.3	22.5–24.1	23.4	22.4–24.4	-0.37	-1.69 to -0.95	0.672
Creatinine (mg/dl)	1.4	1.3–1.4	1.4	1.3–1.5	-0.07	-0.17 to 0.04	0.236
Bilirubin (mg/dl)	1.4	1.3–1.5	1.7	1.6–1.9	-0.21	-0.416 to -0.012	0.038
Continuous flow device (%)	99.7	99.2–100	98.8	97.3–100	1.00	0.998 to 1.02	0.602

CI: confidence interval; CVP: central venous pressure; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; MD: mean difference; PCWP: pulmonary capillary wedge pressure; RR: risk ratio; TR: tricuspid regurgitation; TVS: tricuspid valve surgery.

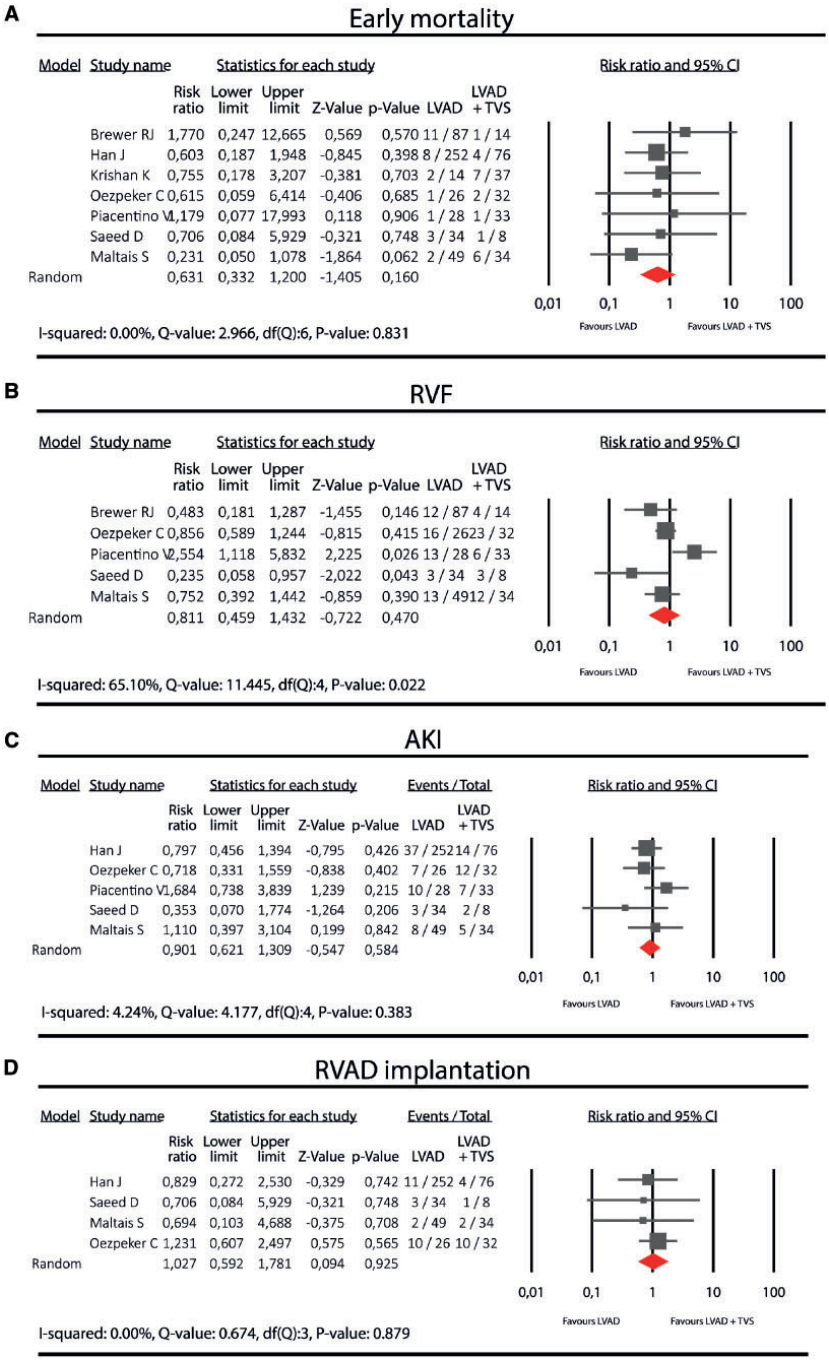

Figure 2: (A–D) Forest plots of early mortality (A), Right ventricular failure (RVF) (B), Acute kidney injury (AKI) (C) and Right ventricualr assist device (RVAD) implantation (D). CI: confidence interval; LVAD: left ventricular assist device; RR: risk ratio; TVS: tricuspid valve surgery.

Late outcomes

Seven studies (Supplementary Material, References S1–S3, S5, S6, S8 and S9) reported KM curves that could be pooled. The pooled KM curves showed comparable late survival in patients undergoing LVAD implantation with and without concomitant TVS (Fig. 3). The 1-, 2- and 3-year survival rates are 77.9 ± 3.0%, 71.8 ± 3.9% and 57.3 ± 6.0% in the LVAD+ TVS group and 82.2 ± 1.9%, 73.3 ± 2.6% and 58.1 ± 5.2% in the LVAD group, respectively. Pooled HR of concomitant TVS for late mortality is 1.13 [95% CI (0.68–1.90), *P*-value = 0.634] with I^2 = 47.1%, *Q*-value 11.344 and *P*-value 0.078 (Supplementary Material, Fig. S3). Additionally, 3 studies reported late mortality and follow-up (Supplementary Material, References S4, S6 and S7). The linearized occurrence rate of mortality in these studies was comparable in the group undergoing LVAD + TVS [43%/year, 95% CI (32–59)] compared with isolated LVAD implantation [36%/year, 95% CI (25–52)].

Data on late RVF are scarce; only 2 studies reported late RVF (Supplementary Material, References S3 and S6). Han et al. (Supplementary Material, Reference S3) found no significant differences in the cumulative readmission for RVF between patients with and without concomitant TVS during LVAD implantation (*P* = 0.95). Moreover, Oezpeker et al. (Supplementary Material, Reference S6) also found no differences in RVF at 1 year after LVAD implantation between patients receiving LVAD compared with LVAD +TVS [odds ratio 1.23 (0.18–8.44), *P* = 0.830].

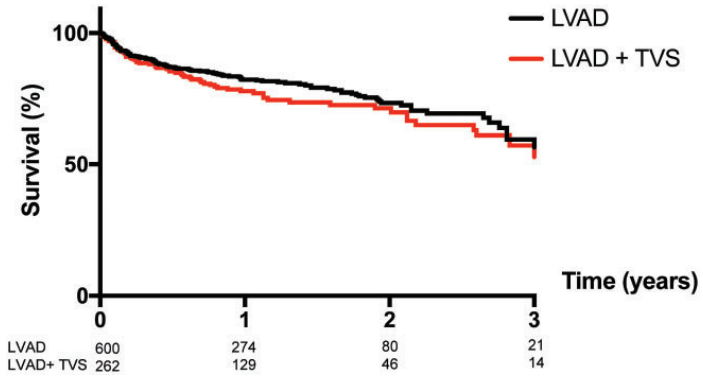

Figure 3: A pooled Kaplan–Meier curve of survival of patients undergoing LVAD implantation with or without TVS. Patients are censored at heart transplant. As Piacentino et al. (Supplementary Material, Reference S8) contained more patients than Piacentino et al. (Supplementary Material, Reference S7), more patients are included in the Kaplan–Meier analysis than in the meta-analysis. LVAD: left ventricular assist device; TVS: tricuspid valve surgery.

DISCUSSION

This meta-analysis showed that there are no significant differences in early mortality, RVF, acute kidney failure, hospital stay and RVAD implantation between patients receiving isolated LVAD implantation versus LVAD + TVS. Not surprisingly, CPB time was longer in patients receiv-

ing concomitant TVS. In addition, late mortality and late RVF were comparable for patients with and without TVS during LVAD implantation. To the best of our knowledge, this is the first systematic review that pools late survival using KM curves.

Our results can be interpreted two-fold. First, one could argue that despite the fact that patients receiving concomitant TVS are sicker at baseline, concomitant TVS results in comparable outcomes as isolated LVAD implantation, and thus, TVS during LVAD may be beneficial. Several authors have mentioned this reasoning (Supplementary Material, References S2, S4, S5 and S7). Second, one could argue that LVAD alone is also able to improve the loading conditions of the heart, and TVS does not have clinical relevance. It is difficult to discriminate between these 2 interpretations as the ideal control group (patients with severe TR and impaired RVF at baseline undergoing isolated LVAD implantation) is rarely compared with patients undergoing LVAD + TVS in the literature, as is also indicated by the differences in pooled baseline characteristics. Nevertheless, the pooled data show that additional TVS is not associated with worse outcomes. Therefore, we question the clinical impact of the pop-off valve hypothesis, which states that the tricuspid valve regurgitation serves as a 'pop-off', reducing right ventricular afterload (Supplementary Material, References S1 and S4). The results of this meta-analysis agree in this respect with a prior systematic review that focused on early outcomes [14].

Severe TR is associated with impaired right ventricle function [15], and RVF is uniformly recognized as a risk factor for adverse events and mortality following LVAD implantation [16]. These 2 observations raise important questions. Does TR impact outcomes by itself or is it merely a marker for the severity of the right ventricular dysfunction? If so, does TVS improve right ventricular function? Some data suggest that TVS improves right ventricular function in the setting of functional TR [17, 18], adding to the rationale that TVS may be beneficial. However, whether this is true in the setting of LVAD implantation remains unclear.

Complicating matters, significant TR can reduced to insignificant TR after optimizing loading conditions through diuretics use [3]. Therefore, baseline TR grade as sole operation criteria might not be sufficient. Dreyfus et al. [19] proposed that the decision of TVS should be based on annulus dilatation rather than TR grade in patients with functional TR. Some centres have adopted this approach in their decision-making process whether to operate on the TV during LVAD implantation (Supplementary Material, References S2 and S4). Current guidelines on management of TR recommend consideration of tricuspid valve repair if moderate or greater TR is present [20].

The data of the STS and the INTERMACS registries have been used to shed some light on routinely repairing the tricuspid valve if significant TR is present [21, 22]. Analysing the STS registry, Robertson et al. reported that patients undergoing TVS had a higher postoperative risk of renal failure, dialysis, reoperation, greater total transfusion requirement and a higher rate of hospital length of stay >21 days. They concluded that routinely operating on the tricuspid valve based on TR grade should be avoided [21]. Our recent article confirms also the increased risk of RVF if the CPB time is increased [23]. Increased CPB is a marker for a difficult situation,

subsequently requiring extended surgery, which may lead to RVF. We agree, therefore, with their suggestion to seek additional selection criteria for TVR. Nonetheless, their results should be interpreted with some caution, since they did not adjust for preoperative RVF, except for TR grade. Song et al. [22] showed comparable survival of patients undergoing TVS during LVAD implantation versus isolated LVAD implantation using the INTERMACS database. On the one hand, multicentre studies include more patients, increasing statistical power, and on the other hand, TR measurement and quantification remain challenging, and adding different centres with different operators results in less reliable data. This point was also raised by Shah [22, 24] commenting on the publication of the INTERMACS data. Furthermore, a limitation is that these multicentre studies were not designed to specifically address these research questions. Therefore, data on tricuspid valve function, time of assessment and reason for TVR are not collected uniformly or not available at all, which is expected to have resulted in significant bias. The study on the STS database attempted to adjust for baseline differences using a propensity score model. However, data on right heart function, except for TR grade in their model, were not included.

Additionally, the data from HeartMate II and ADVANCE trials have been retrospectively reviewed to assess the impact of TVS during LVAD implantation. Although patients undergoing TVS in the HeartMate II trial had worse baseline characteristics (higher CVP, higher CVP/PWCP ratio and lower right ventricular stroke work index) both early survival and late survival were comparable. The incidence of early RVAD implantation and early RVF was higher in the LVAD + TVS group [25]. However, the data from the ADVANCE trial showed that patients with moderate or severe TR receiving TVS have a lower incidence of late RVF when compared with patients with moderate or severe TR undergoing isolated LVAD implantation [26], suggesting that patients undergoing TVS may be at higher risk of early RVF, but this reverses during follow-up.

We speculate that TR is part of an interplay of RVF, pulmonary pressures, systemic volume status and kidney function. Subsequently, TVS may only be beneficial in patients who have not reached the point-of-no-return but are sick enough to require TVS. For example, patients with TR and risk factors for postoperative RVF, but not yet with full-blown RVF, may benefit more if TVS is able to improve right ventricular function or prevent further decrease in right ventricular function post-implantation. Therefore, identifying these patients should be a focus of further research, because clear insight in which subpopulation within the TR population may benefit from TVS remains yet to be elucidated. A randomized clinical trial including all patients with TR is not feasible, and multiple clinical trials in different subpopulations within the TR population would be a costly endeavour. However, newer innovative designs are rising that can possibly provide answers on this matter [27]. Currently, a clinical trial (NCT02537769) is being performed to assess the effect of TVS on patients with mild–moderate TR at baseline. This is already a subset of the general TR population; nevertheless it may be a subset which does not benefit from TVS. Therefore, it may still be elucidating to gain insights in the natural history of TR after LVAD implantation and to seek additional selection criteria for concomitant TVS.

Limitations

This study is a systematic review and meta-analysis of observational studies, which all are retrospective in nature. Therefore, the inherent limitations of meta-analysis and pooling retrospective data apply to this study [28]. Moreover, serious risk of bias due to confounding was found in most studies using the ROBINS-I tool. However, this bias mostly favours the LVAD group, further suggesting that there may be benefit of concomitant TVS that underlies our findings of comparable outcomes. Despite the inclusion of multiple studies, the sample size remains modest, possibly with too little power to show true differences. Funnel plots did not show clear evidence of publications bias. However, the small number of studies precludes unambiguous conclusions. Considerable heterogeneity was present in the RRs of early RVF, CBP and in the late mortality, including the pooled HRs. Unfortunately, exploring heterogeneity with meta-regression was not possible due to limited number of studies. The RVF heterogeneity may be explained by the fact that some studies included patients less prone to postoperative RVF in the LVAD group, resulting in different RRs. For example, Piacentino et al. (Supplementary Material, Reference S7) only included patients >moderate TR, and in the cohort of Maltais et al. (Supplementary Material, Reference S5), TR differed in groups, whereas TR is found to be a predictor of postoperative RVF after LVAD implant [29]. Additionally, CBP had significant heterogeneity, which can partly be explained by the fact that in the cohort of Maltais et al. (Supplementary Material, Reference S5), patients did not undergo other concomitant procedures (e.g. aortic valve procedure), whereas in the cohort of Han et al. (Supplementary Material, Reference S3), nearly half the population underwent concomitant procedures. Because of differences in postoperative care and censoring due to heart transplantation, the heterogeneity found in late mortality can be explained.

CONCLUSION

Concomitant TVS during LVAD implantation is not associated with worse outcome when compared with LVAD implantation, and some data indicate that it may be beneficial. However, current literature is unable to offer a definitive answer, as the majority the compares unmatched groups. Additional effort should be made to identify which patients will benefit most from adding TVS to LVAD implantation.

ACKNOWLEDGEMENTS

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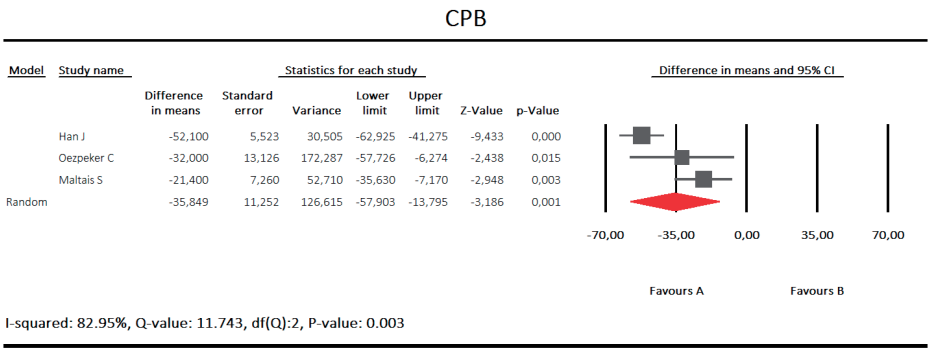
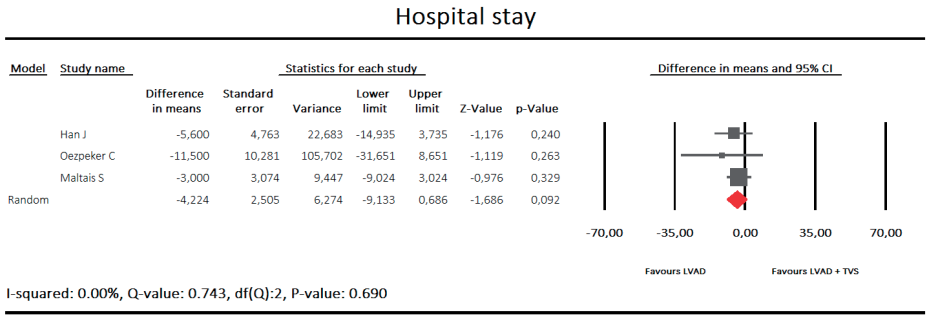
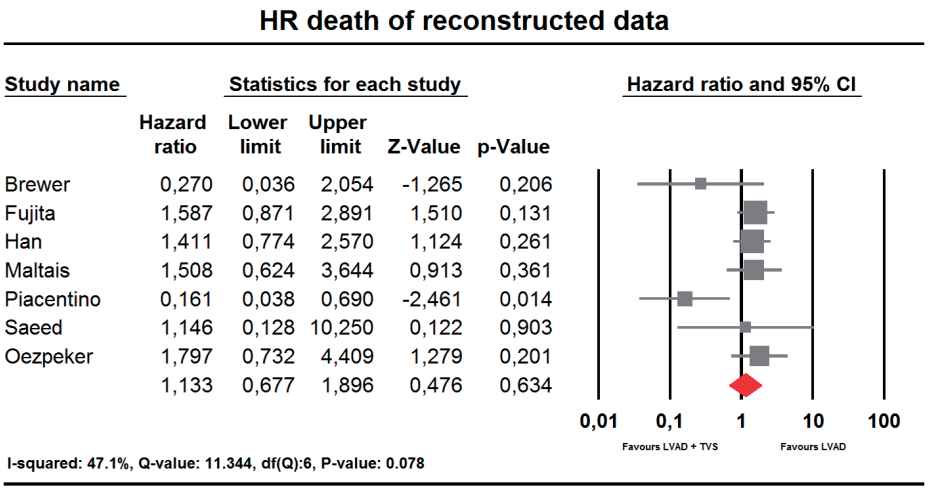
SUPPLEMENTARY MATERIAL



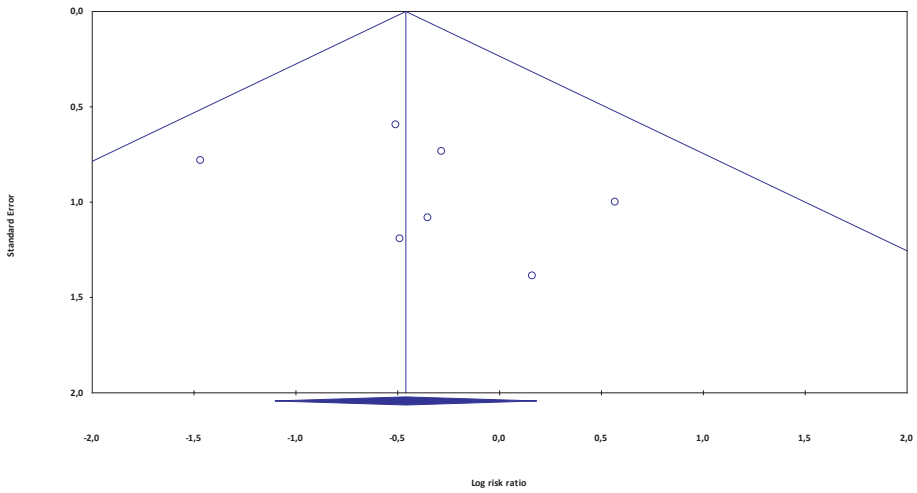
Supplementary Figure 1: Forest plot of cardiopulmonary bypass time.



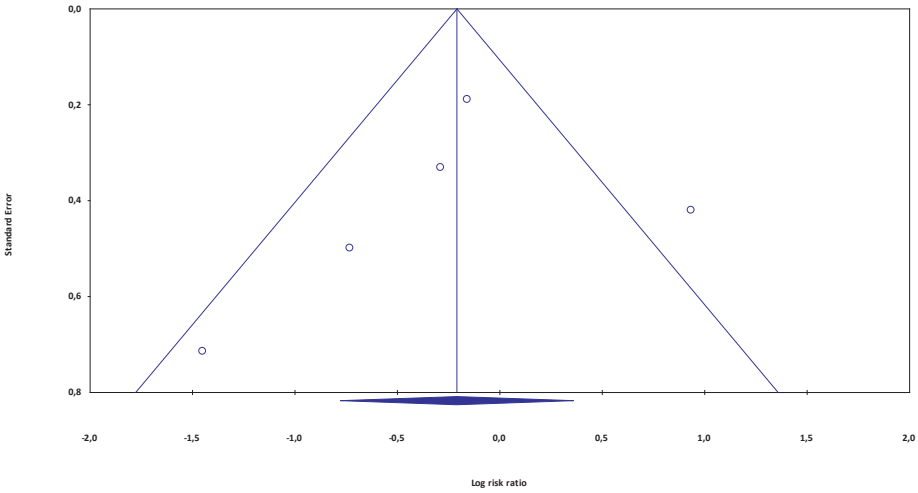
Supplementary Figure 2: Forest plot of length of hospital stay.



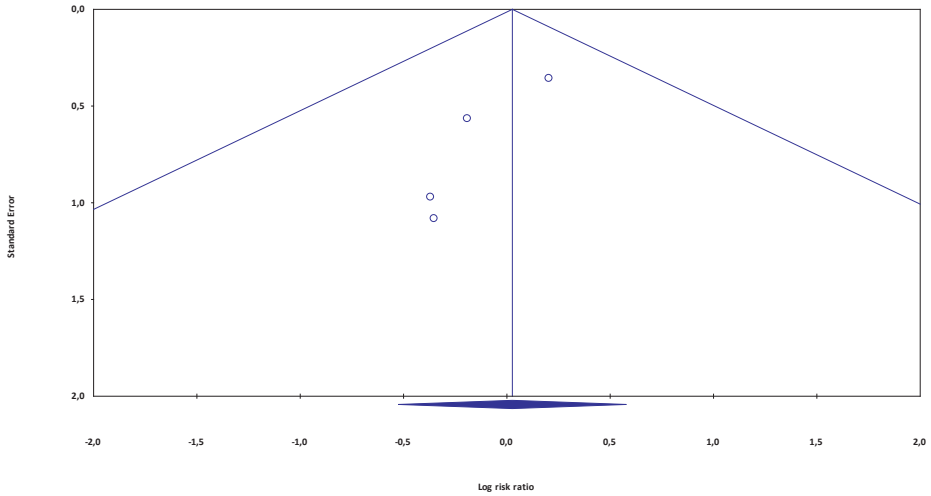
Supplementary Figure 3: Forest plot of constructed hazard ratio of late mortality of patients receiving isolated LVAD implant vs LVAD + TVS.



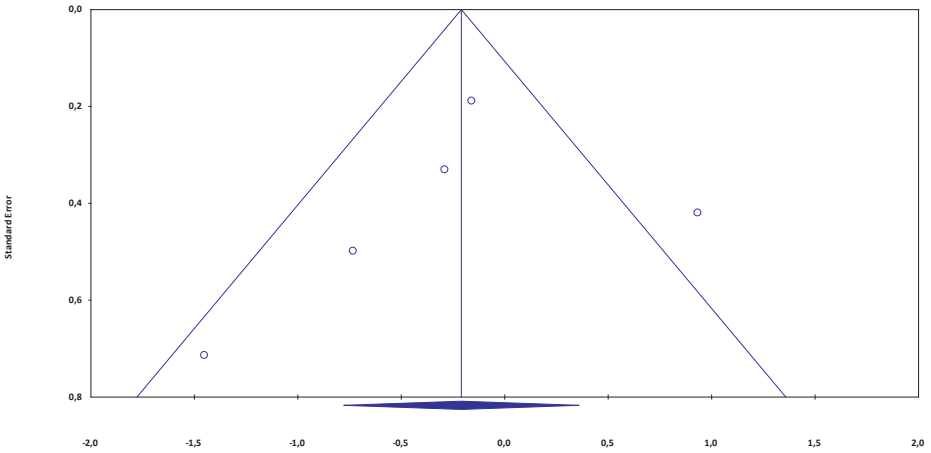
Supplementary Figure 4: Funnel plot of Early Mortality.



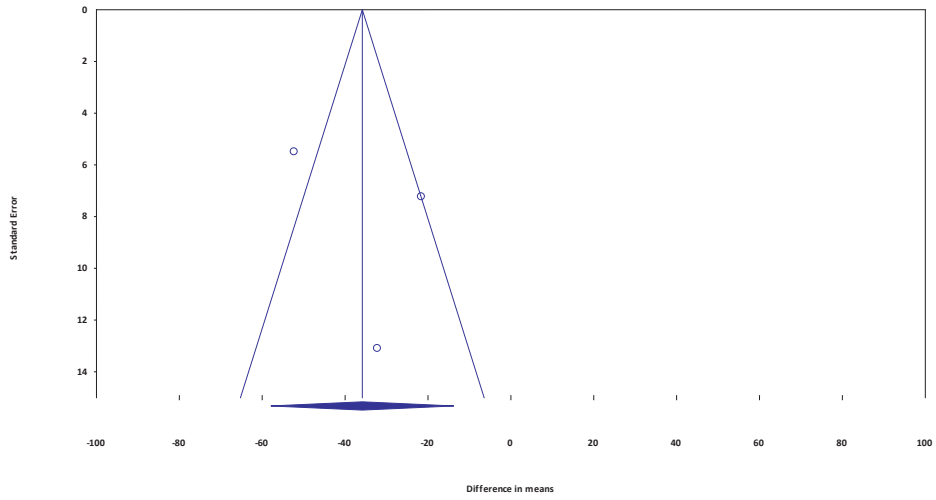
Supplementary Figure 5: Funnel plot of Acute Kidney Failure .



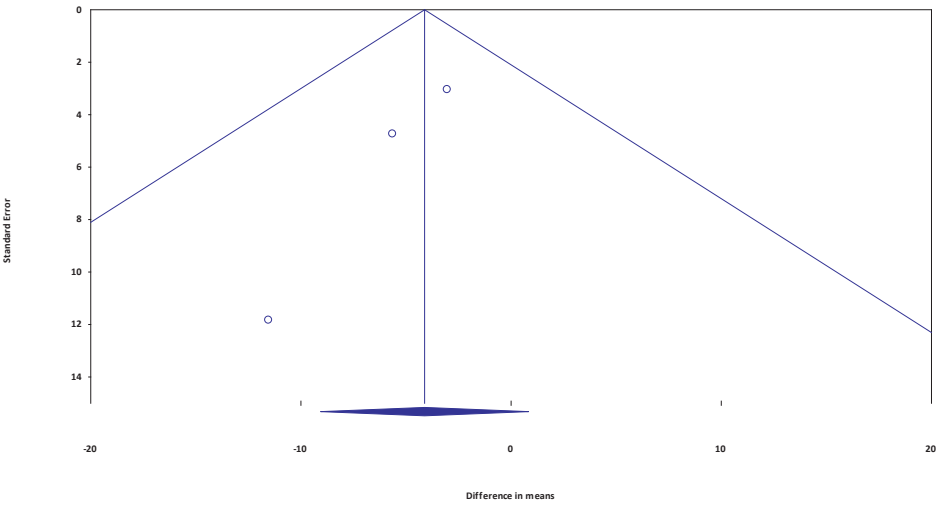
Supplementary Figure 6: Funnel plot of RVAD implantation.



Supplementary Figure 7: Funnel plot of right ventricular failure.



Supplementary Figure 8: Funnel plot of cardiopulmonary bypass time.



Supplementary Figure 9: Funnel plot of length of hospital stay.

Supplementary Table 1: ROBIN-I risk of bias judgements of the outcome Early mortality in all studies. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

Early mortality							
Study	**Brewer RJ**	**Han J**	**Krishan K**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to confounding	**SR**	**MR**	**SR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**SR**	**MR**	**MR**	**MR**	**MR**	**MR**	**MR**
Overall	**SR**	**MR**	**SR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 2: ROBIN-I risk of bias judgements of the outcome RVF in all studies. RVF: right ventricular failure. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

RVF					
Study	**Brewer RJ**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to cofounding	**SR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**MR**	**MR**	**MR**	**MR**	**MR**
Bias in selection of reported results	**SR**	**MR**	**MR**	**MR**	**MR**
Overall	**SR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 3: ROBIN-I risk of bias judgements of the outcome AKI in all studies. AKI: Acute kidney injury. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

AKI					
Study	**Han J**	**Oezpeker C**	**Piacentino V**	**Saeed D**	**Maltais S**
Bias due to cofounding	**MR**	**MR**	**SR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**MR**	**MR**	**MR**	**MR**	**MR**
Overall	**MR**	**MR**	**SR**	**SR**	**SR**

Supplementary Table 4: ROBIN-I risk of bias judgements of the outcome RVAD implantation in all studies. RVAD: Right ventricular assist device. LR: low risk, MR: moderate risk, SR: serious risk, CR:critical risk, NI: No information

RVAD implantation				
Study	**Han J**	**Oezpeker C**	**Saeed D**	**Maltais S**
Bias due to cofounding	**MR**	**MR**	**SR**	**SR**
Bias due to participant selection	**LR**	**LR**	**LR**	**LR**
Bias due to classification of interventions	**LR**	**LR**	**LR**	**LR**
Bias due to deviations from intended interventions	**LR**	**LR**	**LR**	**LR**
Bias due to missing data	**LR**	**LR**	**LR**	**LR**
Bias in measurements of outcome	**LR**	**LR**	**LR**	**LR**
Bias in selection of reported results	**MR**	**MR**	**MR**	**MR**
Overall	**MR**	**MR**	**SR**	**SR**

SUPPLEMENTARY TEXT 1

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('ventricular assist device'/exp OR 'heart assist device'/de OR (((ventricular OR lv OR assist*) NEAR/3 device*) OR lvad OR vad OR Heartware* OR HeartMate OR Levacor OR Novacor OR Ventrassist):ab,ti) AND ('tricuspid valve disease'/exp OR 'tricuspid valve repair'/de OR 'tricuspid valve'/de OR 'tricuspid annuloplasty'/de OR (tricuspid* OR (atrioventricular NEAR/3 (valve* OR right)) OR (functional* NEAR/3 regurgit*)):ab,ti)

Medline Ovid 268

("Heart-Assist Devices"/ OR (((ventricular OR lv OR assist*) ADJ3 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist).ab,ti,kf.) AND ("Tricuspid Valve Prolapse"/ OR "Tricuspid Valve Stenosis"/ OR "tricuspid valve"/ OR "Tricuspid Valve Insufficiency"/ OR (tricuspid* OR (atrioventricular ADJ3 (valve* OR right)) OR (functional* ADJ3 regurgit*)).ab,ti,kf.)

Web of science 237

TS=(((((ventricular OR lv OR assist*) NEAR/2 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist)) AND ((tricuspid* OR (atrioventricular NEAR/2 (valve* OR right)) OR (functional* NEAR/2 regurgit*))))

Cochrane CENTRAL 8

((((ventricular OR lv OR assist*) NEAR/3 device*) OR lvad OR vad OR Heartware* OR HeartMateOR Levacor OR Novacor OR Ventrassist):ab,ti) AND ((tricuspid* OR (atrioventricular NEAR/3 (valve* OR right)) OR (functional* NEAR/3 regurgit*)):ab,ti)

Google scholar 100

"ventricular|lv|assist device|devices"|lvad|vad|Heartware|HeartMate|Ventrassist tricuspid|"atrioventricular valve"|"functional regurgit"

SUPPLEMENTARY TEXT 2

S1. Brewer RJ, Cabrera R, El-Atrache M, Zafar A, Hrobowski TN, Nemeh HM, et al. Relationship of tricuspid repair at the time of left ventricular assist device implantation and survival. Int J Artif Organs. 2014;37(11):834-8.

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9

Clinical impact and 'natural' course of uncorrected tricuspid regurgitation after implantation of a left ventricular assist device: an analysis of the European Registry for Patients with Mechanical Circulatory Support (EUROMACS)

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EJCTS, October 2020

ABSTRACT

Objectives

Data on the impact and course of uncorrected tricuspid regurgitation (TR) during left ventricular assist device (LVAD) implantation are scarce and inconsistent. This study explores the clinical impact and natural course of uncorrected TR in patients after LVAD implantation.

Methods

The European Registry for Patients with Mechanical Circulatory Support was used to identify adult patients with LVAD implants without concomitant tricuspid valve surgery. A mediation model was developed to assess the association of TR with 30-day mortality via other risk factors. Generalized mixed models were used to model the course of post-LVAD TR. Joint models were used to perform sensitivity analyses.

Results

A total of 2496 procedures were included (median age: 56 years; men: 83%). TR was not directly associated with higher 30-day mortality, but mediation analyses suggested an indirect association via preoperative elevated right atrial pressure and creatinine (P = 0.035) and bilirubin (P = 0.027) levels. Post-LVAD TR was also associated with increased late mortality [hazard ratio 1.16 (1.06–1.3); P = 0.001]. On average, uncorrected TR diminished after LVAD implantation. The probability of having moderate-to-severe TR immediately after an implant in patients with none-to-mild TR pre-LVAD was 10%; in patients with moderate-to-severe TR pre-LVAD, it was 35% and continued to decrease in patients with moderate-to-severe TR pre-LVAD, regardless of pre-LVAD right ventricular failure or pulmonary hypertension.

Conclusions

Uncorrected TR pre-LVAD and post-LVAD is associated with increased early and late mortality. Nevertheless, on average, TR diminishes progressively without intervention after an LVAD implant. Therefore, these data suggest that patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade.

ABBREVIATIONS

CI	**Confidence interval**
EUROMACS	**European Registry** for Patients with Mechanical Circulatory Support
LVAD	**Left ventricular** assist device
RA	**Right atrium**
RV	**Right ventricular**
RVF	**Right ventricular** function
SEM	**Structural equation** model
TR	**Tricuspid regurgitation**

INTRODUCTION

Tricuspid regurgitation (TR) is common in patients with end-stage heart failure undergoing left ventricular assist device (LVAD) implant [1]. Most studies addressing TR after an LVAD implant focus on comparing patients with and without tricuspid valve surgery concomitant with an LVAD implant [2]. However, it is still unclear what the 'natural' course of post-LVAD TR is, and which patients will potentially benefit most from concomitant tricuspid valve surgery. TR has been reported to decrease after an LVAD implant [3–5], but it is not known whether this occurs in all patients uniformly or only in subgroups. Assessing the course and clinical impact of TR after LVAD is important, because it may provide a rationale to perform, or to refrain from performing, tricuspid valve surgery during LVAD implantation. Therefore, this study explores the evolution of TR after an LVAD implant in patients who did not undergo concomitant tricuspid valve surgery. Furthermore, we explored the impact of the preoperative and postoperative TR grade on early (30-day) and late mortality using the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database. We hypothesized that pre-LVAD TR is part of an interplay with other risk factors [e.g. right ventricular (RV) failure, pulmonary hypertension, renal and/or liver function] and that TR may be associated with 30-day mortality by increasing these risk factors. Therefore, we performed a mediation analysis. To account for the dynamic nature of TR after LVAD implantation and potential survival bias, the longitudinal evolution of TR was modelled and linked to survival under the joint modelling framework.

METHODS

Data source

EUROMACS is a registry of the European Association for Cardio- Thoracic Surgery. In this registry, all relevant clinical, echocardiographic haemodynamic and laboratory parameters of patients who require mechanical circulatory support have been collected prospectively since January 2011. Participating centres (Supplementary Material, Table S1) were allowed to enter

data before 2011 retrospectively. Detailed descriptions of the database and collection procedure were provided previously [6].

Patients

All patients operated between 2005 and 2018 were identified. Patients under 18 years of age, with no recorded pre-LVAD TR grade and with concomitant tricuspid valve surgery were excluded from analysis (Supplementary Material, Fig. S1). Additionally, we excluded patients with a planned durable RV assist device, biventricular assist device or total artificial heart implant. Patients were followed until death or the end of the study. Patients were censored at heart transplant or explant.

Outcome

The main outcomes that were assessed were 30-day mortality, late mortality (defined as death after 30 days) and TR grade (5-point system: none–trivial–mild–moderate–severe).

Statistical analyses

Continuous data are presented as mean (standard deviation) (Gaussian distribution) or median (interquartile range) (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). Comparisons among continuous variables were made with the one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Continuous data outside 3 standard deviations were considered erroneous and removed (Supplementary Material, Table S2). Comparisons of categorical variables were made with the χ^2 test or with the Fisher's exact test, as appropriate. Due to multiple testing (34 tests), a Bonferroni correction was applied, considering $P = 0.0014$ as significantly different. Data with <50% missing values were imputed using multiple imputation (Supplementary Material, Text S1 and Tables S3 and S4).

Univariable and multivariable ordinal proportional odds regression models were used to explore determinants associated with TR at baseline. A forwards stepwise modelling strategy was applied in which all covariates with *P*-value <0.10 were entered into the multivariable model.

We hypothesized that the effect of TR on 30-day mortality was mediated by well-known risk factors. Therefore, mediation analysis with a structural equation model (SEM) was performed. The selected variables incorporated into the model included right atrial pressure, creatinine and bilirubin levels and the international normalized ratio (all were incorporated as continuous variables), and were based on previous literature [7–9]. Using SEM, one can compute direct and indirect associations (associations via other variables) on outcomes by specifying a pathway. The conceptual pathways are shown in Fig. 1. A comprehensive explanation of mediation analyses with SEM is provided in Supplementary Material, Text S1. Late mortality was calculated and visualized using the Kaplan–Meier method, and a log-rank test was performed to compare strata. Modified Clark's C, denoted as C*, was used to calculate completeness of follow-up [10].

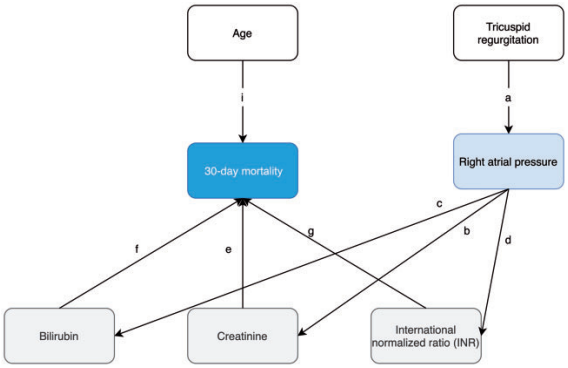

Figure 1: Path diagram of the structural equation model with table of regressions. Paths are indicated by labels a–h, which correspond to the labels in Table 3. Arrows denote the direction of the regression [e.g. tricuspid regurgitation predicts right atrial pressure (path a), which in term predicts creatinine level (path b)]. INR: internationalized normal ratio.

Evolution of tricuspid regurgitation

Logistic mixed models were used to assess longitudinal evolution of TR grade over time (Supplementary Material, Text S1). Subgroup analysis was done for patients with moderate-to-severe TR pre-LVAD. In these patients, separate models containing RV ejection fraction impairment, pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnosis (time elapsed since first cardiac diagnosis) and pre-LVAD right atrium (RA) pressure were developed to investigate the association of these variables with the course of post- LVAD TR. All analyses were done in R (version 3.6.3) (R Project for Statistical Computing: https://www.r-project.org/).

Sensitivity analyses

It is possible that a portion of the dropout of patients is caused by deaths due to TR, resulting in informative censoring (survival bias). In this case, the dropout is not random, thus leading to bias in the mixed model results. Therefore, a sensitivity analysis was performed in which the dynamic longitudinal evolution of TR was inserted into a Cox model under the joint modelling framework. Modelling these entities together alleviates possible bias due to missing values that are missing not at random (i.e. survival bias). The other baseline covariates inserted in the Cox model were based on information from previously published articles; only the current value parameterization of TR was investigated [11, 12]. Several other sensitivity analyses were conducted to test the robustness of the model estimates. These analyses included: exclusion of patients with pre-LVAD extracorporeal membrane oxygenation and patients with postoperative durable RV assist device. Additionally, centre heterogeneity was accounted for in the random effects by performing a mixed model with patients nested in hospitals.

RESULTS

The database contained 3948 procedures. After applying the exclusion criteria, 2411 patients undergoing 2496 procedures were included (Supplementary Material, Fig. S1). In total, 1892 patients had recorded late follow-up (>30 days) with a median of 1.3 interquartile range (0.5–2.6) years, with a completeness of 85% (C*).

Baseline characteristics

Baseline characteristics stratified to TR grade are presented in Table 1. Nearly all the baseline characteristics differed significantly between patients with none-to-mild TR compared to those with moderate-to-severe TR, even after the Bonferroni correction. Seventy-three potential determinants were tested in univariable ordinal regression models, and 12 determinants remained significant in multivariable analyses. Among others, a higher TR grade at baseline was significantly associated with more peripheral oedema, other pulmonary and mitral valve dysfunction, higher RA pressure, more loop diuretics and worse right ventricular function (RVF) (Supplementary Material, Table S5).

Table 1: Baseline characteristics stratified to pre-left ventricular assist device TR grade

	None-to-mild TR	Moderate-to-severe TR	*P*-value
Demographics			
n	1690	806	
Age (years)	56.00 (47.00–62.00)	56.00 (46.00–62.00)	0.71
Male gender, *n* (%)	1416 (83.8)	657 (81.5)	0.17
Body surface area (m^2)	1.99 (1.83–2.12)	1.92 (1.78–2.08)	<0.001
White race, *n* (%)	1234 (86.3)	626 (86.2)	0.97
Ischaemic aetiology HF, *n* (%)	620 (43.3)	251 (35.2)	<0.001
≥2 Years since first diagnosis	811 (60.3)	494 (70.4)	<0.001
Destination therapy	294 (17.5)	128 (15.9)	0.36
Ascites	96 (8.5)	94 (16.9)	<0.001
Rhythm, *n* (%)			0.001
Sinus	796 (58.1)	341 (49.6)	
Atrial fibrillation	225 (16.4)	130 (18.9)	
Paced	28 (2.0)	28 (4.1)	
Other	322 (23.5)	189 (27.5)	
INTERMACS profile, *n* (%)			<0.001
1	238 (14.7)	79 (10.1)	
2	538 (33.3)	259 (33.2)	
3	457 (28.3)	205 (26.3)	
≥4	384 (23.7)	237 (30.4)	

Table 1: Baseline characteristics stratified to pre-left ventricular assist device TR grade (continued)

	None-to-mild TR	Moderate-to-severe TR	*P*-value
IABP, *n* (%)	173 (12.0)	58 (8.1)	0.008
ECMO, *n* (%)	183 (11.2)	50 (6.5)	<0.001
Ventilator (%)	224 (15.6)	52 (7.3)	<0.001
Medication, *n* (%)			
Loop diuretics	1060 (78.8)	588 (86.7)	<0.001
Use of ≥3 inotropes	182 (13.0)	93 (13.3)	0.91
Laboratory values			
Serum creatinine (mg/dl)	106.00 (84.00–146.00)	106.00 (82.00–144.00)	0.43
ASAT (U/l)	33.00 (22.00–70.00)	30.00 (21.00–55.00)	0.002
Total bilirubin (mg/dl)	1.18 (0.74–1.90)	1.40 (0.90–2.27)	<0.001
Albumin (g/dl)	499.91 (410.07–579.60)	521.64 (440.50–579.60)	0.010
Haemoglobin (g/dl)	12.00 (10.30–13.60)	11.75 (10.20–13.30)	0.17
Haemodynamics			
RA pressure (mmHg)	10.00 (6.00–14.00)	11.00 (8.00–16.00)	<0.001
PCWP (mmHg)	24.00 (17.00–30.00)	25.00 (20.00–30.00)	0.005
PAP, systolic (mmHg)	51.00 (38.00–62.00)	53.00 (41.75–65.00)	0.003
Echocardiography			
TAPSE (mm)	15.00 (12.00–17.00)	14.00 (11.00–16.00)	<0.001
No aortic regurgitation, *n* (%)	1043 (67.8)	397 (54.8)	<0.001
Severe mitral regurgitation, *n* (%)	162 (11.1)	223 (30.3)	<0.001
LVEF grade <20%, *n* (%)	779 (57.2)	431 (64.2)	0.010
RVF			<0.001
Normal	279 (24.4)	89 (15.6)	
Mild	334 (29.2)	105 (18.4)	
Moderate	389 (34.1)	274 (48.1)	
Severe	140 (12.3)	102 (17.9)	

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile range).

ASAT: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; HF: heart failure; IABP: intra-aortic balloon pump; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; LVEF: left ventricular ejection fraction; PAP: pulmonary atrial pressure; PCWP: pulmonary capillary wedge pressure; RA: right atrium; RVF: right ventricular function; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

Pre-left ventricular device tricuspid regurgitation and early mortality

In total, 271 (10.9%) patients died within 30 days. The 30-day mortality was comparable between patients with none-to-mild TR versus moderate-to-severe TR (10.8% vs 10.9%; *P* = 0.99). Procedural and hospital outcomes in patients with none-to-mild and moderate-to-severe TR are presented in Table 2.

Table 2: Procedural characteristics and early outcomes

	None-to-mild TR	Moderate-to-severe TR	*P*-value
Device			0.005
HeartMate II LVAS	484 (29.5)	186 (24.2)	
HeartWare HVAD	841 (51.3)	452 (58.8)	
HeartMate3	241 (14.7)	95 (12.4)	
Other	74 (4.5)	36 (4.7)	
CPB time	79.00 (58.00–108.00)	80.00 (60.00–111.00)	0.22
ICU/CCU stay (days)	10.00 (5.00–23.00)	10.00 (5.00–22.00)	0.81
Hospital stay (days)	29.00 (21.00–43.00)	31.00 (21.00–44.00)	0.18
Discontinuation of IV inotropes (days) (%)			0.30
1–7	558 (55.0)	295 (58.4)	
8–13	184 (18.1)	97 (19.2)	
14–27	168 (16.6)	73 (14.5)	
>27	103 (10.1)	38 (7.5)	
Temporary RVAD	66 (3.9)	39 (4.8)	0.32
30-Day mortality, *n* (%)	184 (10.9)	87 (10.8)	>0.99

Normally distributed variables are presented as means (standard deviations) and not normally distributed variables are medians (interquartile ranges).
CCU: coronary care unit; CPB: cardiopulmonary bypass; ICU: intensive care unit; IV: intravenous; LVAS: left ventricular assist system; RVAD: right ventricular assist device; TR: tricuspid regurgitation.

The conceptual paths of the SEM are shown in Fig. 1 and the regression estimates and significance, in Table 3. Overall, the model fitted well, as indicated by the fit indices in Table 3. Although the total effect of TR on 30-day mortality was insignificant, the path TR to RA pressure to creatinine was significantly associated with 30-day mortality ($P = 0.035$) (Table 3). Additionally, the path TR to RA pressure to bilirubin was significantly associated with 30-day mortality ($P = 0.027$) (Table 3). However, the path TR to RA pressure to international normalized ratio was not associated with 30-day mortality ($P = 0.057$) (Table 3).

Pre-left ventricular assist device tricuspid regurgitation and late mortality

A total of 626 of 2410 thirty-day survivors died during the long-term (>30 days) follow-up period. Survival after 30 days, stratified to none-to-mild TR versus moderate-to-severe TR at baseline, is presented in Fig. 2 and differed significantly between strata ($P = 0.015$).

The Spearman correlation between pre-LVAD TR and pre-LVAD RVF was 0.22 ($P < 0.001$). Therefore, these variables were combined into 1 variable. In Fig. 3 the population is stratified to different levels of right ventricle dysfunction with or without significant TR. Three years after implant, the Kaplan–Meier survival estimate was lower in patients with both moderate-to-severe TR and RVF [54%, 95% confidence interval (CI) 47–61] compared to patients with

good RVF and none-to-mild TR (68%, 95% CI 64–73). In a sensitivity analysis with only complete cases, the group with both moderate-to-severe TR and RVF pre-LVAD had survival and hazard ratios comparable to those of patients with none-to-mild TR and moderate-to-severe RVF pre-LVAD (Supplementary Material, Figs S2 and S3). RVF did seem to be conditionally missing based on observed variables (Supplementary Material, Table S6).

Table 3: Estimates of the paths of the structural equation model

Regressions	Path[a]	β-Estimate (95% CI)	*P*-value
Mortality ~			
Bilirubin	f	0.056 (0.003–0.080)	>0.001
Creatinine	e	0.001 (0.001–0.001)	>0.001
INR	g	0.121 (0.033–0.209)	0.007
Age	i	0.016 (0.010–0.021)	>0.001
TR per 1 grade	h	-0.047 (-0.101 to 0.007)	0.087
RA pressure ~			
TR	a	0.805 (0.464–1.146)	>0.001
Bilirubin ~			
RA pressure	c	0.048 (0.023–0.072)	0.002
Creatinine ~			
RA pressure	b	1.159 (0.341–1.977)	0.015
INR ~			
RA pressure	d	0.011 (0.003–0.019)	0.011
Indirect effects of TR			
Direct effect	h	-0.047 (-0.101 to 0.007)	0.087
RA pressure—creatinine	a–b–e	0.001 (0.001–0.001)	0.035
RA pressure—bilirubin	a–c–f	0.002 (0.001–0.003)	0.027
RA pressure—INR	a–d–g	0.001 (0.000–0.001)	0.058
Total effect		-0.043 (-0.098 to 0.012)	0.12
Fit measures			
χ^2		>0.001	
Non-normed fit index		0.95	
Comparative fit index		0.98	
Root mean square error of approximation (95% CI)		0.051 (0.037–0.065)	
Standardized root mean square residual		0.065	

[a]Paths correspond to the paths specified in Fig. 1.

CI: confidence interval; INR: internationalized normal ratio; RA: right atrium; TR: tricuspid regurgitation.

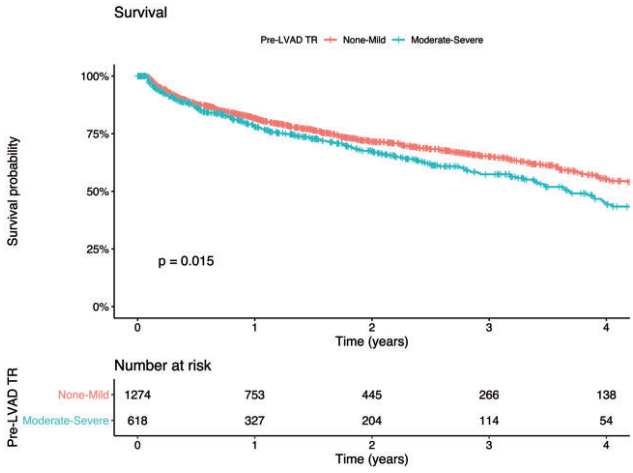

Figure 2: Kaplan–Meier curve of late survival (includes only 30-day survivors) after LVAD implant stratified to pre-LVAD TR grade. LVAD: left ventricular assist device; TR: tricuspid regurgitation.

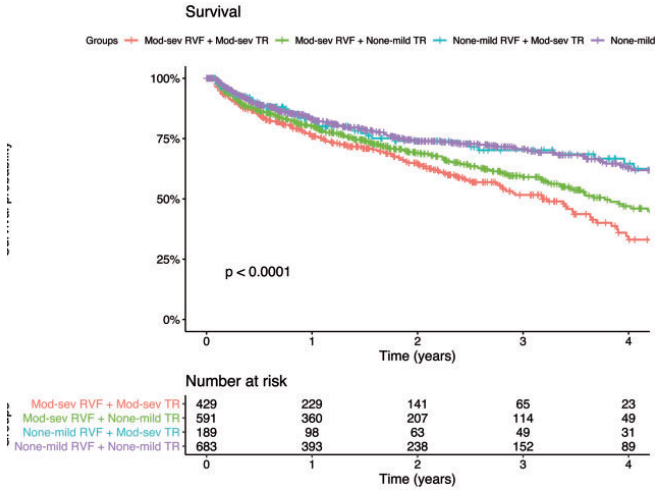

Figure 3: Kaplan–Meier curve of late survival (includes only 30-day survivors) after left ventricular assist device implant stratified to pre-left ventricular assist device TR grade with or without right ventricular dysfunction. Of note, data from the first imputed data set are used. RVF: right ventricular failure, mod: moderate; sev: severe; TR: tricuspid regurgitation.

Evolution of tricuspid regurgitation

During the follow-up period, 914 (48%) patients had 1 or more echocardiograms, with 3113 echocardiograms in total (mean 3.4, range 1–8) (Supplementary Material, Fig. S4). Figure 4A presents the probabilities of having moderate-to-severe TR after an LVAD implant, stratified to pre-LVAD TR severity. The odds of moderate-to-severe TR after an LVAD implant decreased over

time and became comparable after ~1.4 years in patients with moderate-to-severe TR pre-LVAD versus patients with none-to-mild TR pre-LVAD.

In patients with moderate-to-severe TR pre-LVAD, no significant differences were observed in the course of TR post-LVAD among different levels of pre-LVAD RV ejection fraction impairment, pre-LVAD pulmonary hypertension, pre-LVAD mitral regurgitation, pre-LVAD rhythm, duration of cardiac diagnoses, an implantable cardioverter-defibrillator or pre-LVAD RA pressure (Supplementary Material, Figs S5–S11), except for patients with idiopathic dilated myopathy. In these patients post-LVAD TR decreased faster compared to patients with other diagnoses (Fig. 4B), but the odds of moderate-to-severe TR became comparable after ~2.5 years. The difference in the odds of moderate-to- severe TR was observed predominantly in patients with other diagnoses (e.g. myocarditis and toxic or postpartum myopathy) compared to patients with idiopathic dilated myopathy (Fig. 4B). To gain insight into the possibility of informative censoring (survival bias), the longitudinal evolution of TR was jointly modelled with a survival model and compared with the estimates of the mixed model (Supplementary Material, Table S7). Some sensitivity was observed in both the effect size and standard errors (Supplementary Material, Table S8); however, the direction of the effect did not change, nor did the significance. Hence, the decrease in the probability of TR after LVAD cannot be solely explained by survival bias.

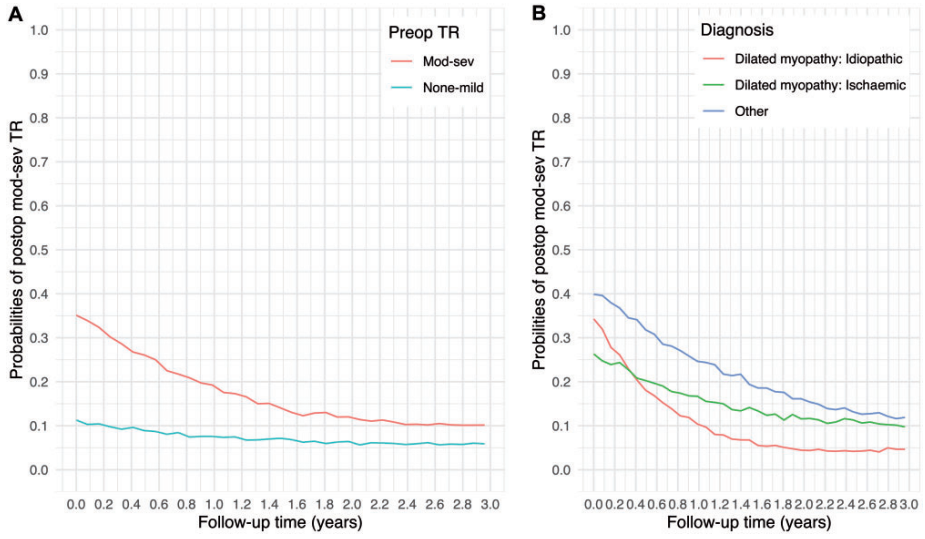

Figure 4: (A) Effects plot of the probability of TR after left ventricular assist device (LVAD) implant stratified to pre-LVAD. (B) Effects plot of the evolution of TR after LVAD (in patients with moderate-to-severe TR pre-LVAD) TR. mod-sev: moderate to severe; postop: postoperative; preop: preoperative; TR: tricuspid regurgitation.

Post-left ventricular assist device tricuspid regurgitation and mortality

Moderate-to-severe TR post-LVAD was associated with increased mortality (hazard ratio 1.16, 95% CI 1.06–1.30; *P* = 0.001), as estimated by the joint model adjusted for several baseline variables including RV dysfunction (Supplementary Material, Table S7).

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the outcomes. Estimates of the evolution of TR did not change considerably if patients with pre-LVAD ECMO were excluded (Supplementary Material, Tables S9 and S10). Including the centre as a random effect did not change estimates (Supplementary Material, Table S11). Furthermore, centres that tended to repair the tricuspid valve in the setting of moderate-to-severe TR pre-LVAD had similar evolutions of post-LVAD TR in patients without tricuspid valve intervention compared to centres that were not inclined to repair the tricuspid valve (Supplementary Material, Fig. S12). Excluding patients with an RV assist device implant during the follow-up period did not considerably change the estimates of the longitudinal evolution or of survival (Supplementary Material, Tables S12 and S13).

DISCUSSION

This study explores the clinical impact of pre-LVAD and post-LVAD TR on 30-day and late mortality and the course of post- LVAD TR in the survivors. Interesting observations were noted: both pre- and post-LVAD TR seemed to be associated with reduced survival. Nevertheless, on average, TR resolved ‘spontaneously’ after an LVAD implant, which was not solely due to survival bias.

Early and late mortality

We hypothesized that TR is part of an entire pathway that may lead to higher 30-day mortality, i.e. mediated by other variables. To gain insight in this hypothesis, we developed a conceptual model with several paths (Fig. 1). When this model was tested, it fit well, suggesting that TR may not be directly related to 30-day mortality but that by increasing other risk factors it is indirectly associated with 30-day mortality. Notably, we did not include RVF in the pathways because of the circular relation with the severity of TR, which cannot be modelled. The impaired RVF can lead to TR due to RV/annulus dilation, but also the other way around due to volume or pressure overload [7]. Furthermore, TR was chosen in the model because TR is associated with renal dysfunction in the literature [9].

The investigators of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) found TR to be associated with reduced late survival [13]. Assessing the Kaplan–Meier curve of the combined variables, it seems that pre-LVAD-impaired RVF is the

driving factor in late mortality after an LVAD implant; however, impaired RVF accompanied by TR resulted in an even worse survival. These data may suggest that pre-LVAD TR in the setting of impaired RVF adds extra late risk, which can partly be explained by the negative spiral that ensues when TR is present in the setting of impaired RVF, leading to more dysfunction. Furthermore, TR together with impaired RVF is associated more with renal failure than with isolated TR or impaired RVF alone [14, 15]. Nevertheless, it has to be noted that confounding may be present here, and, in a sensitivity analysis with complete cases, pre-LVAD RVF did seem to be the driving factor regardless of pre-LVAD TR. RVF was conditionality missing upon other observed baseline variables, suggesting the missing at random mechanism. Multiple imputation is more valid in missing-at-random scenarios [16].

Evolution of tricuspid regurgitation

TR decreases without intervention after an LVAD implant, and this decrease is not solely based on patients dying of TR. Overall, an immediate decrease of ~65% is observed from moderate-to-severe TR to non-to-mild TR in patients with moderate-to-severe TR pre-LVAD. Other studies comparing point estimates over time noted comparable results [1, 4]. The decrease in TR may be explained by the fact that LVAD support reduces pulmonary pressures, subsequently reducing the pressure overload of the right ventricle, which leads to right ventricle remodelling and regression of the tricuspid valve annulus dilatation. The remodelling in turn leads to resolution of functional TR.

Furthermore, it seems that TR decreases more quickly in patients with idiopathic cardiomyopathy compared to other cardiomyopathies. However, later in the follow-up period, this difference disappears. Furthermore, these results can be explained by confounding because the models were univariable, and some misclassifications in TR grade will be present, which can bias outcome in the small subgroups.

Clinical implications and rationale for eventual tricuspid valve surgery

The observations of this study in respect to concomitant tricuspid valve surgery can be interpreted in 2 ways. First, one can argue that concomitant surgery of the tricuspid valve is warranted, because both preoperative and postoperative TR are associated with increased mortality. It has to be noted that this study by design cannot establish a causal relationship between TR and mortality, and TR may just be a marker of significant RVF. Second, one can argue that a less aggressive strategy is warranted because, on average, the TR will resolve after LVAD implantation without any further intervention.

Current guidelines advise consideration of tricuspid valve surgery in the presence of moderate or severe TR at baseline. Current practice notwithstanding, we may be overtreating patients with unnecessary concomitant tricuspid valve surgery if we follow the guidelines. This deficit also may explain why previous studies comparing patients with and without concomitant tricuspid valve surgery were unable to find an effect [2]. Some patients will not benefit because

TR will resolve without an intervention. Therefore, the key point seems to be appropriate patient selection, taking into account the aetiology of TR, the severity of RV dysfunction and the underlying myocardial disease when deciding to perform concomitant surgery. Anwer et al. [17] proposed that atrial fibrillation should be included in this decision process. We were not able to show a significant effect of pre-LVAD atrial fibrillation on the odds of significant TR post-LVAD with the subgroup analyses, but there were only a few patients in the atrial fibrillation group. Functional TR has a chance to reduce spontaneously, whereas primary TR (e.g. caused by a pacemaker or an implantable cardioverter-defibrillator lead) probably will not. Furthermore, functional TR has not only been caused by tricuspid valve annular dilatation but also by valve tethering [18]. In the case of severe tethering, tricuspid annuloplasty may not be enough to reduce TR [19].

Future perspectives

Future studies should focus on understanding the different mechanisms and concomitant factors contributing to significant TR and finding the appropriate predictors of TR after LVAD implantation, preferably in a longitudinal prospective dedicated data set encompassing RV functional and dimensional, pulmonary and haemodynamic parameters. Therefore, we recently set up the Serial Multiparametric Evaluation of Right Ventricular Function After Left Ventricular Assist Device Implantation (EuroEchoVAD) study (see clinicaltrails.org, NCT03552679) to investigate the evolution of RVF, TR and other echocardiographic parameters before and after LVAD implantation. The findings of the study will enhance the prediction of the early and late development of postoperative RVF, the course of TR severity and the subsequent mortality and morbidity. Furthermore, novel transcatheter devices to treat tricuspid valve regurgitation are on the horizon. These devices have the potential to become interesting addenda in the treatment of functional TR in the setting of LVAD implantation. However, several challenges need to be addressed before they can enter daily clinical practice [20].

Limitations

This study has several limitations common to retrospective registry

analyses. EUROMACS is not designed to address the specific questions in this study. Therefore, there is a limited amount of data collected with a focus on the right ventricle, or these data are not uniformly collected. Furthermore, it has to be emphasized that misspecification may be present in a registry and that follow-up is suboptimal, which can introduce bias. We prevented more loss of data by imputation of the missing data in order to generate more power in the analysis. Nevertheless, some variables could not be imputed due to excessive missingness, and we could not use the longitudinal trajectory of TR in the imputation model. Additionally, follow-up data on TR were not collected at prespecified, regular intervals and assessing TR remains challenging [21]. However, we used mixed models, which can handle these unstructured data sets, and TR was dichotomized in these models to create a more robust measurement.

Unfortunately, in some subgroups, the sample size was small, and it was not known if patients had tricusispid valve surgery during the follow-up period. Advanced path models are used to shed some light on the impact of TR on 30-day mortality via other variables. However, due to the circular relationship with RVF, the true effect of TR on mortality may be impossible to estimate. Thereafter, the mechanism of TR was not recorded in the registry. Presumably, most of the TR is functional in nature, supported by the fact that TR is associated with RVF and its symptoms/treatment.

CONCLUSIONS

Moderate-to-severe TR pre-LVAD is positively correlated with worse RVF pre-LVAD and is associated with worse late mortality. However, overall, TR decreases after the LVAD is implanted, regardless of pre-LVAD pulmonary hypertension or right ventricle function. Hence, in the majority of the patients, additional tricuspid valve surgery may be redundant. Therefore, patient selection for concomitant tricuspid valve surgery should not be based solely on TR grade alone. Further studies are urgently needed to tackle this clinical dilemma in the era of durable mechanical circulatory support.

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SUPPLEMENTARY MATERIAL

CONTENTS

SUPPLEMENTARY TEXT 1: ELABORATION MEDIATION. MULTIPLE IMPUTATION AND MIXED-MODELS

Mediation analysis

Historically medical statistics have been focused to describe the relation between independent and dependent variables. However, in order to understand the mechanism that underlie a phenomena a more causal approach is warranted. Furthermore – if the purpose of the study is to assess the impact of a single risk factor – not addressing known causal pathways in multivariable models may result in spurious estimates, because a confounder has a two-way effect (e.g. it is an underlying factor which can both affect the outcome as well as the variable of interest). A mediator can only be affected by the variable of interest (and not the other way around). Therefore, we conducted mediation analysis. These analysis were initially developed by Baron and Kennedy (1). However, in the following decades multiple methods were developed to address mediation.

Structural equation model

We used a structural equation model (SEM), frequently used in behavioral sciences (2). These models are mainly used to work with latent variables (e.g. "motivation"), which cannot be measured directly, but can also be used in mediation analyses, in which all variables are measured (3). A SEM contains exogenous variables (variables that are not predicted by others) and endogenous variables (variables that are predicted). In a SEM a endogenous variable can be both an independent variable (predictor) or dependent variable (predicted). A common way to present a SEM is with a path diagram. In this diagram the arrows denote the presumed causal relation. Curved two-headed arrows present the covariation between variables. The R statistical package "lavaan" was used to conduct the median analysis (4). This package can handle categorical data. Notably, exogenous ordinal data should be incorporated as numerical data. The WLSMV estimator is used when categorical data is incorporated in the model. This estimator uses diagonally weighted least squares to estimate the model parameters, however it will use the full weight matrix to compute robust standard errors, and a mean- and variance-adjusted test statistic (4).

Several fit indices exist to give an indication of the fit of a SEM. The most common used is the chi-squared, in which a $p>0.05$ is an indication of a good fit. However, in large samples the chi-squared is nearly always significantly different (5). Other measures are:

Comparative fit Index

A value ranging from 0 to 1 of which >0.95 is an indication of a good fit.

Non-normed Fit Index

>0.95 is an indication of a good fit

Root Mean Square Error of Approximation

If higher limit of the confidence interval is <0.08 the model is considered well fitted.

Standardized Root Mean Square Residual

<0.08 is an indication of a good fit.

Generalized mixedmodels

All models had random intercepts for patients. Natural splines for time were added to establish flexibility over time. The marginal probabilities were obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest 3000 patients are generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities is taken as estimate.

All models contained the following covariates: time (with splines), the risk factor and the interaction between the risk factor and time.

Missing values

Multiple imputation by chained equations using the statistical "MICE" package in R was used to impute missing values (6). All baseline variables with < 50% missing were imputed, above 50% missing was considered excessive missingness (Supplementary Table 3). Imputations were done based upon the other baseline variables. In case of highly correlated variables the variable with highest clinical value was chosen as predictor (Supplementary Table 4). Correlation was tested with Pearson R or Spearman rho, as appropriate. Five imputed datasets were generated using this method using 5 iterations each. Convergence was visually checked in convergence plots. The imputations were visually checked by strip plots and density plots. The imputed datasets were used for the logistic regression models, structural equation models, ordinal regression models. Estimates, standard errors and model comparison tests were pooled according to Rubins' rules (7). In the cox model part of the joint model the first imputed dataset was used. In a sensitivity analyses the estimates and variance was compared with the pooled estimate and variance according to Rubins rules, which was comparable.

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Supplementary Table 1: List of participating centers as of 31 December 2016

Country	City, Hospital
Austria	Innsbruck, Universitätskliniken
Azerbaijan	Baku, Central Clinic Hospital
Belarus	Minsk, National Institute 'Cardiology'
Belgium	Aalst, Onze Lieve Vrouwenziekenhuis
	Gent, Universitair Ziekenhuis Gent
	Leuven, Katholieke Universiteit Leuven
Czech Republic	Prague, Institute for Experimental Cardiac Surgery (IKEM)
	Brno, Center for Cardiovascular and Transplant Surgery
Denmark	Århus, Århus University Hospital Skejby
	Copenhagen, Rigshospitalet
France	Le Plessis-Robinson, Centre Chirurgical Marie Lannelongue
Germany	Berlin, Deutsches Herzzentrum Berlin
	Lübeck, Universitätsklinikum Schleswig Holstein
	Bad Oeynhausen, Herz- und Diabeteszentrum Nordrhein-Westfalen
	Hamburg, Universitätsklinikum Eppendorf
	Freiburg, Universitäts Herzzentrum Freiburg - Bad Krozingen
	Jena, Universitäts-Herzzentrum Thüringen
	Karlsburg, Klinikum Karlsburg
	Köln, Universitätsklinikum Köln, AöR
Greece	Athens, Onassis Cardiac Surgery Center
	Thessaloniki, Aristotle University of Thessaloniki
Hungary	Budapest, Heart Center of the Semmelweis University
	Budapest, Gottsegen György Hungarian Institute of Cardiology
Italy	Bologna, Ospedale S. Orsola
	Rome, Ospedale San Camillo
	Milan, Ospedale Niguarda Ca'Granda
	Bergamo, Ospedale Papa Giovanni XXIII
	Naples, Ospedale dei Colli
	Palermo, ISMETT
	Rome, Ospedale Pediatrico Bambino Gesù
	Torino, Regina Margherita Children's Hospital
Kazakhstan	Astana, National Research Cardiac Surgery Center
Netherlands	Groningen, Universitair Medisch Centrum Groningen
	Rotterdam, Erasmus Medisch Centrum
	Utrecht, Universitair Medisch Centrum Utrecht
Norway	Oslo, Rikshospitalet
Poland	Warsaw, Childrens Memorial Hospital
	Zabrze, Silesian Heart Center

Supplementary Table 1: List of participating centers as of 31 December 2016 (continued)

Country	City, Hospital
Spain	Pamplona, Clínica Universidad de Navarra
	ESPAMACS, Madrid, collective of 7 hospitals
Switzerland	Bern, University Hospital Bern (Inselspital)
	Zürich, Kinderspital Zürich
Turkey	Izmir, Ege University School of Medicine
	Istanbul, Florence Nightingale Hospital
	Ankara, Bashkent University Hospital
	Ankara, Yüksek Ihtisas Hospital

Supplementary Table 2: Number of removed variables

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
Age	53.39	16.62	90.16	0
LVSF	11.13	-8.12	30.38	3
TAPSE	14.53	1.96	27.09	11
Systolic BP	101.14	50.81	151.46	15
Diastolic BP	65.05	28.6	101.5	20
BSA	2.28	-6.04	10.6	29
Pulmonary artery systolic pressure	52.58	-3.56	108.72	15
Pulmonary artery diastolic pressure	26.42	-6.42	59.26	21
RA pressure	11.41	-11.23	34.06	14
Pulmonary artery wedge pressure	23.83	-2.49	50.14	3
PVR	284.66	-386.64	955.96	10
Sodium	131.14	29.2	233.08	4
Potassium	4.25	-11.44	19.94	3
Blood Urea Nitrogen	61.82	-61.54	185.18	28
Creatinine	206.07	-2797.03	3209.16	13
ALAT	163.6	-1814.26	2141.46	23
ASAT	310.75	-4179.29	4800.79	27
LDH	610.45	-3586.34	4807.24	24
Total bilirubin	2.17	-30.08	34.42	4
Pro BNP	10090.11	-25295.82	45476.05	20
Cholesterol	3.86	-10.87	18.6	1
WBC	35.72	-1443.86	1515.29	6
Reticulocytes	12.95	-39.79	65.69	3
Hemoglobin	15.12	-44.04	74.29	55
Platelet	208.59	-55.41	472.6	22
INR	1.61	-3.71	6.93	6
PTT	41.12	-25.67	107.9	32

Supplementary Table 2: Number of removed variables (continued)

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
pH	13.45	-621.82	648.72	1
Lactate	4.99	-38.27	48.26	16
BicarbonatHCO3	24.16	11.17	37.14	14
CRPC reactive protein	11.09	-157.12	179.3	18
LVEDD2	63.08	-36.33	162.48	6
Pulmonary Artery Pressure Mean	35.97	-30.71	102.66	1
Pa Capillary Wedge Pressure	25.04	0.99	49.08	0

Supplementary Table 3: Missing data (alphabetic order)

Variable	Count missing	Percentage missing
ACE inhibitors	469	18,.8
Acenocoumarol	1152	46.2
Age	22	0.9
Albumin	1290	51.7
Aldosterone antagonist	508	20.4
Amiodarone	529	21.2
Anticoagulant therapy	537	21.5
Antiplatelet drugt herapy	605	24.2
Aortic regurgitation	234	9.4
ARB	508	20.4
Ascites	807	32.3
Betablockers	500	20.0
Bicarbonat HCO3	1352	54.2
Bloodtype	15	0.6
Blood Urea Nitrogen	641	25.7
Bosentan	1095	43.9
BSA	353	14.1
Cancer Other Than Local SkinCancer	342	13.7
Cardia cArrest	337	13.5
Cardiac Index	528	21.2
Cardiac Output	1419	56.9
Cardiac Surgery	329	13.2
Cholesterol	1824	73.1
Connective Tissue Or Inflammatory	383	15.3
COPD	337	13.5
CPB Time	249	10.0
Creatinine	633	25.4
CRPC reactive protein	574	23.0
Cumadine	2155	86.3

Supplementary Table 3: Missing data (alphabetic order) (continued)

Variable	Count missing	Percentage missing
ICD	257	10.3
Diabetes	135	5.4
Dialysis	165	6.6
Diastolic BP	483	19.4
ECG rhythm	437	17.5
ECMO	90	3.6
Ethnic origin	340	13.6
Feeding Tube	410	16.4
Gender	0	0.0
Hemoglobin	415	16.6
History Of Neurological Event	373	14.9
History Of Previous Alcohol Abuse	1367	54.8
Hospital stay	562	22.5
IABP	341	13.7
Iloprost	1096	43.9
INR	362	14.5
INTERMACS class	99	4.0
Intubation	332	13.3
Lactate	1704	68.3
LDHP	852	34.1
Loop diuretics	472	18.9
LVEDD2	453	18.1
LVEDV	1975	79.1
LvEf Percent	405	16.2
LVESD	1277	51.2
LVESV	2059	82.5
LVSF	2101	84.2
Major Infections	344	13.8
Major MI	339	13.6
Marcumar	1892	75.8
Marital status	710	28.4
Mitral regurgitation	299	12.0
Multiple intropes	393	15.7
Neseritide	519	20.8
Nitric Oxide	527	21.1
NT Pro BNP	1670	66.9
Number of inotropes	403	16.1
Pa Capillary Wedge Pressure	2468	98.9
pH	1263	50.6
Phenprocoumon	967	38.7

Supplementary Table 3: Missing data (alphabetic order) (continued)

Variable	Count missing	Percentage missing
Platelet	448	17.9
Positive Blood Cultures	578	23.2
Potassium	509	20.4
Primary Diagnosis	350	14.0
PTT	536	21.5
Pulmonary artery diastolic pressure	1169	46.8
Pulmonary Artery Pressure Mean	1091	43.7
Pulmonary artery systolic pressure	1155	46.3
Pulmonary artery wedge pressure	1323	53.0
Pulmonary Regurgitation	854	34.2
PVR	1748	70.0
RA pressure	1214	48.6
Reason For Admission	306	12.3
Reticulocytes	2273	91.1
Rhesusfactor	15	0.6
R value at peak	2473	99.1
RVEF	784	31.4
RvEf Percent	1382	55.4
ASAT	469	18.8
ALAT	1043	41.8
Sildenafil	1056	42.3
Smoking History	1066	42.7
Sodium	508	20.4
SVR	1842	73.8
Symptomatic Peripheral Vascular Disease	371	14.9
Systolic BP	719	28.8
TAPSE	1395	55.9
Time since first cardiac diagnosis	449	18.0
Total bilirubin	560	22.4
Transfusion History	1572	63.0
Tricuspid regurgitation	0	0.0
Ultrafiltration	336	13.5
Ventilation	704	28.2
Ventilator	346	13.9
Peripheral edema	544	21.8
VO max	2355	94.4
Warfarin	1132	45.4
WBC	365	14.6

Supplementary Table 4: Variables included in multiple imputation

Included in imputation	
Rhesusfactor	BSA
Gender	Pulmonary artery systolic pressure[2]
Mitral regurgitation	Pulmonary artery diastolic pressure[2]
Tricuspid regurgitation	RA pressure
Aortic regurgitation	Sodium
Peripheral edema	Potassium
ECG rhythm	Blood Urea Nitrogen
Neseritide	Creatinine
ARBO	ALAT[3]
Amiodarone	ASAT
ACE inhibitors	LDH
Betablockers	Total bilirubin
Aldosterone antagonist	WBC
Loopdiuretics	Hemoglobin
Phenprocoumon	Platelet
Antiplatelet drug therapy	INR
Anticoagulant therapy	PTT
Nitric Oxide	CRPC reactive protein
Time since first cardiac diagnosis	LVESD
Primary Diagnosis	LvEf Percent
ICD	Pulmonary Artery Pressure Mean
Cardiac Arrest	Diastolic BP
Dialysis	Systolic BP
Intubation[1]	*Legend*
Major MI	1: Not a predictor due to high correlation with Ventilation
Cardiac Surgery	
Positive Blood Cultures	2: Not a predictor due to high correlation with Pulmonary Artery Pressure Mean
Major Infections	
IABP	3: Not a predictor due to high correlation ASAT
Ultrafiltration	
Ventilator	
Feeding Tube	
ECMO	
INTERMACS class	
Diabetes	
COPD	
Symptomatic Peripheral Vascular Disease	
Connective Tissue Or Inflammatory	
Carotid Artery Disease	

Supplementary Table 4: Variables included in multiple imputation (continued)

Included in imputation
History Of Neurological Event
Cancer Other Than Local Skin Cancer
Smoking History
RVF
Ascites
Pulmonary Regurgitation
Sildenafil
Iloprost
Bosentan
Multiple Intropes
Age

Supplementary Table 5: Uni- multivariable ordinal logistic regression

	Univariable		Multivariable	
Characteristic	OR (95% CI)	P – value	OR (95% CI)	P – value
Bloodtype A	Reference			
Bloodtype AB	1.13 (0.81 to 1.57)	0.46	-	-
Bloodtype B	1.02 (0.82 to 1.26)	0.89	-	-
Bloodtype O	0.95 (0.81 to 1.12)	0.55	-	-
Rhesusfactor Positive	0.98 (0.81 to 1.2)	0.88	-	-
Male gender	0.97 (0.8 to 1.18)	0.79	-	-
No mitral regurgitation	Reference			
Trivial mitral regurgitation	1.68 (1.16 to 2.43)	0.007	1.62 (1.07 to 2.47)	0.025
Mild mitral regurgitation	4.87 (3.43 to 6.91)	<0.001	3.34 (2.25 to 4.94)	<0.001
Moderate mitral regurgitation	8.35 (5.96 to 11.68)	<0.001	5.23 (3.59 to 7.61)	<0.001
Severe mitralregurgitation	15.2 (10.4 to 22.21)	<0.001	9.62 (5.97 to 15.5)	<0.001
No aortic regurgitation	Reference			
Trivial aortic regurgitation	1.69 (1.41 to 2.02)	<0.001	1.22 (0.97 to 1.54)	0.088
Mild aortic regurgitation	2.53 (2 to 3.2)	<0.001	1.5 (1.12 to 2.02)	0.008
Moderate aortic regurgitation	2 (1.3 to 3.06)	0.002	1.47 (0.88 to 2.47)	0.14
Severe Aortic regurgitation	1.53 (0.74 to 3.15)	0.25	0.76 (0.35 to 1.62)	0.46
No peripheral edema				
Mild peripheral edema	1.55 (1.27 to 1.9)	<0.001	1.39 (1.06 to 1.82)	0.018
Moderate peripheral edema	1.85 (1.48 to 2.31)	<0.001	1.27 (0.99 to 1.62)	0.057
Severe peripheral edema	1.56 (1.21 to 2.01)	0.001	1.36 (1 to 1.85)	0.048
Sinus	Reference			
Atrial fibrillation	1.22 (0.98 to 1.52)	0.071	1.22 (0.96 to 1.56)	0.10
Other	1.59 (0.92 to 2.74)	0.094	1.35 (0.77 to 2.38)	0.28

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
Paced	1.48 (1.22 to 1.8)	0	1.12 (0.86 to 1.45)	0.38
Medication on admission				
Neseritide	0.55 (0.27 to 1.12)	0.088	0.87 (0.21 to 3.55)	0.81
ARB	0.75 (0.59 to 0.96)	0.025	0.8 (0.6 to 1.07)	0.12
Amiodarone	0.8 (0.66 to 0.97)	0.022	0.82 (0.68 to 1)	0.055
ACE inhibitors	1.01 (0.83 to 1.24)	0.92	-	-
Beta-blockers	1.26 (1.08 to 1.48)	0.004	0.96 (0.75 to 1.24)	0.76
Aldosterone antagonist	1.31 (1.1 to 1.57)	0.004	0.97 (0.81 to 1.16)	0.70
Loop diuretics	1.56 (1.28 to 1.9)	<0.001	1.38 (1.13 to 1.69)	0.002
Phenprocoumon*	0.91 (0.63 to 1.33)	0.60		
Antiplatelet drug therapy (yes vs no)	0.63 (0.53 to 0.74)	<0.001	0.83 (0.68 to 1.01)	0.057
Anticoagulant therapy drugs (yes vs no)	0.8 (0.67 to 0.94)	0.009	0.88 (0.68 to 1.13)	0.29
Nitric Oxide	0.58 (0.38 to 0.91)	0.020	0.96 (0.43 to 2.13)	0.90
Sildenafil	0.98 (0.78 to 1.24)	0.87	-	-
Iloprost	0.9 (0.69 to 1.16)	0.38	-	-
Bosentan	1.12 (0.92 to 1.38)	0.25	-	-
Multiple inotropes (>2)	0.84 (0.67 to 1.06)	0.13	-	--
-Cardiac diagnosis less than one month	Reference			
Cardiac diagnosis one month to a year	2.1 (1.6 to 2.75)	<0.001	1.01 (0.7 to 1.46)	0.96
Cardiac diagnosis one to two years	3.77 (2.65 to 5.35)	<0.001	1.27 (0.82 to 1.96)	0.28
Cardiac diagnosis over two years	3.36 (2.66 to 4.23)	<0.001	1.13 (0.75 to 1.68)	0.55
Primary diagnosis: Coronary artery disease	Reference			
Primary diagnosis: Idiopathic dilated myopathy	2.18 (1.63 to 2.92)	<0.001	1.31 (0.98 to 1.75)	0.066
Primary diagnosis: Ischemic dilated myopathy	1.2 (0.91 to 1.58)	0.20	1.08 (0.81 to 1.42)	0.61
Primary diagnosis: Other dilated myopathy	1.45 (1.09 to 1.93)	0.010	1.34 (1.01 to 1.78)	0.045
ICD Device	1.61 (1.39 to 1.88)	<0.001	1.31 (0.98 to 1.75)	0.066
Cardiac arrest	0.47 (0.33 to 0.66)	<0.001	1.17 (0.92 to 1.47)	0.20
Dialysis	0.8 (0.53 to 1.22)	0.31	0.77 (0.54 to 1.09)	0.13
Intubated	0.46 (0.36 to 0.58)	<0.001	0.97 (0.72 to 1.3)	0.83
Major MI	0.57 (0.47 to 0.7)	<0.001	1.12 (0.86 to 1.46)	0.38
Cardiac surgery	1.02 (0.81 to 1.29)	0.84	-	-
Positive blood cultures	0.52 (0.38 to 0.71)	<0.001	0.76 (0.48 to 1.21)	0.23
Major Infections	0.52 (0.39 to 0.7)	<0.001	0.93 (0.62 to 1.37)	0.69
IABP	0.56 (0.44 to 0.72)	<0.001	0.86 (0.63 to 1.18)	0.34
Ultrafiltration*	0.72 (0.49 to 1.07)	0.099	1.47 (0.87 to 2.48)	0.14
Ventilator*	0.41 (0.31 to 0.55)	<0.001	-	-
Feeding tube	0.32 (0.24 to 0.43)	<0.001	0.7 (0.46 to 1.07)	0.096

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
ECMO	0.46 (0.36 to 0.59)	<0.001	0.91 (0.62 to 1.34)	0.64
INTERMACS class 1	Reference			
INTERMACS class 2	1.81 (1.43 to 2.3)	<0.001	1.07 (0.76 to 1.51)	0.69
INTERMACS class 3	1.77 (1.39 to 2.26)	<0.001	1.06 (0.74 to 1.53)	0.73
INTERMACS class >4	2.41 (1.88 to 3.09)	<0.001	1.18 (0.81 to 1.72)	0.37
Diabetes	1.12 (0.95 to 1.31)	0.19	-	-
COPD	0.87 (0.65 to 1.16)	0.33	-	-
Symptomatic peripheral vascular disease	0.8 (0.57 to 1.14)	0.21	-	-
connective tissue or inflammatory disease	0.99 (0.34 to 2.85)	0.98	-	-
Carotid Artery Disease	1.01 (0.53 to 1.93)	0.97	-	-
Prior neurological event: None	Reference			
Prior neurological event: CVA	0.87 (0.65 to 1.15)	0.32	-	-
Prior neurological event: ICB	0.62 (0.28 to 1.36)	0.22	-	-
Prior neurological event: TIA	0.83 (0.55 to 1.25)	0.36	-	-
Cancer other than local skin cancer	0.98 (0.66 to 1.46)	0.92	-	-
Smoking history	0.51 (0.43 to 0.6)	<0.001	0.75 (0.59 to 0.94)	0.016
RVEF: Normal	Reference			
RVEF: Mild impairment	1.51 (1.2 to 1.91)	0.001	1.4 (1.09 to 1.79)	0.009
RVEF: Moderate impairment	2.79 (2.19 to 3.57)	<0.001	2.33 (1.74 to 3.12)	<0.001
RVEF: Severe impairment	2.92 (2.18 to 3.92)	<0.001	2.96 (2.18 to 4.01)	<0.001
Ascites	1.48 (1.08 to 2.04)	0.020	1.07 (0.8 to 1.43)	0.62
No Pulmonary regurgitation	Reference			
Trivial Pulmonary regurgitation	1.78 (1.48 to 2.15)	<0.001	1.28 (1.05 to 1.55)	0.013
Mild Pulmonary regurgitation	4.43 (3.39 to 5.79)	<0.001	2.73 (2.12 to 3.5)	<0.001
Moderate Pulmonary regurgitation	8.03 (5.28 to 12.21)	<0.001	4.47 (2.88 to 6.93)	<0.001
Severe Pulmonary regurgitation	4.02 (1.66 to 9.75)	0.006	3.05 (1.31 to 7.13)	0.015
Continuous variables				
Age per 10 years	0.97 (0.92 to 1.03)	0.39	-	-
Systolic BP per 10 mmHg	0.93 (0.88 to 0.98)	0.011	0.94 (0.9 to 0.99)	0.027
Diastolic BP per 10 mmHG	1.03 (0.97 to 1.1)	0.36	-	-
BSA	0.21 (0 to 8.59)	0.39	-	-
Pulmonary artery systolic pressure per 10 mmHG	1.16 (1.1 to 1.23)	<0.001	-	-
Pulmonary artery diastolic pressure per 10 mmHG	1.26 (1.15 to 1.37)	<0.001	-	-
RA pressure per 1 mmHG	1.04 (1.03 to 1.06)	<0.001	1.05 (1.02 to 1.08)	0.009
Sodium per 50	0.77 (0.64 to 0.91)	0.003	0.82 (0.67 to 1)	0.050
Potassium per 10	0.86 (0.34 to 2.21)	0.75	-	-
Blood urea nitrogen per 50	0.93 (0.84 to 1.03)	0.16	-	-
Creatinine per 50	0.98 (0.94 to 1.02)	0.33	-	-

Supplementary Table 5: Uni- multivariable ordinal logistic regression (continued)

	Univariable		Multivariable	
*ALAT per 50	0.98 (0.97 to 1)	0.031	-	-
ASAT per 50	0.99 (0.98 to 1)	0.019	1.01 (1 to 1.02)	0.14
LDH per 50	0.97 (0.96 to 0.98)	<0.001	0.98 (0.96 to 1)	0.027
Total bilirubin per 1	1.05 (1.01 to 1.09)	0.01	1.02 (1 to 1.07)	0.336
WBC per 10	0.95 (1 to 1.04)	0.28	-	-
Hemoglobin	0.98 (0.95 to 1.01)	0.27	-	-
Platelet per 50	0.98 (0.94 to 1.04)	0.56	-	-
INR per 1	0.95 (0.86 to 1.05)	0.30	-	-
PTT per 1	0.99 (0.98 to 0.99)	<0.001	0.99 (0.99 to 1)	0.014
LVESD per 1	1 (1 to 1.01)	0.46	-	-
LvEfPercent per 1	1 (0.99 to 1.01)	0.83	-	-
PulmonaryArteryPressureMean per 10	1.02 (1.01 to 1.02)	0.003	1 (0.85 to 1.17)	0.966

Supplementary Table 6: Baseline variables stratified to missing versus not missing of right ventricular function (RVF).

	RVF Missing	RVF not missing	P-value
Demographics			
n	784	1712	
Age, y			
Male sex, n (%)	617 (78.7)	1456 (85.0)	<0.001
Body surface area, m2	1.98 [1.83, 2.12]	1.96 [1.81, 2.11]	0.200
White race, n (%)	458 (89.5)	1402 (85.3)	0.003
Ischemic etiology HF, n (%)	231 (46.4)	640 (38.8)	0.008
≥2 years since first diagnosis	312 (61.5)	993 (64.5)	0.001
Destination therapy	105 (13.4)	317 (18.5)	0.002
Ascites	19 (7.2)	171 (12.0)	0.031
Rhythm, n (%)			<0.001
• Sinus	200 (42.0)	937 (59.2)	
• Atrial fibrillation	64 (13.4)	291 (18.4)	
• Paced	191 (40.1)	320 (20.2)	
• Other	21 (4.4)	35 (2.2)	
INTERMACS profile, n (%)			<0.001
• 1	118 (16.8)	199 (11.7)	
• 2	283 (40.3)	514 (30.3)	
• 3	187 (26.6)	475 (28.0)	
• ≥4	115 (16.4)	506 (29.9)	
IABP, n (%)	77 (15.1)	154 (9.4)	<0.001
ECMO, n (%)	80 (10.5)	153 (9.3)	0.406
Ventilator (%)	78 (15.3)	198 (12.1)	0.071

Supplementary Table 6: Baseline variables stratified to missing versus not missing of right ventricular function (RVF). (continued)

	RVF Missing	RVF not missing	P-value
Medication, n (%)			
• Loopdiuretics, n (%)	368 (78.8)	1280 (82.2)	0.111
• Use of ≥3 inotropes, n (%)	112 (23.3)	163 (10.0)	<0.001
Laboratory values			
• Serum creatinine, mg/dL	106.00 [84.00, 139.00]	107.00 [83.00, 146.00]	0.474
• ASAT, U/L	35.00 [23.00, 72.75]	31.00 [22.00, 62.00]	0.015
• Total bilirubin, mg/dL	1.20 [0.79, 2.00]	1.24 [0.80, 2.00]	0.652
• Albumin, g/dL	494.11 [405.72, 594.09]	507.15 [420.21, 579.60]	0.969
• Hemoglobin, g/dL	11.30 [9.90, 13.10]	12.10 [10.43, 13.70]	<0.001
Hemodynamic			
• RA pressure, mmHg	10.00 [6.00, 15.00]	10.00 [7.00, 15.00]	0.550
• PCWP, mmHg	23.00 [17.00, 29.00]	25.00 [18.00, 30.00]	0.049
• PAP, systolic, mmHg	48.00 [37.00, 59.00]	52.00 [40.00, 65.00]	0.003
Echocardiographic			
• TAPSE, mm	15.00 [13.00, 18.00]	14.00 [12.00, 17.00]	0.001
• No aortic regurgitation, n (%)	490 (66.6)	950 (62.3)	0.005
• Severe mitral regurgitation, n (%)	100 (19.1)	285 (17.0)	0.098
• LVEF grade <20%, n (%)	233 (51.8)	977 (61.7)	<0.001

Supplementary Table 7: Estimates and standard errors of the mixed model compared to the longitudinal outcome of the joint-model. Both models contained time, with a spline function (1 knot), TR at baseline and their interaction.

Characteristic	Mixed model		Joint model	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-1.826 (0.496)	<0.001	-1.832 (0.146)	<0.001
Time spline 1	-3.028 (0.987)	0.002	-4.504 (0.748)	<0.001
Time spline 2	3.406 (1.065)	0.001	2.966 (1.616)	0.061
Baseline TR	5.876 (0.81)	<0.001	5.848 (0.254)	<0.001
Baseline TR: Time spline 1	-9.979 (1.595)	<0.001	-8.372 (1.072)	<0.001
Baseline TR: Time spline 2	1.05 (1.939)	0.59	2.832 (2.314)	0.21

The direction of effects did not change between the two models and significance remains similar between the two groups, except for the second spline for time, which is not significant in the joint model. Hence, some sensitivity is present, but course over time is comparable between the two models.

Supplementary Table 8: Estimates of the joint model survival part. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR

Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.03 to 1.06)	<0.001
Male gender	0.83 (0.55 to 1.28)	0.43
Moderate-to-Severe baseline TR	0.84 (0.62 to 1.25)	0.29
Destination therapy	1.04 (0.66 to 1.58)	0.84
Intermacs score (cubic)	0.66 (0.5 to 0.86)	<0.001
ICD	0.98 (0.72 to 1.33)	0.87
Blood urea nitrogen	1 (0.99 to 1)	0.49
Creatinine	1 (1 to 1)	0.24
Sodium	1 (0.99 to 1)	0.25
Pre-LVAD RV function (lin)	1.33 (0.86 to 2.02)	0.19
Ascitis	1.27 (0.81 to 1.94)	0.26
Moderate-to-severe post LVAD TR*	1.16 (1.06 to 1.28)	0.005

Supplementary Table 9: Sensitivity analyses of the generalized mixed model in which patients with preoperative ECMO were excluded.

Characteristic	Mixed model with ECMO patients		Mixed model without ECMO patients	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-2.178 (0.801)	0.007	-2.638 (0.857)	0.002
Time spline 1	-4.117 (1.59)	0.010	-3.32 (1.69)	0.049
Time spline 2	1.948 (1.57)	0.21	2.017 (1.634)	0.22
Baseline TR	5.129 (1.269)	<0.001	5.664 (1.347)	<0.001
Baseline TR: Time spline 1	-7.23 (2.532)	0.004	-8.381 (2.685)	0.002
Baseline TR: Time spline 2	1.362 (2.6)	0.60	1.384 (2.71)	0.61

Supplementary Table 10: Sensitivity analyses of the survival part of the joint model of in which patients with preoperative ECMO were excluded. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR

Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.03 to 1.06)	<0.001
Male gender	0.8 (0.48 to 1.31)	0.35
Moderate-to-Severe baseline TR	0.89 (0.61 to 1.29)	0.55
Destination therapy	1.02 (0.67 to 1.48)	0.84
Intermacs score (cubic)	0.75 (0.55 to 1.03)	0.07
ICD	1.11 (0.76 to 1.7)	0.63
Blood urea nitrogen	1 (0.99 to 1)	0.49

Supplementary Table 10: Sensitivity analyses of the survival part of the joint model of in which patients with preoperative ECMO were excluded. *time varying covariate as estimated by a mixed model containing time in a Spline function with 1 knot and baseline TR (continued)

Characteristic	Hazard ratio (95% confidence interval)	P-value
Creatinine	1 (1 to 1)	0.54
Sodium	1 (0.99 to 1.01)	0.71
Pre-LVAD RV function (lin)	1.22 (0.81 to 1.93)	0.37
Ascitis	1.18 (0.71 to 1.87)	0.53
Moderate-to-severe post LVAD TR*	1.14 (1.03 to 1.27)	0.008

Supplementary Table 11: Sensitivity analyses of a mixed model containing random intercept for patients versus random intercept for center and patient. Laplace approximation was used in both models. Akaike information criterion for the model with random intercept for patients was 1774 whereas this was 1776 for the model with random intercept for both patient and center.

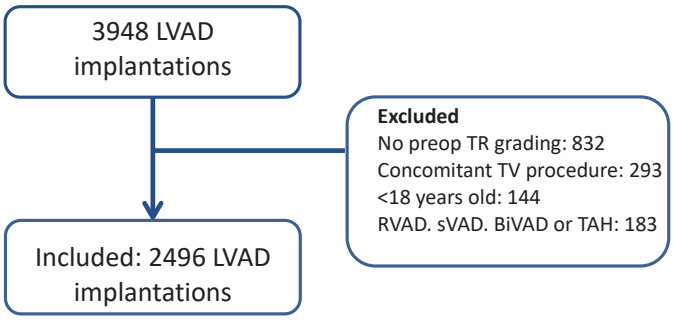
Characteristic	Mixed model with random intercept patients		Mixed model without with nested random effect patient and center	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-5.231 (1.035)	<0.001	-5.202 (1.036)	<0.001
Time spline 1	-3.378 (1.874)	0.071	-3.391 (1.873)	0.070
Time spline 2	3.56 (1.977)	0.072	3.534 (1.973)	0.073
Baseline TR	6.704 (1.579)	<0.001	6.694 (1.578)	<0.001
Baseline TR: Time spline 1	-11.572 (3.123)	<0.001	-11.542 (3.123)	<0.001
Baseline TR: Time spline 2	1.722 (3.86)	0.67	1.723 (3.849)	0.654

Supplementary Table 12: Sensitivy analyses of estimates of the mixed model excluding patients that underwent RVAD during follow-up. Of the 914 patients that had echocradiorapich follow-up 12 patients were excluded.

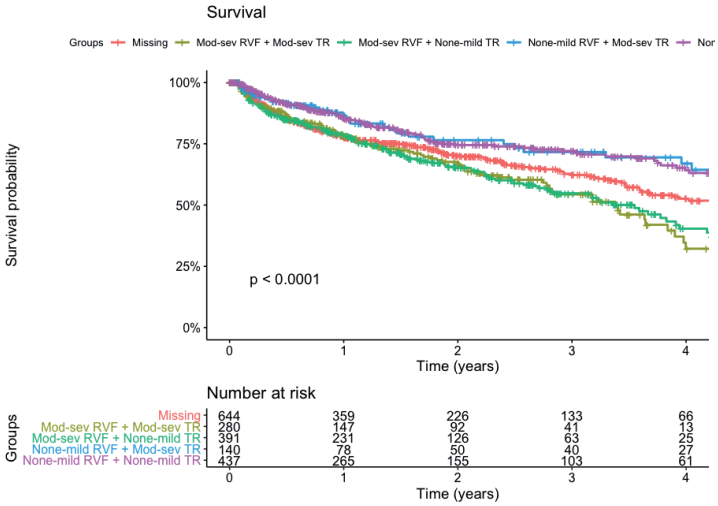
Characteristic	Mixed model all patiens		Mixed model excluding patients with RVAD during follow-up	
	Estimate (SE)	*P-value*	*Estimate (SE)*	*P-value*
Intercept	-2.178 (0.801)	0.007	-2.262 (0.804)	0.005
Time spline 1	-4.117 (1.59)	0.01	-3.929 (1.593)	0.014
Time spline 2	1.948 (1.57)	0.21	1.941 (1.567)	0.22
Baseline TR	5.129 (1.269)	<0.001	5.235 (1.27)	<0.001
Baseline TR: Time spline 1	-7.23 (2.532)	0.004	-7.422 (2.534)	0.003
Baseline TR: Time spline 2	1.362 (2.6)	0.60	1.346 (2.59)	0.60

Supplementary Table 13: Sensitivity analyses of estimates of the mixed model excluding patients that underwent durable right ventricular assist device during follow-up. Of the 914 patients that had echocardiographic follow-up 12 patients were excluded.

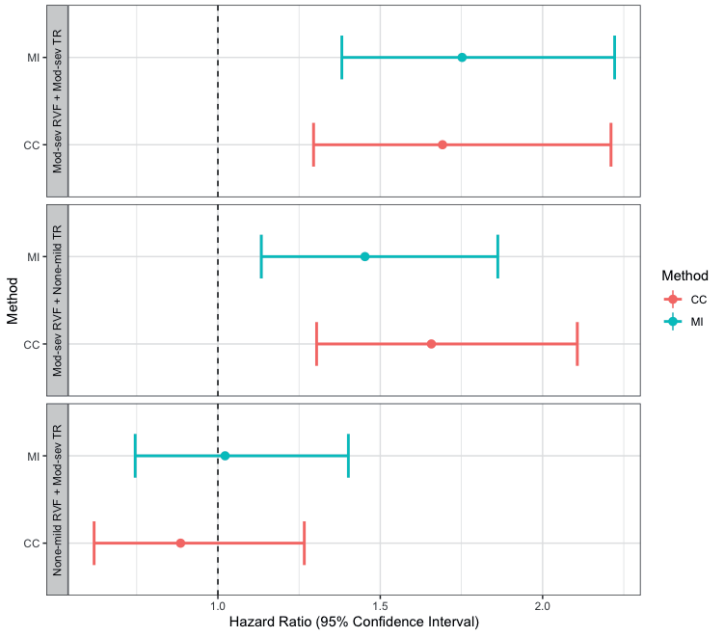
Characteristic	Hazard ratio (95% confidence interval)	P-value
Age	1.04 (1.02 to 1.06)	<0.001
Male gender	0.86 (0.55 to 1.32)	0.50
Moderate-to-Severe baseline TR	0.87 (0.61 to 1.22)	0.44
Destination therapy	1.08 (0.75 to 1.63)	0.71
Intermacs score (cubic)	0.71 (0.54 to 0.93)	0.024
ICD	0.96 (0.66 to 1.38)	0.82
Blood urea nitrogen	1 (0.99 to 1)	0.65
Creatinine	1 (1 to 1.01)	0.12
Sodium	0.99 (0.99 to 1)	0.16
Pre-LVAD RV function (lin)	1.36 (0.87 to 2.02)	0.14
Ascitis	1.37 (0.86 to 2.19)	0.22
Moderate-to-severe post LVAD TR*	1.15 (1.03 to 1.29)	0.010



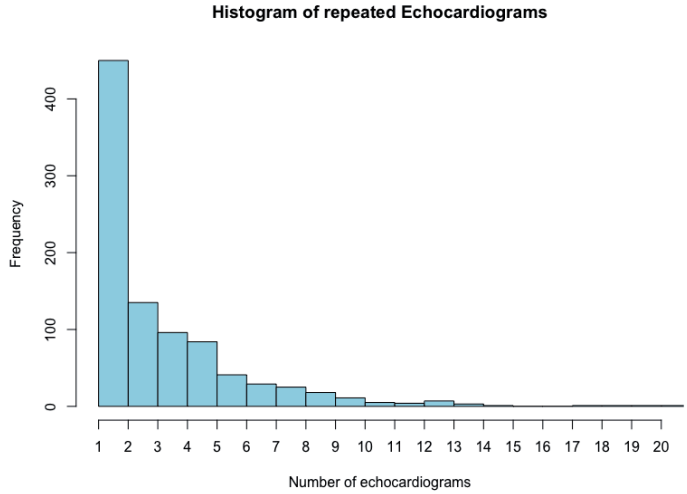
Supplementary Figure 1: Flowchart of inclusion. TR: tricuspid regurgitation, TV: tricuspid vavle, RVAD: right ventricular assist device, sVAD: single ventricle assist device, BiVAD: biventricular assist device, TAH: total artificial heart



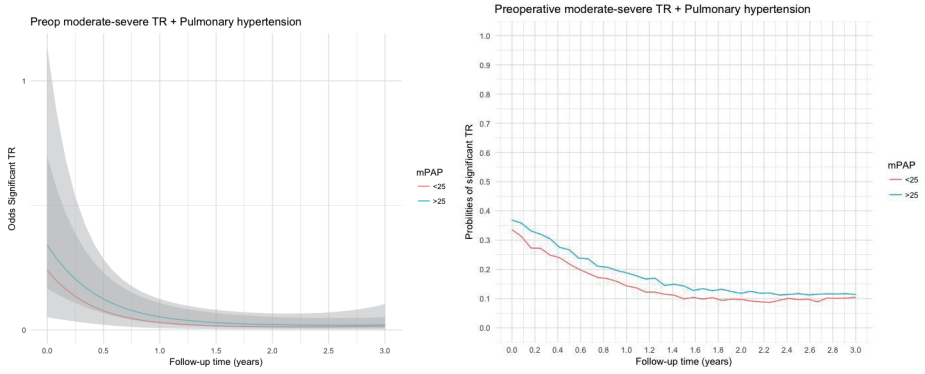
Supplementary Figure 2: Kaplan Meier curve with complete case analyses with missing RVF and a category.



Supplementary Figure 3: Cox proportional hazard ratios derived from complete case (CC) analyses versus multiple imputation (MI). The reference was the group of patient with none-to-mild tricuspid regurgitation and none-to-mild right ventricle dysfunction at baseline.

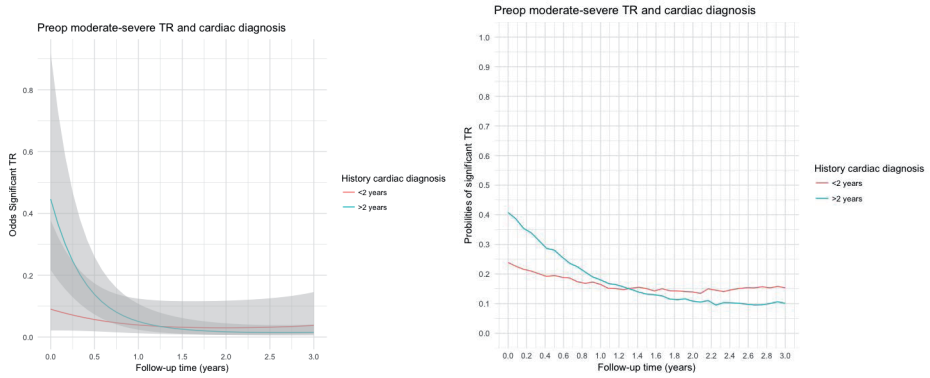


Supplementary Figure 4: Histogram of repeated echocardiograms



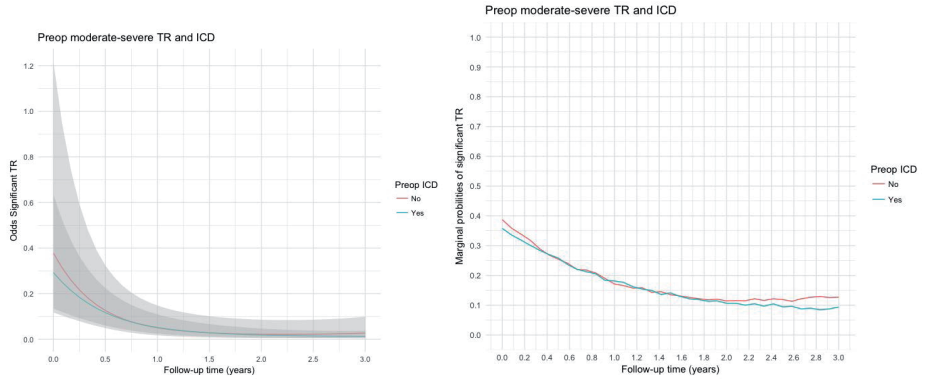
Year	mPAP	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	>25	849	572	391	270	188	132	95
	<25	166	127	83	52	27	15	6
Patients remaining	>25	251	190	140	114	85	64	46
	<25	46	36	26	20	14	8	4

Supplementary Figure 5ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with or without pulmonary hypertension. No significant differences are found when mean Pulmonary pressure or systolic pulmonary pressure is entered in the model as linear continuous variable. Significant TR = moderate-to-severe tricuspid regurgitation



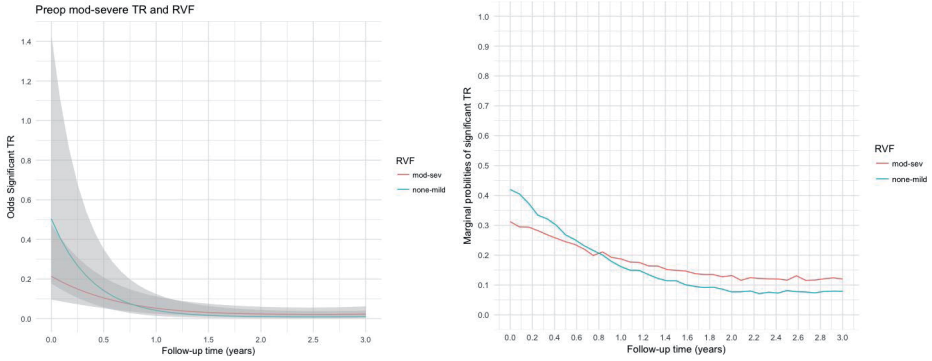
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	>2 years	798	542	365	245	162	111	76
	<2 years	217	157	109	77	53	36	25
Patients remaining	>2 years	216	164	118	97	69	52	36
	<2 years	81	62	48	37	30	20	14

Supplementary Figure6ab: Effect plots of subgroup moderate-to-severe TR >2 or <2 years cardiac diagnosis. Significant TR = moderate-to-severe tricuspid regurgitation



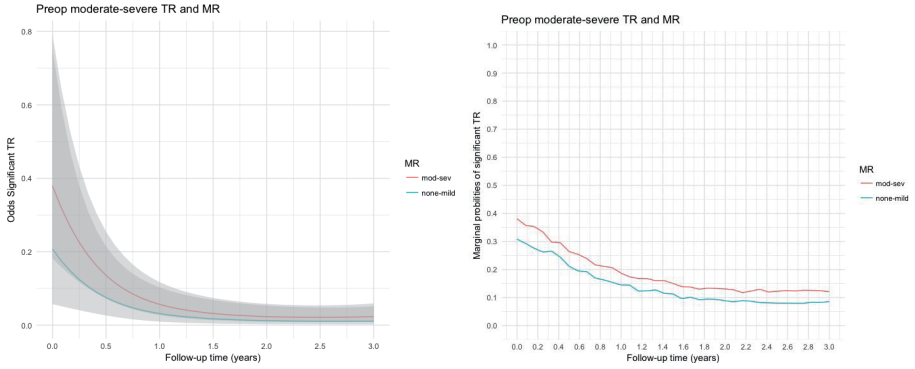
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	No ICD	743	505	338	223	147	91	54
	ICD	272	194	136	99	68	56	47
Patients remaining	No ICD	200	150	110	90	64	45	26
	ICD	97	76	56	44	35	27	24

Supplementary Figure 7ab: Effect plots of subgroup moderate-to-severe TR with our without pre-LVAD ICD. Significant TR = moderate-to-severe tricuspid regurgitation



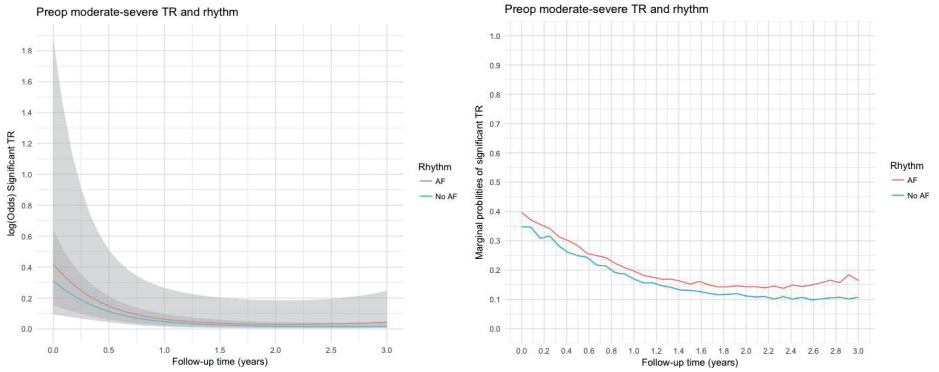
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	None-mild RVF	342	218	149	106	76	57	45
	Mod-sev RVF	673	481	325	216	139	90	56
Patients remaining	None-Mild RVF	94	71	51	44	36	30	23
	Mod-sev RVF	203	155	115	90	63	42	27

Supplementary Figure 8ab: Effect plots of subgroup moderate–to-severe TR with none-mild RVF or moderate-severe RV dysfunction. Significant TR = moderate-to-severe tricuspid regurgitation



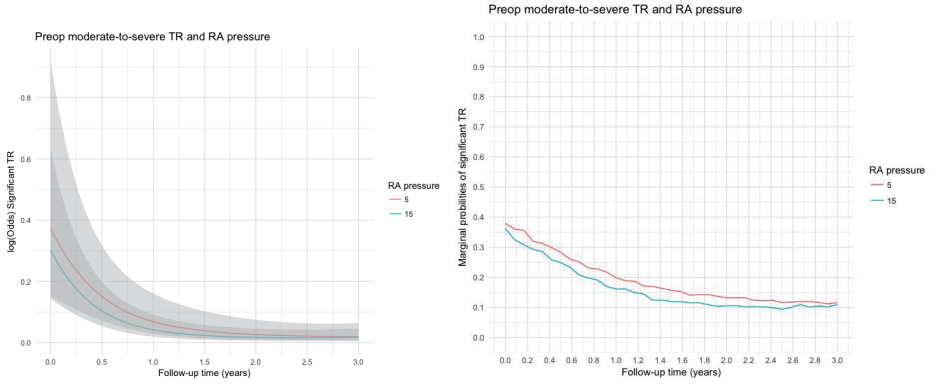
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	None-mild MR	257	185	128	91	62	44	29
	Mod-sev MR	758	514	346	231	153	103	72
Patients remaining	None-Mild MR	82	64	43	36	26	21	12
	Mod-sev MR	215	162	123	98	73	51	38

Supplementary Figure 9ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with moderate-severe mitral regurgitation (MR) or none-mild MR. Significant TR = moderate-to-severe tricuspid regurgitation



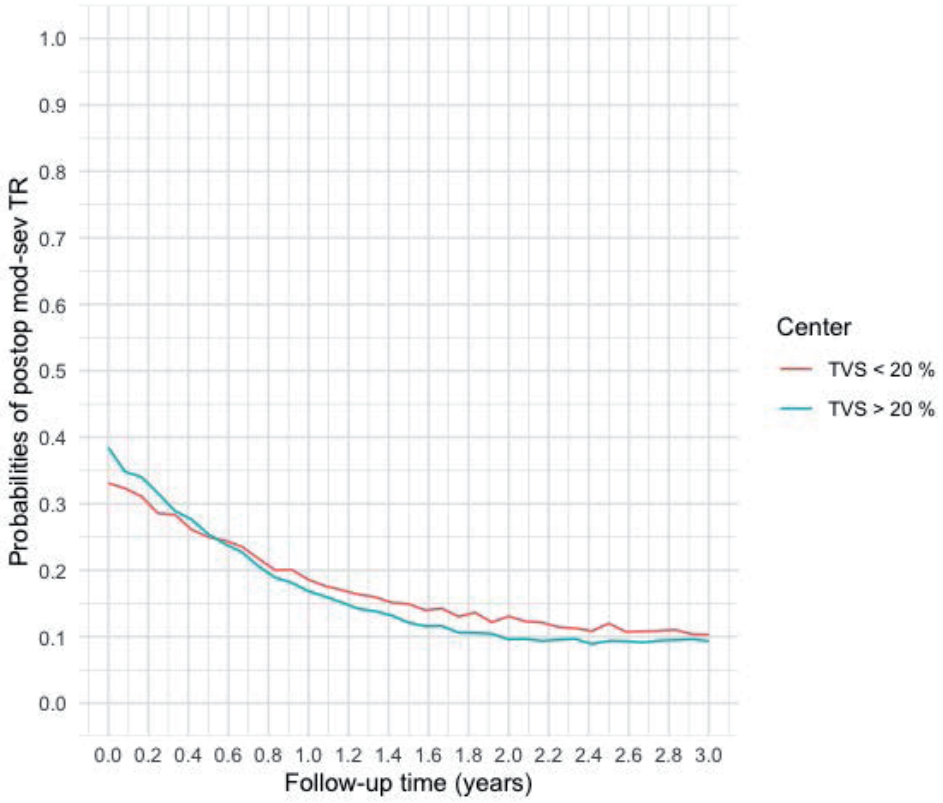
Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	AF	130	80	50	34	21	18	14
	No AF	885	619	424	288	194	129	87
Patients remaining	AF	44	30	20	16	10	9	8
	No AF	253	196	146	118	89	63	42

Supplementary Figure 10ab: Effect plots of subgroup pre-LVAD moderate-to-severe TR with or without pre-LVAD AF. Significant TR = moderate-to-severe tricuspid regurgitation



Year	Diagnosis	0	0.5	1	1.5	2	2.5	3.0
Echo remaining	RA peressue 5	130	80	50	34	21	18	14
	RA presure 15	44	30	20	16	10	9	8
Patients remaining	RA peressue 5	253	196	146	118	89	63	42
	RA presure 15							

Supplementary Figure 11ab: Effect plots of pre-LVAD moderate-to-severe TR and (right atrium) RA pressure (5 mmHg and 15 mmHg are chosen as example). RA pressure was modeled as continuous variable. Significant TR = moderate-to-severe tricuspid regurgitation



Supplementary Figure 12: Effectplot of subgroup pre-LVAD moderate-to-severe TR stratified to centers that performed concomitant tricuspid valve surgery in >20% of cases in patients with pre-LVAD moderate-to-severe TR versus centers that performed tricuspid valve surgery in <20% of cases in these patients. Of note, only patients without tricuspid valve intervention are included in this analyses.

10

Outcomes after tricuspid valve surgery concomitant with left ventricular assist device implantation in the EUROMACS registry: a propensity score matched analysis

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EJCTS, 2020

ABSTRACT

Objectives

Tricuspid regurgitation (TR) is common in patients receiving a left ventricular assist device (LVAD). Controversy exists as to whether concomitant tricuspid valve surgery (TVS) is beneficial in currently treated patients. Therefore, our goal was to investigate the effect of TVS concomitant with a LVAD implant.

Methods

The European Registry for Patients with Mechanical Circulatory Support was used to identify adult patients. Matched patients with and without concomitant TVS were compared using a propensity score matching strategy.

Results

In total, 3323 patients underwent LVAD implantation of which 299 (9%) had TVS. After matching, 258 patients without TVS were matched to 258 patients with TVS. In the matched population, hospital deaths, days on inotropic support, temporary right ventricular assist device implants and hospital stay were comparable, whereas stay in the intensive care unit was higher in the TVS cohort (11 vs 15 days; $P = 0.026$). Late deaths ($P = 0.17$), cumulative incidence of unexpected hospital readmission ($P = 0.15$) and right heart failure ($P = 0.55$) were comparable between patients with and without concomitant TVS. In the matched population, probability of moderate-to-severe TR immediately after surgery was lower in patients with concomitant TVS compared to patients without TVS (33% vs 70%; $P = 0.001$). Nevertheless, the probability of moderate-to-severe TR decreased more quickly in patients without TVS ($P = 0.030$), resulting in comparable probabilities of moderate-to-severe TR within 1.5 years of follow-up.

Conclusions

In matched patients, TVS concomitant with LVAD implant does not seem to be associated with better clinical outcomes. Concomitant TVS reduced TR significantly early after LVAD implant; however, differences in probability of TR disappeared during the follow-up period.

INTRODUCTION

Implantation of a left ventricular assist device (LVAD) improves survival, functional status and quality of life in patients with end-stage heart failure [1, 2]. In these patients tricuspid regurgitation (TR) is common [3], and current guidelines recommend consideration of tricuspid valve surgery (TVS) when moderate-to-severe TR is present [4]. Nevertheless, controversy exists whether concomitant TVS is associated with better outcomes, because contemporary studies are hampered by small sample sizes and are biased due to baseline differences [5]. In this study, we investigated the clinical outcomes after TVS concomitant with LVAD implantation compared to propensity score matched controls using the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). Furthermore, we assessed the postoperative course of TR in patients with and without concomitant TVS.

METHODS

Study design

The EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. In this registry all relevant clinical, echocardiographic, haemodynamic and laboratory parameters of patients who require mechanical circulatory support have been collected prospectively since January 2011. Participating centres were allowed to enter data acquired before 2011 retrospectively, making this study an ambispective cohort study. Detailed descriptions of the database and the collection procedure were provided previously [6].

Patients

All patients operated on between 1995 and 2018 were identified. Patients <18 years old and with planned right ventricular (RV) or biventricular were excluded from analysis. Additionally, patients with single ventricle physiology were excluded (Supplementary Material, Fig. S1).

Study outcome

The main outcomes that were assessed were early (both 30-day and hospital deaths separately) and late deaths. A late death was defined as death after 30 days, regardless of hospital admission status. Furthermore, unplanned hospital readmission and right heart failure were assessed. Right heart failure was defined according to the INTERMACS adverse event definitions [7]. Patients were censored at heart transplant, death and when lost to follow-up. Lastly, the course of the probability of moderate-to-severe TR was evaluated in patients with and without TVS.

Missing values

Multiple imputation by chained equations using the statistical MICE package in R was used to impute missing values [8] Selected baseline variables with <55% missing values were imputed; >55% missing values was considered excessive missingness (Supplementary Material, Table S1). Nevertheless, 51 out of the 67 imputed variables (76%) had <30% missing values. An exception was made for the variable tricuspid annular plane systolic excursion (62% missing), because this variable is highly important in the setting of TVS, and it was reasonable to assume it could be imputed based on observed variables, such as the RV ejection fraction (missing mechanism: missing at random). Imputations were done based on the other baseline variables. In the case of highly correlated variables, the variable with the highest clinical value was chosen as the predictor (Supplementary Material, Table S2). Correlation was tested with Pearson R or Spearman rho, as appropriate. Five imputed datasets were generated with this method using 5 iterations each. The imputations were visually checked by strip plots and density plots, and no major deviations were noted between imputed data and complete data (e.g. tricuspid annular plane systolic excursion: Supplementary Material, Fig. S2). Analyses were done on each dataset separately and pooled according to Rubin's rules [9]. In baseline comparisons of the matched groups, continuous data were transformed to the approximate Gaussian distribution and were pooled according to Rubin's rules.

Statistical analyses

Continuous data are presented as mean ± standard deviation (Gaussian distribution) or median [interquartile range (IQR)] (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). Comparisons among continuous variables were made with the Student's *t*-test or the Mann–Whitney test, as appropriate. Continuous data outside 3 standard deviations were considered erroneous and removed (Supplementary Material, Table S3). Comparisons of categorical variables were made with the χ^2 test or with the Fisher's exact test, as appropriate. Propensity score matching was used to balance baseline differences, because the main interest of this study is the treatment effect in a typical treated patient instead of a population level treatment effect [10]. The parsimonious propensity score model was developed using least absolute shrinkage and selection operator regression [11]. This machine learning analysis technique shrinks unimportant covariates to zero. The parsimonious model comprised all non-zero covariates. In total, 62 variables were offered to the least absolute shrinkage and selection operator model, which selected 15 variables (Supplementary Material, Table S4). Thereafter, 9 variables were added due to clinical significance and to achieve satisfactory balance (Supplementary Material, Table S5). The final propensity score model contained 24 variables (Supplementary Material, Tables S5 and S6). One-on-one matching without replacement was performed, and the caliper was set at 0.15. For the main outcome, a sensitivity analyses was performed with the caliper set at 0.001. Standard mean difference before and after matching was used to assess covariate balance. Late survival was calculated

and visualized with the Kaplan–Meier method; both cohorts were compared with the log-rank test. Because some patients had no recorded follow-up, a sensitivity analysis was performed to test the robustness of the log-rank test under different missing mechanisms. Unplanned hospital readmission and right heart failure were considered competing risks with death, and Fine and Gray competing risk models were used to calculate cumulative incidences. Gray's tests were used to quantify significant differences among cohorts. Generalized mixed models were used to analyse repeated echocardiograms. Further details regarding the mixed models are provided in Supplementary Material, Text S1. Follow-up completeness was calculated using the modified Clark C (C*) [12]. All analyses were done in R (R core team 2017, Vienna, Austria) with the use of statistical packages 'glmnet', 'Matching', 'survival', 'cmprsk', 'splines' and 'lme4'.

RESULTS

In total, 3323 procedures were included [3024 (91%) without TVS and 299 (9%) with TVS]. In the TVS cohort, 292 (97%) patients had a tricuspid valve repair, and 7 (3%) patients had a tricuspid valve replacement (6 mechanical and 1 biological). After propensity score matching, 258 procedures without TVS surgery were matched to 258 procedures with additional TVS. Density plots of the propensity score in the unmatched and matched cohorts are presented in Fig. 1. In patients who survived 30 days and had recorded late follow-up information, the mean follow-up time was 1.7 ± 1.5 years with a completeness of 86% (C*).

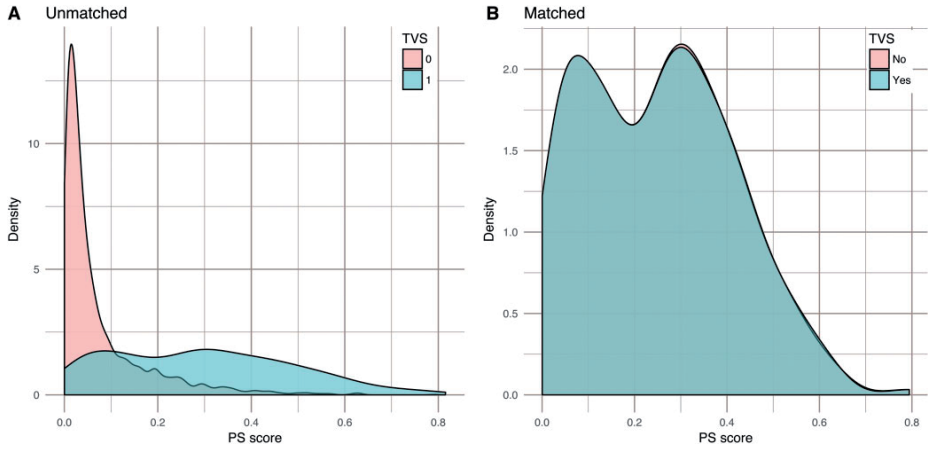

Figure 1: Density of propensity score in the (A) unmatched and (B) matched cohorts. PS: propensity score; TVS: tricuspid valve surgery.

Patient characteristics

Patient characteristics are presented in Table 1. In the unmatched cohort, patients who did not undergo TVS had, among others, significantly less TR, more ischaemic cardiomyopathy and better kidney and liver function. In the matched cohort, no significant differences in baseline characteristics were noted. In addition, the overall absolute standard mean difference before matching was 18.7 and after matching, it was 4.9 (Supplementary Material, Table S7).

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts

	Unmatched groups[a]			**Matched groups**[b]		
	No TVS	**TVS**	***P*-value**	**No TVS**	**TVS**	***P*-value**
n	3024	299		258	258	
Age (years), median (IQR)	56.00 (47.00–62.00)	57.00 (47.50–63.00)	0.044	56.00 (47.00–64.00)	57.00 (47.25–63.00)	0.74
Male sex, *n* (%)	2519 (83.3)	235 (78.6)	0.048	205 (79.5)	202 (78.3)	0.83
Body surface area (m^2), median (IQR)	1.96 (1.81–2.12)	1.96 (1.85–2.12)	0.80	1.94 (1.79–2.11)	1.96 (1.84–2.11)	0.75
White, *n* (%)	2271 (87.4)	248 (95.8)	0.003	247 (95.7)	245 (95.0)	>0.99
Aetiology (%), *n* (%)			<0.001			0.77
Coronary artery disease	252 (10.0)	24 (9.3)		20 (7.8)	26 (10.1)	
Idiopathic disease	614 (24.5)	100 (38.8)		95 (36.8)	97 (37.6)	
Ischaemic disease	1011 (40.3)	62 (24.0)		66 (25.6)	65 (25.2)	
Other	632 (25.2)	72 (27.9)		77 (29.8)	70 (27.1)	
≥2 Years since first diagnosis, *n* (%)	1546 (63.5)	188 (75.5)	0.001	190 (73.6)	192 (74.4)	0.90
Destination therapy, *n* (%)	467 (16.9)	47 (15.9)	0.72	42 (16.9)	43 (16.8)	>0.99
Ascites, *n* (%)	198 (10.3)	36 (18.0)	<0.001	55 (21.3)	56 (21.7)	0.90
Rhythm, *n* (%)			0.084			0.99
Sinus	1337 (55.4)	119 (47.8)		128 (49.6)	120 (46.5)	
Atrial fibrillation	397 (16.4)	44 (17.7)		45 (17.4)	49 (19.0)	
Paced	613 (25.4)	80 (32.1)		82 (31.8)	82 (31.8)	
Other	68 (2.8)	6 (2.4)		3 (1.2)	7 (2.7)	
INTERMACS class, *n* (%)			<0.001			0.90
1	427 (15.0)	19 (6.4)		17 (6.6)	20 (7.8)	
2	942 (33.2)	118 (40.0)		101 (39.1)	93 (36.0)	
3	738 (26.0)	92 (31.2)		80 (31.0)	80 (31.0)	
≥4	733 (25.8)	66 (22.4)		60 (23.3)	65 (25.2)	
IABP, *n* (%)	287 (11.3)	17 (6.6)	0.030	24 (9.3)	15 (5.8)	0.34

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts (continued)

	Unmatched groups[a]			Matched groups[b]		
ECMO, *n* (%)	306 (10.9)	22 (7.5)	0.097	18 (7.0)	19 (7.4)	>0.99
Ventilator (%), *n* (%)	377 (14.8)	19 (7.5)	0.002	18 (7.0)	26 (10.1)	>0.99
Medication, *n* (%)						
Loop diuretics, *n* (%)	1886 (80.5)	218 (86.9)	0.018	213 (82.6)	224 (86.8)	0.82
Use of ≥3 inotropes, *n* (%)	198 (10.5)	23 (11.2)	0.87	51 (19.8)	33 (12.8)	0.79
Laboratory values, median (IQR)						
Serum creatinine (mg/dl)	107.00 (83.00–150.00)	115.00 (90.50–150.00)	0.035	109.50 (84.00–152.75)	114.00 (88.00–150.00)	0.51
ASAT (U/l)	33.00 (23.00–75.00)	35.00 (25.00–57.00)	0.41	34.00 (24.00–67.75)	34.00 (25.00–55.00)	>0.99
Total bilirubin (mg/dl)	1.20 (0.78–2.00)	1.69 (1.14–2.50)	<0.001	1.50 (0.90–2.55)	1.53 (1.05–2.28)	0.92
Albumin (g/dl)	507.15 (420.21–579.60)	507.15 (449.91–574.16)	0.54	507.15 (405.72–579.60)	507.15 (434.70–579.60)	0.82
Haemoglobin (g/dl)	11.80 (10.20–13.60)	11.40 (10.07–13.03)	0.11	11.70 (9.83–13.20)	11.40 (10.00–13.28)	0.65
Haemodynamic values, median (IQR)						
RA pressure (mmHg)	10.00 (7.00–15.00)	13.00 (9.50–17.00)	<0.001	12.00 (8.00–16.00)	13.00 (9.00–16.00)	0.63
PCWP (mmHg)	24.00 (18.00–30.00)	25.00 (20.75–29.25)	0.085	24.00 (18.00–30.00)	24.50 (20.00–29.00)	0.21
PVR	231.50 (137.00–354.75)	267.00 (166.75–372.50)	0.11	262.00 (177.00–368.00)	276.50 (160.00–372.50)	0.71
SVR	1262.00 (896.25–1676.50)	1446.50 (1102.75–1908.00)	0.001	1317.00 (1021.00–1590.00)	1300.00 (1062.50–1858.00)	0.38
PAP, systolic (mmHg)	51.00 (39.00–64.00)	49.50 (40.00–63.00)	0.71	52.00 (40.00–63.00)	52.00 (40.00–65.00)	0.66
Echocardiographic results						
TAPSE (mm), median (IQR)	14.00 (12.00–17.00)	15.00 (12.00–18.00)	0.28	14.00 (11.00–17.00)	14.00 (12.00–17.00)	0.63
No aortic regurgitation, *n* (%)	1469 (63.5)	151 (55.7)	0.060	146 (56.6)	148 (57.4)	0.98
Severe mitral regurgitation, *n* (%)	392 (17.4)	77 (30.4)	<0.001	76 (29.5)	66 (25.6)	0.83

Table 1: Characteristics of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts (continued)

	Unmatched groups[a]			Matched groups[b]		
Tricuspid regurgitation, *n* (%)			<0.001			0.79
None	286 (11.4)	4 (1.4)		8 (3.1)	4 (1.6)	
Trivial	504 (20.1)	14 (4.8)		15 (5.8)	15 (5.8)	
Mild	907 (36.2)	34 (11.7)		39 (15.1)	37 (14.3)	
Moderate	564 (22.5)	113 (38.8)		96 (37.2)	112 (43.4)	
Severe	243 (9.7)	126 (43.3)		100 (38.8)	90 (34.9)	
LVEF (%), median (IQR)	19.00 (15.00–23.00)	20.00 (15.00–25.00)	0.029	20.00 (15.00–24.00)	20.00 (15.00–23.00)	0.85
RVF, *n* (%)			<0.001			0.89
Normal	400 (22.1)	21 (10.7)		37 (14.3)	31 (12.0)	
Mild	460 (25.4)	44 (22.3)		45 (17.4)	52 (20.2)	
Moderate	700 (38.6)	96 (48.7)		124 (48.1)	114 (44.2)	
Severe	252 (13.9)	36 (18.3)		52 (20.2)	61 (23.6)	

[a]Data and tests on complete cases.

[b]Data from first imputed dataset; P-values from tests are derived from the pooled analyses.

ASAT: aspartate aminotransferase; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IQR: interquartile range; LVEF: left ventricular ejection fraction; PAP: pulmonary atrial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RA: right atrium; RVF: right ventricle function.; SVR: systemic vascular resistance; TAPSE: tricuspid annular plane systolic excursion; TVS: tricuspid valve surgery.

Hospital outcome

Hospital outcomes are presented in Table 2. In the unmatched cohort, cardiopulmonary bypass time (80 vs 118 min; $P < 0.001$), intensive care unit (ICU) stay (10 vs 15 days; $P < 0.001$), hospital stay (30 vs 34; $P = 0.001$) and days on inotropic support (>14 days: 24.7% vs 32.4%) were longer in the patients who underwent TVS. In the matched cohorts, these variables were all comparable, except for cardiopulmonary bypass time (85 vs 116 min; $P < 0.001$) and ICU stay (11 vs 15 days; $P = 0.026$) (Table 2). Additionally, in the matched groups, the 30-day mortality risk [13.6%, 95% confidence interval (CI) 9.5–18.6 vs 10.0%, 95% CI 6.5–14.4; $P = 0.27$] and hospital mortality risk (20.2%, 95% CI 14.7–24.7 vs 16.5%, 95% CI 13.0–22.6; $P = 0.41$) were comparable between the patients with and without concomitant TVS. Sensitivity analyses with the caliper at 0.001 did not change point estimates greatly (Supplementary Material, Table S8).

Table 2: Hospital outcomes of patients with or without concomitant tricuspid valve surgery in matched and unmatched cohorts

	Unmatched groups			Matched groups		
	No TVS	**TVS**	***P*-value**	**No TVS**	**TVS**	***P*-value**
n	3024	299		258	258	
CPB time (min), median (IQR)	80 (58–111.5)	118 (94–157)	<0.001	84.50 (61.00–114.50)	115.50 (92.25–157.75)	<0.001
Device brand, *n* (%)			<0.001			0.93
HeartMate II	776 (27.4)	120 (40.4)		102 (39.5)	96 (37.2)	
HeartWare HVAD	1481 (52.3)	117 (39.4)		112 (43.4)	113 (43.8)	
HeartMate III	414 (14.6)	58 (19.5)		42 (16.3)	47 (18.2)	
Other	160 (5.7)	2 (0.7)		2 (0.8)	2 (0.8)	
Hospital deaths, *n* (%)	452 (15.2)	55 (18.8)	0.58	50 (20.2)	45 (16.5)	0.41
30-Day deaths, *n* (%)	306 (11.9)	32 (11.0)	0.72	32 (13.6)	25 (10.0)	0.27
Temporary RVAD support, *n* (%)	138 (4.5)	23 (7.7)	0.024	22	16	0.40
Days of inotropic support, *n* (%)			0.013			0.29
1–7	993 (56.6)	92 (48.2)		11 (7.0)	13 (7.7)	
8–13	321 (18.3)	37 (19.4)		85 (53.8)	85 (50.6)	
14–27	276 (15.7)	48 (25.1)		27 (17.1)	41 (24.4)	
>27	158 (9.0)	14 (7.3)		33 (20.9)	29 (17.3)	
Ongoing	6 (0.3)	0 (0.0)		2 (1.3)	0 (0.0)	
ICU/CCU stay, median (IQR)	10 (5–23)	15 (6–53)	<0.001	11.00 (5.00–24.00)	15.00 (6.00–31.00)	0.026
Hospital stay, median (IQR)	30 (21–46)	34 (25–53)	0.001	33.00 (22.00–54.00)	34.50 (24.75–52.25)	0.38

CCU: cardiac care unit; CPB: cardiopulmonary bypass; ICU: intensive care unit; IQR: interquartile range; RVAD: right ventricular assist device; TVS: tricuspid valve surgery.

Late outcome

In total, 2522 patients had recorded late follow-up and did not die within 30 days (no TVS: 2263 and TVS: 259 patients); 809 patients died during the follow-up period (Supplementary Material, Fig. S3). Kaplan–Meier survival curves are shown in Fig. 2A, B. Unmatched patients with and without concomitant TVS had comparable late survival rates ($P = 0.41$). Additionally, cumulative incidence plots are shown in Figs 3A and B and 4A and B. In unmatched patients, cumulative incidence of unplanned hospital readmission from any cause and cumulative incidence of right heart failure were higher in the TVS cohort (Figs 3A and 4A); *P*-value = 0.006 and *P*-value = 0.011, respectively.

In the matched cohort, 226 patients with TVS survived 30 days and had recorded late follow-up versus 204 matched controls, 128 of whom died during the follow-up period. Late

survival was comparable between patients with and without TVS (*P* = 0.17) (Fig. 2B). Notably, the curves diverged after ~1 year of follow-up with 2-year survival estimates of 75.6% (95% CI 69.3–82.5) in the no TVS cohort and 63.2% (95% CI 55.3–72.2) in the TVS cohort, but still with overlapping CIs. In total, 22 patients in the matched control group and 7 patients in the TVS cohort did not have recorded follow-up information. Sensitivity analyses revealed that only in the scenario in which all missing patients in the no TVS cohort survived and in which all in the TVS cohort died, the log-rank test results differed significantly (Supplementary Material, Table S9). Sensitivity analyses with the caliper set at 0.001 did not considerably change point estimates (Supplementary Material, Table S8). In the matched cohorts, cumulative incidence of unplanned hospital readmissions (*P* = 0.15) and right heart failure (*P* = 0.55) were comparable between patients with and without concomitant TVS (Figs 3B and 4B).

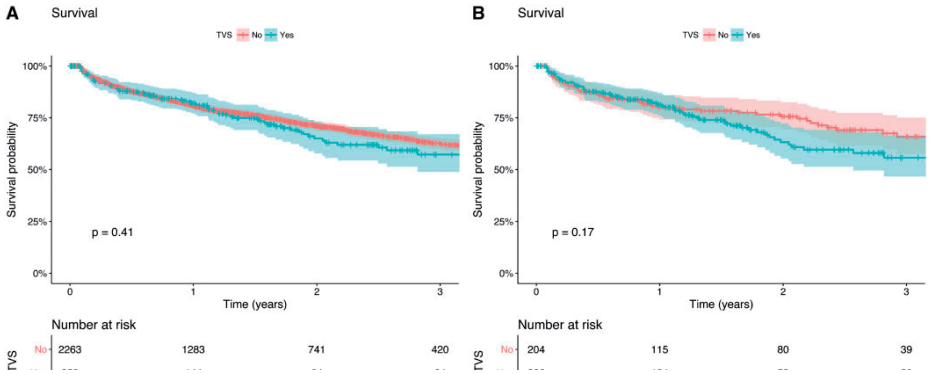

Figure 2: Kaplan–Meier curve of patients who survived 30 days in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

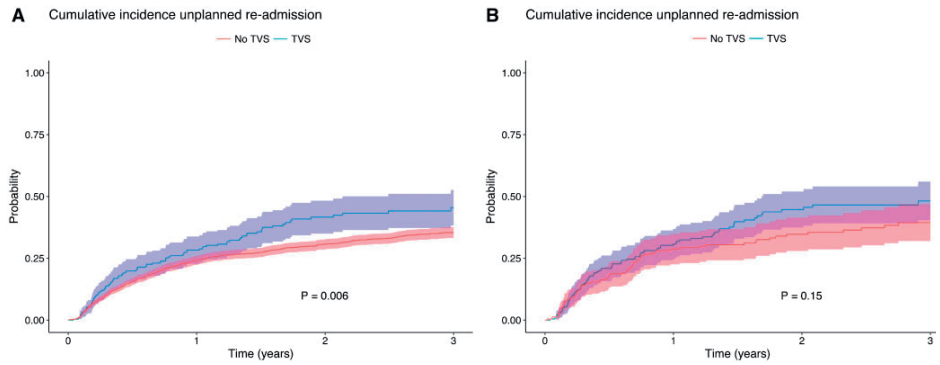

Figure 3: Cumulative incidence estimated by the Fine and Gray model with death as the competing risk of unexpected hospital readmission in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

Evolution of tricuspid regurgitation

In total, 1219 patients had 3956 recorded echocardiograms during the follow-up period (mean: 3.2 echocardiograms, range: 1–28). Figure 5A presents the probability of moderate-to-severe TR over time in the unmatched cohorts. In the matched cohorts, 224 patients had 725 recorded echocardiograms (mean 3.2, range 1–21) that could be used in the mixed models. Immediately after LVAD implantation, patients who underwent TVS had a significantly lower probability of moderate-to-severe TR (33% vs 70%; *P* = 0.001) (Fig. 5B). Nevertheless, during follow-up, the probability of moderate-to-severe TR decreased more quickly in the no TVS cohort compared to the TVS cohort (*P* = 0.030), resulting in comparable probabilities within 1 year of follow-up.

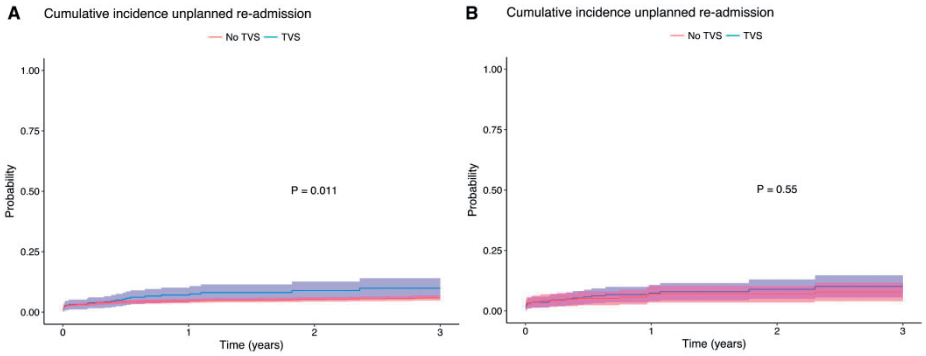

Figure 4: Cumulative incidence estimated by the Fine and Gray model with death as the competing risk of right heart failure in the (A) unmatched and (B) matched cohorts. TVS: tricuspid valve surgery.

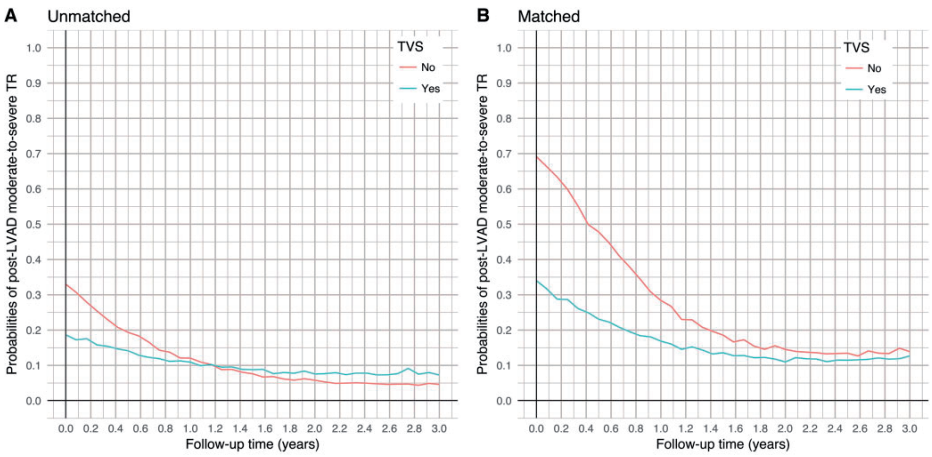

Figure 5: Course of the probability of moderate-to-severe tricuspid regurgitation over time in the (A) unmatched and (B) matched cohorts estimated by the mixed model. LVAD: left ventricular assist device; TR: tricuspid regurgitation; TVS: tricuspid valve surgery.

DISCUSSION

We evaluated outcomes of concomitant TVS during LVAD implantation in the largest European LVAD registry. In the matched cohort, comparable risks and rates of mortality, days on inotropic support, cumulative incidence of unexpected readmission and right heart failure were noted. Not surprisingly, cardiopulmonary bypass time was longer in the TVS cohort. Furthermore, patients who underwent concomitant TVS stayed longer in the ICU compared to patients who did not undergo TVS. Immediately after surgery the probability of moderate-to-severe TVS was significantly lower in the TVS cohort; however, this difference disappeared during the follow-up period.

Patients undergoing TVS are significantly different from patients without concomitant TVS. Patients undergoing TVS presented as less acute patients with a longer history of cardiac diagnosis and fewer ischaemic aetiologies (among others), which is also illustrated by different densities in propensity scores (Fig. 1). Hence, patients undergoing TVS seemed to be a select subgroup in the overall LVAD population. It has to be noted that conclusions regarding treatment effect in this study only apply to this subgroup and may not apply in other subgroups within the LVAD population.

Prior analyses of the Society of Thoracic Surgeons database and the INTERMACS database revealed results comparable to our results [13, 14]. Patients receiving TVS who were recorded in the Society of Thoracic Surgeons database stayed longer in the ICU. RV assist device implant and hospital mortality risks were comparable in this cohort [13].

The investigators of the INTERMACS database noted comparable rates of late survival in patients with preoperative moderate-to-severe TR with and without concomitant TVS [14]. Moreover, a recent systematic review, pooling mostly small retrospective studies, found no differences in early and late survival risks/rates [5]. Interestingly, both in retrospective studies and INTERMACS database studies, it was noted that pre-LVAD moderate-to-severe TR was associated with poorer late survival rates [3, 14, 15]. Regarding the latter observation, it seems peculiar that eliminating TR does not result in a better outcome. Two hypotheses may explain these paradoxical results. First, TVS may not sustainably reduce post-LVAD TR. Song et al. found a relatively high rate of recurrent TR in patients who received concomitant TR. Additionally, there are reports that LVAD support exacerbates TR due to a leftward shift of the interventricular septum and increased venous return [16, 17]. Nevertheless, our results support the idea that TVS reduces TR soon after the operation, but that in patients without concomitant TVS, TR also decreases in the following months. Second, it may be that TR does not cause death in most cases. It is known that TR is frequently caused by RV dilatation in response to elevated pulmonary pressures [18]. Therefore, TR may merely be a symptom or a marker of RV damage secondary to long-standing pulmonary hypertension or primary RV damage caused by the underlying ischaemic or cardiomyopathic diseases. By treating TR, one may be treating the symptom rather than the causing factor of mortality and morbidity (e.g. RV dysfunction). To

some extent, our findings support this theory because favourable RV remodelling is observed in patients with an LVAD implant without concomitant TVS [19, 20]. This finding would inherently be paired with a reduction of TR, even without an intervention, assuming that the TR is functional in nature.

In this respect, the cause of TR (primary or secondary) is important. Primary TR, caused by structural valve damage or interfering pacemaker/implantable cardioverter defibrillator leads, will certainly not reduce itself and may even cause RV dysfunction [21]. Therefore, we propose that this aspect be taken into account in the decision process whether to perform concomitant TVS. Robertson et al. [13] suggested that the decision to perform concomitant TVS should not be solely based on the pre-LVAD TR grade. Our data and reports in the current literature support this suggestion, because our results and multiple other studies were do not to show any benefit from concomitant TVS. Current guidelines suggest consideration of concomitant TVS in all patients with pre-LVAD moderate-to-severe TR, which may not be necessary. Nevertheless, if one follows the trends in concomitant TVS for functional TR during left-sided valve surgery, it has become clear that TR in some cases is not reduced or even becomes worse [22, 23]. The remaining challenge is now to adequately identify these patients in the LVAD population.

Strengths and limitations

The strength of this study is the relatively large sample size compared to those reported in the current literature. Additionally, the EUROMACS registry records serial echocardiograms, which made it possible to analyse the change in TR over time. In contrast to previous studies, we accounted for the within-patient correlations in our analyses of the postoperative course of TR over time using advanced statistical modelling. This study has several important limitations. First, the database is not designed to specifically address concomitant TVS in patients with LVAD implants. Therefore, important factors, such as the cause of TR or the reasons for intervention, were not collected. This lack may introduce selection bias, because these factors could not be captured in the propensity model. Furthermore, the surgeon and institutional preferences can introduce selection bias. Although the majority of variables of interest had below 30% missing values, we accepted up to 55% missing values. On the other side, the EUROMACS database collects many variables, making it more plausible that missing data could be predicted from the other observed variables, thereby strengthening the missing-at-random assumption. In addition, since last year, the EUROMACS investigators intensified their quality control measures to reduce missingness in the future [24]. Furthermore, assessing TR remains challenging: TR is subject to loading conditions, which means TR severity is highly dynamic [25]. Unfortunately, it was impossible to analyse patients receiving a tricuspid valve replacement compared to a tricuspid valve repair due to the small numbers. Some differences could be due to chance because of multiple testing. Propensity score matching reduces the sample size and therefore may reduce the power of the tests. Nevertheless, we utilized a matching technique because the main interest of this study was the effect of treatment in a typical treated patient. Some

patients in the matched population had no recorded follow-up information. Nevertheless, sensitivity analyses did not change the direction of the conclusions in most of the hypothetical missing scenarios.

CONCLUSIONS

Patients undergoing concomitant TVS differ significantly from patients without TVS. In matched patients, concomitant TVS during LVAD implant does not seem be associated with better clinical outcomes. Concomitant TVS reduced TR significantly early after LVAD implant; however, differences in probability of TR disappeared during the follow-up period. Using current selection criteria, TVS does not seem beneficial.

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SUPPLEMENTARY MATERIAL

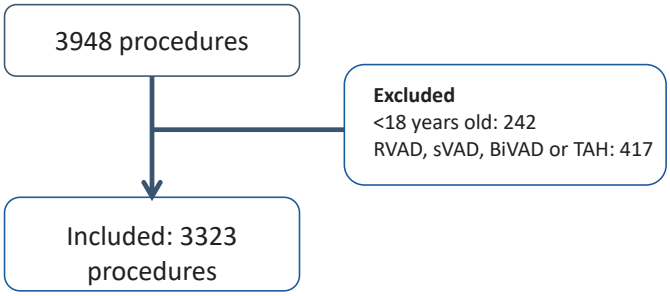
CONTENTS

SUPPLEMENTARY TEXT 1

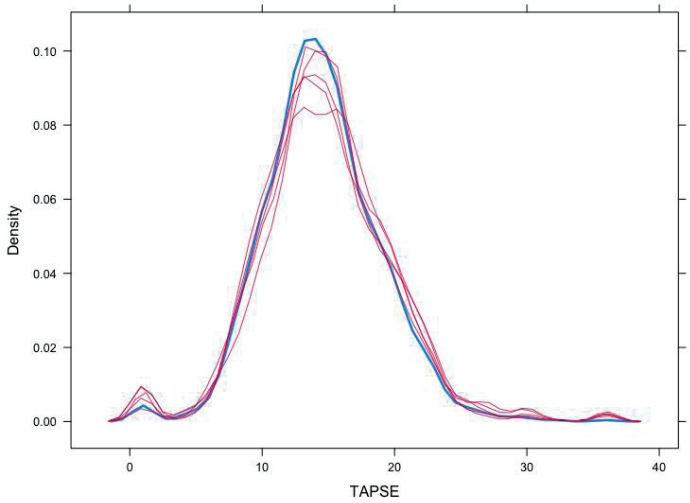
Generalized mixed-models

All models had random intercepts for patients. Natural cubic splines for time were added to establish flexibility over time. All models contained the following covariates: time (with splines), tricuspid valve surgery (yes/no) and the interaction between tricuspid valve surgery and time. The number of knots for the splines was determined using a backwards approach starting with 3 knots to 0 knots. Models were compared by likelihood ratio tests. One knots proved to be sufficient.

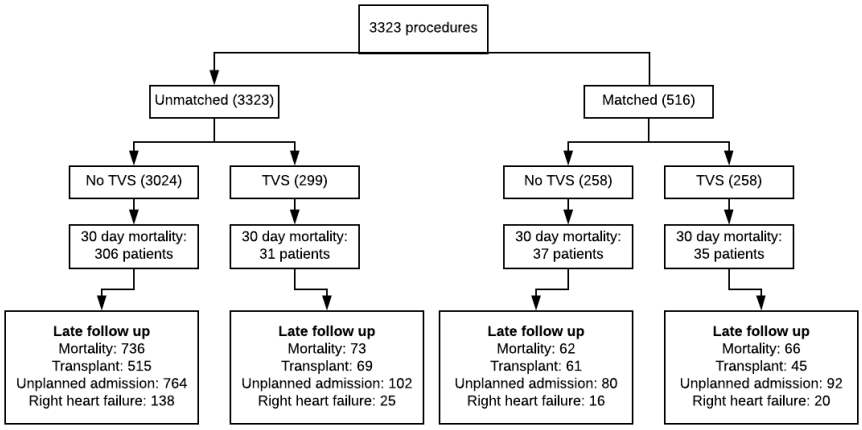
The marginal probabilities for the effect plot were obtained using a Monte Carlo sampling procedure. For each combination of follow-up time and covariate of interest 3000 patients are generated with random effect values coming from the normal distribution $N(0, \sigma_b^2)$, where σ_b^2 denotes the estimated variance of the random effects from the model. The mean of the 3000 calculated probabilities is taken as estimate.



Supplementary Figure 1: Flowchart of included patients



Supplementary Figure 2: Kernel density plot of complete data of tricuspid annular plane systolic excursion (blue line) and imputed data of the 5 imputed datasets (red lines).



Supplementary Figure 3: Flow diagram of mortality, transplants and events in unmatched and matched cohorts.

Supplementary Table 1: Missing data (alphabetic order)

Variable	Count missing	Precentage missing (%)
ACE inhibitors	737	22,2
Acenocoumarol	1608	48,4
Age	44	1,3
Albumin	1858	55,9
Aldosterone antagonist	1258	37,9
Amiodarone	813	24,5
Anticoagulant therapy	1302	39,2
Antiplatelet drugt herapy	822	24,7
Aortic regurgitation	738	22,2
ARB	805	24,2
Ascites	1218	36,7
Betablockers	776	23,4
Bicarbonat HCO3	1877	56,5
Bloodtype	18	0,5
Blood Urea Nitrogen	1013	30,5
Bosentan	1538	46,3
BSA	504	15,2
Cancer Other Than Local SkinCancer	539	16,2
Cardia cArrest	515	15,5
Cardiac Index	787	23,7
Cardiac Output	2009	60,5
Cardiac Surgery	506	15,2
Cholesterol	2506	75,4
Connective Tissue Or Inflammatory	581	17,5
COPD	516	15,5
CPB Time	399	12,0
Creatinine	923	27,8
CRPC reactive protein	778	23,4
Cumadine	2886	86,8
ICD	80	2,4
Diabetes	249	7,5
Dialysis	295	8,9
Diastolic BP	737	22,2
ECG rhythm	659	19,8
ECMO	212	6,4
Ethnic origin	465	14,0
Feeding Tube	614	18,5
Gender	0	0,0
Hemoglobin	633	19,0

Supplementary Table 1: Missing data (alphabetic order) (continued)

Variable	Count missing	Precentage missing (%)
History Of Neurological Event	557	16,8
History Of Previous Alcohol Abuse	1838	55,3
Hospital stay		
IABP	521	15,7
Iloprost	1540	46,3
INR	550	16,6
INTERMACS class	188	5,7
Intubation	508	15,3
Lactate	2275	68,5
LDH	1201	36,1
Loop diuretics	729	21,9
LVEDD2	947	28,5
LVEDV	2726	82,0
LvEf Percent	823	24,8
LVESD	1941	58,4
LVESV	2814	84,7
LVSF	2854	85,9
Major Infections	525	15,8
Major MI	515	15,5
Marcumar	2517	75,7
Marital status	1060	31,9
Mitral regurgitation	814	24,5
Neseritide	1247	37,5
Nitric Oxide	824	24,8
NT Pro BNP	2347	70,6
Number of inotropes	1233	37,1
Pa Capillary Wedge Pressure	3292	99,1
pH	1768	53,2
Phenprocoumon	1379	41,5
Platelet	720	21,7
Positive Blood Cultures	853	25,7
Potassium	730	22,0
Primary Diagnosis	556	16,7
PTT	803	24,2
Pulmonary artery diastolic pressure	1712	51,5
Pulmonary Artery Pressure Mean	1652	49,7
Pulmonary artery systolic pressure	1715	51,6
Pulmonary artery wedge pressure	1938	58,3
Pulmonary Regurgitation	1438	43,3

Supplementary Table 1: Missing data (alphabetic order) (continued)

Variable	Count missing	Precentage missing (%)
PVR	2405	72,4
RA pressure	1798	54,1
Reason For Admission	445	13,4
Reticulocytes	3032	91,2
Rhesusfactor	18	0,5
R value at peak	3298	99,2
RVEF	1314	39,5
ASAT	751	22,6
ALAT	1412	42,5
Sildenafil	1490	44,8
Smoking History	1466	44,1
Sodium	727	21,9
SVR	2499	75,2
Symptomatic Peripheral Vascular Disease	549	16,5
Systolic BP	1066	32,1
TAPSE	2061	62,0
Time since first cardiac diagnosis	638	19,2
Total bilirubin	881	26,5
Transfusion History	2074	62,4
Tricuspid regurgitation	528	15,9
Tricuspid valve surgery	0	0,0
Ultrafiltration	517	15,6
Ventilation	1019	30,7
Ventilator	529	15,9
Peripheral edema	865	26,0
VO max	3167	95,3
Warfarin	1577	47,5
WBC	545	16,4

Supplementary Table 2: Variables used in imputation

Imputed variables	
ACE inhibitors	Nitric Oxide
Age	Platelet
Albumin[1]	Positive Blood Cultures[1]
Aldosterone antagonist	Potassium
Amiodarone	Primary Diagnosis
Anticoagulant therapy drugs status	PTT
Aortic regurgitation	Pulmonary artery diastolic pressure[1]
ARB	Pulmonary Artery Pressure Mean

Supplementary Table 2: Variables used in imputation (continued)

Imputed variables	
Ascites	Pulmonary artery systolic pressure[1]
Betablockers	Pulmonary artery wedge pressure[1]
Bloodtype	Pulmonary Regurgitation
Blood Urea Nitrogen[1]	RA pressure
BSA	Rhesusfactor
Cancer Other Than Local Skin Cancer	RVEF
Cardiac Arrest	ASAT
Carotid Artery Disease	ALAT[1]
Connective Tissue Or In flammatory	Sodium
COPD	Symptomatic Peripheral Vascular Disease
Creatinine	Systolic BP
CRPC reactive protein	TAPSE[1]
ICD	Time since first cardiac diagnosis
Diabetes	Total bilirubi
Dialysis	Tricuspid regurgitation
Diastolic BP[1]	Volume Status peripheral edema
ECG rhythm	White blood cell count
ECMO	Mitral regurgitation
Ethnic origin	Multiple intropes
Feeding Tube[1]	Legend
Gender	1: not a predictor due to high correlation with other variables
Hemoglobin	
History Of Neurological Event	
IABP	
INR	
INTERMACS Patient Profile	
Intubation[1]	
LDH	
Loop diuretics	
LvEf Percent	
Major Infections	
Major MI	

Supplementary Table 3: Overview of data continuous outside 3 standard deviations

	Mean	Mean - 3SD	Mean + 3 SD	#removed variables
Age	53.53	16.88	90.19	0
LVSF	11.12	-8.97	31.2	6
TAPSE	15.93	-27.15	59	14
Systolic BP	100.44	50.02	150.86	20
Diastolic BP	64.69	27.65	101.73	22
BSA	2.22	-5.41	9.85	32
Pulmonary artery systolic pressure	52.52	-3.5	108.55	17
Pulmonary artery diastolic pressure	26.81	-23.52	77.13	5
RA pressure	11.65	-10.77	34.07	16
Pulmonary artery wedge pressure	24	-2.3	50.3	4
SVR	1337.62	-819.7	3494.93	7
PVR	279.27	-375.68	934.22	13
Cardiac Index	1.04	-3.08	5.16	6
Cardiac Output	4	-3.65	11.65	4
Sodium	131.67	39.67	223.68	6
Potassium	4.34	-12.4	21.07	6
Blood Urea Nitrogen	61.98	-68.71	192.68	26
Creatinine	204.02	-2823.53	3231.57	15
ALAT	226.42	-3847.52	4300.36	16
ASAT	346.72	-4170.23	4863.66	37
LDH	628	-3583.7	4839.69	32
Total bilirubin	2.14	-26.99	31.28	6
Albumin	623.23	-1629.7	2876.17	38
NT Pro-BNP	10047.39	-26451.64	46546.41	24
Cholesterol	3.75	-9.69	17.18	1
WBC	34.04	-1433.06	1501.14	7
Reticulocytes	10.79	-37.64	59.22	3
Hemoglobin	16.28	-88.56	121.11	66
Platelet	206.05	-55.82	467.92	26
INR	1.61	-3.17	6.4	11
PTT	41.09	-28.16	110.33	38
pH	12.21	-553.52	577.94	1
Lactate	4.57	-35.65	44.79	21
BicarbonatHCO3	24.23	10.84	37.61	17
CRPCreactiveprotein	51111614.32	-7685840681.11	7788063909.75	1
LVEDD2	64.88	-42.31	172.07	22
LVESD	58.12	-89.77	206.01	14
LVEDV	250.44	-69.98	570.86	4
LVESV	193.51	-89.48	476.5	3
LvEf Percent	18.65	-5.39	42.68	26
Pulmonary Artery Pressure Mean	35.86	-26.6	98.33	1
Pa Capillary Wedge Pressure	24.94	-0.73	50.6	0

Supplementary Table 4: All variables originally offered to the Lasso logistic model

Variable	Type
Bloodtype	Categorical
Rhesusfactor	Categorical
Age	Continuous
Gender	Categorical
Mitral regurgitation	Categorical
Tricuspid regurgitation	Categorical
Aortic regurgitation	Categorical
Systolic blood pressure	Continuous
Volume Status peripheral edema	Categorical
Cardiac rhythm	Categorical
BSA	Continuous
Neseritide	Categorical
ARB	Categorical
Amiodarone	Categorical
ACE inhibitors	Categorical
Betablockers	Categorical
Aldosteroneantagonist	Categorical
Loop diuretics	Categorical
Anticoagulant therapy drugs status	Categorical
Nitric Oxide	Categorical
Sodium	Continuous
Potassium	Continuous
Creatinine	Continuous
ASAT	Continuous
LDH	Continuous
Total bilirubin	Continuous
White blood cell count	Continuous
Hemoglobin	Continuous
Platelet	Continuous
INR	Continuous
PTT	Continuous
CRPC reactive protein	Continuous
Time since first cardiac diagnosis	Categorical
Ethnic origin	Categorical
Primary Diagnosis	Categorical
Current ICD Device	Categorical
Cardiac Arrest	Categorical
Dialysis	Categorical
Intubation	Categorical

Supplementary Table 4: All variables originally offered to the Lasso logistic model (continued)

Variable	Type
Major MI	Categorical
Positive Blood Cultures	Categorical
Major Infections	Categorical
IABP	Categorical
ECMO	Categorical
INTERMACS Patient Profile	Categorical
Diabetes	Categorical
COPD	Categorical
Symptomatic Peripheral Vascular Disease	Categorical
Connective Tissue Or Inflammatory Disease	Categorical
Carotid artery Disease	Categorical
History of Neurological Event	Categorical
Cancer Other than local skin cancer	Categorical
Device brand LVAD	Categorical
RVEF	Categorical
Ascites	Categorical
Pulmonary Regurgitation	Categorical
LvEf Percent	Continuous
Pulmonary Artery Pressure Mean	Continuous
RA pressure	Continuous
TAPSE	Continuous
Pulmonary artery wedge pressure	Continuous
Albumin	Continuous

Supplementary Table 5: Variables included in propensity score model

Variable	Type	Selection
Tricuspid regurgitation	Categorical, 5 levels	By Lasso
Systolic BP	Continuous, linear	By Lasso
Volume Status peripheral edema	Categorical, 3 levels	By Lasso
ACE inhibitors	Categorical, 2 levels	By Lasso
Beta blockers	Categorical, 2 levels	By Lasso
PTT	Continuous, linear	By Lasso
Ethnic origin	Categorical, 2 levels	By Lasso
Primary Diagnosis	Categorical, 4 levels	By Lasso
Current ICD Device In Place	Categorical, 2 levels	By Lasso
Intubation	Categorical, 2 levels	By Lasso
Major MI	Categorical, 2 levels	By Lasso
Device Brand LVAD	Categorical, 4 levels	By Lasso
Pulmonary Regurgitation	Categorical, 5 levels	By Lasso

Supplementary Table 5: Variables included in propensity score model (continued)

Variable	Type	Selection
RA pressure	Continuous, linear	By Lasso
Potassium	Continuous, linear	Due covariate imbalance
LVEF	Continuous, linear	Due covariate imbalance
INTERMACS Patient Profile	Categorical, 4 levels	Due clinical significance
Age	Continuous, linear	Due clinical significance
TAPSE	Continuous, linear	Due covariate imbalance
ECMO	Categorical, 2 levels	Due covariate imbalance
Albumin	Continuous, linear	Due clinical significance
ECG rhythm	Categorical, 4 levels	Due covariate imbalance
Total bilirubin	Continuous, multiple fractional polynomial: Total bilirubin^-2 +Total bilirubin^-1	Due covariate imbalance
BSA	Continuous, linear	Due covariate imbalance

Supplementary Table 6: Estimates of included variables in PS model

Characteristic	log(OR), [95% CI]
(Intercept)	-6,62 [-8,991 to -4,348]
Tricuspid regurgitation: Trivial	0,328 [-0,73 to 1,612]
Tricuspid regurgitation: Mild	0,436 [-0,526 to 1,67]
Tricuspid regurgitation: Moderate	2,126 [1,203 to 3,34]
Tricuspid regurgitation: Severe	3,058 [2,12 to 4,281]
Systolic blood pressure	-0,016 [-0,025 to -0,006]
Peripheral edema: Mild	-0,54 [-0,965 to -0,133]
Peripheral edema: Moderate	-0,022 [-0,411 to 0,357]
Peripheral edema: Severe	0,139 [-0,27 to 0,539]
ACE inhibitors	-0,375 [-0,702 to -0,056]
Beta blockers	-0,207 [-0,515 to 0,101]
PTT	0,012 [0,003 to 0,022]
Ethnic origin: Caucasian vs other	0,915 [0,346 to 1,55]
Primary Diagnosis: Idiopathic	0,188 [-0,332 to 0,733]
Primary Diagnosis: Ischemic	-0,326 [-0,858 to 0,226]
Primary Diagnosis: Other	0,08 [-0,461 to 0,642]
ICD	0,403 [0,058 to 0,755]
Intubation	-0,55 [-1,138 to -0,002]
Major MI	-0,599 [-1,169 to -0,072]
HeartWare HVAD	-0,635 [-0,951 to -0,319]
Other	-2,329 [-4,164 to -1,107]
Thoratec - HeartMate III	-0,145 [-0,546 to 0,248]
Pulmonary Regurgitation: Trivial	0,479 [0,143 to 0,815]

Supplementary Table 6: Estimates of included variables in PS model (continued)

Characteristic	log(OR), [95% CI]
Pulmonary Regurgitation: Mild	0,118 [-0,268 to 0,499]
Pulmonary Regurgitation: Moderate	-0,252 [-0,925 to 0,374]
Pulmonary Regurgitation: Severe	-1,432 [-2,882 to -0,366]
RA pressure	0,014 [-0,009 to 0,037]
Potassium	0,203 [0,055 to 0,36]
LvEf Percent	0,025 [0,004 to 0,046]
INTERMACS 2 - Progressive decline	0,734 [0,166 to 1,34]
INTERMACS 3- Stable but inotrope dependent	0,603 [0,01 to 1,232]
INTERMACS 4/7	0,54 [-0,098 to 1,208]
Age	0,017 [0,004 to 0,03]
TAPSE	0,014 [-0,018 to 0,046]
ECMO	0,207 [-0,435 to 0,823]
Albumin	0 [0 to 0,001]
ECG: Atrial fibrillation	0,059 [-0,335 to 0,444]
ECG: Other rhythm	-0,159 [-1,12 to 0,67]
ECG: Paced	-0,341 [-0,701 to 0,016]
I(Bilirubin^-2)	0,034 [0,017 to 0,054]
I(Bilirubin^-1)	-0,495 [-0,787 to -0,218]
BSA	0,234 [-0,33 to 0,809]

Supplementary Table 7: Standard mean differences before and after matching. *means of 5 imputed datasets

names	Standard mean difference before matching*	Standard mean difference after matching*
BSA	6,1	4,1
Age	15,3	4,4
Gender	11,8	2,8
Creatinine	6,3	3,7
Ascites	18,6	2,9
Loop diuretics	20,1	5,8
Multiple inotropes	2,4	10,0
ASAT	6,7	2,0
Total bilirubin	17,0	8,7
Hemoglobin	9,9	9,8
RA pressure	34,6	4,6
LVEF Percent	10,8	2,0
IABP	17,6	12,1
ECMO	12,8	2,3
Pulmonary artery systolic pressure	4,4	4,3
Asian	38,6	3,3

Supplementary Table 7: Standard mean differences before and after matching. *means of 5 imputed datasets (continued)

names	Standard mean difference before matching*	Standard mean difference after matching*
White	35,3	5,4
Other race	11,0	5,7
Idiopathic etiology	27,3	1,1
Ischemic etiology	34,1	6,8
Other etiology	6,3	10,2
History cardiac diagnosis one month to a year	30,4	1,4
History cardiac diagnosis one to two years	12,1	0,8
History cardiac diagnosis over two years	12,1	8,0
Atrial fibrillation	3,2	0,4
Other rhythm	3,4	6,4
Paced rhythm	14,1	0,4
INTERMACS class II	6,6	4,0
INTERMACS class III	24,7	5,9
INTERMACS class ≥IV	5,9	3,3
MR trivial	42,7	0,8
MR mild	21,7	4,3
MR moderate	8,1	7,4
MR severe	9,4	5,5
TR trivial	124,2	0,6
TR mild	55,3	8,5
TR moderate	14,0	10,5
TR severe	34,1	6,8
RVF mild	37,6	2,9
RVF moderate	12,3	7,2
RVF severe	12,7	3,4
AR trivial	7,7	0,9
AR mild	14,4	1,0
AR moderate	13,4	6,0
AR severe	1,4	9,2
TAPSE	3,2	6,0
Pulmonary artery wedge pressure	24,8	7,2
Albumin	1,1	2,5

Supplementary Table 8: Sensitivity analyses with caliper set at 0.001

	TVS (n=117)	No TVS (n=117)	p-value
30-day mortality	10.4% (5.3 to 17.9)	7.9% (3.4 to 14.3)	0.69
Hospital mortality	21.2% (10.2 to 24.4)	16.4% (13.6 to 30.6)	0.47
Late mortality $_{\text{KM estimate at 2 years}}$	68.3% (57.7 to 80.4)	60.3 (50.4 to 72.1)	0.18*

TVS: Tricuspid valve surgery. *Derived from log-rank test

Supplementary Table 9: Sensitivity analyses survival (matched patients)

Scenario	P-value log-rank
No TVS: all 22 missing survived 3 year *TVS*: all 7 patients survived 3 years	0.059
No TVS: all 22 missing died at 0.5 year *TVS*: all 7 patients died at 0.5 year	0.86
No TVS: all 22 missing died at 1 year *TVS*: all 7 patients died at 1 year	0.75
No TVS: all 22 missing died at 2 years *TVS*: all 7 patients died at 2 years	0.31
No TVS: all 22 missing died at random time points *TVS*: all 7 patients died at random time points	0.59
No TVS: all 22 missing survived at 3 years *TVS*: all 7 patients died at random time points	0.007*
No TVS: all 22 died at random time points *TVS*: all 7 patients survived at 3 years	0.77
No TVS: 11 patients of 22 died at random time points *TVS*: 3 patients of 7 died at random time points	0.28

In the matched cohort 22 patients without TVS and 7 patients with TVS did not had recorded follow-up. In order to test the robustness of the log-rank test of the kaplan-meier analyses different scenarios were tested under different missing mechanism including missing not at random. The linearized occurrence rate of death was calculated using the formula: number of events/ total patients years and was 19% patient-year.
Therefore: expected alive at 3 years no TVS: 22*0.81^3 ≈ 11 and in TVS cohort: 7*0.81^3 ≈ 4

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Biatrial vs Bicaval Orthotopic Heart Transplantation: A Systematic Review and Meta-Analysis

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Background

Orthotopic heart transplantation (OHT) is the gold standard treatment in end-stage heart disease. Controversy remains whether bicaval OHT is superior to biatrial OHT in both early and late outcomes. This study aimedto provide an overviewof the early andlate outcomes in patients who underwent a bicaval or biatrial OHT.

Methods

A systematic literature search was performed for articles published before December 2017. Studies comparing adult patients undergoing biatrial OHT and bicaval OHT were included. Early outcomes were pooled in odds ratios and late outcomes were pooled in rate ratios. Late survival was visualized by a pooled Kaplan- Meier curve.

Results

A total of 36 publications were included in the meta-analysis, counting 3555 patients undergoing biatrial OHT and 3208 patients undergoing bicaval OHT. Early outcomes in mortality, tricuspid regurgitation, mitral regurgitation, and permanent pacemaker implantation differed significantly in favor of the bicaval OHT patients. Long-term survival was significantly better in patients undergoing bicaval vs biatrial OHT (hazard ratio, 1.32; 95% confidence interval, 1.1-1.6; *P* = .008). Also, late tricuspid regurgitation was less frequently seen in the bicaval OHT patients (rate ratio, 2.14; 95% CI, 1.17- 3.94; *P* = .014).

Conclusions

This systematic review with metaanalysis shows that bicaval OHT results in more favorable early and late outcomes for patients undergoing a bicaval OHT compared with a biatrial OHT. Therefore, bicaval OHT should be considered as preferable technique for OHT.

INTRODUCTION

Orthotopic heart transplantation (OHT) remains the gold standard for patients with end-stage heart failure.[1] The standard biatrial OHT technique was introduced by Lower and Shumway in 1960[2] and is still widely used because of its relative simplicity. This technique only requires 2 anastomoses to the atria of the recipient. Yacoub and colleagues[3] introduced the bicaval OHT technique in 1989, and it has gained popularity since. The bicaval technique requires a single left atrial anastomosis and separate caval suture lines. However, controversy regarding the preferred surgical OHT technique remains. There is a broad variety of studies that describe potential differences in outcome between the 2 surgical techniques. The biatrial technique tends to be less technical challenging for cardiac implantation, which results in a reduced ischemic time of the allograft.[4,5] However, the biatrial technique is known for worse hemodynamics because of the redundant atrial tissue and an increased risk of atrial arrhythmias in the postoperative period. The bicaval technique is more complicated and, therefore, might require a longer operation times. However, the bicaval technique leads to improved hemodynamics and a lower incidence of atrial arrhythmias in the postoperative period.[6,7] Unfortunately, most reported studies are insufficiently powered to detect important differences. Therefore, a systematic review and meta-analysis was conducted to assess the possible advantages in early and late posttransplantation outcomes in patients who underwent biatrial OHT compared with bicaval OHT.

MATERIAL AND METHODS

Search Strategy

To establish an overview of reported outcome, a systematic literature search, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, was conducted (Supplemental Text 1).[8] Search terms were developed in collaboration with a dedicated librarian in our center. On December 15, 2017, Embase, MEDLINE, Cochrane, Web of Science, and Google Scholar were searched (search terms are provided in Supplemental Text 2). Inclusion and exclusion criteria were defined a priori. Randomized controlled trials and observational studies concerning adult patients undergoing OHT comparing the standard biatrial OHT and the bicaval OHT were included. Studies with less than 20 patients, poster publications, abstracts, and conference summaries were excluded. Studies with less than 20 patients were excluded because these studies were most likely early experiential series and do not reflect the general population. Posters and abstracts were not included because these formats did not undergo extensive peer reviewing. In the case of overlapping study populations, the study with the most patient-years of follow-up were selected. Exceptions were made for studies that reported on more outcomes of interest. Furthermore, non-English studies were excluded. Two

researchers (C.F.Z. and K.M.V.) independently reviewed abstracts and full texts in an unblinded standardized manner. In case of disagreement to include a study, an agreement was negotiated.

Data Extraction

Study design, year of surgery, and follow-up (patient-years and mean) were documented. If follow-up was not provided, patient-years were calculated by multiplying the number of patients with the mean follow-up (or median if the mean was not provided). The baseline characteristics extracted from the individual studies are displayed in Supplemental Table 1. In addition, the following procedural characteristics were extracted: cardiopulmonary bypass time, aortic cross-clamp time, length of hospital stay, and ischemic time. The following post-transplantation outcomes were extracted and documented as early (in-hospital or <30 day[s]) or late (out-of-hospital or >30 days): mortality, tricuspid regurgitation, mitral regurgitation, and pacemaker implantation. The length of hospital stay was defined as the day the patient received the OHT till the day the patient was dismissed from the hospital after the transplant. The individual study definitions were used to define the outcomes. Data were independently extracted by 2 authors (C.F.Z. and T.S.). The Newcastle–Ottawa Scale was used to assess the methodological quality of the studies.[9]

Statistical Analyses

Log-transformed inverse variance–weighted pooled baseline characteristics were calculated. To compare baseline and procedural characteristics, in cases of descriptive data, odds ratios (ORs) were used, and in cases of categorical data, mean differences were used. The ORs and mean differences were calculated with the use of a fixed-effects model, as the goal was to compute comparisons for the identified population, and not to generalize to other populations, and an assessment of baseline characteristics similar in most cases.[10] A *P* value less than .05 was considered statistically significant and a 95% confidence interval (CI) was calculated. Continuous data were presented as mean with 95% CI and discrete variables were presented as percentage with 95% CI. Random-effects models using the DerSimonian-Laird method were used to pool outcomes.[11] ORs were used for dichotomous data for early outcomes, and rate ratios (RRs) were used for dichotomous data for late outcomes. The Cochrane Q statistic and I^2 were used to assess heterogeneity. Egger's test and funnel plots were used to assess the risk of publication bias.[12] Comprehensive Meta-Analysis v2.2.064 (Biostat, Engelwood, NJ) was used to calculate the pooled outcomes and to generate forest and funnel plots. Patient survival was visualized in a pooled Kaplan-Meier (KM) curve derived from the originally published KM curves using the method described by Guyot and colleagues.[13] The Engauge Digitizer v10.0[14] was used to create a list of coordinates of the KM curve, and an algorithm written in R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria) was employed to reconstruct the original patient data. Thereafter, GraphPad Prism version 7.00 for Windows (GraphPad Software, San Diego, CA) was used to plot the pooled KM curve. The reconstructed data were used to

obtain hazard ratios (HRs) of late mortality in the biatrial and bicaval groups by univariable Cox regression. Thereafter, the HRs were pooled using Comprehensive Meta-Analysis. In order to evaluate whether studies before the year 2000 yielded different conclusions compared with contemporary studies, a subgroup analysis was performed.

RESULTS

The literature search resulted in 3648 studies, of which 45 articles met the inclusion criteria. Owing to overlapping data, 9 studies had to be excluded, resulting in 36 inclusions for the meta-analysis (Figure 1). References are represented together with the baseline characteristics of all individual studies in Supplemental Table 1 (References S1-S36). The meta-analysis included 6763 patients who had underwent OHT, of whom 3555 (52.6%) received a biatrial OHT and 3208 (47.4%) received a bicaval OHT. The median year of operation in the biatrial group was 1996 (range, 1988-2005) and in the bicaval group was 1998 (range: 1990-2005). Of the 36 studies, 32 were observational studies and 4 studies were randomized (References S1, S4, S14, and S17 in Supplemental Table 1). The biatrial group contained 1911 patients who had reported a mean follow-up time of 6.2 ± 8.8 years, encompassing 11,833 patient-years. The bicaval group contained 1935 patients who had reported a mean follow-up time of 6.5 ± 10.2

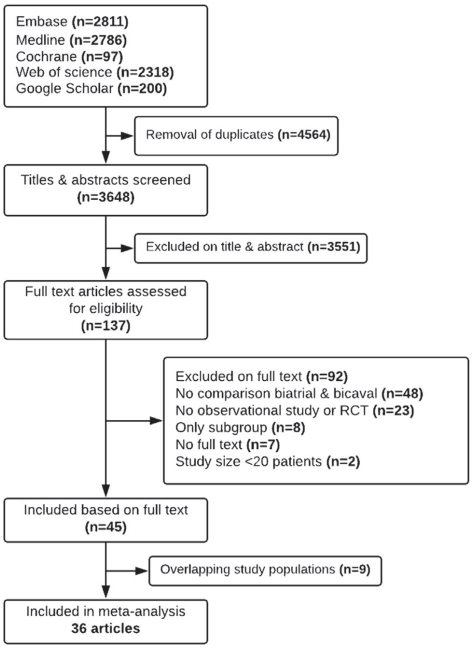

Figure 1. Flowchart of included studies in the meta-analysis.

years, encompassing 12,601 patient-years. All studies scored between 5 and 9 points on the Newcastle–Ottawa Scale and most studies lost points on comparability (Supplemental Table 1).

Baseline and Procedural Characteristics

Pooled baseline and procedural characteristics of the 6763 patients included in the meta-analysis are shown in Table 1.

Table 1. Pooled Baseline and Procedural Characteristics of Included Studies

Variable	Biatrial (n = 3555)	Bicaval (n = 3208)	OR/MD (95% CI)	*P* Value	Studies Reported	I^2 (%)
Age, y[a]	50.5 (50.0-51.0)	50.3 (49.8-50.8)	–0.63 (–1.42 to 0.16)	.118	23	54.0
Male, %[b]	82.6 (81.0-84.2)	77.6 (75.6-79.5)	1.31 (1.12 to 1.55)	.002	27	47.8
Systolic PAP, mm Hg[a]	40.7 (38.8-42.6)	41.7 (39.6-43.8)	–1.64 (–4.55 to 1.28)	.272	6	48.0
CVP, mm Hg[a]	5.37 (5.10-5.63)	3.48 (3.22-3.75)	1.01 (0.62 to 1.41)	<.001	9	76.6
Ischemic etiology, %[b]	39.5 (37.1-41.9)	36.8 (34.2-39.5)	1.10 (0.94 to 1.28)	.245	19	0.0
Diabetes, %[b]	29.6 (25.5-34.1)	26.6 (22.2-31.6)	1.10 (0.79 to 1.52)	.573	5	52.9
CPB, min[a]	116.5 (103.3-129.6)	126.8 (111.0-142.5)	–9.90 (–21.7 to 1.9)	.099	11	90.2
Aortic cross-clamp time, min[a]	64.7 (53.3-76.1)	75.0 (58.5-91.6)	–10.15 (–20.8 to 0.5)	.062	6	93.4
Ischemia time, min[a]	164.7 (162.8-166.6)	174.8 (165.8-183.9)	–16.7 (–27.7 to –4.3)	.007	25	93.8
Length of hospital stay, d[a]	26.2 (19.3-33.2)	25.1 (17.4-32.9)	1.07 (–2.82 to 4.95)	.590	7	70.0

[a]MD [b]OR

Values are median (interquartile range).

CI, confidence interval; CPB, cardiopulmonary bypass time; CVP, central venous pressure; MD, mean difference; OR, odds ratio; PAP, pulmonary artery pressure.

Early Outcomes

A forest plot containing the individual and pooled ORs for the early outcomes of mortality, tricuspid regurgitation, mitral regurgitation, and pacemaker implantation is presented in Figures 2A to 2D. The pooled early mortality in the biatrial group was 12.5% (95% CI, 8.3%-18.4%) and in the bicaval group was 8.8% (95% CI, 4.8%-15.5%), with an OR of 1.47 (95% CI, 1.0-2.2; *P* = .048). Furthermore, early moderate-to-severe tricuspid regurgitation, early moderate-to-severe mitral regurgitation, and need of early pacemaker implantation were observed more frequently in the biatrial OHT group (Table 2).

Table 2. Pooled Early and Late Outcomes

Outcome	Variable	Biatrial (n = 3555)	Bicaval (n = 3208)	OR/RR (95% CI)	*P* Value	Studies Reported	I^2 (%)
Early	Mortality	12.5 (8.30 to 18.4)	8.80 (4.8 to 15.5)	1.47 (1.0 to 2.2)[a]	.048	10	4.7
	Tricuspid regurgitation	42.8 (30.8 to 55.7)	28.5 (20.2 to 38.6)	1.92 (1.4 to 2.7)[a]	<.001	13	52.6
	Mitral regurgitation	11.1 (3.6 to 29.7)	6.9 (2.4 to 17.9)	2.13 (1.3 to 3.5)[a]	.002	6	12.1
	Pacemaker implantation	19.2 (12.2 to 28.7)	8.6 (4.8 to 15.0)	2.49 (1.5 to 4.2)[a]	.001	14	34.8
Late	Mortality	4.9 (1.1 to 8.7)	4.1 (0.3 to 7.8)	1.77 (1.2 to 2.6)[b]	.004	4	0
	Tricuspid regurgitation	6.3 (3.9 to 8.6)	1.2 (0.5 to 2.0)	2.14 (1.2 to 3.9)[b]	.014	8	79.5
	Mitral regurgitation	0.4 (–0.4 to 1.3)	0.4 (–0.3 to 1.0)	1.23 (0.6 to 2.4)[b]	.528	6	0
	Pacemaker implantation	3.3 (1.3 to 5.4)	1.4 (2.0 to 2.5)	1.93 (0.9 to 4.1)[b]	.083	8	41.5

[a]OR; [b]RR.

Values are % (95% CI) for early outcomes and linearized occurrence rate as percentage per patient year (95% CI) for late outcomes. CI, confidence interval; OR, odds ratio; RR; rate ratio.

Late Outcomes

The meta-analyses contained 10 studies (References S13, S14, S18, S21, S22, S26, S27, S32, S33, and S36 in Supplemental Table 1) that reported KM curves that could be pooled. The KM curves showed differences in late mortality between the biatrial and bicaval groups (Figure 3). The 2-year, 5-year, and 10-year survival rates were 80.0% ± 0.1%, 71.0% ± 0.1%, and 60.1% ± 0.2% in the biatrial group and 84.3% ± 0.01%, 76.8% ± 0.1%, and 71.2% ± 0.2% in the bicaval group, respectively. Pooled HR for late mortality showed a significantly higher risk in the biatrial group, with an HR of 1.32 (95% CI, 1.1-1.6; *P* = .008) and an I^2 of 38.0%. The linearized occurrence rates of late outcomes of the individual transplant groups are presented in Table 2. Data on late tricuspid regurgitation were reported in 8 studies and showed a significant difference in favor of the bicaval group, with a linearized occurrence RR of 2.14 (95% CI, 1.17-3.94; *P* = .014) (Supplemental Figure 1A). Late mitral regurgitation was reported in 6 studies, with a linearized occurrence RR of 1.23 (95% CI, 0.64-2.37; *P* = .528) (Supplemental Figure 1B). Late pacemaker implantation was reported in 8 studies and had a linearized occurrence RR of 1.93 (95% CI, 0.92-4.10; *P* = .083) (Supplemental Figure 1C).

Subgroup Analysis

Subgroup analysis of the 4 randomized controlled trials was only possible for early permanent pacemaker implantation, as other outcomes were reported in less than 3 individual studies and no pooling attempt was made. Early permanent pacemaker implantation was comparable

in these 3 studies. Subgroup analysis of the observational studies did not lead to a change in significance in any of the outcomes. Subgroup analyses of studies published before and after year 2000 did not lead in changes in significance in any of the outcomes.

Publication Bias and Sensitivity Analysis

Early and late outcomes did not show publication bias according to Egger's test. Funnel plots are presented in Supplemental Figures 2A to 2D for early outcomes and Supplemental Figures 3A to 3C for late outcomes. Leave-one-out sensitivity analysis did not change the significance of all outcomes.

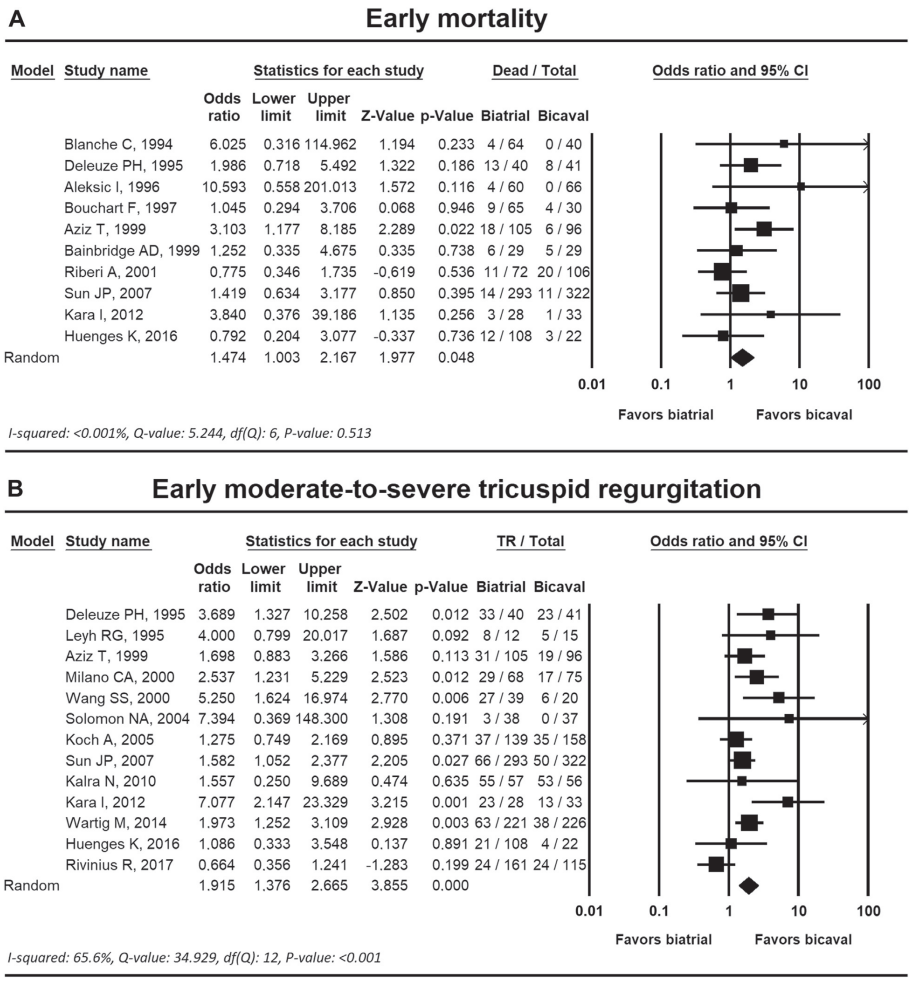

Figure 2. Forest plots of (A) early mortality, (B) moderate-to-severe tricuspid regurgitation (TR), (C) moderate-to-severe mitral regurgitation (MR), and (D) permanent pacemaker (PM) implantation. CI, confidence interval.

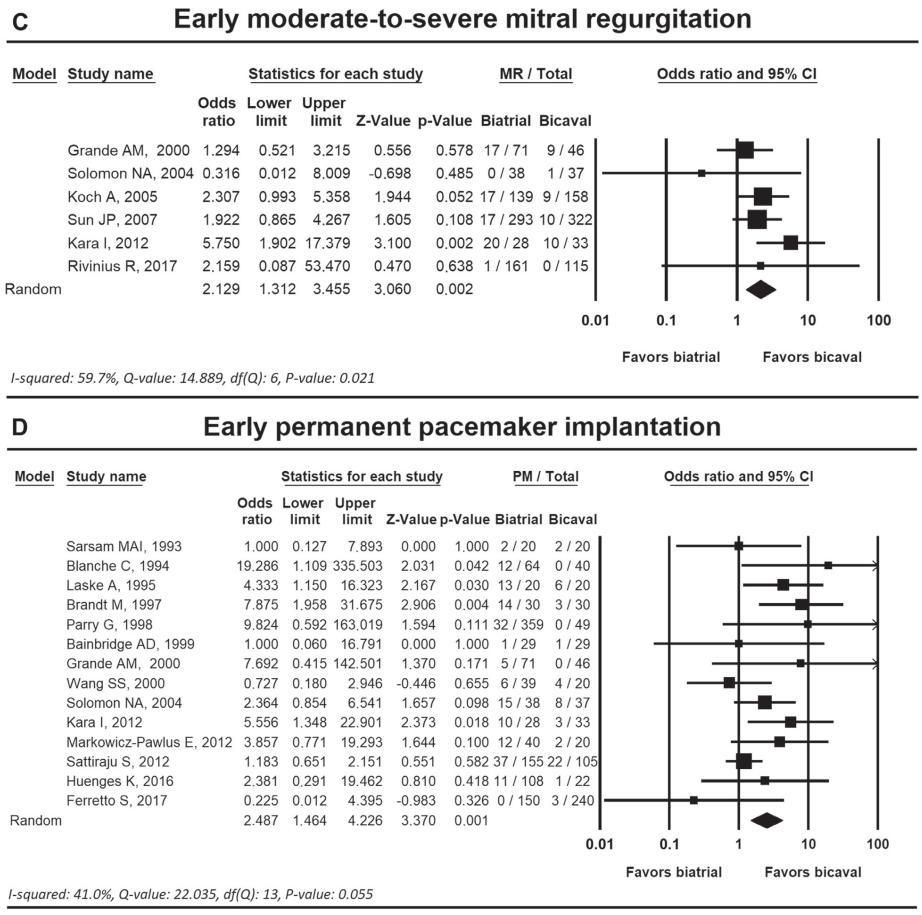

Figure 2. (continued).

COMMENT

This systematic review and meta-analysis shows that the bicaval technique is associated with superior early and late survival, less early and late tricuspid regurgitation, less early mitral regurgitation, and reduced early need of permanent pacemaker implantation.

Although bicaval OHT can be considered the preferable technique to perform an OHT, there are still many centers worldwide where the biatrial approach is preferred.[15] More than a decade ago, Schnoor and colleagues[6] performed a meta-analysis and concluded that early outcomes in the bicaval technique have beneficial effects in comparison with the biatrial technique. More recent overviews of the literature have presented similar conclusions.[16,17] However, little is known about the difference between these 2 techniques with regard to late outcomes.[6] Our meta-analysis confirms the association of the bicaval technique with better outcomes in the

short term. Moreover, this meta-analysis, with novel contemporary statistics, shows clinically relevant beneficial effects of the bicaval technique in the long term as well.

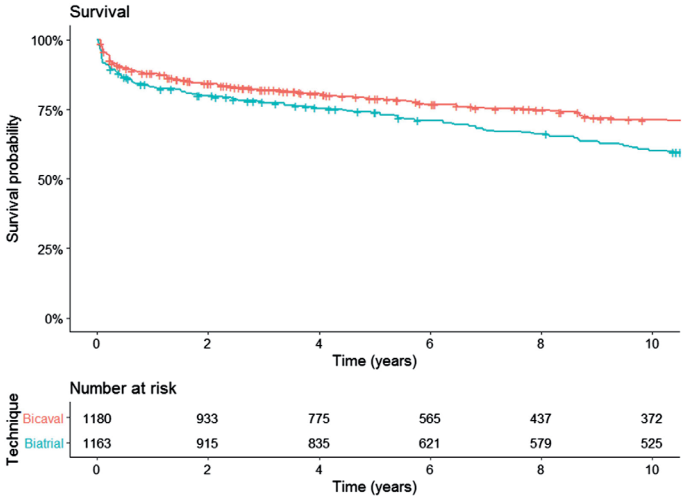

Figure 3. Pooled Kaplan-Meier curve of patient survival after bicaval (red) or biatrial (green) heart transplantation.

Ischemia Time

There was a significant difference in the ischemia time between the 2 transplanted groups. Although statistically different, the absolute time difference was only 10 minutes. Cardiopulmonary bypass time and aortic cross-clamp time did not differ significantly. The prolonged ischemia time could be explained by the duration of transport or waiting time before or during the operation. In a retrospective study, Russo and colleagues[18] reviewed ischemia time in 33,640 OHT recipients in the United Network for Organ Sharing (UNOS) database performed between 1987 and 2004 and found no difference in long-term survival (10 years) between prolonged ischemia time (3.50-5.49 hours) and limited ischemia time (0.00-3.49 hours). Taking these observations into account, it seems implausible that a 10-minute difference would lead to major changes in postoperative outcomes. Nevertheless, as in some selected cases, such as in reoperative heart transplantation or abnormal caval veins, a biatrial approach may still be preferred.

Mortality

A significant difference was found in both early mortality and late survival between the 2 transplanted groups in favor of the bicaval group. Davies and colleagues[19] reviewed the UNOS database data between 1997 and 2007 and reported a higher survival rate in the bicaval vs biatrial group after 10 years (57.4% vs 51.1%). The survival rate in the present meta-analysis is

higher when compared with Davies and colleagues (71.2% vs 60.1%).[19] This could be due to the fact that Davies and colleagues[19] used the UNOS database, whereas the individual studies in this meta-analysis mostly reviewed their own patients. Thereby, a strong improvement of the posttransplant care has been seen in the last decade, which has resulted in increased long-term survival.[20] However, both our meta-analysis and the registry study provide a higher survival rate in the bicaval group after 10 years of follow-up.

Tricuspid Regurgitation

This study shows a significant difference in early and late tricuspid regurgitation in favor of the bicaval group. Moderate-to-severe tricuspid regurgitation is usually caused by donor-recipient size mismatch, right ventricular failure due to pretransplant pulmonary hypertension, and right ventricular dysfunction due to donor heart rejections.[21] The cause of donor-recipient size mismatch is mainly a problem of the atria, and the biatrial technique may induce tricuspid regurgitation due to changes in atrial geometry. The bicaval technique only uses the left atrium and both caval veins to perform the anastomosis and, therefore, the technique may prevent tricuspid regurgitation.[3] Moreover, moderate-to-severe tricuspid regurgitation after OHT could also been caused by torn leaflets and ruptured chordae due to surveillance endomyocardial biopsies in the years after transplantation.[22,23] It has been shown that patients with no or mild tricuspid regurgitation have better survival than do those with moderate or severe tricuspid regurgitation.[24] Moderate-to-severe tricuspid regurgitation was, as confirmed byour analysis, reportedmore often in the biatrial group and therefore could have contributed to a higher mortality rate in this group.[25-27] However, the optimal treatment of posttransplant severe tricuspid regurgitation is very cumbersome and still not well defined. Generally, because severe tricuspid regurgitation remains asymptomatic for a long time, it is not unusual that conservative treatment is preferred to surgical treatment, probably missing the optimal timing of tricuspid surgery.[28] Therefore, reduction of occurrence of tricuspid regurgitation by bicaval OHT might be a suitable approach for this post-OHT problem.

Mitral Regurgitation

Mitral regurgitation post OHT is still not well studied. Mitral regurgitation could be caused by a mismatch in size between the donor heart and native heart, early allograft rejection, left ventricular failure after OHT, and a dilated left atrium.[29-31] In our study, early mitral regurgitation occurred more frequently in the biatrial transplant group (Figure 2D). However, in late outcomes, no mitral regurgitation was observed. The treatment of mitral regurgitation depends on the severity and symptoms of the patients. Symptomatic severe mitral regurgitation is associated with excess mortality and frequent heart failure.[32,33] Despite these poor outcomes, only a minority of the affected patients undergo some kind of treatment.[32]

Permanent Pacemaker Implantation

Early after OHT, sinus node dysfunction and atrioventricular conduction abnormalities are frequently encountered, with some cases in need of permanent pacemaker implantation.[34] Increased ischemic time, a higher donor age, frequent episodes of rejection, and the anatomy of the blood supply to the sinoatrial node are denoted as causes of sinus node and atrioventricular conduction abnormalities after OHT.[35-39] However, the most commonly stated cause is surgical trauma at time of transplantation.[40] Our systematic review and meta-analysis confirms this hypothesis, showing a significant decrease in requirement of early permanent pacemaker implantation in the bicaval group. This is in line with the retrospective study of Davies and colleagues[19] that showed a higher early pacemaker implantation risk in patients who underwent the biatrial OHT vs bicaval OHT after discharge from the hospital (5.1%vs. 1.9%). Although Davies and colleagues[19] also found a higher rate of late pacemaker implantation in the biatrial group, this could not be confirmed in the present study. This may be explained by the fact that only a few studies reported late permanent pacemaker implantation, resulting in insufficient power to show a difference. Another explanation could be that the differences in pacemaker implantation are only presented in the early postoperative period and become comparable with a longer follow-up period. This was also observed by Herre and colleagues,[34] who noted comparable findings to this meta-analysis.

Strengths and Limitations

The majority of studies were retrospective in nature, which made them prone to selection bias.[41] This was confirmed by the fact that most studies scored 6 points on the Newcastle–Ottawa Scale and no points on comparability. Publication bias may have led to an underestimation of the pooled estimates when studies with relatively poor outcomes are not published. However, funnel plots and the Egger's test found no indication for the presence of publication bias. Notwithstanding, some publication bias may be present based on visual inspection of the funnel plots. There was moderate-to-substantial heterogeneity between studies in most outcomes, which may potentially have led to inaccurate results. Another limitation was caused by the limited availability of posttransplant clinical data about the number and severity of rejections and cardiac transplant vasculopathy in the 2 groups, as these factors are known to influence the long-term prognosis. Furthermore, studies over a large time span were included in the meta-analysis. Nevertheless, subgroup analyses yielded comparable outcomes of both older and contemporary studies.

Conclusion

This systematic review with meta-analysis provides ample evidence that bicaval OHT is associated with better early and late clinical outcomes, including early and late survival, prevention of tricuspid regurgitation, and need of permanent pacing.

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SUPPLEMENTARY MATERIAL

CONTENT

Supplementary Text 1, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist:

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	21/22
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5

Supplementary Text 1, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist: (continued)

Section/topic	#	Checklist item	Reported on page #
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	22/23/24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	25/26/27
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15/16/24/25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16/17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16/17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENTARY TEXT 2, SEARCH OF THE LITERATURE:

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('heart transplantation'/exp OR 'cardiac graft rejection'/de OR 'cardiac allograft vasculopathy'/de OR (((heart* OR cardiac) NEXT/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))):ab,ti,kw) AND ('biatrial heart transplantation'/de OR 'bicaval heart transplantation'/de OR 'orthotopic transplantation'/de OR (('intermethod comparison'/de OR 'heart atrium'/exp OR 'cava vein'/exp) AND 'surgical technique'/de) OR (biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/6 (method* OR technique* OR approach*) NEAR/6 compar*) OR (technique* NEAR/6 compar*) OR (left NEAR/3 right NEAR/3 (atrium OR atria)) OR (inferior* NEAR/3 superior*)):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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(Heart Transplantation/ OR (((heart* OR cardiac) ADJ (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))).ab,ti,kw.) AND (((Methods/ OR Methods.fs.) AND (exp Heart Atria/ OR exp Venae Cavae/)) OR (biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) ADJ6 (method* OR technique* OR approach*) ADJ6 compar*) OR (technique* ADJ6 compar*)).ab,ti,kw.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane CENTRAL 97

((((heart* OR cardiac) NEXT/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*))):ab,ti,kw) AND ((biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/6 (method* OR technique* OR approach*) NEAR/6 compar*) OR (technique* NEAR/6 compar*) OR (left NEAR/3 right NEAR/3 (atrium OR atria)) OR (inferior* NEAR/3 superior*)):ab,ti,kw)

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TS=(((((heart* OR cardiac) NEAR/1 (transplant* OR allotransplant* OR homotransplant* OR graft* OR homograft* OR allograft*)))) AND ((biatrial* OR bicaval* OR orthotopic* OR intermethod* OR ((surgical* OR operat*) NEAR/5 (method* OR technique* OR approach*) NEAR/5 compar*) OR (technique* NEAR/5 compar*) OR (left NEAR/2 right NEAR/2 (atrium OR atria)) OR (inferior* NEAR/2 superior*))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird*) NOT (human* OR patient*))) AND DT=(article) AND LA=(english)

Google scholar

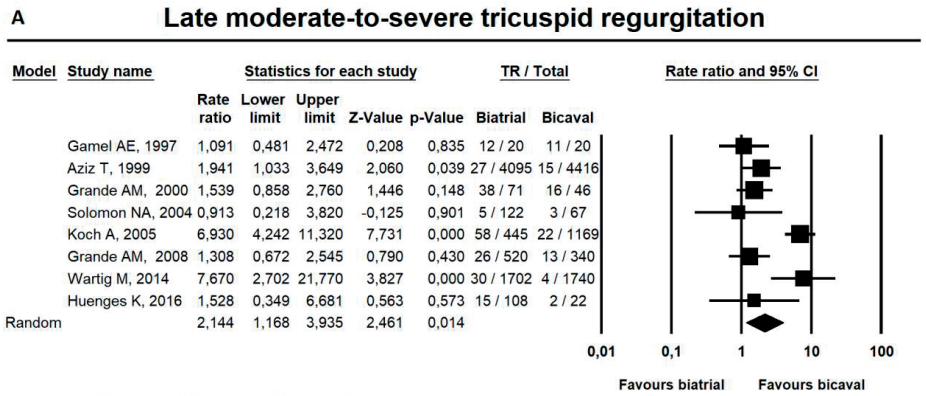
"heart|cardiac transplantation|allotransplantation|homotransplantation|graft|homograft|allograft" biatrial|bicaval -pig -animal -nonhuman -canine

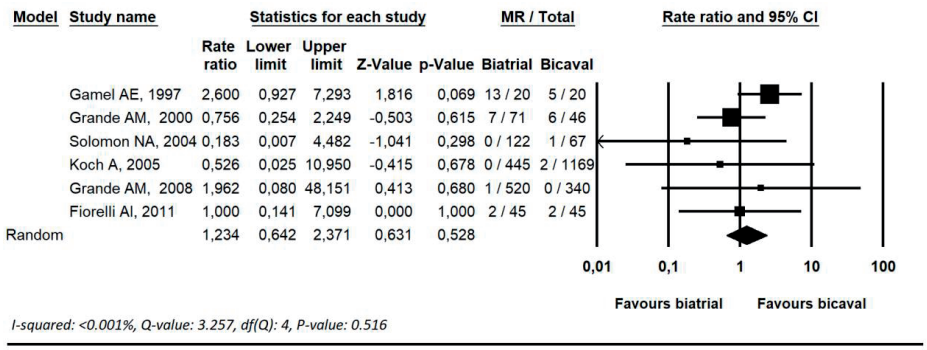
Supplementary Table 1: Baseline characteristics of the individual studies including study references (S1-S36).

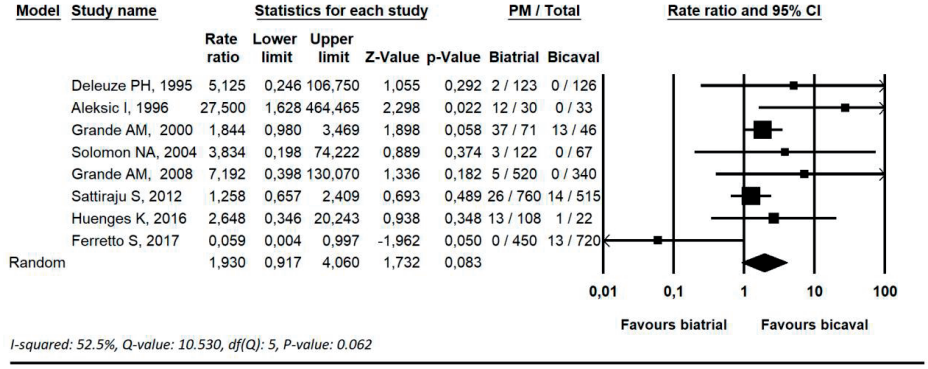
Publication, Supplementary Material Reference (S)	Year	Design	Group size, n (biatrial/ bicaval)	Male % (biatrial/ bicaval)	Ischemic aetiology % (biatrial /bicaval)	Follow-up, years (biatrial/ bicaval)	Median year of operation (biatrial /bicaval)	Points in Newcastle-Ottawa-Scale (Selection/ Comparability/ Outcome)
Sarsam M.A.I. et al., S1	1993	Prospective randomized	20 / 20					4 / 0 / 2
Bizouarn P. et al., 1994, S2	1994	Retrospective cohort	11 / 9	91 / 100	73 / 56	0.0055 / 0.0055	1991.5 / 1991.5	4 / 0 / 2
Blanche C. et al., S3	1994	Retrospective cohort	64 / 40	83 / 93	59 / 65		1989.5 / 1992	4 / 0 / 2
Deleuze P.H. et al., S4	1995	Prospective randomized	40 / 41	80 / 83	38 / 39	3.08 / 3.08	1992 / 1992	4 / 0 / 3
Laske A. et al., S5	1995	Prospective cohort	20 / 20	90 / 80	35 / 40			4 / 0 / 1
Leyh R.G. et al., S6	1995	Retrospective cohort	12 / 15	83 / 93				4 / 0 / 2
Aleksic I. et al., S7	1996	Retrospective cohort	60 / 66	82 / 92		0.5 / 0.5	1990 / 1992.5	4 / 0 / 2
Gamel A.E. et al., S8	1997	Retrospective cohort	20 / 20	65 / 75	55 / 45	1 / 1	1993.5 / 1993.5	4 / 0 / 2
Beniaminovitz A. et al., S9	1997	Retrospective cohort	10 / 10					4 / 0 / 1
Bouchart F. et al., S10	1997	Retrospective cohort	65 / 30		32 / 23		1990.5 / 1990.5	4 / 0 / 1
Brandt M. et al., S11	1997	Retrospective cohort	30 / 30	87 / 90		0.75 / 0.75	1992.5 / 1992.5	4 / 0 / 3
Parry G. et al., S12	1998	Retrospective cohort	359 / 49	84 / 84				4 / 0 / 2
Aziz T et al., S13	1999	Retrospective cohort	105 / 96	84 / 88	56 / 66	39 / 46	1993.5 / 1993.5	4 / 0 / 3
Bainbridge A.D. et al., S14	1999	Prospective randomized	29 / 29	86 / 86				4 / 0 / 2
Grande A.M. et al., S15	2000	Retrospective cohort	71 / 46	80 / 80	35 / 30	1 / 1		4 / 0 / 3
Milano C.A. et al., S16	2000	Retrospective cohort	68 / 75	76 / 75	46 / 53		1993 / 1997	4 / 0 / 1
Wang S.S. et al., S17	2000	Prospective randomized	39 / 20	72 / 75	28 / 35		1998 / 1998	4 / 0 / 1

Supplementary Table 1: Baseline characteristics of the individual studies including study references (S1-S36). (continued)

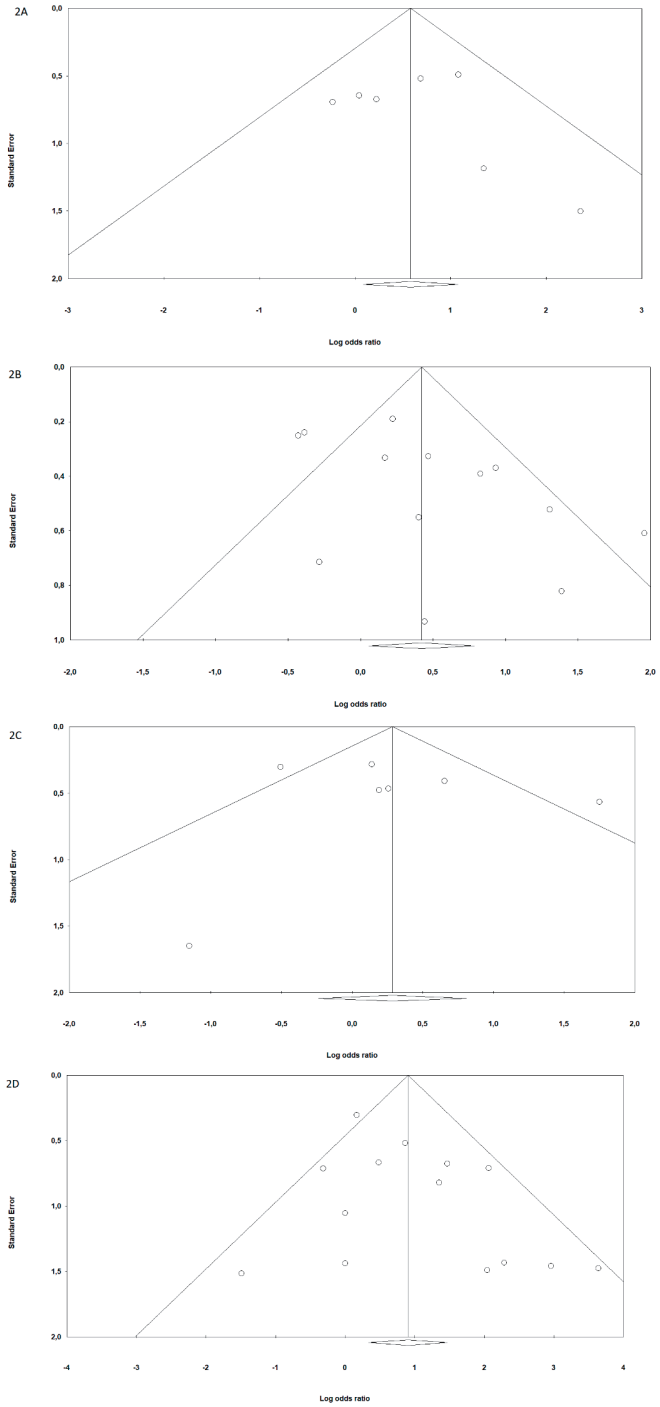
Publication, Supplementary Material Reference (S)	Year	Design	Group size, n (biatrial/ bicaval)	Male % (biatrial/ bicaval)	Ischemic aetiology % (biatrial /bicaval)	Follow-up, years (biatrial/ bicaval)	Median year of operation (biatrial /bicaval)	Points in Newcastle-Ottawa-Scale (Selection/ Comparability/ Outcome)
Riberi A. et al., S18	2001	Retrospective cohort	72 / 106			8.7 / 5.9	1992 / 1992	4 / 0 / 3
Solomon N.A. et al., S19	2004	Retrospective cohort	38 / 37	76 / 81	32 / 30	3.2 / 1.8	1998.5 / 1998.5	4 / 0 / 3
Koch A. et al., S20	2005	Retrospective cohort	139 / 158		30 / 27	3.2 / 7.4	1996 / 1996	4 / 0 / 3
Park K.Y. et al., S21	2005	Retrospective cohort	13 / 25	77 / 68	8 / 12		1995 / 1999.5	4 / 0 / 3
Sun J.P. et al., S22	2007	Retrospective cohort	293 / 322	92 / 73	38 / 33	3.8 / 3.8	1998.5 / 1998	4 / 2 / 3
Grande A.M. et al., S23	2008	Retrospective cohort	52 / 34	83 / 82		10 / 10	1996 / 1996	4 / 0 / 3
Kalra N. et al., S24	2010	Retrospective cohort	57 / 56	70 / 73				4 / 0 / 2
Fiorelli A.I. et al., S25	2011	Retrospective cohort	15 / 15	87 / 60	40 / 20	3 / 3	1992 / 2004.5	4 / 0 / 3
Jung S.H. et al., S26	2011	Retrospective cohort	53 / 148			6.4 / 6.4	2000 / 2000	4 / 0 / 3
Dell'Aquila A.M. et al., S27	2012	Retrospective cohort	117 / 99	89 / 93	50 / 58	10.5 / 5.2	1998.5 / 1998.5	4 / 0 / 3
Kara I. et al., S28	2012	Retrospective cohort	28 / 33	86 / 79			1998.5 / 1998.5	4 / 0 / 2
Markowicz-Pawlus E. et al., S29	2012	Retrospective cohort	40 / 20					4 / 0 / 1
Sattiraju S. et al., S30	2012	Retrospective cohort	155 / 105	79 / 75		4.9 / 4.9	2002 / 2002	4 / 2 / 3
Kim G.S. et al., S31	2014	Retrospective cohort	53 / 148				2000 / 2000	4 / 0 / 3
Wartig M. et al., S32	2014	Retrospective cohort	221 / 226	80 / 73	33 / 23	7.7 / 7.7	1996.5 / 1996.5	4 / 2 / 3
Huenges K et al., S33	2016	Retrospective cohort	108 / 22	82 / 95	45 / 41	1 / 1	2005 / 2005	4 / 0 / 3
Ferretto S. et al., S34	2017	Retrospective cohort	150 / 240	87 / 80		3 / 3	1999 / 1999	4 / 0 / 2
Mallidi H.R. et al., S35	2017	Retrospective cohort	767 / 683				1998 / 1998	4 / 0 / 2
Rivinius R. et al., S36	2017	Retrospective cohort	161 / 115	81 / 72	32 / 32	0.08 / 0.08	2000.5 / 2000.5	4 / 2 / 3



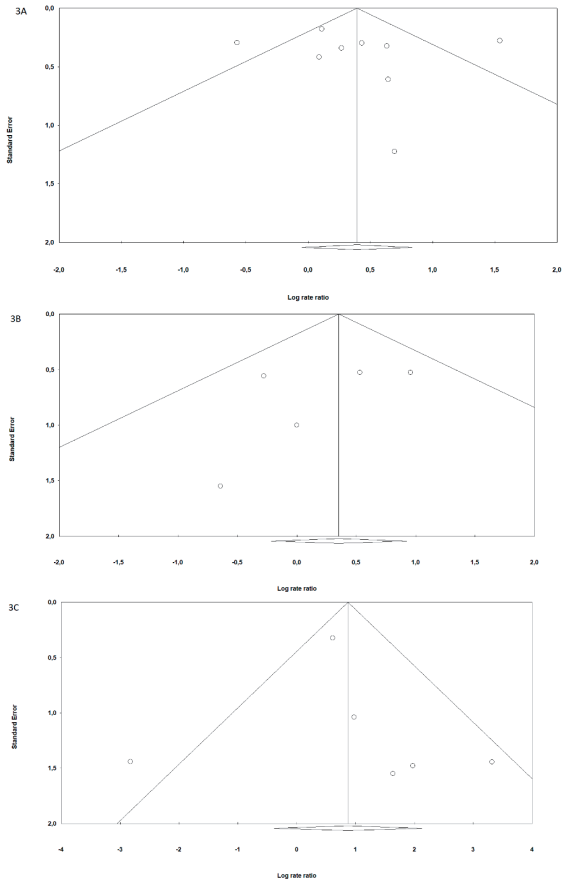




Supplementary Figure 1: (A-C) Forest plots of late moderate-to-severe tricuspid regurgitation (A), moderate-to-severe mitral regurgitation (B) and permanent pacemaker implantation (C). CI: confidence interval; TR: tricuspid regurgitation; MR: mitral regurgitation; PM: permanent pacemaker implantation.



Supplementary Figure 2: (A-D) Funnel plots of early mortality (A), early tricuspid regurgitation (B), early mitral regurgitation (C) and early permanent pacemaker implantation (D).



Supplementary Figure 3: (A-C) Funnel plots of late tricuspid regurgitation (A), late mitral regurgitation (B) and late permanent pacemaker implantation (C).

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S12.Parry G, Holt ND, Dark JH, McComb JM. Declining need for pacemaker implantation after cardiac transplantation. PACE - Pacing and Clinical Electrophysiology. 1998;21(11 II):2350-2.

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The clinical impact of tricuspid regurgitation in patients with a biatrial orthotopic heart transplant

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ABSTRACT

Introduction

Tricuspid regurgitation (TR) is common in patients with after biatrial orthotopic heart transplant (OHT). Nevertheless, the clinical impact and long-term sequel of TR remains unclear. In this study, we aim to elucidate the clinical impact and long-term course of TR, taking into account its dynamic nature.

Methods

All consecutive adult patients undergoing biatrial OHT (1984-2017) and with an available follow-up echocardiogram were included in this study. Mixed-models were used to model the evolution of TR. Thereafter, the mixed-model was inserted into a Cox model, under the joint-model framework, in order to address the association of the dynamic TR with mortality.

Results

In total, 572 patients were included (median age: 50 years, males:74.9%). Approximately 32% of patients had moderate-to-severe TR immediately after surgery. However, this declined to approximately 11% at 5 years and 9% at 10 years after of surgery, adjusted for survival bias. Pre-implant mechanical support was associated with less TR during follow-up, whereas concurrent LV dysfunction was significantly associated with more TR during follow-up. Survival at 1, 5, 10, 20 years was 97±1%, 88±1%, 66±2% and 23±2%, respectively. The presence of moderate-to-severe TR during follow-up was associated with higher mortality (HR:1.07,95%CI[1.02-1.12],p=0.006). The course of TR was positively correlated with the course of creatinine (R=0.45).

Conclusion

TR during follow-up is significantly associated with higher mortality and worse renal function. Nevertheless, probability of TR is the highest immediately after OHT and decreases thereafter. Therefore, it may be reasonable to refrain from surgical intervention for TR during earlier phase after OHT.

INTRODUCTION

Tricuspid regurgitation (TR) is common in patients post biatrial orthotopic heart transplant (OHT) (1). Risk factors for TR after OHT include endomyocardial biopsies, allograft rejection, mismatch between the donor heart size and pericardial cavity dimensions (2-4). Additionally, several studies identified a biatrial anastomoses technique (vs a bicaval anastomoses) as independent risk factor for TR after OHT (3, 5, 6). Nevertheless, the clinical impact of TR remains unclear, partly because post-OHT TR is a dynamic disease that changes over time in individual patients. Due to these complex characteristics the clinical impact of post-OHT TR cannot be approached using traditional statistical tools. In this study, we aim to elucidate the clinical impact and long-term course of TR, taking into account its dynamic nature, by using novel statistical models to link the course of post-OHT TR to survival and renal function.

METHODS

Patients

Consecutive patients that underwent biatrial OHT from 1984 to 2016 in Erasmus MC were included in this retrospective cohort study (n=687). Patients whom echocardiograms results were not retrievable or had recorded echocardiograms without TR measurements were excluded (n=115) resulting in 572 patients eligible for analyses. Of note, most patients that died within 30 days did not have a TR measurement on echocardiogram and, therefore, were excluded. (Supplementary Figure 1). None of the patients received tricuspid valve interventions during follow-up. Approval from the local Medical Ethical Committee was obtained to conduct this study (MEC-2017-421).

Data collection

Baseline characteristics were extracted from our institutional OHT database. Additionally, all echocardiographic measurements and creatinine measurements were collected longitudinally via automated extraction from the electronic patient records. Furthermore, echocardiographic measurements were supplemented with data acquired from paper patient records. The Dutch municipal civil registry was checked for the survival status.

Study outcome

The main outcome of this study is mortality in relation to the changing TR severity over time. Secondary outcomes include: the evolution of post-OHT TR grade and the evolution of post-OHT creatinine in relation to the changing TR severity.

Operation

All patients were operated with the biatrial anastomoses technique described in 1960 by Lower and Shumway (7). This technique entails an incision in the right atrium from the inferior vena cava toward the right atrial appendage to avoid sino-atrial node injury.

Statistics

Continuous data are presented as mean ± standard deviation (Gaussian distribution) or median [interquartile range (IQR)] (nonGaussian distribution). Categorical data are presented as frequencies (percentage).

Logistic mixed-effect models were used to assess probability of TR over time and investigate determinants of the longitudinal evolution over time. These models included random intercept and slope effects to capture the correlation of the repeated measurements in each patient. Natural splines with 2 knots placed at the 1st and 3rd quartiles were used to allow for flexibility of the subject-specific trajectories over time. Splines allow for non-linear trajectories over time. This is achieved by allowing a different spline-coefficient for each time interval defined by the knots (e.g. two knots define 3 such intervals). Survival probabilities were estimated and visualized by the Kaplan-Meier method. A joint model was developed to investigate determinants of mortality. More specifically, the mixed-effects model of TR and a relative risk model for the hazard of death (e.g. Cox model) were jointly modelled using shared-random effects. The subject-specific estimated longitudinal profiles were included in the relative risk model as predictors. Joint modelling has several benefits, such as the appropriate inclusion of endogenous covariates in relative risk models (TR), reduced bias and increased efficiency, while it can be used to derive dynamic predictions (8). At time point *t* one can investigate the effect of the current value of TR, the effect of the slope of TR (at which speed probability of TR is changing at time point *t*) and the cumulative effect of TR. Predictors were selected based upon clinical knowledge and availability. Left ventricle function, pacemaker, dialysis and number of rejection episodes after one year were included as exogenous time-varying covariates.

Global-local shrinkage priors were used for the regression coefficients of the relative risk sub-model for the selection of the current value of TR as predictor and this is presented in the article (Supplementary Table 1-3).

The longitudinal evolution of TR probability was correlated to the longitudinal evolution of creatinine by multivariate (multiple outcomes) mixed modelling. Correlation tests were done on the random effects D matrix.

Sensitivity analyses including both the mixed-effect model for right ventricle function and TR as predictors in the joint model and a model including year of surgery were performed in order the these the robustness of the estimates.

Missing baseline data used in the analyses was considered completely at random, and complete case analyses was performed. Creatinine at baseline had highest missing values (n=29, 5%). A. p-value <0.05 was considered statistically significant. Statistical analyses were done in

R (R core team 2017, Vienna, Austria) with the use of statistical packages "GLMMadaptive", "splines", "JointAI", "survival" and "JMbayes".

RESULTS

In total, 572 patients were included in this study. Baseline characteristics are presented in Table 1. Given the dynamic character of TR over time, baseline characteristics are not stratified on post-OHT TR grade. On average patients were 50 years old and 74.9% was male. Most frequently cyclosporine / prednisone (26.4%) and tacrolimus / prednisone (21.3%) are prescribed as immunosuppressive maintenance therapy. Median follow-up was 10.4 years (IQR: 6.4-15.3). Two patients were lost in follow-up, resulting in a completeness of 99.5% (C).

Table 1: Pre-, peri-, postoperative characteristics

Characteristics	N=572
Recipient Age (median, IQR)	50.23 [41.87, 56.32]
Donor age (median, IQR)	33.00 [22.00, 44.00]
Receiver female sex (n,%)	143 (25.1)
Donor female sex (n,%)	277 (49.0)
Primary diagnosis (n,%)	
Non ischemic	275 (49.4)
Ischemic	254 (45.6)
Other	28 (5.0)
Creatinine (median [IQR])	114.00 [93.00, 136.00]
Immunosuppression (n,%)	
Cyclosporine + azathioprine + prednisone	70 (12.3)
Cyclo+ MMF+ prednisone	32 (5.6)
Cyclosporine + prednisone	150 (26.4)
Tacrolimus+prednisone	121 (21.3)
tacrolimus+MMF	21 (3.7)
Other	175 (30.8)
Number of prior cardiac operations (n,%)	
0	415 (72.8)
1	125 (21.9)
2	26 (4.6)
3	4 (0.7)
Urgency (n,%)	
0	370 (65.1)
1	99 (17.4)
2	93 (16.4)

Table 1: Pre-, peri-, postoperative characteristics (continued)

Characteristics	N=572
3	6 (1.1)
Pre HTx diabetes (n,%)	35 (6.4)
Pre HTx mechical assistance (%)	
None	517 (92.8)
LVAD	33 (5.9)
ECMO	2 (0.4)
IABP	5 (0.9)
Ischemia time (median [IQR])	170.00 [143.00, 203.00]
Re-exploration for bleeding (n,%)	77 (13.5)
Dialysis* (%)	94 (16.8)
Pacemaker* (%)	70 (12.5)
Number rejection first year 1(median [IQR])	1.00 [1.00, 2.00]

*Number of patients that received a pacemaker or dialysis during follow up

Tricuspid regurgitation evolution

In total, 8826 echocardiograms were collected (range: 1-50, mean: 15.4) and all echocardiograms are used in the analyses. The model predicting the evolution of TR over time is presented in Table 2. Probability of TR changed over time, as indicated by the significant times estimates (Table 2). The evolution of the probability of moderate-to-severe TR over time, as estimated by the mixed-model, is presented in Figure 1. On average, approximately 32% of patients have moderate-to-severe TR immediately after surgery. However, this declines to approximately 11% after 5 years and 9% after 10 years of surgery. Pre-implant mechanical support was significantly associated with lower probability of moderate-to-severe TR during follow-up (Table 2). Additionally, a worse LV function at the time of the TR measurement was significantly associated with a higher probability of moderate-to-severe TR (Table 2). Strikingly, the number of rejections in the first year was not associated with a higher probability of moderate-to-severe TR.

Table 2: Estimates of logistic mixed-model part of the joint model to predict moderate-to-severe TR over time.

Variable	OR	95% CI	P value
Intercept	0.10	(0.01; 1.35)	0.090
Spline 1 of time[1]	0.23	(0.09; 0.56)	<0.001
Spline 2 of time[1]	0.03	(0.01; 0.13)	<0.001
Spline 3 of time[1]	0.18	(0.02; 1.22)	0.080
Receiver age	0.98	(0.95; 1.01)	0.138
Donor age	1.02	(0.99; 1.05)	0.114
Receiver female sex	0.77	(0.36; 1.59)	0.466
Donor female sex	1.66	(0.86; 3.18)	0.130

Table 2: Estimates of logistic mixed-model part of the joint model to predict moderate-to-severe TR over time. (continued)

Variable	OR	95% CI	P value
Ischemia time	0.96	(0.89; 1.04)	0.344
Cardiac reoperation	0.99	(0.56; 1.76)	0.952
Urgency 1 vs 0	1.40	(0.56; 3.55)	0.456
Urgency 2/3 vs 0	0.63	(0.27; 1.46)	0.322
No mechanical assistance prior HTx	6.29	(1.47; 27.31)	0.014
Pre HTx diabetes	0.60	(0.19; 1.94)	0.394
Number rejection first year	1.02	(0.88; 1.19)	0.742
Mildly impaired LV function vs normal[2]	1.73	(1.32; 2.31)	<0.001
Moderately impaired LV function vs normal[2]	4.03	(2.29; 7.18)	<0.001
Severely impaired LV function vs normal[2]	9.54	(2.82; 38.46)	<0.001
Pacemaker[2]	1.12	(0.59; 2.07)	0.718
Creatinine	1.00	(1; 1.01)	0.374

1: Time was modelled in an non-linear way with a spline function. CI: confidence interval, OR: odds ratio. 2: At the time of TR measurment (time-varying covariate)

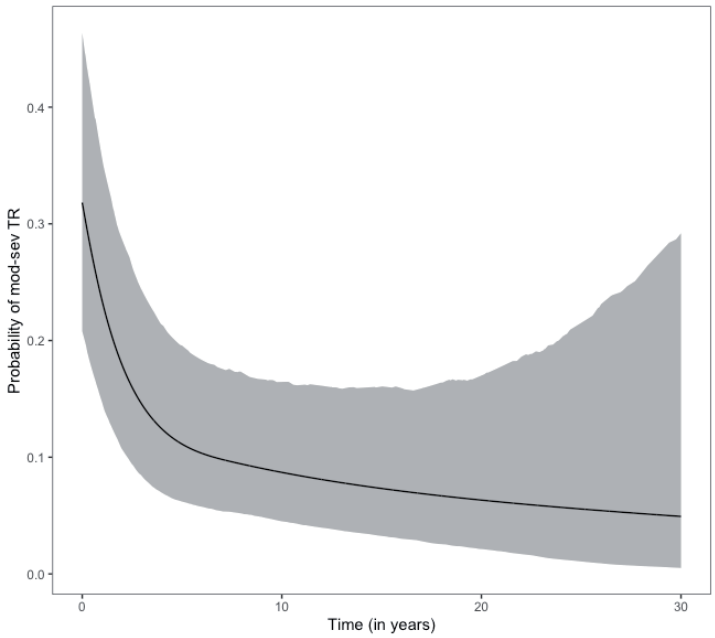

Figure 1: The marginal probability of moderate-to-severe TR during follow-up for an average patient.

Mortality

During follow-up 357 patients died of which 5 (0.9%) within 30 days. Survival at 1, 5, 10, 20 years was 97±1%, 88±1%, 66±2% and 23±2%, respectively (Figure 2). The presence of moderate-to-severe TR during follow-up was associated with higher mortality (Table 3). Table 3 presents the estimates of the joint model. A higher age, the presence of pre-OHT diabetes, recipient female sex and dialysis were significantly associated with mortality during follow-up. Moderate-to-severe TR remained significant a sensitivity analyses in which left ventricular dysfunction was incorporated in the Cox model as time-varying covariate (Supplementary Table 4).

Figure 3ab presents a dynamic survival probability plot for two patients. The first patients developed moderate-to-severe TR after approximately 3 years. At this moment, the survival probability of 10 years later is estimated to be 77% (Figure 3a). The second patient did not develop moderate-to-severe TR at 3 years, and the survival probability of 10 years later for this patients is estimated to be 81% (Figure 3b).

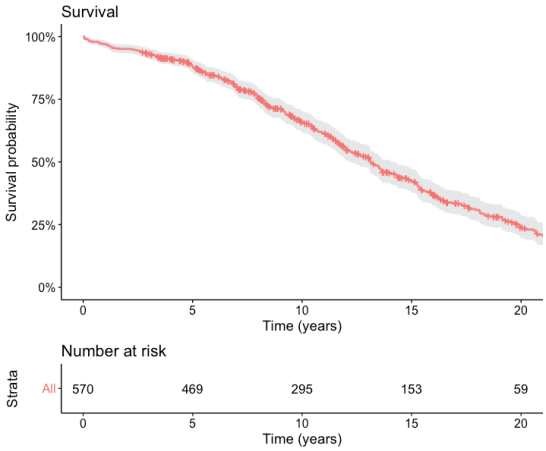

Figure 2: A Kaplan-Meier curve of overall survival.

Table 3: Estimates of the joint-model survival part

Variable	HR	95% CI	P value
Receiver age	1.04	(1.03; 1.06)	<0.001
Receiver female sex	1.44	(1.02; 2.03)	0.046
Donor female sex	1.05	(0.78; 1.44)	0.768
Ischemia time	1.00	(1; 1.01)	0.064
Cardiac reoperation	1.22	(0.91; 1.6)	0.174
Urgency1 vs 0	0.90	(0.61; 1.31)	0.590
Urgency2 vs 0	0.78	(0.48; 1.22)	0.270
Urgency3 vs 0	12.26	(2.32; 55.12)	0.012
No mechanical assistance prior HTx	0.75	(0.28; 2.19)	0.580

Table 3: Estimates of the joint-model survival part (continued)

Variable	HR	95% CI	P value
Donor Age	0.99	(0.98; 1.01)	0.372
Non-ischemic CMP vs ischemic	1.17	(0.82; 1.66)	0.364
Other diagnosis vs ischemic	1.15	(0.55; 2.15)	0.668
Pre HTx diabetes	2.30	(1.3; 3.8)	<0.001
Creatinine	1.00	(1.00; 1)	0.096
Pacemaker[1]	1.00	(0.64; 1.52)	0.972
Dialysis[1]	1.81	(1.27; 2.5)	0.002
Mod-sev TR	1.07	(1.02; 1.13)	0.006

1: Time-varying covariate

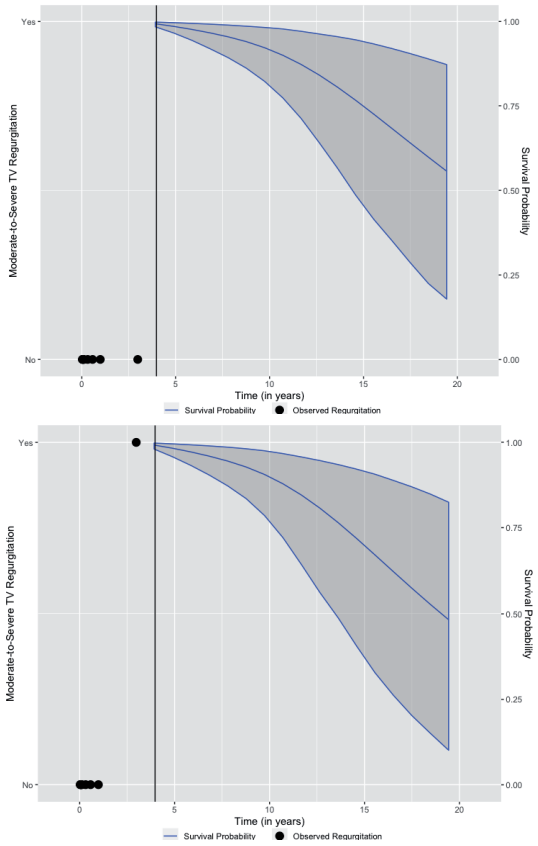

Figure 3ab: A dynamic plot of two patients (A and B). Patient A develops TR after 3 years and patient B does not develop TR after 3 years.

Kidney function

Creatinine was collected at 4426 times simultaneously with an echocardiogram. The longitudinal evolution of creatinine is presented in Figure 4 as estimated by a mixed-model containing only the variable time with a spline function.

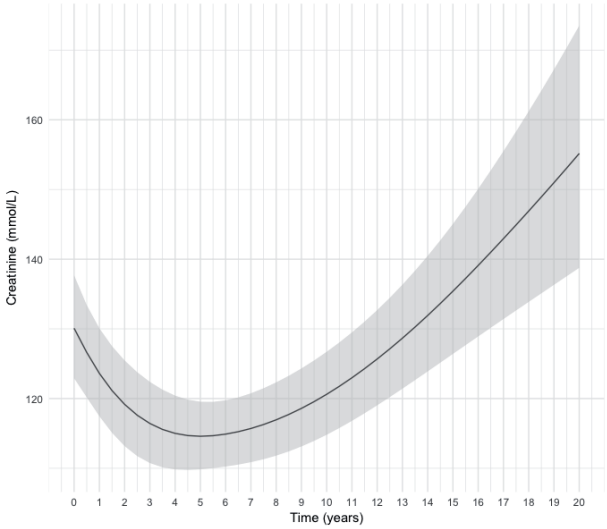

Figure 4: The predicted evolution of creatinine after HTx

The random slope of moderate-to-severe TR was highly positively correlated to the slope of creatinine (R = 0.45), meaning that if the probability moderate-to-severe TR increases, creatinine levels also increase in an individual patient. The intercept (starting point) of TR was not highly correlated the intercept (starting point) of creatinine (R = 0.04). The correlation matrix is shown in Supplementary Table 5.

The current value of post-OHT moderate-to-severe TR was found to be predictive for dialysis dependence (HR 1.21 95% CI [1.04 to 1.44], *P* = 0.012) as estimated by a simple joint-model adjusting for baseline creatinine, sex and age (Supplementary Table 6).

Sensitivity analyses

In a multivariate joint model including both the longitudinal evolution of dichotomized right ventricle function and of moderate-to-severe TR, only moderate-to-severe TR was found to be a significant predictor of mortality, whereas right ventricle function was not. It has to be noted that right ventricle function was only recorded in 1216 of 8826 echocardiograms leaving relatively little data for the analyses (Supplementary Table 7-8). Including year of surgery in the model of longitudinal evolution and Cox model did not change the significance or estimate of the longitudinal predictor of moderate-to-severe TR for mortality (Supplementary Table 9 – 10).

DISCUSSION

This study investigated the long-term course of moderate-to-severe TR and its impact on mortality and renal function. We found that moderate-to-severe TR during follow-up was associated with higher mortality and progressive decline of renal function. Specifically, moderate-to-severe TR was found to be a risk factor for dialysis. To the authors knowledge, this is the first study that accounts for the dynamic nature of TR during follow-up.

TR evolution

The etiology of TR after OHT is multifactorial in nature (3). In older studies higher pulmonary pressures after OHT and endomyocardial biopsies were mainly found to be associated with TR (3, 9-11). Furthermore, the biatrial surgical technique is found to be associated with more TR in multiple studies (12).

In our study, left ventricular dysfunction at the time of TR measurement was significantly associated with the higher probabilities of moderate-to-severe TR, probably because worse LV function causes higher pulmonary pressures, subsequently leading to RV dysfunction and dilatation, leading to functional TR. Moreover, we noted that patients who have mechanical assistance (LVAD, ECMO, IABP) prior OHT have a lower probability of post-OHT moderate-to-severe TR. It has been observed that left ventricular assist devices effectively unload the left ventricle and reduce pulmonary pressures (13). Hence, patients with pre-OHT mechanical assistance will probably have lower pulmonary pressures, resulting in less right ventricle dysfunction, annulus dilation and, secondary TR immediately after OHT.

Other studies noted initially a decrease in TR severity after OHT, but a relative increase later in follow up, or even a gradual increase in TR over time (5, 11, 14). This study did not replicate these results. Nevertheless, change over time was not significantly decreasing over time later in follow-up. The results of prior studies can partly be explained by the used methodology, which does not take into account the correlations within patients vs between patients nor does take into account the dropout of patients (either due to death or censoring), whereas the joint modeling framework does take these phenomena into account.

Mortality & Morbidity

In this cohort we only included patients with a follow-up echocardiogram, as the focus was on evolution of TR. Previously we reported the outcomes of the entire cohort (15). In patient who die early an echocardiogram may not be performed or TR in this echocardiogram is not recorded, explaining the low 30-day mortality (0.9%) in this subset of the entire cohort (Supplementary Figure 1).

Previous studies noted that TR at discharge was associated with impaired late morality (5, 16). Two other studies examined late TR and noted contradicting results in regard to the association with mortality (14, 17). This study models the dynamic nature of TR over time and

the association with mortality. During follow-up developing TR is associated with higher probability of mortality. The dynamic predictions estimated that developing TR at 3 years after OHT is paired with a 4% reduction in survival 10 years later compared to a patient who does not develop TR, given that all the other variables are similar.

The observed association of TR with mortality does not inherently imply a causal association. An important factor in in this interplay is right ventricular dysfunction. In a sensitivity analyses right ventricle function was not found to be a significant predictor of mortality. However, eyeballing the right ventricle function is difficult and the analyses be underpowered to detect differences. Moreover, it is complicated to make causal inference in regard to right ventricular dysfunction and TR due to their circular relationship; TR leads to right ventricular dysfunction, which leads to dilatation, in turn leading to more TR. One needs to backtrack which phenomena starts first and starts the negative spiral, which is difficult to do in retrospective studies. Nevertheless, previous studies claim that it is the TR that may lead to right ventricular dysfunction (1, 14, 18).

Moreover, we could also link the longitudinal evolution of TR probabilities to the longitudinal evolution of creatinine. Previous studies also found an association between renal function and TR (17). It is still debatable whether it is the TR or right ventricular dysfunction causing the renal dysfunction, however TR may contribute to renal dysfunction by increasing venous congestion (19) and the combination of TR and right ventricular dysfunction is found to predictive of impaired renal function (20). Furthermore, in a recent study Karam et al. noted stabilization of renal function and improvement of liver function in patients undergoing transcatheter tricuspid valve repair, suggesting a beneficial effect of eliminating TR (21).

Clinical implications

In most cases symptomatic TR is managed with usual heart failure treatments, but in refractory cases a surgical intervention becomes necessary (1). Literature regarding surgery for TR after OHT is scarce. Nevertheless, it has been shown that surgery in these patients can be performed safely (22, 23). The authors who linked discharge TR to impaired survival suggest to surgically intervene if TR is not resolved by discharge (5). However, our data shows that it may be reasonable to wait longer, as probability of TR continues to decrease after discharge, and TR usually remains asymptomatic for years (4). Notwithstanding, our data shows that after approximately five years post-OHT the decrease probability of moderate-to-severe TR negates. In patients with persistent TR at five years post-OHT surgical intervention may be most beneficial, assuming the association of TR and mortality / renal function is causal in nature.

A small randomized clinical trial (n=60) in which patients received either prophylactic tricuspid annuloplasty vs. no annuloplasty concomitant to OHT noted a better cardiac survival in the annuloplasty groups, if they combined early and late deaths (18). No overall survival difference was noted. Furthermore, opportunities arise with emerging trans-catheter devices to treat TR, since this population may be an interesting potential target population for trans-

catheter approaches (25). However, these devices still need to be validated in this complex subgroup of patients. Other authors advocate the use of bicaval anastomosis by default to prevent TR in the first place (6, 24).

Strengths and limitations

The major advantage of this study is that we were able to collect 8826 echocardiograms, enabling us to use advanced statistical methods to model the dynamic nature of TR and making less biased inference of the impact of TR during follow-up on mortality. Several limitations apply to this study common in retrospective analyses. We did not consider cardiac allograft vasculopathy (CAV) explicitly in this study since CAV is diagnosed by coronary angiography and, therefore, there is a delay between development and diagnosis of CAV. Nevertheless, CAV manifests as LV dysfunction, which we were able to analyze, hence CAV is implicitly considered. Patients who died without an TR measurement on echocardiogram were excluded, which can introduce selection bias. Assessing TR remains challenging, but we dichotomized this variable to create a more robust measurement. Moreover, we it was not possible to determine the cause of TR (e.g. biopsy related vs functional). Lastly, LV function, pacemaker and dialyses were incorporated in the models as a time-varying exogenous variable, while in fact these variables are more likely to be endogenous.

Conclusions

TR during follow-up is significantly associated with higher mortality and progressive decline of renal function / end-stage renal failure. Nevertheless, probability of TR is the highest immediately after OHT and decreases thereafter. Therefore, it may be reasonable to refrain from surgical intervention during early phase after OHT with bi-atrial anastomoses.

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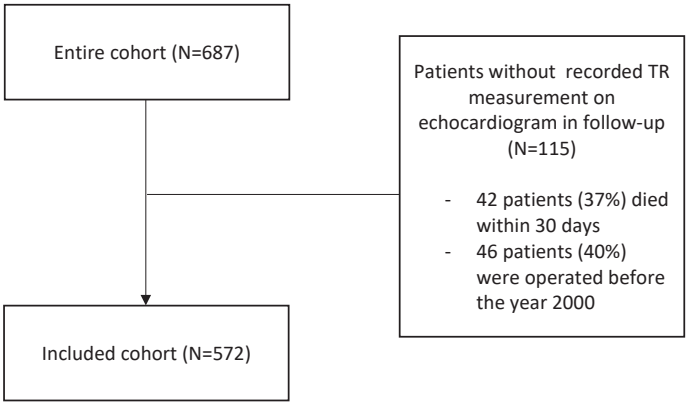
SUPPLEMENTARY MATERIAL

CONTENTS



Supplementary Figure 1: Flowchart of included patients.

Supplementary table 1: Estimates of the relative hazard model (cox) in the joint-model using the horseshoe global-local shrinkage prior and value, slope and area under the curve association structures.

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.050
Receiver female sex	1.25	(0.95; 1.77)	0.186
Donor female sex	1.03	(0.86; 1.26)	0.820
Ischemia time	1.00	(1; 1.01)	0.036
Cardiac reoperation	1.17	(0.95; 1.53)	0.198
Urgency1 vs 0	0.98	(0.73; 1.22)	0.870
Urgency2 vs 0	0.89	(0.56; 1.18)	0.544
Urgency3 vs 0	6.98	(1.02; 26.60)	0.042
No mechanical assistance prior HTx	0.83	(0.32; 1.23)	0.608
Donor Age	0.99	(0.98; 1.01)	0.404
Non-ischemic CMP vs ischemic	1.05	(0.86; 1.38)	0.656
Other diagnosis vs ischemic	1.09	(0.81; 1.75)	0.710
Pre HTx diabetes	2.17	(1.16; 3.79)	0.010
Creatinine	1.00	(1; 1)	0.026
Pacemaker[1]	1.02	(0.80; 1.36)	0.888
Dialysis[1]	1.64	(1.09; 2.30)	0.020
Mod-sev TR (value)	1.07	(1.01; 1.15)	0.010
Mod-sev TR (slope)	0.97	(0.35; 1.95)	0.978
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.046

Supplementary table 2: Estimates of the relative hazard model (cox) in the joint-model using the ridge global-local shrinkage prior and value, slope and area under the curve association structures. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.060
Receiver female sex	1.41	(0.97; 1.97)	0.066
Donor female sex	1.04	(0.76; 1.42)	0.802
Ischemia time	1.00	(1; 1.01)	0.064
Cardiac reoperation	1.22	(0.90; 1.62)	0.188
Urgency1 vs 0	0.93	(0.63; 1.38)	0.722
Urgency2 vs 0	0.76	(0.47; 1.21)	0.232
Urgency3 vs 0	7.57	(1.42; 32.30)	0.022
No mechanical assistance prior HTx	0.63	(0.24; 1.68)	0.308
Donor Age	0.99	(0.98; 1.01)	0.302
Non-ischemic CMP vs ischemic	1.14	(0.84; 1.61)	0.402
Other diagnosis vs ischemic	1.15	(0.59; 2.07)	0.618
Pre HTx diabetes	2.45	(1.53; 3.96)	0.002
Creatinine	1.00	(1; 1)	0.040
Pacemaker[1]	1.03	(0.66; 1.56)	0.902
Dialysis[1]	1.78	(1.21; 2.49)	0.006
Mod-sev TR (value)	1.09	(1.02; 1.15)	0.006
Mod-sev TR (slope)	0.95	(0.53; 1.42)	0.770
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.050

Supplementary table 3: Estimates of the relative hazard model (cox) in the joint-model using value, slope and area under the curve association structures but with no shrinkage. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.01	(1.00; 1.03)	0.158
Receiver female sex	1.44	(0.96; 2.12)	0.074
Donor female sex	1.03	(0.76; 1.43)	0.904
Ischemia time	1.00	(1; 1.01)	0.112
Cardiac reoperation	1.24	(0.91; 1.70)	0.218
Urgency1 vs 0	0.92	(0.62; 1.37)	0.720
Urgency2 vs 0	0.77	(0.44; 1.22)	0.308
Urgency3 vs 0	8.74	(1.39; 48.33)	0.028
No mechanical assistance prior HTx	0.67	(0.23; 2.15)	0.474
Donor Age	0.99	(0.98; 1.01)	0.348
Non-ischemic CMP vs ischemic	1.15	(0.81; 1.67)	0.442
Other diagnosis vs ischemic	1.12	(0.56; 2.15)	0.752
Pre HTx diabetes	2.52	(1.46; 4.22)	<0.001
Creatinine	1.00	(0.99; 1)	0.070
Pacemaker[1]	1.01	(0.65; 1.50)	0.918

Supplementary table 3: Estimates of the relative hazard model (cox) in the joint-model using value, slope and area under the curve association structures but with no shrinkage. 1: exogenous time-dependent covariate (continued)

Variable	HR	95% CI	P value
Dialysis[1]	1.83	(1.26; 2.64)	0.002
Mod-sev TR (value)	1.12	(1.03; 1.22)	0.010
Mod-sev TR (slope)	0.53	(0.07; 3.27)	0.546
Mod-sev TR (area)	1.00	(1.00; 1.00)	0.046

Supplementary table 4: Estimates of the relative hazard model (cox) in the joint-model with left vertical function as time-varying covariate predicting mortality. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1.04	(1.03; 1.06)	<0.001
Receiver female sex	1.16	(0.84; 1.64)	0.344
Donor female sex	1.37	(1.03; 1.82)	0.04
Ischemia time	1.00	(1; 1)	0.534
Cardiac reoperation	1.49	(1.08; 2.03)	0.012
Urgency1 vs 0	1.16	(0.78; 1.78)	0.436
Urgency2 vs 0	0.80	(0.49; 1.3)	0.356
Urgency3 vs 0	11.69	(2.08; 45.83)	0.018
No mechanical assistance prior HTx	1.66	(0.63; 4.58)	0.296
Donor Age	0.98	(0.97; 0.99)	<0.001
Non-ischemic CMP vs ischemic	1.19	(0.85; 1.62)	0.272
Other diagnosis vs ischemic	0.92	(0.48; 1.75)	0.764
Pre HTx diabetes	1.43	(0.85; 2.27)	0.136
Creatinine	1.00	(1; 1)	0.658
Pacemaker[1]	0.99	(0.66; 1.45)	0.932
Dialysis[1]	1.37	(0.94; 2.03)	0.102
Moderately/severe LV function vs normal[1]	110.23	(53.51; 252.98)	<0.001
Mod-sev TR	1.07	(1.02; 1.12)	0.008

1: Time-varying covariate

Supplementary table 5: Random correlation matrix of the multivariate longitudinal model with creatinine and tricuspid regurgitation. Random effect were: intercept for patients and slope over time in both models. No splines were added in the random effects for time in order to enhance interpretability.

	Intercept TR	Random slope TR	Random slope creatinine	Intercept creatinine
Intercept TR	1	X	X	X
Random slope TR	0.1791	1	X	X
Random slope creatinine	-0.6112	0.4540	1	X
Intercept creatinine	0.0464	0.0775	-0.5634	1

Supplementary table 6: Estimates for the relative hazard model (cox) a in the joint model predicting dialysis.

Variable	OR	95% CI	P value
Reciever Age	0.99	(0.97; 1.02)	0.546
Baseline creatinine	1.00	(0.99; 1.01)	0.784
Receiver female sex	0.58	(0.26; 1.21)	0.150
Moderate-to-severe TR	1.21	(1.04; 1.44)	0.012

Supplementary table 7: Estimates for the relative hazard model (cox) a in the joint model predicting mortality, with both longitudinal evolution of right ventricular function and moderate-to-severe TR as predictor. The current value parametrization was used in both predictors. 1: exogenous time-dependent covariate

Variable	HR	95% CI	P value
Receiver age	1,04	(1; 1,07)	0.028
Receiver female sex	1,64	(0,87; 3,27)	0.12
Donor female sex	0,92	(0,45; 1,81)	0.82
Ischemia time	1,01	(1; 1,01)	0.026
Cardiac reoperation	1,08	(0,57; 1,97)	0.82
Urgency1 vs 0	0,34	(0,12; 0,86)	0.020
Urgency2 vs 0	0,37	(0,14; 0,94)	0.036
Urgency3 vs 0	3,50	(0,22; 34,2)	0.32
No mechanical assistance prior HTx	0,40	(0,08; 2,53)	0.33
Donor Age	1,00	(0,97; 1,03)	0.84
Non-ischemic CMP vs ischemic	1,06	(0,57; 1,95)	0.85
Other diagnosis vs ischemic	1,17	(0,15; 7,83)	0.88
Pre HTx diabetes	3,16	(1,32; 7,08)	0.012
Creatinine	1,00	(0,99; 1,01)	0.93
Pacemaker[1]	1,03	(0,46; 2,22)	0.95
Dialysis[1]	2,44	(1,16; 4,95)	0.014
Right ventricle dyfunction	1,02	(0,93; 1,13)	0.63
Mod-sev TR	1,06	(1,02; 1,12)	0.002

Supplementary table 8: Estimates for the logistic mixed-effects model part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate

Variable	Log(OR)	Log(95% CI)	P value
Intercept	-3,24	(-15,24; 23.964)	0.736
Spline 1 of time[1]	-2,24	(-4,613; -0.245)	0.026
Spline 2 of time[1]	-9,60	(-13,239; -6.197)	<0.001
Spline 3 of time[1]	-8,45	(-13,605; -4.063)	<0.001
Receiver age	-0,05	(-0,095; -0.004)	0.028
Donor age	0,04	(-0,004; 0)	0.064
Receiver female sex	-1,23	(-2,502; -)	0.042

Supplementary table 8: Estimates for the logistic mixed-effects model part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate (continued)

Variable	Log(OR)	Log(95% CI)	P value
Donor female sex	1,01	(-0,08; 2.156)	0.064
Ischemia time	-0,01	(-0,025; 0)	0.096
Cardiac reoperation	0,10	(-0,796; 1.004)	0.84
Urgency 1 vs 0	0,96	(-0,39; 2.371)	0.18
Urgency 2/3 vs 0	0,03	(-1,286; 1.441)	0.96
No mechanical assistance prior HTx	5,43	(1,779; 9.868)	0.006
Pre HTx diabetes	-0,37	(-2,194; 1.495)	0.69
Number rejection first year	0,08	(-0,2; 0.342)	0.50
Mildly impaired LV function vs normal[2]	0,27	(-0,194; 0.714)	0.26
Moderately impaired LV function vs normal[2]	1,54	(0,676; 2.359)	0.002
Severely impaired LV function vs normal[2]	4,31	(2,26; 6.859)	<0.001
Pacemaker[2]	-0,56	(-2,257; 1.264)	0.50
Creatinine	0,01	(0,001; 0.024)	0.044
Year of surgery	-0,01	(-0,016; 0.004)	0.32

Supplementary table 9: Estimates for relative hazard model (cox) part from the joint model predicting mortality with year as predictor. 1: exogenous time-dependent covariate

Variable	OR	95% CI	P value
Receiver age	1,04	(1,02; 1,06)	<0.001
Receiver female sex	1,49	(1; 2,19)	0.046
Donor female sex	1,09	(0,78; 1,49)	0.60
Ischemia time	1,00	(1; 1,01)	0.098
Cardiac reoperation	1,24	(0,91; 1,67)	0.18
Urgency1 vs 0	0,83	(0,53; 1,27)	0.39
Urgency2 vs 0	0,80	(0,45; 1,35)	0.38
Urgency3 vs 0	10,67	(1,26; 56,75)	0.034
No mechanical assistance prior HTx	0,59	(0,21; 1,91)	0.36
Donor Age	0,99	(0,98; 1,01)	0.33
Non-ischemic CMP vs ischemic	1,18	(0,8; 1,67)	0.36
Other diagnosis vs ischemic	1,05	(0,52; 2,13)	0.90
Pre HTx diabetes	2,27	(1,3; 4)	0.004
Creatinine	1,00	(0,99; 1)	0.096
Pacemaker[1]	0,99	(0,61; 1,58)	0.94
Dialysis[1]	1,75	(1,19; 2,53)	0.004
Year of surgery	1,00	(1.00; 1.00)	0.14
Mod-sev TR	1,06	(1,02; 1,12)	0.006

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Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review

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EHJ, August 2019

ABSTRACT

Tricuspid regurgitation (TR) is a frequent and complex problem, commonly combined with left-sided heart disease, such as mitral regurgitation. Significant TR is associated with increased mortality if left untreated or recurrent after therapy. Tricuspid regurgitation was historically often disregarded and remained undertreated. Surgery is currently the only Class I Guideline recommended therapy for TR, in the form of annuloplasty, leaflet repair, or valve replacement. As growing experience of transcatheter therapy in structural heart disease, many dedicated transcatheter tricuspid repair or replacement devices, which mimic well-established surgical techniques, are currently under development. Nevertheless, many aspects of TR are little understood, including the disease process, surgical or interventional risk stratification, and predictors of successful therapy. The optimal treatment timing and the choice of proper surgical or interventional technique for significant TR remain to be elucidated. In this context, we aim to highlight the current evidence, underline major controversial issues in this field and present a future roadmap for TR therapy.

INTRODUCTION

Tricuspid regurgitation (TR) is commonly detected on echocardiography.[1] Moderate/severe TR is associated with an increased risk for cardiac and all-cause mortality.[2,3] A recent meta-analysis demonstrated that moderate/severe TR is associated with a two-fold increased mortality risk compared with no/mild TR, which seems to be independent of pulmonary pressures and right heart failure (HF).[4] Topilsky et al.[5] reported that quantitative measures of TR were associated with increased mortality in patients with left ventricular (LV) systolic dysfunction. These evidences may push towards an earlier indication of correction of TR.

Tricuspid regurgitation remains undertreated as a result of our limited understanding of the disease and how to quantify it.[6–8] Surgery is currently the only Class I Guideline Recommended therapy for TR,[9,10] which is most often performed during left-sided heart surgery. Previous estimates indicate that <1% of patients undergo tricuspid valve (TV) surgery.[11] The operative mortality of isolated TV surgery could be high due to the late referral, multiple comorbidities, and right ventricle (RV) remodelling.[12,13] Due to the paucity of evidence, American and European guideline recommendations for the management of TR are limited, and the timing for surgical intervention is still debated.[9,10] As the management of valvular heart disease moves towards less invasive surgical and transcatheter therapies, several techniques and devices are applied to the TV.[14,15] Nevertheless, many aspects of TR are little understood. In this context, we aim to highlight controversial issues and present a future roadmap for TR therapy.

PATHOPHYSIOLOGY OF TRICUSPID REGURGITATION AND RATIONALE FOR THERAPY

With the growing incidence of atrial fibrillation,[16] the use of intracardiac devices,[17] and the global epidemic of valvular heart disease, the prevalence of TR is likely to increase.[18] Recently, Topilsky et al.[19] reported the prevalence of TR (0.55%) in a community setting which was about one-fourth of all left-sided valve disease and similar to the prevalence of aortic stenosis. The distribution pattern of TR was primary in 14.6% and secondary in 85.4% of patients.[19] Primary TR results from primary abnormalities of the TV apparatus and can be divided into congenital and acquired disease. The latter may include rheumatic disease, carcinoid disease, infective endocarditis, degenerative, or iatrogenic disease from implantable device lead-induced TV injury/dysfunction or RV endomyocardial biopsy.[20] Secondary TR is due to annular dilatation (with or without leaflet tethering) or RV dilatation (typically associated with leaflet tethering), with left-sided heart disease and/or pulmonary hypertension being the most frequent aetiologies.[20,21] The disease process of TR is not fully understood and is likely influenced by the underlying aetiology, concomitant heart disease, and haemodynamic abnormalities.[22] Age,

presence of device leads, mild TR at baseline, and receiving left-sided valvular surgery (without concomitant TV surgery) have been shown as predictors of development of significant TR.[23]

Currently, long-term data on the beneficial effect of isolated surgical TV therapy compared to medical therapy remains scarce.[24] According to data from theNational Inpatient Sample files from 2004 to 2013 in the USA, isolated TV surgery was performed in 15% of all patients who underwent TV surgery, with high in-hospital mortality rate (8–10%) that has remained unchanged over the 10-year period.[12,13] This suboptimal outcome is likely related to comorbidities and referral timing rather than to the risk of isolated TV surgery.[25,26] Furthermore, residual or late significant TR after mitral valve replacement is independently associated with poor outcome.[27] Adding TV repair during left-sided heart surgery did not increase surgical risk and could result in reverse RV remodelling with reduction of symptoms.[28–30] Therefore, a more aggressive approach to correct concomitant TR in the presence of annular dilatation may reduce the chance of late TR progression after left-sided valve surgery.

SPECIFIC ANATOMICAL CONSIDERATIONS INTERFERING WITH TRICUSPID VALVE

The TV is a complex apparatus consisting of leaflets, tricuspid annulus, tendinous cords, papillary muscles, and the associated RV. The normal tricuspid annulus is a saddle-shaped ellipsoid surrounded by several critical anatomical structures, including the atrioventricular node, right coronary artery, coronary sinus ostium, and non-coronary sinus of Valsalva (Figure 1A). Multiple TV structural abnormalities may be encountered as a result of different aetiologies with various morphological changes. Tricuspid annulus dilation, right atrium/RV dilation, and leaflet malcoaptation are the most common changes in secondary TR.When tricuspid annulus dilation occurs, its shape becomes more circular and planar (Figure 1B).[31,32] It is usually observed in the anatomical location of anterolateral free wall and posterior border. Leafletmalcoaptation may occur due to inadequate leaflet length to cover the dilated annulus, or in the absence of adequate chordal redundancy resulting in leaflet tethering. The region of malcoaptation occurs often centrally or extends from the anteroseptal commissure towards the posteroseptal commissure.[32,33]

GUIDELINE RECOMMENDATIONS FOR TRICUSPID REGURGITATION THERAPY

Tricuspid regurgitation often presents as a component of a complex heart disease and its clinical manifestations range from subtle symptoms to advanced HF with multiorgan involvement. At the far end of the disease spectrum, there may be a point of no return where irreversible

RV dysfunction persists regardless of therapy. Therefore, a timely therapy is essential to avoid worsening of causative pathology and the onset of complications caused by TR. However, the indication and optimal timing of surgery remain controversial due to insufficient evidence.

The comparison of the American[32] and the European guidelines[9] for the management of TR is provided in the Supplementary material online, Table S1. In both guidelines, most of the Classes I and IIa indications for intervening on significant TR require concomitant leftsided valve surgery. Isolated TV surgery is recommended in patients with severe TR who are either symptomatic or are developing progressive RV dilatation/dysfunction.[9] Nevertheless, patients with severe TR are often asymptomatic for a long period of time and symptoms are not specific, contributing to late referral for surgery.[34] Recently, an extended five-stage classification of secondary TR was proposed to help categorize the severity of disease presenting late in the disease process.[15] Symptoms, severity of TR, leaflet coaptation, tethering, annular remodelling, and RV function need to be evaluated to determine the timing and options of treatment.

On the other hand, the 'optimal medical treatment' has not yet been defined for right-sided HF. Recently, the American Heart Association released a scientific statement on evaluation and management of right-sided HF.[35] Based on the document, medical treatment of right-sided HF should focus on volume management (diuretics and renal replacement therapies), afterload reduction (pulmonary vasodilators) and, if needed, mechanical circulatory support.

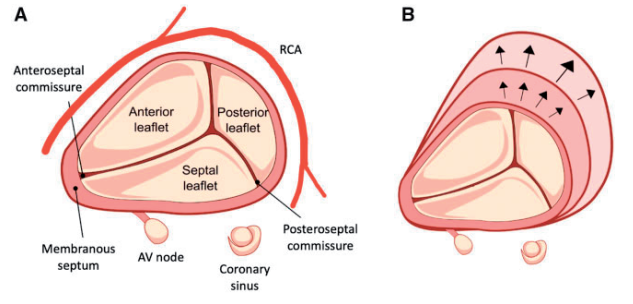


Figure 1. Anatomical structure of the tricuspid valve. (A) Normal and (B) dilated tricuspid annulus.

RISK STRATIFICATION AND HEART TEAM DECISION-MAKING

In the past decades several models were developed to predict outcome in cardiac surgery.[36] Nevertheless, until recently, no specific risk model addressed isolated TV surgery. LaPar et al.[37] used the Society of Thoracic Surgeons (STS) database to develop a risk score for patients undergoing TV surgery. They included age, sex, stroke, haemodialysis, LV ejection fraction, chronic lung disease, New York Heart Association functional class, reoperation, and operative characteristics in their models. Although the authors developed well-discriminated and calibrated models, they could not include indices of RV dysfunction and liver dysfunction, because these

data were simply not collected. Testing these models will require large clinical datasets, however, datasets like the STS database are currently designed for the majority of patients (with left-sided valve surgery) and do not specifically address the right heart.[38] Therefore, we propose a standardized approach and risk stratification process for heart team decision-making. Our proposed stepwise assessment is as follows (Take home figure):

Step 1: Patient demographics (age and sex).

Step 2: Clinical symptoms (New York Heart Association functional class).

Step 3: Comorbidities [stroke, major organ dysfunction (lung, kidney, and liver)].

Step 4: Cardiac pathological remodelling (TR severity, local remodelling of TV, RV remodelling, pulmonary vascular resistance, and left-sided heart disease).

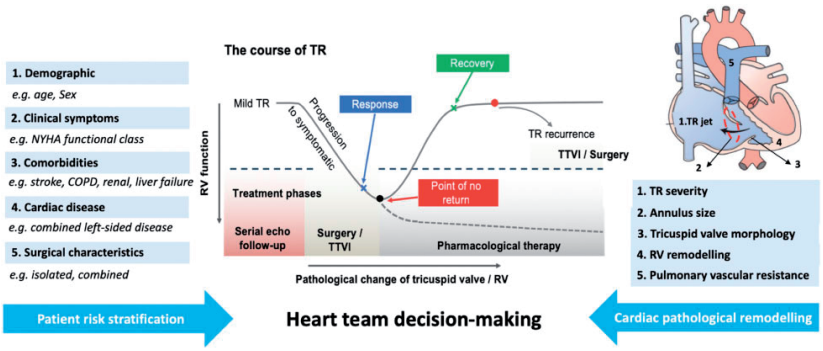
Step 5: Surgical or interventional characteristics (isolated, combined, elective, or emergent).

Step 6: Combining 3R's (Risk, Reversibility, and Recurrence) information to allocate patient profiles.

Step 7: Decision-making by the multidisciplinary heart team to provide appropriate treatment (surgical, minimal invasive surgical, transcatheter, pharmacological, or palliative).

IMAGING ASSESSMENT FOR TRICUSPID REGURGITATION TREATMENT

Imaging assessment for TR treatment runs in three phases: (i) patient assessment for decision-making; (ii) peri-operative/peri-interventional planning and guidance; and (iii) assessing therapeutic efficacy and durability during follow-up.



Take home figure. Heart team decision-making for treatment of tricuspid regurgitation. COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; RV, right ventricle; TR, tricuspid regurgitation; TTVI, transcatheter tricuspid valve intervention.

Imaging for decision-making in patients with tricuspid regurgitation

A stepwise approach using multimodality imaging to assessment of TR is shown in Table 1. First, determining the presence of TR, as well as the TV morphology and aetiology. Second is to evaluate TR severity. Third is to assess the haemodynamic impact in terms of regurgitant volume and coexisting pressure overload. Fourth is to identify the presence (and severity) of associated left-sided heart disease. Finally, to assess the presence (and severity) of RV remodelling. Two-dimensional echocardiography, including tissue Doppler imaging and RV strain, is currently the most widely used imaging modality (Table 2). Three-dimensional techniques such as three-dimensional echocardiography, cardiovascular magnetic resonance, or multislice computed tomography are powerful tools for assessing the TV annulus, as well as the RV and LV size and global function.[39]

The current echocardiographic criteria for grading TR only consider three grades of severity: mild, moderate, and severe.[40] In the SCOUT trial,[41] despite the severity of TR reduced from 'severe' to 'severe', the equivalent quantitative reduction of a 'grade' of TR was associated with an increase in stroke volume and improved quality of life. Therefore, an extended five-grade scale of 'mild, moderate, severe, massive, and torrential' has been proposed to accommodate

Table 1. Five-stepwise approach for evaluations of patients with suspected or established tricuspid regurgitation

Target	Imaging modalities needed to evaluate
Tricuspid valve morphology (TV annulus dilatation and leaflet tethering)	TTE and TOE (2DE and 3DE)
TR severity	2DE/3DE with Doppler, CMR if unclear
Haemodynamic impact	2DE with Doppler
Preload (RV filling)	2DE and M-mode for longitudinal function
Afterload (pulmonary atrial pressure and pulmonary vascular resistance) RV size and function	3DE for RV volumes
Left-sided heart disease	2DE/3DE
Right heart remodelling and function	Ideally 3D modality for RV size and function CMR or 4D MSCT or 3DE > 2DE 3DE >> 2DE For preclinical studies and first-in-man studies or small efficacy studies, CMR and 4D CT may be appropriate. For Large studies and routine care, 3DE is good alternative

2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiog-raphy; CMR, cardiovascular magnetic resonance; MSCT, multislice computed tomography; RV, right ventricle; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

the large variability amongst patients with severe TR.[42] Moreover, recent publications have shown that the current cut-off values for quantitative parameters used to assess TR severity are inadequate to quantify the burden on the RV and it is likely that lower threshold values of

effective regurgitant orifice area (EROA) and regurgitant volume define severe TR.[43] This finding was also supported by the study of Bartko et al.[44] showing a significant increase in mortality and morbidity for EROA ≥0.2 cm^2 and regurgitant volume ≥20mL in HF patients with reduced ejection fraction. This may potentially impact the therapeutic decision-making, particularly timing for intervention.

Table 2. Advantages and limitations of imaging modalities in TR assessment

Imaging technique	Main advantages	Main limitations
2DE	Real-time, versatile, high frame rate	Insufficient for 3D complex structures such as TV annulus, LV, and RV size and function
3DE	Both simultaneous multi-plane imaging and real-time 3D imaging. 3DE is an excellent tool for quantification of ventricular volume and function	Lower frame rate than in 2DE, currently less spatial resolution compared to 2DE, inability to assess tissue characterization such as calcifications or fibrosis
TOE (2DE and 3DE)	Real-time intra-procedural planning and guidance	Four levels of imaging allow a comprehensive evaluation of the valve: mid-oesophageal, deep-oesophageal, transgastric, and deep-transgastric
CMR	TV severity, perfusion, fibrosis, tissue characterization, and chamber quantification	Less versatile
MSCT	Superb resolution, calcification, excellent tool for TV annulus and preplanning, best to assess radiopaque surgical, and percutaneous implants	Radiation and less versatile

2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; CMR, cardiovascular magnetic resonance; LV, left ventricle; MSCT, multislice computed tomography; RV, right ventricle; TOE, transoesophageal echocardiography; TV, tricuspid valve.

Imaging for peri-operative/peri-interventional planning and guidance

Transthoracic echocardiography (TTE) supported by transoesophageal echocardiography (TOE) is the main tool for preplanning. For transcatheter therapy targeting the leaflets such as edge-to-edge repair, TOE, particularly using transgastric views is essential for assessment of leaflet morphology, coaptation gap, device landing zones and location of main TR jet. Transoesophageal echocardiography guides procedural planning and allows for outcome prediction.[45] For annuloplasty devices, intracardiac echocardiography may be an alternative,[46] especially when TOE images are suboptimal.

Multislice computed tomography could aid in TV preplanning for transcatheter therapies mimicking surgical annuloplasty, spacer devices, and transcatheter TV replacement.[47] It allows for accurate measurement of the TV annulus, device landing zone, relationship between the annulus and right coronary artery, annular tissue quantity and quality, and access selection and guidance.[48]

Imaging of therapeutic efficacy and durability

Surgical success of TV repair is defined, by imaging in the immediate post-operative period as reduction in TR severity to mild or less and reduction of TV annulus diameter. In the long run, reverse RV remodelling, if present, as well as reduction of the RV afterload, are important imaging endpoints. These are correlated to patients' symptomatic and functional improvement. In contrast, the need for reintervention or mortality is the main clinical endpoints reflecting failure of repair. Ideally, the imaging results of successful transcatheter repair should match those of surgical repair. However, most candidates for transcatheter TV repair are currently patients with advanced RV dysfunction and are often beyond the point of complete repair.

TRICUSPID REGURGITATION THERAPY—SURGICAL PERSPECTIVE

Tricuspid valve repair (annulus, leaflets, and sub-valvular apparatus)

In the setting of secondary TR with primarily annular dilation, a reduction annuloplasty is the most commonly used surgical approach. Now, almost abandoned, the first suture annuloplasty was described by Kay et al.[49] This 'bicuspidization' technique is done by tightening a suture from the anteroposterior commissure to the posteroseptal commissure (Figure 2).[49] The second technique was described by De Vega et al.[50] It consists of two parallel lines of running sutures starting at the posteroseptal commissure at the annulus level. The suture follows the annulus with a stitch approximately every 5mm to the fibrous trigone. Thereafter, a pledget is placed and the suture is reversed.[50] Nowadays, TV annuloplasty using a rigid ring is the most often applied technique, which provides a lower recurrent rate of significant TR compared to suture or flexible ring annuloplasty.[51,52] However, the use of a rigid ring was associated with an increased risk of early ring dehiscence.[53] Ideally, a ring annuloplasty should meet the following criteria: (i) restoring the three-dimensional shape of the annulus to reduce leaflet stress and tethering; (ii) addressing the remodelling along the RV free wall and also be 'open' at the septal leaflet sector to protect the conduction system; and (iii) being flexible to maintain annular dynamicity and prevent ring dehiscence.[54,55]

In case of severe leaflet tethering, an annuloplasty alone is usually not sufficient to ensure adequate repair.[56] Dreyfus et al.[57] described an anterior leaflet augmentation technique to address the tethering. An edge-to-edge technique similar to the Alfieri stitch in mitral valve repair has been performed resulting in a triple 'clover-like' orifice.[58] In addition, several case reports exist on neochordae repair of the TV.[59,60] Various other repair techniques specifically addressing a primary cause (e.g. Ebstein anomaly or endocarditis) are reported in literature.[61,62]

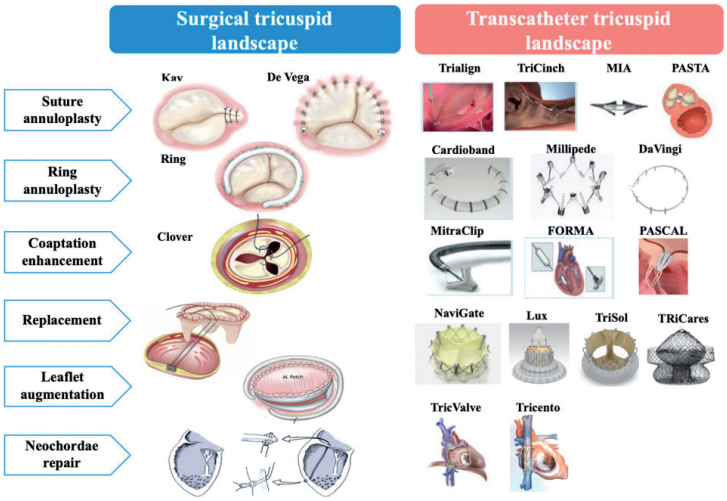


Figure 2. Surgical and transcatheter treatments for tricuspid regurgitation. Direct suture annuloplasty: Trialign™ (Mitralign Inc., Tewksbury, MA, USA), TriCinch™ (4Tech Cardio Ltd., Galway, Ireland), MIA™ (Micro Interventional Devices Inc., Newtown, PA, USA), pledget-assisted suture tricuspid valve annuloplasty (PASTA). Ring annuloplasty: Cardioband (Edwards Lifesciences, Irvine, CA, USA), IRIS (Millipede Inc., Santa Rosa, CA, USA), DaVingi (Cardiac Implants Ltd, Israel). Coaptation enhancement: edge-to-edge with MitraClip® (Abbott Vascular, Santa Clara, CA, USA), PASCAL (Edwards Lifesciences), FORMA (Edwards Lifesciences). Valve replacement: NaviGate (NaviGate Cardiac Structures, Inc., Lake Forest, CA, USA), Lux (Ningbo Jenscare Biotechnology Co., Ltd., Ningbo, China), Trisol (Trisol Medical, Haifa, Israel), TRiCares (TRiCares SAS, Paris, France), TricValve® (P&F Products & Features GmbH, Vienna, Austria), Tricento® (NVT GmbH, Hechingen, Germany and NVT AG, Muri, Switzerland).

Tricuspid valve replacement

Tricuspid valve replacement is usually reserved for patients with primary TV disease. Nevertheless, the latest consensus is that patients with severe RV dysfunction, very large annulus, or severe tethering may be better served with TV replacement.[63] A recent meta-analysis showed comparable outcomes in terms of survival, reoperation, and prosthetic valve failure after TV replacement between biological and mechanical valves. Nonetheless, mechanical prostheses had a higher risk of thrombosis.[64] These results were derived from observational and retrospective studies. Randomized studies are needed to determine which type of valve is better for TV replacement. Currently, biological prostheses are preferred and offer an option for future transcatheter valve-in-valve implantation.

Surgical controversies

The best timing of surgery in patients with TR remains in question. Repairing the TV in patients with a dilated tricuspid annulus (intraoperative ≥70mm, TTE ≥40mm) without significant TR during left-sided heart surgery has been debated[65] since 2005 when this concept was initially presented by Dreyfus et al.[28] This debate is partly fuelled by the lack of evidence for the validity of the conversion of 70mm as measured intraoperatively to 40mm on TTE.[66] Furthermore, since the TV annulus is not planar, even small variations in the ultrasound beam plane may result in

substantial differences in the measurement.[67] The question as to whether repairing a TV with dilated annulus in patients with trace or mild TR at the time of planned mitral valve surgery could improve clinical outcomes will be explored in an ongoing randomized trial (ClinicalTrials.gov identifier: NCT02675244).

As for patients with late or recurrent significant TR after previous left-sided surgery, current guidelines consider this is a Class IIa indication for TV surgery. Yet it has been shown that reoperation on the TV may be associated with a high mortality.[68,69] In combination with multiple co-existing comorbidities or old age, many surgeons are reluctant to operate on these patients, especially if pulmonary hypertension or RV failure is present.[27]

Predictors of a successful surgical tricuspid valve repair

From the surgical perspectives, a successful TV repair is mild or less TR after surgery. Several studies aimed to identify predictors for recurrent TR after surgery (Table 3). Most studies found severe TR and suture annuloplasty are risk factors of recurrent TR after TV repair. Nevertheless, these studies use survival analyses in the context of repeated measures, which is not the preferred approach.[78] Navia et al.[79] used advanced statistical modelling for repeated echocardiography and showed a higher grade of TR, larger TV annuloplasty ring, presence of pacemaker leads, mitral valve replacement rather than repair, depressed LV function, and advanced LV remodelling to predict TR recurrence. As far as TV morphology is concerned, the tethering distance was found to predict recurrent TR after annuloplasty.[56] As tethering is usually present among inoperable patients who might be the first target population of transcatheter therapy, the question whether a transcatheter annuloplasty alone will be sufficient need to be answered.

Table 3. Risk factors of recurrent tricuspid regurgitation

Study	Risk factors				
	De Vega vs. ring annuloplasty HR (95% CI)	Severe TR at baseline HR (95% CI)	Higher PASP HR (95% CI)	Female gender HR (95% CI)	Atrial fibrillation HR (95% CI)
Ren (2015)[70]	1.47 (1.0–1.9)	NS	1.54 (1.1–2.0)	NS	—
Lin (2014)[71]	7.2 (2.7–15.4)	3.6 (1.7–12.1)	NS	NS	9.4 (2.3–94.0)
Ratschiller (2015)[72]	—	3.0 (1.2–7.8)	—	2.5 (1.0–5.9)	4.3 (1.0–18.3)
Gatti (2016)[73]	2.2 (1.1–4.3)	1.2 (0.6–2.4)	1.3 (0.6–2.9)	—	—
Yoda (2011)[74]	—	8.23[a]	NS	—	NS
Jung (2010)[75]	—	—	—	—	NS
Murashita (2014)[76]	10.7 (3.7–31.0)[b]	2.8 (1.4–5.7)[b]	—	—	—
Ghanta (2007)+	0.64 (0.1–1.2)[c]	4.0 (3.4–4.7)	1.0 (0.9–1.0)	—	—

—, not reported; CI, confidence interval; HR, hazard ratio; NS, not significant upon univariate analyses; PASP, pulmonary arterial systolic pressure; TR, tricuspid regurgitation.

[a]No confidence interval reported.

[b]Only univariable cox regression model.

[c]Kay vs. Ring annuloplasty.

TRICUSPID REGURGITATION THERAPY—INTERVENTIONAL PERSPECTIVE

Following the success of transcatheter aortic valve therapy, there is a large interest in developing transcatheter TV devices. Multiple novel technologies are currently invented for transcatheter TV therapy. Most of these devices are yet in the preclinical or early clinical assessment.[14]

Patient selection

The number of patients treated within these transcatheter TV therapy pilot studies is still limited, and most enrolled patients are inoperable or at 'high surgical risk' with chronic secondary TR (Supplementary material online, Table S2). Considering the heterogenous nature of TR, patient selection by a multidisciplinary heart team is paramount to optimize clinical results and effectiveness of transcatheter TV therapy. We summarized potential target population for future studies investigating whether those patients would benefit from TV interventions (Supplementary material online, Table S3).[80] As to patients with primary TR, there are only few case reports and some patients with primary TR within TriValve registry.[81] There is insufficient evidence regarding feasibility of transcatheter intervention in this heterogeneous population. An individualized approach is mandatory.

Anatomical challenges

The most common anatomical changes in significant TR are annulus dilatation and leaflet tethering. Specific anatomical considerations should be assessed according to different therapeutic targets. We summarize the potential anatomical and pathophysiological constraints of transcatheter TV interventions.

(1) Challenges during catheter navigation

a. The angulation between the annular plane and the superior and inferior venae cava complicates the transvenous access.

b. The loss of anatomical landmarks under pathologic conditions (right atrial and ventricular dilation) complicates catheter navigation and interferes with proper positioning of repair/replacement devices.

c. Pre-existing device leads could interfere with device delivery and deployment.

d. Imaging views and quality, which depends on numerous patient characteristics (i.e. mechanical valves in place, chest deformation, oesophageal anatomy/pathologies) but also on the device used for repair.

(2) Difficultly in proper sizing

a. Tricuspid annulus is significantly larger than other valves and is influenced by volume status which might preclude appropriate sizing and device selection.

b. Flexibility and fragility of the annulus and the surrounding myocardium counteracts fixation and long-term stability of transcatheter TV replacement devices.

(3) Increased risk of thrombosis

a. The low pressure and slow flow in the right heart chambers might provoke device thrombosis.

Approaches for transcatheter tricuspid valve interventions

As shown in Figure 2, most of devices for transcatheter TV therapy are designed to mimic surgical techniques. Currently, themost widely used technique is the edge-to-edge repair using the MitraClip device (Abbott, Santa Clara, CA, USA) in TV position to improve leaflet coaptation.[82] Nevertheless, transcatheter repair cannot replace all the types of surgical repair, and several vendors are currently developing transcatheter heart valves for TV replacement. Despite the growing experience in transcatheter TV interventions, we would like to emphasize that clinical data on most of the devices are not sufficient to conclude on their safety and efficacy.When evaluating these early clinical data, the following issues should be addressed:

(1) Patients enrolled in first-in-man studies differ markedly in terms of TR severity, EROA, vena contracta area, with some studies focusing on severe TR as compared to torrential TR. This has to be considered when efficacy in TR reduction and potential for clinical improvements of different devices/approaches are assessed.

(2) General application and comparison between studies are hindered by the differences in study design.

(3) Clinical and echocardiographic endpoints, device and procedural success, and optimal TR reduction should be clearly defined.

(4) Most of the surgical data on the TV are derived from patients who underwent left-sided heart surgery which is not fully transferable to dedicated transcatheter interventions.

LESSONS LEARNT FROM TRANSCATHETER LEFT-SIDED VALVE THERAPY

Aortic valve

Transcatheter aortic valve replacement has been an established first-line therapy for high-risk and could be an alternative therapy for surgery in patients with aortic stenosis and intermediate and more recently low risk.[83,84] With the progress of transcatheter valve therapy, balloon-expandable transcatheter heart valves, which were designed for the aortic position are now being applied for degenerated bioprostheses in TV position.[85,86] Off-label heterotopic heart valve implantation in the superior/inferior vena cava (preferred is one valve in the inferior vena cava) is currently being tested in patients who are inoperable or at very high surgical risk for TV replacement.[87,88] Furthermore, dedicated orthotopic/heterotopic devices for TR are in development.[89] Navia et al.[90] reported the first-in-man results of the NaviGate valve. Several patients received this bioprothesis with excellent TR reduction.[91] Conduction disturbances requiring pacemaker implantation has been reported in one patient.[14] Tricuspid valve surgery carries

a significant risk of conduction disorders requiring permanent pacemaker implantation.[92] Whether transcatheter TV therapy, particular annuloplasty, and valve replacement, would encounter similar issues is yet unknown.

Mitral valve

Transcatheter therapy for severe functional mitral regurgitation (FMR) associated with HF has increased rapidly recently. Results of two clinical outcome trials, MITRA-FR and COAPT were published.[93,94] Both trials randomly assigned patients with FMR to MitraClip plus guideline-directed optimal medical treatment (GDMT) or GDMT only. MITRA-FR failed to demonstrate the benefit ofMitraClip procedure in terms of a composite endpoint (all-cause death or unplanned hospitalization for HF). Conversely, the COAPT trial showed that the MitraClip procedure significantly reduced HF rehospitalizations and all-cause death during 2-year follow-up. The COAPT trial applied a prespecified approach by a group of HF specialists to evaluate GDMT prior to randomization, and therefore, this trial had a long enrolment period. The conflicting results of the two studies reflect the importance of patient selection before irreversible HF ensues, optimization of medical therapy and the role of a multidisciplinary heart team. The MitraClip device has been applied to the tricuspid position. The feasibility and safety of edge-to-edge TV repair using the MitraClip device has been reported.[45,81]

The Cardioband system (Edwards Lifesciences, Irvine, CA, USA) is a transcatheter direct annuloplasty device that mimics surgical repair. The feasibility study in symptomatic patients with FMR demonstrated that Cardioband implantation was effective in reducing mitral regurgitation and was associated with improvement in HF symptoms.[95] The ACTIVE randomized trial is ongoing to compare Cardioband implantation plus GDMT to GDMT alone in patients with significant FMR (ClinicalTrials.gov identifier: NCT03016975). The tricuspid Cardioband device has CE mark approval and is the first commercially available transcatheter device for the treatment of significant TR. In the TRI-REPAIR study, Cardioband implantation provided favourable clinical and functional outcomes at 6 months.[96]

Nevertheless, how to define an optimal repair is still an unsolved issue. In the recent published mid-term outcomes of TriValve registry including 312 patients with severe TR,[82] procedural success (defined as patient alive at the end of the procedure, with the device successfully implanted and delivery system retrieved, with a residual TR grade ≤2 by the investigators) was achieved in 72.8% of patients and was independently associated with increased mortality. The definition of successful repair remains discrepant across studies investigating transcatheter devices (Supplementary material online, Table S4). In order to adequately compare clinical outcomes after surgical or transcatheter therapy, definitions of clinical endpoints including technical, device, procedural as well as patient success should be refined and standardized in future studies.

CONCLUSIONS

With the development of transcatheter therapy, there has been an increasing focus on the treatment of significant TR. Although early safety and efficacy results of transcatheter TV therapy are encouraging, remaining uncertainties including grade of TR severity (quantitative and qualitative), patient selection, risk stratification, timing of intervention, and definition of successful repair warrant further investigations. Due to the complex nature and interaction between TR and HF, the question as to whether a timely transcatheter TV therapy, a minimal invasive intervention, may change the disease process and improve clinical outcomes remains to be answered in prospective studies. This manuscript uses a novel heart-team approach via a comprehensive and a balanced focus on uncertainties, controversies, step-by-step recommendations, and endpoints definitions in TR therapy. Therefore, it provides a framework for randomized clinical trials and registries in the field of transcatheter TV therapy. Since there is no document on the Tricuspid Valve Academic Research Consortium yet, we believe that this work will pave the road as the foundation for such a needed document.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1. Comparison of guidelines for the management of tricuspid regurgitation

	ACC/AHA guideline[1]	ESC/EACTS guideline[2]
Medical therapy		
Class IIa	Diuretics can be useful for patients with severe TR and signs of right-sided HF (stage D). (Level of Evidence: C)	
Class IIb	Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional TR (stages C and D). (Level of Evidence: C)	
Surgical therapy		
Class I	Surgery is indicated in patients with: • Severe TR undergoing left- sided valve surgery.	Surgery is indicated in patients with: • **Primary** o Severe primary TR undergoing left-sided valve surgery. o Severe symptomatic isolated primary TR without severe RV dysfunction. • **Secondary** o Severe secondary TR undergoing left-sided valve surgery.
Class IIa	• TV repair can be beneficial for patients with mild, moderate, or greater functional TR at the time of left-sided valve surgery with either tricuspid annular dilation or prior evidence of right HF.	Surgery should be considered in patients with: • **Primary** o Moderate primary TR undergoing left-sided valve surgery. o Asymptomatic or mildly symptomatic patients with severe isolated primary tricuspid TR and progressive RV dilatation or deterioration of RV function. • **Secondary** o Mild or moderate secondary TR with a dilated annulus (≥40 mm or > 21 mm/m2 by 2D echocardiography) undergoing left-sided valve surgery. o After previous left-sided surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe TR who are symptomatic or have progressive RV dilata- tion/dysfunction, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension.
Class IIb	• Tricuspid valve repair maybe considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery. (Level of Evidence: C) • Tricuspid valve surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction. • Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms due to severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction. (Level of Evidence: C)	Surgery may be considered in patients with: • **Secondary** o Mild or moderate secondary TR when undergoing left-sided valve surgery even in the absence of annular dilatation when previous recent right-HF has been documented.

Supplemental Table 2. Summary of Inclusion Criteria of Studies on Transcatheter Therapies for Tricuspid Regurgitation

SCOUT II (NCT03225612)	**TRILUMINATE** (NCT03227757)	**TRI-REPAIR** (NCT02981953)	**4Tech** (NCT03294200)
Trialign	**MitraClip**	**Cardioband**	**TriCinch**
• **Chronic functional tricuspid regurgitation** with a minimum of moderate tricuspid regurgitation • ≥18 and ≤85 years old • NYHA II, III, or ambulatory IV • Symptomatic despite Guideline Directed medical Therapy, at minimum, patient on diuretic use • patient is at high risk for open heart valve surgery • LVEF ≥35% • Tricuspid valve annular diameter ≤55 mm (or 29 mm/m^2)	• ≥ 18 years and ≤ 90 years • NYHA Functional Class II (conditional), III, or ambulatory IV • No indication for left-sided or pulmonary valve correction. • The Site Heart Team concur the benefit-risk analysis supports intervention of Valvular heart disease and that the subject is at high risk for tricuspid valve surgery. • In the judgement of the TVRS implanting investigator, femoral vein access is determined to be feasible and can accommodate a 25 Fr catheter. • Subject fulfill the echocardiographic Inclusion Criteria • Subjects with moderate or greater (≥2+) Tricuspid Regurgitation determined by the assessment of a qualifying transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) confirmed by the Echocardiography Core Lab (ECL). • Subjects with moderate TR will only be included in the trial if moderate TR is accompanied by a tricuspid annular diameter of ≥ 40mm as measured by the site heart team echocardiographer. • Subjects with tricuspid valve anatomy determined to be suitable for implantation determined by the site heart team.	• **Chronic functional tricuspid regurgitation** with annular diameter ≥ 40 mm with valve Systolic pulmonary pressure ≤ 60mmHg • ≥18 years old • NYHA Class II-IVa • Symptomatic despite Guideline Directed Medical Therapy; at minimum patient on diuretic regimen • LVEF ≥ 30% • Patient is willing and able to comply with all specified study evaluations • The Local Site Heart Team concur that surgery will not be offered as a treatment option • Transfemoral access of the Cardioband is determined to be feasible	• Moderate to severe functional tricuspid regurgitation, defined as: severity 2+ to 4+ (according to semi-quantitative echocardiographic color flow doppler evaluation); and Annular diameter ≥ 40 mm confirmed by echocardiography • ≥ 18 years old • Subject has read and signed the informed consent prior to study related procedures. • Willing and able to comply with all required follow-up evaluations and assessments. • The 'Heart Team' assessment recommends TriCinch Coil Implantation • NYHA Classification ≥ II. • LVEF ≥ 30%. • Heart failure symptoms despite on optimized medical therapy by the local heart team; at minimum subject on diuretic use • Subject has suitable anatomy for investigational device implantation as per imaging requirements

Supplemental Table 3. Potential target population for future studies investigating "whether those groups would benefit from transcatheter tricuspid valve interventions"

Patient phenotype	Rationale
Severe TR undergoing mitral valve edge-to-edge repair	TR could be improved after treatment for MR, but it remains unchanged or deteriorates in some patients[3] and results in a higher mortality rate.[4] Similarly to the conventional surgical approach, the benefits of simultaneous or staged transcatheter treatment for MR and TR should be investigated in selected patients.[5]
Prior left-heart valve surgery	Patients with residual or late significant TR after left-heart valve surgery have higher mortality rates compared to patients with mild or less TR.[6] However, the risk of reoperation for significant TR after left-sided heart valve surgery could be high.[7]
Post-heart transplantation TR	Post-heart transplantation TR could be caused by iatrogenic trauma during endomyocardial biopsy[8] and increases mortality rate.[9]
High-risk patients with severe AS undergoing TAVI	In a large TAVI registry, 24% had significant TR.[10] Residual significant TR is associated with mortality.[11, 12]
Pacemaker/defibrillator lead-induced TV damage	The incidence of worsening TR post device implantation is around 25%.[13] Transcatheter TV therapy plus leadless pacemaker implantation was performed in a case report.[14]
Elderly patients with long-standing AF with "idiopathic" high-grade TR	Clinical features of chronic AF related functional TR include extremely old age, female sex, lower pulmonary artery pressure, prominent enlarged right atrium and excessive dilated tricuspid annulus with impaired contractility.
Prior surgical TV repair	The recurrence of significant TR after surgical TV repair was common.[15] However, the risk of reoperation could be high.[16] Off-label use of transcatheter valve-in-ring was reported in 20 patients.[17] The procedure was effective in reducing TR. However, paravalvular regurgitation was common after procedure and often required transcatheter treatment with occlusion devices in that registry.

Supplemental Table 4. Summary of Definition of Device Success of Studies on Transcatheter Therapies for Tricuspid Regurgitation

Study	Device	Study design	Definition of device/ procedure success
SPACER (NCT02787408)	Forma	Prospective • registry	• Tricuspid regurgitation reduction compared to baseline and tricuspid valve gradient ≤ 5 mmHg
TRILUMINATE (NCT03227757)	MitraClip	Prospective registry	Echocardiographic tricuspid regurgitation reduction at least 1 grade
SCOUT II (NCT03225612)	Trialign	Prospective registry	Successful access, delivery and retrieval of the device delivery system
4Tech (NCT03294200)	TriCinch	Prospective registry	Echocardiographic tricuspid regurgitation reduction at least 1 grade
TRI-REPAIR (NCT02981953)	Cardioband	Prospective registry	Successful access, deployment and positioning of the Cardioband device

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14

General discussion

In the medical literature the tricuspid valve is frequently labeled as the “forgotten valve”, due to the fact that it was believed that tricuspid valve disease was a benign phenomenon (1). Approximately two decades ago, this dogma became controversial. Nevertheless, outcome modelling proved to be difficult using traditional statistical methodology. This thesis aimed to identify determinants of outcome in patients with tricuspid valve disease with the use of advanced statistical tools. In this chapter, the key findings and implications of those results are discussed. Firstly, the clinical implications will be discussed. Secondly, the implications of used methodology in the setting of heart valve disease will be discussed. Lastly, future perspectives and a roadmap for further research are presented.

FUNCTIONAL TRICUSPID REGURGITATION

Surgery for functional tricuspid regurgitation

In this thesis we aimed to summarize and to pool available evidence on outcomes of surgery for functional tricuspid regurgitation. Current literature regarding surgery for functional tricuspid valve regurgitation focuses on concomitant tricuspid valve surgery during left sided valve surgery. In most cases the tricuspid valve is repaired with either a suture or a ring annuloplasty. Both short and long term mortality is acceptable. The results show that the mortality rate of this population is specifically higher in the first year after surgery. Nevertheless, durability is still suboptimal, with considerable residual and recurrent tricuspid regurgitation. Remarkably, these patients are generally not re-operated. The substantial population of patients who are not re-operated could be an interesting target for the innovative percutaneous tricuspid valve repair devices. Furthermore, the results of this study can be used as benchmark for the performance of these novel devices and to inform both physicians and patients about the expected outcome after (concomitant) surgery for functional tricuspid valve disease (**Chapter 2**).

Male-female differences are increasingly more recognized in medical literature. Specifically, is has been shown that females have poorer outcomes compared to males when undergoing coronary artery bypass grafting (2, 3), but comparable outcomes when they undergo isolated mitral valve surgery (4). In this thesis we attempted to unravel male-female differences in tricuspid valve surgery. It was noted that substantial differences exist between males and females in preoperative characteristics. In the subpopulation of patients undergoing (concomitant) tricuspid valve repair, the male population appeared to have more severe cardiac disease. Notwithstanding, in previous studies it was noted that tricuspid regurgitation is more prevalent in females and that females undergo tricuspid valve surgery during left sided valve surgery more frequently (5, 6). This gave rise to an interesting hypothesis; are females more prone to (functional) tricuspid valve regurgitation? Extrapolating this hypothesis to post-surgery outcomes, this may imply females are more prone to recurrent tricuspid regurgitation; a hypothesis which is still heavily debated in current literature (7-10). Further research into this subject

is warranted, as this can have potential implications for the decision to perform concomitant tricuspid valve surgery in females. Regarding the outcomes, sex was not a predictor of hospital mortality. Interestingly, some determinants had a stronger association to hospital mortality in the female population compared to the male population, indicating the usefulness of separate prediction models for males and females (**Chapter 3**).

Tricuspid regurgitation in patient with left ventricular assist device

The use of mechanical support in the form of left ventricular assist devices as therapy for advanced heart failure has become increasingly more common (11). The rapid development and improvement of these devices, together with the growing body of clinical experience, resulted in improved outcomes after left ventricular assist device implantation (11). Nowadays, left ventricular assist device therapy is approved destination therapy for patients uneligible for heart transplantation. Tricuspid regurgitation in this population is common (12). The evidence on clinical impact, course of tricuspid regurgitation and the effect of tricuspid valve surgery during left ventricular assist device implantation in these patients remains scarce. Nevertheless, current guidelines recommend consideration of tricuspid valve surgery if moderate-to-severe tricuspid regurgitation is present at the time of left ventricular assist device implantation (13).

We summarized and pooled all contemporary studies comparing patients undergoing concomitant tricuspid valve surgery during left ventricular assist device implantation with patients without tricuspid valve surgery in a systematic manner. Interestingly, outcomes in terms of early and late mortality, right ventricular dysfunction, early right ventricular failure and late right ventricular failure, acute kidney failure, early right ventricular assist device implantation or length of hospital stay were all comparable between patient with and without concomitant tricuspid valve surgery. Nevertheless, assessing and pooling the baseline variables it seemed that patients undergoing tricuspid valve surgery had a more progressive underlying disease, characterized by a higher tricuspid regurgitation grade, central venous pressure and bilirubin levels (**Chapter 8**). Due to the possibility of these confounding factors definitive conclusions cannot be made, however, it can be hypothesized that concomitant tricuspid valve surgery may be beneficial due to comparable outcomes in the setting of a worse preoperative condition.

This hypothesis prompted us to conduct two other studies regarding tricuspid valve regurgitation in patients with a left ventricular assist device (**Chapter 9** and**10**). In these studies the EUROMACS database was used. This is a large international multicenter ambispective database including over 3000 patients and 52 institutions (14). These large numbers enabled us to do advanced statistical modelling in order to provide more reliable estimates of outcome in this population.

Isolating the population who did not undergo tricuspid valve interventions during left ventricular assist device implantation it was noted that preoperative moderate-to-severe tricuspid regurgitation was associated with worse outcome in terms of mortality. Moreover, it seemed that tricuspid regurgitation did not have a direct association with early mortality,

but strengthened the variables which did had an association with mortality, e.g. moderate-to-severe tricuspid regurgitation may lead to worse kidney function resulting in increased early mortality. Noticeably, the probability of moderate-to-severe tricuspid regurgitation decreased over time. This interesting finding can be attributed to the fact pulmonary pressures decrease after left ventricular assist device implantation, resulting in favorable remodeling of the right ventricle and subsequent decrease of tricuspid valve regurgitation. Of note, it may also be the case that patients with tricuspid regurgitation die and the models will depict more patients with decreasing tricuspid regurgitation later in follow-up. Notwithstanding, in both scenarios there must be patients present in which tricuspid regurgitation grade decreases over time. This has implications for the guidelines, as currently surgery is advised in all patients with preoperative moderate-to-severe tricuspid valve regurgitation. Presumably, surgery will not be beneficial in the patients in which tricuspid valve regurgitation decreases without an intervention. This may also explain why in previous studies comparing patient with and without concomitant tricuspid valve surgery no effects were observed. Both arms may be contaminated with patients not in need of tricuspid valve surgery.

Unfortunately, we were not able to find reliable predictors of tricuspid valve regurgitation evolution, although it seemed that tricuspid valve regurgitation decreased more quickly in patients with idiopathic cardiomyopathy compared to other cardiomyopathies (**Chapter 9**).

Previous studies comparing outcomes of patients with and without concomitant tricuspid valve during left ventricular assist device implantation were severely hampered by differences in baseline characteristics (15). In **Chapter 10** a propensity score matching strategy was applied in order to assess the outcomes in a typical treated patient (16). The results show comparable outcomes between the two cohorts. As aforementioned, tricuspid valve regurgitation decreased also in patients who did not receive concomitant tricuspid valve surgery. This further indicates that the choice to perform concomitant tricuspid valve surgery should not be made solely on preoperative tricuspid valve regurgitation.

Functional tricuspid valve regurgitation in patients with a heart transplant

Tricuspid valve regurgitation in patients with a heart transplantation is associated with the number of cardiac biopsies, the anastomosis technique and number of rejection episodes (17, 18). Several studies noted that functional tricuspid regurgitation in patients with a heart transplant is progressive, and that intraoperative tricuspid regurgitation during cardiac transplantation is associated with impaired survival. In **Chapter 11** all studies in the literature comparing anastomosis technique (bicaval vs biatrial) are summarized and pooled. The results of this study confirm that the biatrial technique is associated with early TR, but not with late TR. Additionally, the biatrial technique was associated with higher mortality rates compared to the bicaval technique. Nevertheless, the course and clinical impact of tricuspid regurgitation during follow-up was never addressed correctly in current literature. The results of this thesis show that the probability of tricuspid valve regurgitation is highest immediately after heart

transplantation and decrease thereafter. Determinants associated with higher probabilities of tricuspid valve regurgitation are higher operation urgency, higher donor age, no pre-implant mechanical assist device and a worse LV function at the time of the tricuspid valve regurgitation measurement. Moderate-to-severe tricuspid valve regurgitation during follow was found to be associated with increased mortality (**Chapter 12**). Nevertheless, since the probability declines after follow-up it may be reasonable not to intervene immediately. These conclusions are in contrast with prior recommendations (19). Patients with unchanging moderate-to-severe tricuspid regurgitation could be a target population of novel percutaneous devices (**Chapter 13**)

STRUCTURAL TRICUSPID VALVE DISEASE

In patients with structural tricuspid valve disease repair is often not feasible and a replacement is necessary (20). Tricuspid valve replacement was initially associated with extremely poor outcomes (21). However, outcomes have improved over time. This was confirmed by reviewing our own cohort of patients undergoing tricuspid valve replacement from 1972 till present. The results of this study showed a drastic improvement of early mortality over time (**Chapter 7**).

The implantation of biological versus mechanical prostheses is a topic of controversy in medical literature (22). Optimal prosthesis choice is subject to patient characteristics and preferences (22, 23). Mechanical prostheses are exceptionally durable in design, but require lifelong anticoagulation due to their thrombogenicity, with the risk of bleeding events (too much anticoagulation) and valve thrombosis (too little anticoagulation). On the contrary, biological prostheses do not require anticoagulation, but deteriorate over time, necessitating re-interventions. The inherent characteristics of the two prostheses types have been noted in numerous studies focusing on valves in different positions (24-26). Nevertheless, in the tricuspid valve position the lower risk of deterioration of the mechanical prostheses compared to biological prostheses does not translate to lower risk of re-intervention. This is due the higher incidence of valve thrombosis necessitating re-intervention. Hence, in the tricuspid valve position the benefit of a more durable mechanical valve is largely negated by the substantial risk of re-intervention due to valve thrombosis (**Chapter 2**).

Carcinoid heart disease

In a small subpopulation of patients with structural tricuspid valve disease the underlying etiology is carcinoid heart valve disease. This is caused by a neuro-endocrine tumor that excretes vaso-active peptides that damage the tricuspid valve, resulting in regurgitation, stenosis, or both (27). A previous study noted that in this disease patients die of progressive right heart failure before patients succumb to the cancer (28). Therefore, tricuspid valve replacement is indicated in these patients. Nevertheless, only a few case series exist on this select subset of patients (29-31). In a multicenter setting in the Netherlands we collected data on patients with

tricuspid valve replacement for carcinoid heart disease. Both early and late mortality in the Dutch experience are comparable to the few series previously published (30, 31). In addition, prosthesis choice (mechanical versus biological) in these patients is especially controversial (29); in a relatively small geographical area in the Netherlands some centers opted to implant exclusively mechanical prostheses, whereas other exclusively implant biological prostheses. We attempted to shed some light on this matter by stratifying outcomes to prosthesis type. Comparable outcomes were noted in regard to mortality and morbidity. Nevertheless, tricuspid regurgitation increased significantly more over time patients with a biological prosthesis. Without apparent benefit of one type over the other, it may be advisable to make valve choice in a multidisciplinary team, taking into account expected lifespan, planned treatment for the carcinoid syndrome and neuroendocrine tumor and patient preferences (**Chapter 5**).

Ebstein's anomaly

Ebstein's is a rare congenital heart disease characterized by apical displacement of the tricuspid valve orifice and atrialization of the right ventricle, resulting in tricuspid valve regurgitation and subsequent right heart failure (32). Several techniques have been described to address this congenital heart defect (33-35). In **Chapter 6** we review the experience of Erasmus MC with the technique described by Carpentier and Chavaud, which can be extended to the cone repair as described by Da Silva (33, 34). Using advanced statistical analyses it was shown that outcomes are acceptable with excellent durability of tricuspid valve function. In contrast to previous literature, the use of a ring annuloplasty was found to be association with more tricuspid regurgitation (36). This surprising finding can be explained by confounding by indication or the fact that forcing the newly created tricuspid valve annulus into the predefined shape of a rigid ring may lead to deformation of the neo-annulus and subsequent tricuspid valve regurgitation.

REPEATED MEASUREMENTS OF VALVE (DYS)FUNCTION

In this thesis it is stressed that tricuspid valve regurgitation is a dynamic entity which can fluctuate over time. Furthermore, tricuspid valve regurgitation is heavily load-depended and severity can change rather quickly with administration of diuretics (37). Traditionally, regurgitation is analyzed as freedom from tricuspid valve failure, defined as regurgitation over grade +1 or +2, and considered in time-to-event analyses. First of all, as mentioned previously, tricuspid valve failure is not a hard endpoint, and can vary over time. Secondly, in this setting the occurrence of tricuspid valve failure is a competing risk with mortality. Thirdly, time-to-event analyses consider time as a continuous variable and do not account for the fact that measurements are missing at certain time points. All these points can introduce bias and lead to spurious conclusions. In fact, the use of these methods may severely overestimate the prevalence of tricuspid valve regurgitation in particular. Additionally, the use of traditional regression methods

introduce bias, since these do not take into account the higher correlations within a patient versus between patients.

Other methodology is required to analyze the longitudinal trend of valve function and determinants hereof. Several methods exists to analyze this type of data (38). One of them; mixed-models (linear or generalized) enables researchers to do these kind of analyses, appropriately addressing all characteristics of longitudinal data (**Chapter 5**, **6**, **9**, **10**, **12**). Researchers can model outcomes in a linear way over time, however this is often an oversimplification of the complex cardiovascular system. Therefore, it is advisable to model in a non-linear way. Several approaches to perform non-linear modeling using mixed-modelled are described, which are implemented in Stata and R. Already in 2008 the guidelines on reporting mortality and morbidity advised to use longitudinal models to address valve function over time (39).

COMBINING REPEATED MEASUREMENTS WITH TIME-TO-EVENT ANALYSES

Heart valve function, a longitudinal outcome, is a competing risk with the limited lifespan of a patient, a time-to-event outcome. Furthermore, patient-lifespan can be associated with heart valve dysfunction. Whereas longitudinal models and time-to-event models are well established by now, modelling these outcomes separately does not take into account de dependencies of one another (e.g. a patient has to be alive to develop valve dysfunction) Therefore, a lot of attention in biostatistics has been given to combining longitudinal models with time-to-event models (40). This application is called joint-modelling (**Chapter 12**). In recent years several software packages are designed that implement these novel statistical models. These models open the door to a new era of prediction modelling, with the use of dynamic predictions. Dynamic prediction models can incorporate all sequential measurements of patients and therefore predictions are updated each time a patients visits the physician. The current problem regarding these models is that the statistical methodology is not yet integrated in medical literature or practice. Much effort has to be done to translate these complex analyses in practical and understandable clinical tools.

FUTURE PERSPECTIVES

Historically, tricuspid regurgitation was believed to be benign and often overlooked in surgical strategies. Nevertheless, tricuspid valve regurgitation has gotten more attention in past two decades. Ideally, the course of tricuspid regurgitation can be predicted reliably and medical decisions can be based upon this predicted course. Using traditional statistical techniques it is extremely difficult to predict this course and impacted hereof. Therefore, previous literature

often shows contradictory results and it is still not entirely clear if an intervention for tricuspid valve regurgitation is necessary or redundant. This thesis shows that in the setting of left ventricular assist devices and heart transplantations patients with tricuspid valve regurgitation are a heterogeneous group; and a one-size-fits-all approach may not be the preferred approach. Patient-tailored predictions are necessary in this group of patients. While this thesis adds to the growing body of evidence, still much work has to be done. Especially in the setting of functional tricuspid regurgitation the right ventricle has to be taken into account, as functional tricuspid regurgitation and right ventricular dysfunction are undoubtable coupled. Using this approach in the future it will become common practice to assess every patient individually, with subsequently a patient-tailored treatment plan conforming to their wishes.

In the setting of the rarer structural tricuspid valve diseases, or rare diseases in general, collaboration is key. Small single center cohorts are usually too small to uncover reliable predictors of outcome, and (inter)national multicenter endeavors are needed. Several registries, such as EUROMACS and the national Dutch database of Cardiothoracic Surgery, are excellent starting points for such endeavors. Unfortunately, registry data often does not provide the detailed data needed for specific research questions. International dedicated networks to heart valve disease, such as the Heart Valve Society, are extremely helpful to tackle these questions regarding rare heart valve diseases. These networks should be maintained meticulously, as they are extremely helpful in starting and facilitating these endeavors and disseminating the knowledge obtained from them. The future in heart valve disease research is collaboration.

While optimal patient selection for (concomitant) tricuspid valve surgery is still debated, new transcatheter devices to repair or replace the tricuspid valve are already on the horizon. These devices have the potential to completely redefine the current surgical landscape. Especially in patients not deemed fit for surgery these devices can be of particular benefit. In the setting of functional tricuspid valve regurgitation concomitant to left sided valve disease a potential whole new treatment strategy arises in which the tricuspid valve is conservatively treated during the left sided valve surgery. The patients who develop late tricuspid regurgitation could be treated with novel transcatheter devices. Nevertheless, it still has to be elucidated whether early surgery for tricuspid regurgitation is equivalent to late surgery with transcatheter devices and future research should focus on this question. Furthermore, these devices, although evolving rapidly, are still in their infancy and multiple challenges need to be addressed first before entering in clinical practice. This is elaborately discussed in **Chapter 13**.

In case of a valve replacement, prosthesis choice is still a topic of debate. In certain subgroups of patients there is no evidence for superiority of mechanical prostheses over biological prostheses or vice versa in tricuspid valve replacement (22). Especially in these cases the patient should be involved in the decision process using shared-decision making, as patients may prefer risk of bleeding and trombo-emblic events (mechanical valves) over reoperation risk (biological valves).

Notwithstanding, in the future this discussion may be alleviated altogether with the use of tissue engineered heart valves (41-43). These valves are one of the most promising developments in heart valve disease treatment as they may limit or eliminate all the disadvantages of existing heart valve prostheses (44).

CONCLUDING REMARKS

This thesis adds to the body of evidence regarding surgery in patients with tricuspid valve disease. It demonstrates that outcomes after surgery for tricuspid valve disease are generally acceptable. Additionally, tricuspid valve regurgitation is a dynamic disease which can regress without intervention. This thesis illustrates that the use of advanced statistical methods is helpful or even necessary to gain better insight in longitudinal evolution of heart valve disease and determinants hereof.

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15

SUMMARY

Chapter 1 gives a general introduction to this thesis and describes the aims and brief outline of this thesis.

Chapter 2 provides a contemporary overview of patient and procedural characteristics of tricuspid valve repair and replacement and early and late outcomes in different settings, such as functional tricuspid regurgitation, rheumatic, congenital, carcinoid tricuspid valve disease, iatrogenic tricuspid valve damage, and finally endocarditis of the tricuspid valve. For this purpose a systematic literature review and meta-analysis was conducted including 132 studies published after 2005 and reporting on outcome after tricuspid valve surgery. This thorough review of reported experience with tricuspid valve repair and replacement reveals a strong variation in patient presentation and outcome among the various indications. Interestingly, reoperation rates of mechanical valves and biological valves are comparable.

Chapter 3 presents a contemporary overview of outcomes after tricuspid valve surgery for functional tricuspid regurgitation. The literature was systematically searched resulting in 87 publications encompassing 13,184 patients. Pooled early mortality was 3.9% and late mortality rate was 2.7%/year. Pooled risk of early moderate-to-severe TR at discharge was 9.4% and late moderate-to-severe TR rate after discharge was 1.9%/year. This study show acceptable clinical outcomes, whereas durability is still suboptimal. The results of this study can be used to inform patients and clinicians about the expected outcome after surgery for FTR and can results serve as a benchmark for the performance of emerging transcatheter TV interventions.

Chapter 4 explores male–female differences in baseline and procedural characteristics, and outcomes of patients undergoing isolated or concomitant tricuspid valve (TV) surgery using the database of the Netherlands Association for Cardio-Thoracic Surgery. Substantial differences in patient and procedural characteristics existed between male and female patients undergoing TV surgery, although sex was not a determinant for hospital mortality. Nevertheless, sex interacted with a critical preoperative condition, indicating the usefulness of separate risk factor models for males and females requiring TV surgery.

Chapter 5 describes a multicenter endeavor that evaluates clinical and echocardiographic outcomes in patients who underwent tricuspid valve replacement for carcinoid heart disease stratified to prosthesis type (biological vs mechanical). It was noted that tricuspid valve surgery for CaHD can be performed with acceptable hospital mortality risk. The study showed no apparent benefit of biological valves over mechanical prosthesis or vice versa. Valve choice should be made in a multi-disciplinary team taking into account expected lifespan, planned treatment for the carcinoid syndrome and neuroendocrine tumor and patient preferences.

Chapter 6 details our experience with reconstructive repair for Ebstein anomaly spanning three decades. Modelling longitudinal evolution of tricuspid regurgitation showed no major changes over time and a full cone repair was associated with less tricuspid regurgitation. In terms of clinical outcomes low mortality, morbidity and acceptable reoperation rates were

observed. Therefore, we conclude that in our centre, repair of Ebstein abnomaly is a durable technique to treat patients.

Chapter 7 provides an overview of the change over a 45-year time period in characteristics and outcome of patients with tricuspid valve disease undergoing surgical tricuspid valve replacement. Etiology changed over time from predominantly functional regurgitation to predominantly carcinoid heart disease. Early mortality declined significantly from 35% in 1972-1985 to 6.7% in 2001-2017. Hence, patient characteristics, potential risk factors and patient outcome changed considerably over time in patients undergoing tricuspid valve replacement.

Chapter 8 describes a systematic review and meta-analysis of studies comparing left ventricular assist device implantation with and without concomitant tricuspid valve surgery. In total 8 studies were included and innovative statistical techniques were used to pool Kaplan Meier curves. It was noted that adding TVS during LVAD implantation was not associated with worse outcome. Adding TVS, nevertheless, may be beneficial, as baseline characteristics of patients undergoing LVAD + TVS were suggestive of a more progressive underlying disease, but with comparable short-term outcome and long-term outcome with patients undergoing isolated LVAD.

Chapter 9 explores the clinical impact and course of uncorrected TR in patients after LVAD of patients in the EUROMACS database using innovative longitudinal models and joint-models. The main observations were that Pre-LVAD and post-LVAD TR is associated with increased mortality. Nevertheless, on average, TR decreases without intervention after LVAD implant. Therefore, this study suggests that patient selection for concomitant tricuspid valve surgery should not solely be based on TR grade.

Chapter 10 entails a study in which patients with and without concomitant tricuspid valve surgery in the EUROMACS database were matched upon propensity scores in order to investigate the effects of concomitant tricuspid valve surgery on clinical and echocardiographic outcomes. In matched patients, TVS concomitant with LVAD implant does not seem to be associated with better clinical outcomes. Concomitant TVS reduced TR significantly early after LVAD implant; however, differences in probability of TR disappeared during the follow-up period.

Chapter 11 provides a systematic review of studies in which patients underwent bicaval versus biatrial orthotropic heart transplant. Early outcomes regarding mortality, tricuspid regurgitation, mitral regurgitation and permanent pacemaker implantation differed significantly in favor of the bicaval orthotropic heart transplant patients, as was long term survival and late tricuspid regurgitation. Hence, bicaval orthotropic heart transplant should be considered as the preferable technique.

Chapter 12 describes the clinical impact of tricuspid regurgitation in our own patients with a biatrial orthotopic heart transplant. Using joint-modelling the dynamic post-heart transplant tricuspid regurgitation evolution was linked to the survival. TR during follow-up was significantly associated with higher mortality and morbidity. Nevertheless, probability of TR is the highest

immediately after OHT and decreases thereafter. Therefore, it may be reasonable refrain from surgical intervention during the initial OHT admission.

Chapter 13 entails a review in which the Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy are discussed, including grade of TR severity (quantitativeand qualitative), patient selection, risk stratification, timing of intervention, and definition of successful repair. This manuscript uses a novel heart-team approach via a comprehensive and a balanced focus on uncertainties, controversies, step-by-step recommendations, and endpoints definitions in TR therapy. Therefore, it provides a framework for randomized clinical trials and registries in the field of transcatheter TV therapy.

Chapter 14, the general discussion, discusses the results of the studies and general implications of these results. Furthermore, the research question are answered and future research is proposed.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 bespreekt een algemene inleiding, beschrijft de doelen en een geeft korte schets van de inhoud van dit proefschrift.

Hoofdstuk 2 biedt een hedendaags overzicht van de patiënt- en procedurele kenmerken van zowel reparatie als vervanging van de tricuspidalisklep en beschrijft vroege en late uitkomsten in verschillende situaties, zoals functionele tricuspidalisklep insufficiëntie, reumatisch, aangeboren, carcinoïd tricuspidalisklep ziekte, iatrogene tricuspidalisklep schade en endocarditis van de tricuspidalisklep. Om dit te beschrijven werd een systematische literatuurstudie en meta-analyse uitgevoerd, bevattend 132 onderzoeken die na 2005 werden gepubliceerd, die rapporteerden over de resultaten na een tricuspidalisklep chirurgie. Deze grondige beoordeling van de gerapporteerde ervaring met reparatie en vervanging van de tricuspidalisklep demonstreert een sterke variatie in presentatie en uitkomst van de patiënt met verschillende indicaties. Interessant is dat hoeveelheid re-operaties van mechanische kleppen en biologische kleppen vergelijkbaar zijn.

Hoofdstuk 3 geeft een hedendaags overzicht van de resultaten na een tricuspidalisklep chirurgie voor functionele tricuspidalisklep insufficiëntie. De literatuur werd systematisch doorzocht, wat resulteerde in 87 publicaties met 13.184 patiënten. De gepoolde vroege sterfte was 3,9% en het late sterftecijfer was 2,7% / jaar. Het gepoolde risico van vroege matige-tot-ernstige tricuspidalisklep insufficiëntie bij ontslag was 9,4% en het late matige-tot-ernstige tricuspidalisklep insufficiëntie percentage na ontslag was 1,9% / jaar. Deze studie laat aanvaardbare klinische resultaten zien, terwijl de duurzaamheid nog steeds niet optimaal is. De resultaten van dit onderzoek kunnen worden gebruikt om patiënten en clinici te informeren over de verwachte uitkomst na een operatie voor functionele tricuspidalisklep insufficiëntie kunnen als referentie dienen voor het uitvoeren van opkomende transcatheter tricuspidalisklep interventies.

Hoofdstuk 4 onderzoekt man-vrouw verschillen in patiënt- en procedurele kenmerken, en uitkomsten van patiënten die geïsoleerde of gecombineerde tricuspidalisklep (TV) chirurgie ondergaan met behulp van de database van de Nederlandse Vereniging voor Cardio-Thoracale Chirurgie. Er waren aanzienlijke verschillen in patiënt- en procedurele kenmerken tussen mannelijke en vrouwelijke patiënten die een tricuspidalisklep -operatie ondergingen. Alhoewel geslacht geen bepalende factor was voor ziekenhuissterfte, had geslacht een wisselwerking met kritieke pre-operatieve status, deze was meer bepalend voor ziekenhuissterfte in mannen. Dit geeft het nu aan van afzonderlijke risicofactormodellen voor mannen en vrouwen die een tricuspidalisklep operatie nodig hebben.

Hoofdstuk 5 beschrijft een multicenter samenwerking die klinische en echocardiografische uitkomsten evalueert bij patiënten die een tricuspidalisklep vervanging ondergingen voor carcinoïd hartaandoeningen (CaHD), gestratificeerd naar prothesetype (biologisch versus mechanisch). Er werd gevonden dat een tricuspidalisklep operatie voor CaHD kan worden uitgevoerd met een aanvaardbaar ziekenhuissterfte risico. De studie toonde geen duidelijk

voordeel aan van biologische kleppen ten opzichte van mechanische prothese of omgekeerd. Klepkeuze moet dus worden gemaakt in een multidisciplinair team, rekening houdend met de verwachte levensduur, geplande behandeling van het carcinoïd syndroom en neuro-endocrine tumor en de patiëntvoorkeuren.

Hoofdstuk 6 beschrijft onze ervaring met reconstructieve reparatie voor Ebstein-anomalie die drie decennia beslaat. Modellering van de longitudinale evolutie van tricuspidalisklep insufficiëntie toonde geen grote veranderingen in de tijd en een volledige kegel herstel van de rechter kamer (Cone operation) werd geassocieerd met minder tricuspidalisklep insufficiëntie. In termen van klinische resultaten werden lage mortaliteit, morbiditeit en een acceptabel re-operaties risico waargenomen. Daarom concluderen we dat in ons centrum reparatie van Ebstein- anomalie een duurzame techniek is om patiënten te behandelen.

Hoofdstuk 7 geeft een overzicht van de verandering over een periode van 45 jaar in kenmerken en uitkomst van patiënten met een tricuspidalisklep ziekte die een chirurgische vervanging van de tricuspidalisklep ondergaan. De etiologie veranderde in de loop van de tijd van voornamelijk functionele insufficiëntie naar voornamelijk carcinoïd hartziekte. De vroege sterfte daalde aanzienlijk van 35% in 1972-1985 tot 6,7% in 2001-2017. Zowel de kenmerken van de patiënt, als de riscofactoren (en gewicht van deze factoren) en uitkomsten zijn substantieel veranderd in de afgelopen decennia.

Hoofdstuk 8 beschrijft een systematische review en meta-analyse van studies die de implantatie van het linker kunsthart (LVAD) vergelijken met en zonder gelijktijdige tricuspidalisklep chirurgie (TVS). In totaal werden 8 studies geïncludeerd en werden innovatieve statistische technieken gebruikt om Kaplan Meier-curven te bundelen. Opgemerkt werd dat het toevoegen van tricuspidalisklep chirurgie tijdens LVAD-implantatie niet geassocieerd was met een slechtere uitkomst. Niettemin kan het toevoegen van TVS nuttig zijn, aangezien de uitgangskenmerken van patiënten die LVAD + TVS ondergaan, wijzen op een progressievere onderliggende ziekte, maar met vergelijkbare resultaten op korte termijn en op lange termijn bij patiënten die geïsoleerde LVAD ondergaan.

Hoofdstuk 9 onderzoekt de klinische impact en het verloop van niet-gecorrigeerde tricuspidalisklep insufficiëntie bij patiënten na linker kunsthart (LVAD) implantatie van patiënten in de EUROMACS-database met behulp van innovatie statistiek. De belangrijkste waarnemingen waren dat pre-LVAD en post-LVAD tricuspidalisklep insufficiëntie geassocieerd zijn met verhoogde mortaliteit. Desalniettemin neemt TR gemiddeld af zonder interventie na LVAD-implantatie. Daarom suggereert deze studie dat de selectie van patiënten voor gelijktijdige chirurgie van de tricuspidalisklep gedurende LVAD implantatie niet alleen op tricuspidalisklep insufficiëntie graad moet worden gebaseerd.

Hoofdstuk 10 bevat een studie waarin patiënten met en zonder gelijktijdige tricuspidalisklep chirurgie gedurende kunsthart implantatie in de EUROMACS-database werden gematcht op basis van propensity scores om de effecten van gelijktijdige tricuspidalisklep chirurgie op klinische en echocardiografische resultaten te onderzoeken. Bij gematchte patiënten lijkt

tricuspidalisklep chirurgie gedurende kunsthart implantatie niet geassocieerd te zijn met betere klinische resultaten. In patiënten met gelijktijdige tricuspidalisklep chirurgie werd vroeg na implantatie significant minder tricuspidalisklep insufficiëntie gezien; tijdens de follow-up periode verdwenen de verschillen echter.

Hoofdstuk 11 geeft een systematisch overzicht van studies waarin patiënten bicavale versus biatriale orthotroop harttransplantatie ondergingen. Vroege resultaten met betrekking tot mortaliteit, tricuspidalisklep insufficiëntie, mitralisklep insufficiëntie en permanente pacemaker implantatie verschilden significant in het voordeel van de bicaval orthotrope harttransplantatie, evenals overleving op lange termijn en late tricuspidale regurgitatie. Vandaar dat bicavale orthotrope harttransplantatie als de voorkeurstechniek moet worden beschouwd.

Hoofdstuk 12 beschrijft de klinische impact van tricuspidalisklep insufficiëntie bij patiënten met een biatriale orthotopische harttransplantatie. Met behulp van joint-modelling werd het dynamische post-harttransplantatie tricuspidalisklep insufficiëntie verloop gekoppeld aan de overleving. Tricuspidalisklep insufficiëntie tijdens follow-up was significant geassocieerd met hogere mortaliteit en morbiditeit. Desalniettemin is de waarschijnlijkheid van TR het hoogst onmiddellijk na harttransplantatie en neemt daarna af. Daarom zijn er argumenten om af te zien van chirurgische ingrepen tijdens de eerste harttransplantatie-opname.

Hoofdstuk 13 bevat een overzicht waarin de onzekerheden en uitdagingen in chirurgische en transcatheter tricuspidalisklep therapie worden besproken, waaronder, patiëntselectie, risicostratificatie, timing van interventie en definitie van succesvol herstel. Dit manuscript maakt gebruik van een nieuwe hart-teambenadering en focust op onzekerheden, controverses, en doet stapsgewijze aanbevelingen voor tricuspidalisklep insufficiëntie therapie. Daarom biedt deze review een raamwerk voor gerandomiseerde klinische onderzoeken en registers op het gebied van transkatheter-tv-therapie.

Hoofdstuk 14, de algemene discussie, bespreekt de resultaten van de studies en de algemene implicaties van deze resultaten. Verder wordt de onderzoeksvraag beantwoord en wordt toekomstig onderzoek voorgesteld.

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Mijn promotor professor Bogers

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De Commissie

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ABOUT THE AUTHOR

Kevin Mitchel Veen was born in Zwijndrecht, The Netherlands on July 25th, 1994. In 2012, he started the Bachelor Nanobiology. In 2013 he chose to persue a Bachelor in medicine. Following the completion of a minor in congenital heart disease, he conducted extracurricular research in the field of cardiac surgery parallel to his medical studies. After obtaining his Bachelor of Science in Medicine in August 2016, he was offered a PhD position based upon his previous work at the Department of Cardiothoracic Surgery, Erasmus MC under supervision of prof. dr. J.J.M. Takkenberg and prof.dr. A.J.J.C. Bogers. During his PhD trajectory, he organized the International Conference of Tissue Engineered Heart Valves in 2017 and 2019. In the following years, Kevin not only became the coordinator of the minor congental heart disease, but also the founder of VECTOR — an extracurricular teaching program in the field of cardiology and cardiac surgery. After two years of full-time PhD research, he commenced his Master in medicine and finished his PhD research concurrently. In 2020, he started as a research fellow for the International Consortium for Health Outcomes Measurment (ICHOM) and will play a role in the development of the Standard Set Heart Vavle Disease.

PHD PORTFOLIO

Name PhD student:	Kevin M. Veen
Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	Februari 2017 – June 2019
Title thesis:	Determinants of outcome in patients with tricuspid valve disease
Promotors:	Prof. dr. J.J.M. Takkenberg
	Prof. dr. A.J.J.C. Bogers
Co-promotors:	Mostafa M. Mokhles

Academic education

2013-2016	Bachelor of Science (BSc) in Medicine, Erasmus MC, Rotterdam, The Netherlands	

In-depth courses

2017	ESP09 Regression Analysis	1,9
	ESP66 Logistic Regression	1,4
	COEUR course Vascular Clinical Epidemiology	1,5
	COEUR course Congenital Heart Disease	1,5
2018	ESP72 Joint Models for Longitudinal and Survival Data	0,7

Compulsory PhD courses

	Research Integrity Course	0,3
	CPO-Course on Patient Oriented Research	0,3

Conferences

2017	Heart Valve Society Annual Meeting, Monaco	0,9
	Dutch Association for Thoracic Surgery Biannual Meeting, Anterwerp	0,6
2018	Heart Valve Society Annual Meeting, New York	0,9
	International Conference of Heart Valve Tissue Engineering, Amsterdam	0,3
	Dutch Association for Thoracic Surgery Biannual Meeting,	0,3

	2019 Heart Valve Society Annual Meeting, Sitges	0,9
	International society of heart and lung transplantation, Orlando	1,2
	European society of cardiothoracic surgery, Lisbon	1,2
	2020 Heart Valve Society Annual Meeting, Sitges	0,9
Conference presentations		
	2017 Heart Valve Society Annual Meeting, Monaco	1,2
	2018 Heart Valve Society Annual Meeting, New York	2,4
	International Conference of Heart Valve Tissue Engineering, Amsterdam	0,6
	2019 Heart Valve Society Annual Meeting, Sitges	1,2
	International society of heart and lung transplantation, Orlando	0,6
	European society of cardiothoracic surgery, Lisbon	0,6
	2020 Heart Valve Society Annual Meeting, Abu dahbi	0,6
Treaching		
	2017 Supervision of 2nd year medical students in writing a systematic review	0,6
	2018 Supervision of 2nd year medical students in writing a systematic review	0,6
	Supervision of 3nd year medical students in writing a systematic review	0,6
	2019 Supervision of 3nd year medical students in writing a systematic review	0,6
	Supervision Master student for master thesis	1,8
	Supervision Master student for master thesis	1,8
	Supervision Master student for master thesis	0,6
	Lecture Minor Congenital heart disease	0,6
	2020 Lecture Minor Congenital heart disease	0,6
	Supervision of 3nd year medical students in writing a systematic review	0,6

Meetings			
Various dates		Scientific meetings Department of Cardiothoracic Surgery, Erasmus MC	3,0
Comittees & organisations			
	2017	Founding member VECTOR	3,0
	2018	Board member Inaugural meeting nternational Conference of Heart Valve Tissue Engineering	7,0
	2019	Heart Valve society branding team	3,0
		Chair network LGTBQIA Erasmus MC	2,0
		Organisor Minor Congenital heart disease	5,0
	2020	Board member second meeting international Conference of Heart Valve Tissue Engineering	3,0
		Organisor Minor Congenital heart disease	5,0
Peer reviewer international scientific journals			
		European Heart Journal	0,5
		Annals of Thoracic Surgery	0,5
		European Journal for Cardio-Thoracic Surgery	1,5
		ESC Heart failure	0,5
Total			64,4

LIST OF PUBLICATIONS

This thesis

1. Tricuspid Valve Disease: Surgical Outcome , **Kevin M. Veen**, Jonathan R. G. Etnel, Johanna J. M. Takkenberg, Chapter Practical Manual of Tricuspid Valve Diseases (2018)3.
2. Outcomes after surgery for functional tricuspid regurgitation: a systematic review and meta-analysis, **Kevin M. Veen**, Jonathan R.G. Etnel, Thijs J.M. Quanjel, Mostafa M. Mokhles, Simone A. Huygens, Moniba Rasheed, Frans B.S. Oei, Folkert J. ten Cate, Ad J.J.C. Bogers, and Johanna J.M. Takkenberg, European Heart Journal - Quality of Care and Clinical Outcomes, July 2019
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