# 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.

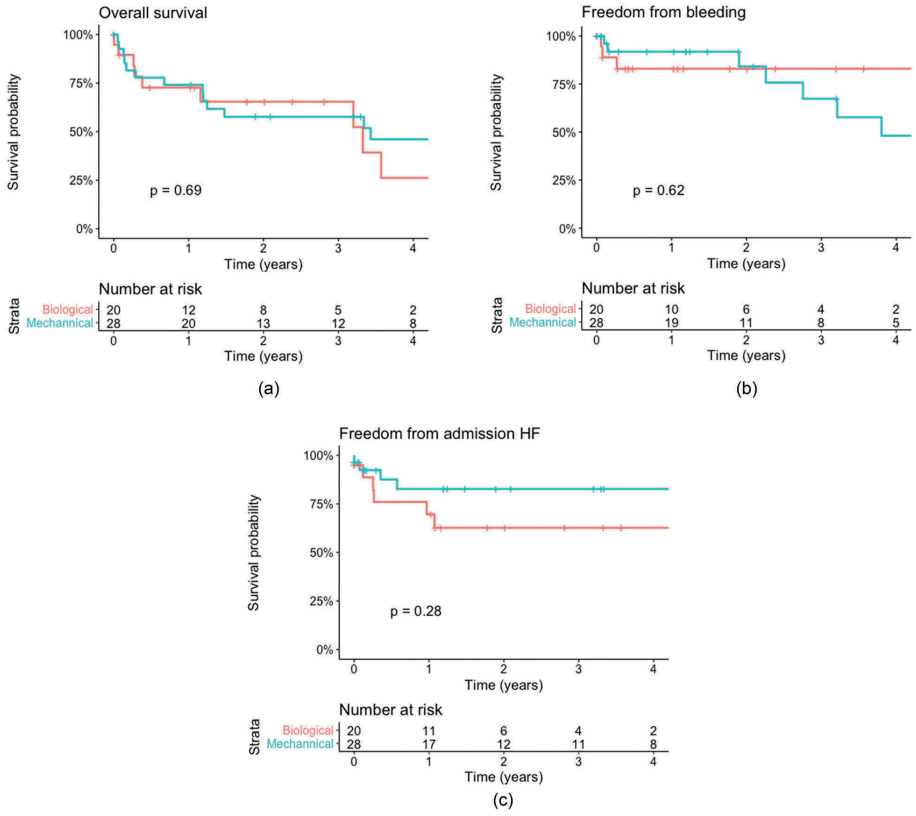


Figure 1. Kaplan–Meier curves of overall survival (a), freedom from bleeding (b) and freedom from heart failure (c). HF = heart failure. Proportional hazard assumption was not violated ($p$ = 0.76, $p$ = 0.13 and $p$ = 0.94).

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.

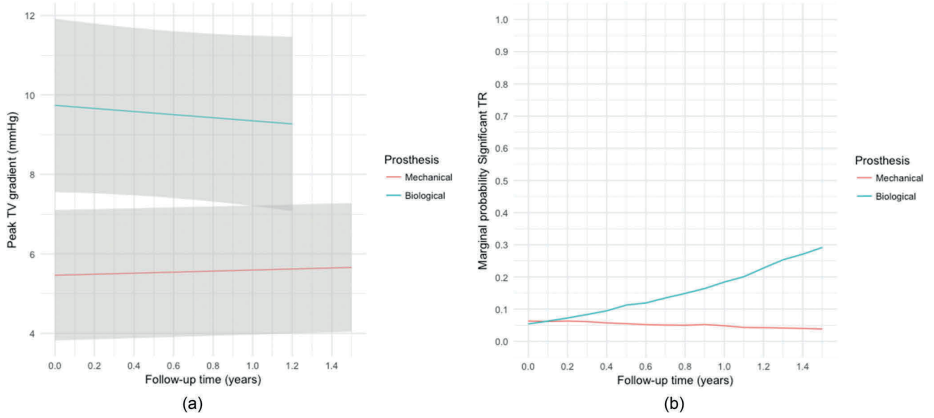


Figure 2. Temporal pattern of Tricuspid valve inflow peak gradient (a) and marginal probability of moderate-to-severe tricuspid regurgitation (b).

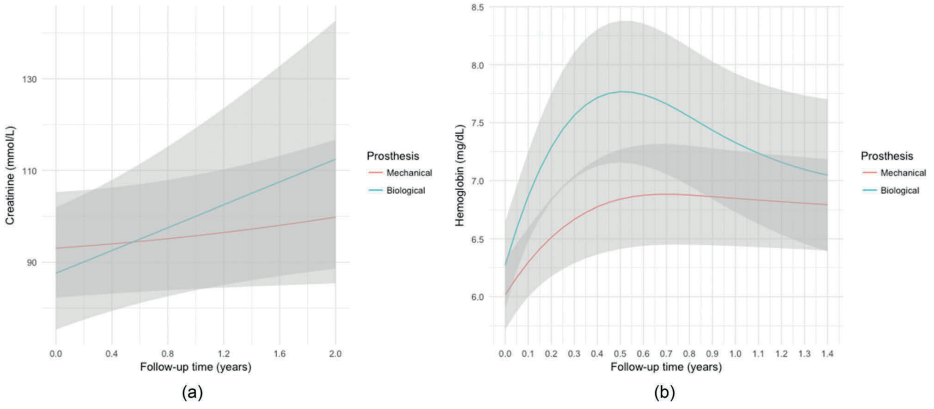


Figure 3. Temporal pattern of creatinine (a) and hemoglobin (b).

## 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 $\sigma_b^2$ 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 |