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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