# 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 trans-catheter 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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