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Impact of kidney function on mortality after transcatheter valve implantation in patients with severe aortic valvular stenosis

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Inhaltsverzeichnis

1. Artikel in gedruckter Originalversion: „Impact of kidney function on mortality after transcatheter valve implantation in patients with severe aortic valvular stenosis“

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Impact of kidney function on mortality after transcatheter valve implantation in patients with severe aortic valvular stenosis

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ABSTRACT

Aims: Transcatheter aortic valve implantation (TAVI) is an accepted alternative for patients with severe aortic valve stenosis who cannot undergo surgery. Acute kidney injury (AKI) is a serious complication in any invasive cardiovascular intervention.
The objectives of the study were to determine (i) the influence of kidney function before TAVI and (ii) the impact of changes in kidney function after TAVI, including acute kidney injury (AKI), on mortality.
Methods and results: A total of 540 patients undergoing TAVI were included. Patients were divided into three groups according to glomerular filtration rate (GFR) before TAVI (A: normal renal function i.e. GFR ≥60 ml/min; B: impaired renal function i.e. GFR 30–59 ml/min; C: severe impaired renal function i.e. GFR <30 ml/min).
Multivariate analysis showed a significant impact of GFR on mortality ($p < 0.0008$). Subgroup analysis showed significant differences between the groups in 30-day (A: 5.4%, B: 9.0%, C: 25.0%) and 12-month mortality (A: 15.0%, B: 32.0%, C: 49%). Patients who had an increase in GFR after TAVI by more than 22% ($p = 0.0068$) had an improved survival rate, whereas a decrease in GFR by more than 15% was associated with an increased mortality rate ($p = 0.0051$). AKI occurred in 30 patients (5.6%), of which 22 patients (73.3%) died within 12 months.
Conclusion: Outcome is significantly related to pre-procedural kidney function. In addition, changes in kidney function after TAVI have a significant impact on mortality. Due to a very poor prognosis in patients with AKI, any effort to prevent this serious complication after TAVI needs to be taken.

1. Introduction

Surgical aortic valve replacement (SAVR) is still the standard treatment for symptomatic aortic valve replacement. Transcatheter aortic valve implantation (TAVI) is now a proven alternative to open heart surgery for those patients considered to have a high surgical risk [1–4]. Adams et al. [5] showed in their study, that TAVI in patients with high surgical risk was associated with a significantly higher 12-month-survival, than SAVR. According to the risk selection criteria, the patient population undergoing TAVI is in a higher age with a higher prevalence of chronic kidney disease (CKD) compared to patients treated by SAVR [6]. The negative impact of impaired kidney function as well as acute kidney injury (AKI) on mortality in patients after cardiac surgery has been described in several studies [7–9]. Recent studies showed that kidney function, especially AKI, significantly influences the outcome in patients after TAVI [10,11]. The revision of the logistic Euro Score [12] and VARC criteria [13] with a more detailed analysis of kidney function already reflects the importance of renal function for risk assessment in patients with severe aortic valvular stenosis. With the current study, we sought to detect risk groups regarding their pre-procedural kidney function. For this concern the aims of the current study were (i) to determine the influence of kidney function before TAVI on patient outcomes in general and (ii) to examine the influence of TAVI on possible changes in kidney function, including acute kidney injury and (iii) to determine the impact of these changes on mortality.

2. Methods

2.1. Patients

Between July 2008 and September 2012, a total of 540 patients (mean age 80.2 ± 7.1 years, logistic Euro Score 24.5 ± 17.9%) were treated by TAVI at our institution. Baseline characteristics, renal function, as well as patient outcomes were retrospectively investigated. Patients were divided into three groups according to their glomerular filtration rate (GFR) before TAVI: A: normal renal function i.e. GFR ≥60 ml/min; B: impaired renal function i.e. GFR 30–59 ml/min; and C: severe impaired renal function i.e. GFR <30 ml/min. TAVI was approved in all patients with severe aortic stenosis, considered either non-operable or at high-risk surgical risk, and all patients provided signed informed consent prior to the procedure.

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2.2. Transcatheter aortic valve replacement

TAVI-procedures have been described in detail in several studies [4,14,15]. The Edwards-SAPIEN or SAPIEN XT valves (ESV) were used in 221 cases and the Medtronic Core Valve (MCV) in 319 cases. The approach was transfemoral in 445 patients, transsubclavian in 40 patients, transapical in 53 patients, and transaortic in 2 patients, respectively. The procedures were done in the vast majority (90%) of the cases in analgosedation (except transapical cases) and a transesophageal echoprobe was only inserted in selected patients (but in all transapical cases) to achieve the best patient comfort. Thus the hemodynamic performance of any TAVI prosthesis was basically derived from invasive hemodynamic data and angiography, respectively. In addition, all patients underwent careful examination of invasive right-/and left-sided hemodynamics with a SwanGanz catheter and arterial pressure lines before and after TAVI (two pigtails). Volume state was assessed according to filling pressures and the RA-pressure was increased by volume substitution (mostly NaCl 0.9%) – if necessary – to a range of 8–16 mm Hg during TAVI.

2.3. GFR- and serum creatinine measurements and definition of acute kidney injury

GFR (MDRD (modification of diet in renal disease) formula) and serum creatinine were measured in all patients before TAVI (<2 days) and after TAVI at the day of the procedure and then continuously until discharge (mean hospital stay was 16.8 ± 12.2 days). The occurrence of AKI during hospitalization was defined according to the Rifle classification [16]. In this classification, AKI is defined as a decrease of GFR by more than 50% or a 2 fold increase in serum-creatinine. In addition, AKI was analyzed according to VARC2. GFR-improvement was defined as an increase in GFR ≥ 1%; GFR-impairment was defined as a decrease of GFR ≤ 1%. This division functioned as a survey in which direction kidney function changes in the whole patient population, as well as in the different groups A, B and C. In addition, more specified values were detected by a ROC-analysis to investigate the coherence between GFR-change and mortality.

2.4. Statistical analysis

Continuous data were described by mean and standard deviation if the variables were normally distributed, or as median, first, and third quartiles if they were not. Differences of metric variables between two groups were analyzed with t-tests, if the data were approximately normally distributed, and with Wilcoxon–Mann–Whitney test in case of non-normally distributed data or very unequal group size. Differences between three and more groups were analyzed by analysis of variance for normally distributed data and the Kruskal–Wallis test otherwise.

Categorical data were described with absolute and relative frequencies. Differences between categorical variables were evaluated with the Chi-square test or with Fisher's exact test in the case of small expected cell frequencies. If three or more groups were compared and the overall tests for group effects were significant, two group comparisons were performed using the multiple comparison adjustment of Bonferroni.

All variables with p-values ≤0.10 in the univariate analysis were used to determine the predictive factors for AKI (Rifle). Variables, which were included in the multivariate analysis, were other than transfemoral approach, anemia, logES, cardiac output (CO) before TAVI, CO after TAVI, CKD, NYHA-class, dialysis in the past medical history, and major vascular complication.

Survival curves were estimated by the Kaplan–Meier method and the log-rank test was used to examine survival differences. The multiple comparison adjustment of Sidak was applied to investigate survival differences between two groups.

All p values are two-sided. For overall tests, $p \leq 0.05$ was considered significant, and for multiple comparisons, adjusted significance levels were used. All calculations were performed with the statistical analysis software SAS (SAS Institute Inc., version 9.3, Cary, NC, USA).

3. Results

A total of 540 patients (mean age 80.2 ± 7.1 years, logistic Euro Score 24.5 ± 17.9%) were treated by TAVI. The demographics and baseline data of all subgroups are shown in Table 1.

3.1. Procedural and hemodynamic data

Overall procedural success with TAVI was 98%. There were 33 (6%) patients with a final grade ≥2+ of aortic regurgitation. Overall, transcatheter heart valve (THV) performance was excellent with a significant reduction of the transaortic gradient (see Table 2). Post-ballooning was performed in 138 patients (26%), 19 patients (4%) were treated with a second THV, and a significant paravalvular leak (PVL ≥ II+) was found in 33 patients (6%) at the conclusion of the procedure. Right heart hemodynamics revealed unchanged pulmonary and pulmonary capillary wedge pressures, whereas the systemic aortic pressures and the cardiac output demonstrated a significant increase (before TAVI 4.31 ± 1.36 l/min vs. after TAVI 4.54 ± 1.49 l/min, $p < 0.0001$). There were 5% major and 18% minor vascular complications. 5.4% of the patients suffered from a cerebrovascular embolic event. 22% of the patients were in need of a pacemaker after TAVI.

3.2. Renal function

Overall baseline glomerular filtration rate (GFR) was 59.1 ± 21.7 ml/min (range: 6 to 90), and there was a moderate increase in GFR after TAVI (day 1: 67.1 ± 22.3 ml/min; discharge 63.6 ± 23.6 ml/min). In patients with normal renal function (group A), there was no significant change in GFR after TAVI (77.29 ml/min vs. 76.6 ml/min; $p = 0.45$). Patients with a moderate impaired renal function (group B) demonstrated a modest increase in GFR (46.17 ml/min vs. 55.72 ml/min; $p < 0.0001$), whereas the most remarkable increase in GFR was found in patients with severe impaired renal function (group C: 19.54 ml/min vs. 27.9 ml/min; $p < 0.0001$) (Figs. 1 and 2). Overall, GFR increased in a

Table 1
Baseline characteristics of patients in groups A, B and C.

	A = 271	B = 215	C = 54	p-Value (A vs. B)	p-Value (A vs. C)
Age n ± SD	79 ± 7.23	81.42 ± 6.45	80.26 ± 8.31	0.0007	0.37
Male gender n/(%)	124 (45.76%)	95 (44.19%)	25 (45.45%)	0.73	0.95
Arterial hypertension	124 (46%)	188 (87%)	47 (87%)	0.61	0.69
Coronary artery disease	159 (89%)	137 (64%)	38 (70%)	0.26	0.12
PCI	51 (19%)	54 (25%)	13 (24%)	0.14	0.4
Porcelain aorta	49 (22%)	36 (21%)	14 (29%)	0.79	0.29
Previous cardiac surgery	51 (19%)	49 (23%)	9 (17%)	0.28	0.71
History of kidney disease	35 (13.0%)	128 (60.0%)	48 (89.0%)	<0.0001	<0.0001
History of dialysis	2 (1.0%)	5 (2.0%)	16 (30.0%)	0.15	<0.0001
Diabetes mellitus n/(%)	78 (28.8%)	61 (28.4%)	22 (40.0%)	0.92	0.08
Hyperlipoproteinemia	114 (42.0%)	89 (41.0%)	17 (31.0%)	0.88	0.15
Atrial fibrillation	113 (42.0%)	102 (47.0%)	27 (50.0%)	0.21	0.26
COPD n/(%)	41 (15.1%)	33 (15.3%)	9 (16.4%)	0.95	0.78
Peripheral artery disease n/(%)	48 (17.7%)	54 (25.1%)	16 (29.1%)	0.046	0.045
Pulmonary hypertension	94 (35.0%)	99 (46.0%)	30 (56.0%)	0.01	0.004
Malignant disease	38 (14.0%)	22 (10.0%)	7 (13.0%)	0.21	0.84
Previous stroke	27 (10.0%)	37 (17.0%)	9 (17.0%)	0.02	0.15
LogEuro-Score n/(%)	20.6% ± 14.0%	26.8 ± 17.6%	34.4% ± 21.4%	<0.0001	<0.0001
Transfemoral n/(%)	183 (67.5%)	138 (64.2%)	40 (27.7%)	0.82	0.80
Creatinine/GFR n ± SD	0.9 ± 0.23/77.1 ± 10.2	1.4 ± 0.78/46.2 ± 8.0	3.3 ± 1.87/19.54 ± 7.27	<0.0001/<0.0001	<0.0001/<0.0001
NTproBNP n ± SD	3696.8 ± 638.4	5278.5 ± 7317.7	31.149.8 ± 55.423.1	0.022	<0.0001
Hemoglobin n ± SD	12.1 ± 1.9	12.1 ± 1.9	10.6 ± 1.4	0.75	<0.0001

Table 2
Procedural data AKI vs. non-AKI.

	AKI	Non-AKI	p-Value
Aortic surface area pre-TAVI (cm^2)	0.92 ± 0.53	0.77 ± 0.31	0.015
Aortic surface area post-TAVI (cm^2)	2.26 ± 0.82	2.01 ± 0.54	0.057
Peak gradient pre-TAVI (mm Hg)	35.8 ± 19.6	43.6 ± 24.7	0.14
Peak gradient post-TAVI (mm Hg)	3.2 ± 3.4	3.6 ± 5.1	0.75
Mean gradient pre-TAVI (mm Hg)	33 ± 13.2	41.4 ± 16.7	0.017
Mean gardient post-TAVI (mm Hg)	7.3 ± 4.5	9.5 ± 7	0.16
LVsys pre-TAVI (mm Hg)	137.23 ± 41.76	157.58 ± 32.31	0.005
LVsys post-TAVI (mm Hg)	122.15 ± 23.56	134.49 ± 25.87	0.04
LVdias pre-TAVI (mm Hg)	15.95 ± 5.02	16.44 ± 6.72	0.74
LVdias post-TAVI (mm Hg)	20.75 ± 6.03	18.94 ± 7.05	0.26
AOsys pre-TAVI (mm Hg)	101.6 ± 30.4	114.1 ± 23.8	0.018
AOsys post-TAVI (mm Hg)	119.1 ± 22.6	130.9 ± 25.2	0.04
AOmean pre-TAVI (mm Hg)	65.7 ± 17.3	73.8 ± 14.7	0.014
AOmean post-TAVI (mm Hg)	70 ± 12.3	79.8 ± 14	0.002
AOdias pre-TAVI (mm Hg)	47.8 ± 12.7	53.6 ± 12.9	0.04
AOdias post-TAVI (mm Hg)	45.5 ± 12.2	54.3 ± 11.3	<0.0001
PAPsys pre-TAVI (mm Hg)	50.7 ± 16.1	44.2 ± 15.6	0.056
PAPsys post-TAVI (mm Hg)	50.8 ± 16.6	45.6 ± 15.7	0.14
PAPmean pre-TAVI (mm Hg)	31.1 ± 10.4	27 ± 9.8	0.063
PAPmean post-TAVI (mm Hg)	30.8 ± 9.8	28 ± 10.2	0.21
PAPdias pre-TAVI (mm Hg)	21.2 ± 7.9	18.5 ± 8	0.118
PAPdias post-TAVI (mm Hg)	20.9 ± 7.1	19.3 ± 8.2	0.4
PCWP pre-TAVI (mm Hg)	20.1 ± 7.7	18.9 ± 8.8	0.5
PCWP post-TAVI (mm Hg)	21.8 ± 6.8	20.3 ± 9.1	0.48
Cardiac output pre-TAVI (l/min)	4.3 ± 1.6	4.3 ± 1.4	0.9
Cardiac output post-TAVI (l/min)	4.4 ± 1.8	4.6 ± 1.5	0.63
RA pre-TAVI (mm Hg)	12.8 ± 8.5	10.5 ± 6	0.21
RA post-TAVI (mm Hg)	14.3 ± 5.8	10.7 ± 5.6	0.007
Procedural success	29 (97%)	498 (98%)	0.61
Paravalvular leakage ≥2+	2 (6.6%)	28 (5%)	0.23
Minor vascular complications	0	95 (19%)	0.009
Major vascular complications	3 (10%)	23 (5%)	0.173
Bleeding	7 (23%)	76 (15%)	0.21

total of 301 patients (55.7%). Interestingly, the cardiac output of these patients showed a significant increase after TAVI (CO before TAVI: 4.25 ± 1.29; CO after TAVI: 4.52 ± 1.4, p< 0.0001; corresponding to a relative increase of CO of 8.8% ± 26.9%). Conversely, patients with a decrease of GFR after TAVI displayed no change in CO (CO before TAVI: 4.24 ± 1.41; CO after TAVI: 4.36 ± 1.59, p = 0.35; ΔCO = 1.9% ± 23.5%). Focusing on patients with a decreased GFR after TAVI, the largest number of patients with a decrease in GFR was found in group A, of which 95 patients (35.1%) had an impairment of renal function at discharge compared to pre-procedural renal function (GFR before TAVI: 75.0 ml/min, GFR at discharge: 59.0 ml/min, p < 0.0001). In accordance to the results of GFR-changes, the most significant decrease of creatinine was found in group C (before TAVI: 3.3 ± 1.87; discharge: 2.95 ± 2.3; p = 0.022). In general, the creatinine values decreased in a total of 199 patients (36.9%).

3.3. Incidence of AKI

In total, 30 patients (5.6%; Rifle-classification) and 15 patients (2.8%; VARC2-definition) developed an AKI (Fig. 3). With regard to VARC 2, AKI stage 1 occurred in 3 patients, stage 2 in 8 patients, and stage 3 in 4 patients, respectively. According to the classification into the three predefined groups (renal function at baseline), AKI (Rifle) occurred in 4.4% (12 patients) of group A, 7.5% (16 patients) of group B and 3.7% (2 patients) of group C. Predictive factors for AKI (Rifle) were anemia, high logistic Euro Score, and major vascular complications (Table 3). A total of 18 (60% from those with AKI) patients had to undergo temporary dialysis. 30-day-mortality of patients with an AKI (Rifle) was 53.3% (16 patients), and 12-month-mortality was 73.3% (22 patients). Interestingly, contrast media volume was not a significant predictor for AKI (p = 0.52), albeit average contrast media volumes were still in a high range, but slightly lower in group C (149 ± 80.8 ml) compared to groups B (168 ± 76.3 ml, p = 0.15) and A (190 ± 78.8 ml; p = 0.003), respectively (Fig. 4).

Regarding the hemodynamics, there were significant differences between patients with AKI (Rifle) vs. without AKI after TAVI (Table 2). Patients without AKI after TAVI had a higher mean aortic blood pressure compared to patients with AKI before (p = 0.014) and after TAVI (p = 0.002). Albeit similar right atrial pressures before TAVI, right atrial pressures were significantly higher in patients with AKI after TAVI compared to patients without AKI (p = 0.007). There was a trend to higher mean pulmonary artery pressure in patients with AKI before TAVI compared to patients without AKI (p = 0.063). In addition, patients with AKI had no improvement of CO after TAVI (increase 0.2%; p = 0.9) compared to patients without AKI (increase 7.2%; <0.0001, Table 2). Furthermore, univariate analysis showed, that a low CO after TAVI was significantly associated with the occurrence of AKI (p = 0.022). Interestingly, severity of aortic stenosis seemed to be less pronounced in patients with AKI compared to patients without AKI (as evidenced by transvalvular gradients and aortic surface area; see Table 2).

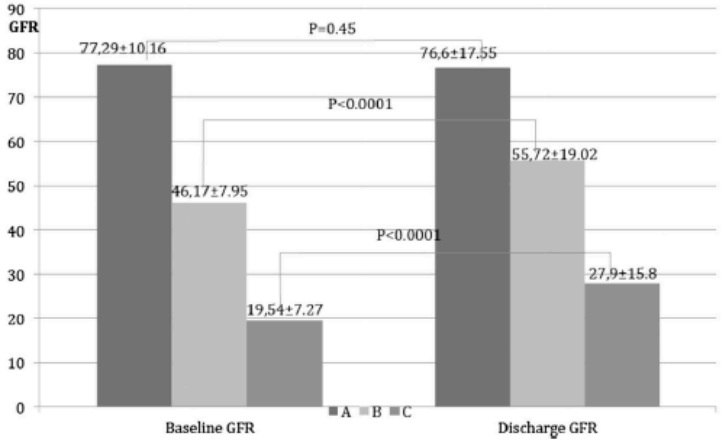

Fig. 1. Baseline GFR and GFR at discharge in groups A, B and C.

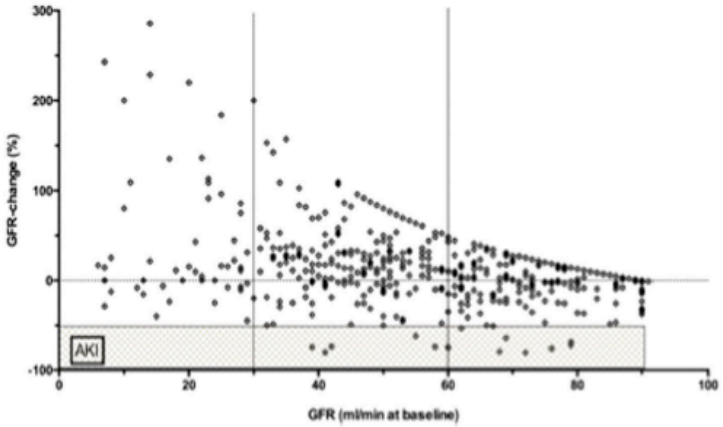

Fig. 2. Change of GFR in groups A, B and C.

3.4. Thirty-day-/and 12-month-outcome

Overall 30-day mortality was 10.2%, and 12-month mortality was 21.5%. Multivariate analysis showed a significant impact of GFR on mortality ($p = 0.0008$) in the whole study group. Further risk factors for mortality were temporary renal dialysis, higher levels of NTproBNP, major vascular complication, dementia, non-femoral access, and arterial hypertension (Table 4). In patients with normal renal function (group A), 30-day survival was 94.6%, and 12-month survival was 85%. In patients with moderate impaired renal function (group B), 91% survived after 30 days and 68% after 1 year. In patients with severe impaired renal function (group C), 30-day survival was 75% and only 51% of the patients survived after 1 year (Fig. 5).

3.5. Mortality and change of kidney function after TAVI

ROC-analysis revealed a statistically significant positive association of GFR-change after TAVI and 12-month mortality. Patients with an increase in GFR ≥22.2% had a lower mortality ($p = 0.0068$), vice versa patients with a GFR decrease ≥14.9% after TAVI displayed a higher mortality ($p = 0.0051$).

Despite the greatest improvement in GFR after TAVI in group C (see above), we observed the highest 30-day and 1-year-mortality compared to the other groups. Subgroup analysis showed that 34 patients (63%) of group C had an increase in GFR and 15 patients (27.8%) had a decrease of GFR after TAVI. Patients with an increase in GFR had a 30-day-mortality of 23.5% and a 12-month-mortality of 41.2%, compared to a numerically higher 30-day-mortality of 33.3% ($p = 0.48$) and 12-month-mortality of 60% ($p = 0.23$) in patients with a declining GFR after TAVI, respectively.

3.6. Predictors for GFR-change

Subgroup analysis with regard to kidney function after TAVI showed the following results: patients with an increase in GFR ≥22.2% (mostly patients of group C) after TAVI had a higher prevalence of major vascular complications ($p = 0.0012$), stroke ($p = 0.03$) and a higher logES ($p = 0.0016$). Predictors for no significant change of GFR after TAVI (ΔGFR −14.9%–+22.2%) were pacemaker before TAVI ($p = 0.007$), anemia ($p = 0.008$) and female gender ($p = 0.003$). Patients with a decrease of GFR ≥14.9% after TAVI had more frequent dialysis in their past medical history ($p = 0.005$) and anemia ($p = 0.04$).

4. Discussion

The main findings of the present study are: (1.) the pre-procedural kidney function is statistically associated with a significantly increased mortality in patients after TAVI, (2.) a change of kidney function after TAVI appears to influence mortality, and (3.) an acute kidney injury is a very strong predictor of 12 month mortality.

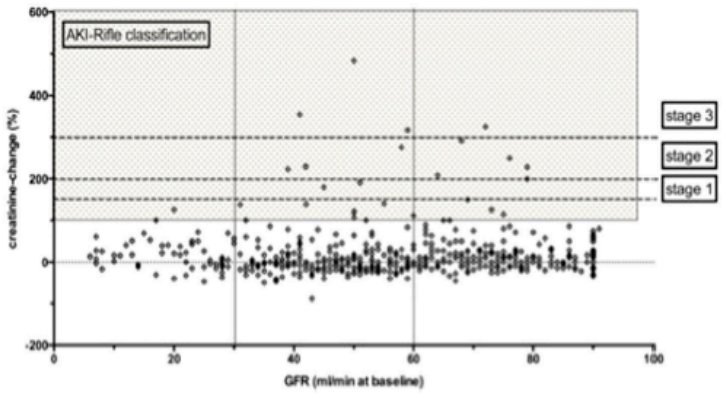

Fig. 3. Incidence of AKI according to baseline-GFR. The incidences of all 3 stages (according to VARC II) are indicated by the individual boundaries with respect to creatinine increase.

Table 3
Dependent predictors for acute kidney injury.

Parameter	p-Value	95% CL
Anemia	0.067	1.083
LogEuro-Score	0.016	3.165
Major vascular complications	0.031	35.740

Table 4
Independent predictors for mortality.

Parameter	p-Value	HR	HR lower CL	HR upper CL
Temporary dialysis	0.0008	4.360	1.846	10.298
NTproBNP	0.0002	1.943	1.373	2.750
CKD	0.0008	2.246	1.401	3.599
Major vascular complication	<.0001	4.647	2.252	9.589
Dementia	0.0020	2.329	1.362	3.984
Femoral access	0.0187	0.472	0.252	0.883
Arterial hypertension	0.0324	0.533	0.300	0.949

4.1. Effect of renal function on mortality

In patients with normal kidney function, 30-day mortality was almost half compared to patients with a moderate reduced pre-procedural kidney function (5.4%, vs. 9%), whereas the mortality in patients with severe reduced kidney function was almost 5-fold increased (5.4% vs. 25%). Accordingly, 12 month-mortality was much lower in group A vs. group B vs. group C (15% vs. 32% vs. 49%). These findings are similar to those of Dumonteil et al. [6]. In their study, the 1-year survival rate in patients with a severe impaired pre-procedural renal function was 62.2%, compared to 91.4% in patients with normal renal function. Comparable results were reported by Yamamoto et al. [17]. In their study, 30-day- and 12-month-mortalities were significantly increased (30 day-mortality: 26.2% and 12 month-mortality: 47.8%) in patients with a higher stage of chronic kidney disease. Sinning and colleagues [18] showed that a pre-procedural serum creatinine level ≥1.58 mg/dl was associated with a 6-fold increased risk of 30-day mortality and a 4-fold increased risk of 1-year mortality. Our data support the conclusion drawn by these authors, that impaired renal function is a strong predictor of 30-day and 12-month mortality in patients undergoing TAVI. Interestingly, patients with severe impaired renal function were excluded from the PARTNER trial [4] — thus, the PARTNER trial results cannot necessarily be extended to patients with severe impaired renal function.

4.2. GFR improvement after TAVI

An improvement of kidney function after TAVI has been described in several other studies [19,20]. Similar to our study, Bagur and colleagues found an increase in GFR after TAVI in 60% of their patients [19]. In our patient population, overall GFR increased in 55.7% of the patients. The largest increase in GFR was found in group C. Comparable results were shown in the study of Keles and colleagues [21]. They reported, that patients with CKD before TAVI demonstrated a significant improvement in renal function after the procedure. Therefore, patients with severe impaired renal function seem to obtain a certain benefit from TAVI with regard to their kidney function. This observation seemed to translate into a reduced mortality in patients with an improvement in kidney function after TAVI, whereas an impairment did not. Although patients of group C had the most remarkable increase in GFR after TAVI in our study, this group had the highest mortality after TAVI. Statistical analysis revealed, that those patients with the most prominent increase in GFR (mostly patients of group C) after TAVI had unfortunately the highest incidence of major vascular complications, stroke and a higher logES at baseline. Thus, the high mortality in group C can be explained by the higher prevalence of co-morbidities and a higher susceptibility for complications in these particular patients.

In addition, our hemodynamic data suggests, that patients with an increase in GFR after TAVI had the largest increase in CO after TAVI, supporting the concept that an improved renal blood flow does preserve renal function. Along these lines, Ljungman et al. [22] showed that GFR was strongly associated with hemodynamic parameters. Their univariate analysis showed a significant relation between renal blood flow and GFR ($p < 0.0001$). Several other studies have shown that cardiac output is a strong determinant of renal function [23,24]. According to these results, a rise in cardiac output after TAVI serves as a protective factor for kidney function as seen in the univariate analysis.

4.3. Acute kidney injury after TAVI

Several studies have shown that AKI is a serious complication after TAVI [25–27]. Thirty patients (5.6%) in our patient population developed AKI (Rifle) after TAVI, and 60% of those temporarily had to undergo dialysis. These patients had a very high mortality (73.3% were deceased after 12 months). No study has as yet shown the coherence between hemodynamic parameters and AKI after TAVI and only very few data exists about the impact of invasive hemodynamics and renal function. Monitoring of systemic arterial pressures is a generally accepted monitoring tool in any surgical intervention, since systemic hypoperfusion is known to be associated with organ failure and procedural mortalities. We found a lower blood pressure before and after TAVI in patients with AKI compared to patients without AKI. This observation underlines the fact, that an invasive monitoring remains mandatory before and after TAVI to prevent systemic hypotension. Nevertheless, periprocedural mean arterial blood pressure was still in an acceptable range in patients with AKI in our study, indicating that other factors remain important contributors to AKI. Accordingly, patients with AKI in our study displayed no change in CO, whereas patients without AKI demonstrated an increase in CO after TAVI. Thus, a rise in CO seems to be an important protective factor against the occurrence of AKI during TAVI. Interestingly, the comparison of the preprocedural severity of aortic stenosis indicated that patients with AKI had less valvular obstruction compared to patients without AKI. Thus, it might be conclusive that the placement of a THV in these patients did provide a lower net increase in aortic surface area with a subsequent lower beneficial impact on cardiac output. Moreover, we found a higher rise in right atrial pressures after TAVI in patients with AKI, possibly indicating some kind of

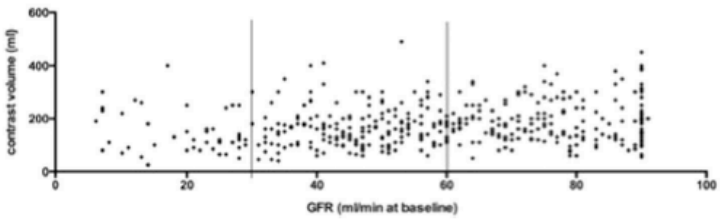

Fig. 4. Contrast media volume in relation to renal function (defined by GFR) in groups A, B and C.

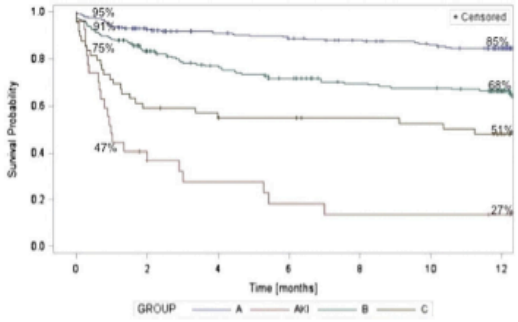

Fig. 5. Mortality after TAVI in groups A, B and C, as well as in patients with AKI.

backward failure compared to patients without AKI. Furthermore, patients with AKI had higher left ventricular end-diastolic pressures after TAVI (despite lower pressures before TAVI), which supports our thesis, that hemodynamics seem to be an important factor for the development of AKI.

Interestingly, Adams and colleagues reported very recently a lower incidence with TAVI compared to SAVR (6.0% vs. 15.1%; $p < 0.001$) [5]. Similarly Bagur et al. [19] evaluated the occurrence of AKI in patients undergoing TAVI in comparison to patients with SAVR. In their study, 9% suffered from AKI after TAVI, whereas SAVR was associated with an incidence of AKI in 26%. In addition, similar to our results, the transapical approach was a major risk factor for AKI. Noble [28] speculated that a transapical TAVI in their study may cause a trauma to the left ventricle, which leads to a decreased left ventricular ejection fraction. Subsequently, hypoperfusion of the kidneys may be a cause for AKI. This hypothesis is supported by a decrease in CO after transapical TAVI ($\Delta CO = -3.7\% \pm 23.9\%$) in our patient population compared to an increase in CO after transfemoral TAVI ($\Delta CO = 7.6\% \pm 25.8\%$).

Until today, several predictive factors for the occurrence of AKI have been proposed. Nuis et al. [11] reported similar to our results, that AKI is a predictor for short- and longterm mortality. They also reported, that the number of blood transfusions was a predictor for AKI. However, multivariate analysis in our study did not show, that blood transfusions were associated with the occurrence of AKI ($p = 0.12$), although blood transfusions were numerically higher in patients with AKI (AKI: 7 patients [23%]; non-AKI: 76 patients [15%]). However, our multivariate analysis showed, that major vascular complications ($p = 0.031$) were strongly associated with post-procedural AKI. Thus, both variables (blood transfusion and vascular complication) are likely to be interrelated, despite the fact that blood transfusion did not reach statistical significance – possibly explained by the low numbers of patients with AKI (statistically underpowered). Barbanti et al. [10] reported in their multicenter study, that especially patients with female gender and baseline renal insufficiency had a high risk for AKI after TAVI. Again, in contrast to their study, we subdivided patients with impaired renal function in two separate groups, with a higher incidence of AKI in group B compared to group C. This finding was unexpected, since many studies have reported a strong correlation between poor renal function and AKI [10,29]. Finally, we did not observe that the volume of contrast media was associated with AKI, an observation that has been previously reported by Goebel et al. [30]. Nevertheless, the average volume of contrast media was still in the upper range in our study and a lower number would have been more than desirable. It might be taken as a limitation of our study, that we didn't perform an intra-procedural transesophageal echo (TEE) in all patients (except in transapical cases). Since the vast majority of procedures were performed under analgosedation, we had to rely on angiography and invasive hemodynamics for evaluation of the performance of the THVs. Nevertheless, post-ballooning to diminish PV leaks was frequently performed and the rate of significant aortic regurgitation was acceptably low in our study, indicating a limited value of intraprocedural TEE if the TAVI is performed appropriately.

4.4. Limitations

This is a single center study with retrospective data collection. Accordingly, despite all precautions, some observation bias cannot be excluded. In addition, we cannot rule out with certainty the possibility that other variables might have influenced the results, which were not analyzed in this study. There is an ongoing controversy if TEE should be mandatorily applied during TAVI. Clearly, TEE does frequently provide important information with regard to the THV performance. Nevertheless, our center believes in a more minimalistic approach, making the patients' comfort in the center (sparing general anesthesia, TEE only in selected cases, etc.). The latter is at the expense of higher contrast media volumes, which may certainly increase the risk of AKI. However, the rate of AKI in our patients was in a lower range with no association to contrast media volume and the study was still sufficiently powered to demonstrate a general effect of TAVI on renal function.

5. Conclusion

Kidney function is a powerful long-term predictor of mortality in patients undergoing TAVI. Patients with severe impaired renal function had the highest mortality after TAVI. Thus, the beneficial effects of TAVI in patients with severe impaired renal function seem to be limited and should be implemented in a decision making process before TAVI. Fortunately, in most patients an improvement in kidney function could be observed after TAVI, translating into a survival benefit after the procedure. Nevertheless, TAVI is associated with a certain risk of AKI with a devastatingly low long-term survival. Therefore, preprocedural renal function should be carefully assessed and any precaution to prevent AKI during TAVI should be implemented in every patient.

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2. Zusammenfassende Darstellung der Publikation

2.1 Einleitung

Die Aortenklappenstenose ist die häufigste erworbene Herzklappenerkrankung (Nkomo et al., 2006) und wird primär durch einen chirurgischen Aortenklappenersatz mit sehr geringen Komplikationsraten kurativ behandelt (Elayda et al., 1993, O'Brien et al., 2009, Schwarz et al., 1982). Dennoch ist insbesondere das Akute Nierenversagen (ANV) eine schwerwiegende Komplikation nach herzchirurgischen Eingriffen (Chertow et al., 1998, Thakar et al., 2005, Rosner and Okusa, 2006). Viele Studien zeigten, dass ein ANV auch nach Transkatheter-Aortenklappenimplantation (TAVI) eine ernstzunehmende Komplikation darstellt, die die Lebenserwartung der Patienten deutlich reduziert (Nuis et al., 2012, Barbanti et al., 2014). So zeigten Bagur et al. in ihrer Studie (ähnlich zu unserer Studie), dass ein ANV nach TAVI eine schwerwiegende Komplikation darstellt, jedoch nach TAVI seltener als nach herzchirurgischem Aortenklappenersatz vorkommt (9,2% vs. 25,9%) (Bagur et al., 2010). Der Wichtigkeit der Nierenfunktion bei der Indikationsstellung für eine TAVI in Hinblick auf postprozedurale Mortalität und Morbidität wird dadurch Rechnung getragen, dass die Nierenfunktion eine besondere Bedeutung bei den Risikostratifizierungssystemen logistischer EuroSCORE (Sedaghat et al., 2013) und VARC (Kappetein et al., 2012) besitzt.
Die Zielsetzung unserer retrospektiven Studie bestand darin, bei einem Patientenkollektiv von 540 Patienten den Einfluss der präprozeduralen Nierenfunktion auf die Mortalität nach TAVI (i), sowie potenzielle Veränderungen der Nierenfunktion einschließlich der Inzidenz eines ANV im Rahmen einer TAVI zu untersuchen (ii). In einer weiteren Fragestellung wurde untersucht, inwieweit eine Veränderung der Nierenfunktion im Rahmen der TAVI Prozedur einen Einfluss auf die Mortalität hat (iii).

2.2 Material und Methode

Zwischen Juli 2008 und September 2012 wurden in der Abteilung für Kardiologie der Asklepios Klinik St. Georg 558 Patienten mittels TAVI versorgt.

Ausgeschlossen von der Studie wurden Patienten bei denen bestimmte Laborwerte, insbesondere die glomeruläre Filtrationsrate (GFR) vor TAVI nicht vorhanden waren (n=18), sodass 540 Patienten in die finale Studie aufgenommen wurden. Die Indikation zur TAVI war in folgenden Fällen gegeben: Patienten mit symptomatischer hochgradiger Aortenklappenstenose mit Dyspnoe, Angina pectoris und Synkopen, Patienten mit asymptomatischer hochgradiger Aortenklappenstenose, aber eingeschränkter linksventrikulärer Ejektionsfraktion, Patienten mit asymptomatischer Aortenklappenstenose und pathologischer Belastungsuntersuchung und bei Patienten mit hochgradiger Aortenklappenstenose mit geringem Druckgradienten (KÖF < 1 cm^2, mittlerer systolischer Gradient < 40 mmHg) und eingeschränkter linksventrikulärer Ejektionsfraktion. Bei allen Patienten wurde die Nierenfunktion durch regelmäßige Blutentnahmen während des Krankenhausaufenthalts systematisch überwacht. Die für diese Arbeit relevanten Werte waren die GFR und das Serumkreatinin vor der Prozedur, am Tag der Prozedur, sowie der Minimal- und Maximalwert bis zur Entlassung. Die Patienten wurden nach ca. vier Wochen, sechs Monaten und zwölf Monaten zur Nachuntersuchung in die kardiologische Ambulanz zur Durchführung erneuter Laborkontrollen einbestellt. Die nach der Entlassung gesammelten Daten ermöglichten es Langzeitergebnisse zu evaluieren. Die GFR wurde nach MRDR (Modification of Diet in Renal Disease)-Formel bestimmt. Alle Patienten wurden bezüglich ihrer GFR in drei Gruppen aufgeteilt (Gruppe A: normale Nierenfunktion, GFR ≥ 60ml/min; Gruppe B: leichte bis mittelgradig eingeschränkte Nierenfunktion, GFR 30-59 ml/min; Gruppe C: hochgradig eingeschränkte Nierenfunktion, GFR ≤ 29ml/min).

2.3 Ergebnisse

Das durchschnittliche Alter der Patienten lag bei 80,2 ± 7,1 Jahren, der logistische EuroSCORE lag durchschnittlich bei 24,5% ± 17,9%. Tabelle 1 zeigt die klinischen Basisdaten und die demographischen Daten der Patienten.

2.3.1 Prozedurale Daten

Die Klappenimplantation wurde in 98% erfolgreich durchgeführt. Die Häufigkeit

von signifikanten paravalvulären Leckagen (PVL) lag bei 6% (33 Patienten). In Bezug auf vaskuläre Komplikationen gab es zwischen den einzelnen Gruppen keine signifikanten Unterschiede. Es zeigte sich jedoch eine erhöhte Tendenz zu Blutungskomplikationen in Gruppe C (24%) im Vergleich zu Gruppe A (16%) (p=0,17) und Gruppe B (14%) (p=0,09).

2.3.2 Hämodynamische Messungen

Bei den Messungen der hämodynamischen Parameter vor Implantation der Klappe zeigten sich einige Unterschiede zwischen den Gruppen A, B und C.
Der transvalvuläre Gradient vor TAVI war am höchsten in Gruppe A (mittlerer Gradient vor TAVI: 43,7 ± 16,4 mmHg) und war nach TAVI bei allen Gruppen signifikant reduziert (mittlerer Gradient vor TAVI: 41 ± 16,7 mmHg; mittlerer Gradient nach TAVI: 9,4 ± 6,7 mmHg; p<0,0001).
Präprozedural war der systemische arterielle Blutdruck in Gruppe C am niedrigsten. Dieser stieg nach TAVI vergleichbar zu Gruppe A und B an. Die standardmäßig durchgeführte Rechtsherzkatheteruntersuchung zeigte bei Patienten der Gruppe C höhere Drücke im kleinen Kreislauf (PAP und PCWP) vor und nach TAVI. Die rechtsatrialen Füllungsdrücke (RA) zeigten einen ausreichenden Volumenstatus in allen Gruppen vor und nach TAVI. Die RA-Drücke waren in Gruppe C vor und nach TAVI im Vergleich zu Gruppe A und B leicht erhöht.

2.3.3 Änderung der Nierenfunktion nach TAVI

Die durchschnittliche GFR aller Patienten vor TAVI lag bei 59,1 ± 21,7 ml/min. Bei 301 Patienten (55,7%) kam es zu einer Verbesserung der Nierenfunktion nach TAVI, bei 69 Patienten (12,8%) fand sich keine Veränderung und bei 169 Patienten (31,3%) verschlechterte sich die Nierenfunktion nach TAVI. Bei Patienten aus Gruppe C verbesserte sich die Nierenfunktion am deutlichsten (GFR vor TAVI: 19,5 ± 7,3; GFR bei Entlassung: 27,9 ± 15,8; p < 0,0001) im Vergleich zu den Gruppen A und B. Bei Patienten mit mittelgradig eingeschränkter Nierenfunktion (Gruppe B) zeigte sich ebenfalls eine Verbesserung der Nierenfunktion nach TAVI (GFR vor TAVI: 46,2 ± 7,9; GFR bei Entlassung: 55,7 ± 19,0; p < 0,0001), wohingegen Patienten der Gruppe A keine wesentliche Veränderung der Nierenfunktion nach TAVI aufwiesen (GFR

vor TAVI: 77,3 ± 10,2; GFR bei Entlassung: 76,6 ± 17,6; p = 0,45) (Abbildung 1 und 2). Es existieren einige Studien, in denen ebenfalls ein Anstieg der GFR nach TAVI beschrieben wird (Bagur et al., 2010, Aregger et al., 2009, Keles et al., 2013). Konform zu unseren Ergebnissen berichteten Keles et al. über eine signifikante Verbesserung der Nierenfunktion nach TAVI bei Patienten mit chronischer Niereninsuffizienz, wiesen aber gleichzeitig auf eine sorgfältige Patientenselektion hin, da diese Patientengruppe auf der anderen Seite auch aufgrund vieler Komorbiditäten ein hohes Risiko für Morbidität und Mortalität haben (Keles et al., 2013). Interessanterweise zeigte sich bei Patienten in unserer Studie, bei denen sich die Nierenfunktion nach der Prozedur verbesserte, auch eine signifikante Verbesserung des Herzzeitvolumens (HZV) nach TAVI (HZV vor TAVI: 4,25 ± 1,29; HZV nach TAVI: 4,52 ± 1,4, p < 0,0001; ΔHZV = 8,8% ± 26,9%). Bei den Patienten, bei denen sich die Nierenfunktion nach TAVI verschlechterte, zeigte sich analog dazu keine Verbesserung des HZV nach TAVI (HZV vor TAVI: 4,24 ± 1,41; HZV nach TAVI: 4,36 ± 1,59, p = 0,35; ΔHZV = 1,9% ± 23,5%).

2.3.4 Akutes Nierenversagen

Ein ANV trat insgesamt bei 30 Patienten nach TAVI auf (5,6%). Bei 18 dieser Patienten (60%) musste eine temporäre Dialyse erfolgen. 11 dieser Patienten (37%) verstarben innerhalb von 12 Monaten. Von den 30 Patienten, die nach TAVI ein ANV entwickelten, war die Mehrheit (16 Patienten, 53,3%) der Gruppe B zuzuordnen. Aus Gruppe A entwickelten 12 Patienten (40%) ein ANV und aus Gruppe C nur 2 Patienten (6,7%) (Abbildung 3). Eine mögliche Erklärung dafür, dass Patienten aus Gruppe B eher ein ANV entwickelten als Patienten aus Gruppe C könnte sein, dass Patienten aus Gruppe C eher eine renale Kontrastmittel-Prophylaxe in Form von intravenöser Hydratation erhielten als Patienten aus Gruppe B. Risikofaktoren für das Auftreten eines ANV waren ein hoher logistischer EuroSCORE (p=0,016) und bedeutsame vaskuläre Komplikationen (p=0,003). Eine Tendenz zeigte sich bei Patienten mit Anämie (p=0,067). Überraschend zeigte sich, dass die applizierte Kontrastmittelmenge (KM) kein Prädiktor für das Auftreten eines ANV war. Die mittlere KM-Menge, die für die Prozedur verwendet wurde, betrug bei Patienten mit ANV 199 ml ± 121,2 ml, bei Patienten ohne ANV wurde durchschnittlich 175 ml ± 75,25 ml

verwendet (p=0,13). Auch im Vergleich der einzelnen Gruppen A, B und C zeigten sich bei der KM-Menge leichte, jedoch nicht signifikante Unterschiede (C:149 ± 80,8 ml; B:168 ± 76,3 ml; A:190 ± 78,8 ml; P1 = 0,15, P2 = 0,003) (Abbildung 4).

2.3.5 Einfluss hämodynamischer Faktoren auf Akutes Nierenversagen

Ein gewisser Einfluss einer veränderten Hämodynamik zeigte sich auch bei Patienten mit Akutem Nierenversagen nach TAVI. So fand sich bei Patienten mit ANV nach TAVI kein Anstieg des HZV nach TAVI (HZV vor TAVI: 4,3 ± 1,5; HZV nach TAVI: 4,4 ± 1,8; ΔHZV = 0,2% ± 18,6%; p = 0,86) im Vergleich zu Patienten ohne ANV (HZV vor TAVI: 4,3 ± 1,4; HZV nach TAVI: 4,6 ± 1,5; ΔHZV= 7,2% ± 26,5%; p < 0,0001) (Tabelle 2). Bisher existieren keine Untersuchungen über einen Zusammenhang zwischen hämodynamischen Parametern und dem Auftreten eines ANV nach TAVI. Sampaio et al. zeigten in ihrer Studie einen Zusammenhang zwischen einem niedrigen HZV und ANV nach herzchirurgischen Eingriffen. Sie beschrieben, dass ein niedriges HZV der bedeutendste Prädiktor für das Auftreten eines ANV ist (Sampaio et al., 2013). Interessant ist auch die Beobachtung von Arreger et al., dass Patienten die einer transapikalen TAVI unterzogen werden ein erhöhtes Risiko für ein ANV aufweisen (Aregger et al., 2009). Redfors et al. zeigten in ihrer Studie über ANV bei Patienten nach herzchirurgischem Eingriff, dass sich die Sauerstoffversorgung und die GFR deutlich verbesserte, wenn der mittlere arterielle Druck von 60 mmHg auf 75 mmHg erhöht wurde (Redfors et al., 2011). Poukkanen et al. berichteten in ihrer Studie, dass die Vermeidung von hypotensiven Phasen (mit einem mittleren arteriellen Druck < 73 mmHg) die Progression eines ANV zu verhindern scheint (Poukkanen et al., 2013). Es zeigte sich bei unserer Patientenpopulation, dass Patienten mit transapikalem Zugang im Durchschnitt ein vermindertes HZV nach TAVI hatten (ΔHZV = -3,7% ± 23,9%). Im Gegensatz dazu kam es bei Patienten mit transfemoralem Zugang zu einer Steigerung des HZV nach TAVI (ΔHZV = 7,6% ± 25,8%). Diese Ergebnsisse zeigen, dass hämodynamische Parameter einen starken Einfluss auf das Auftreten von ANV nach TAVI besitzen könnten und eventuell eine tragende Rolle bei der Früherkennung, bzw. Prävention eines ANV spielen könnten.

2.3.6 Mortalität

Im Patientenkollektiv lag die 30-Tages-Mortalität insgesamt bei 10,2 %, die 12-Monats-Mortalität lag bei 21,5 %. Risikofaktoren für Mortalität sind in Tabelle 4 dargestellt. Die multivariate Analyse zeigte einen starken Zusammenhang zwischen präprozeduraler GFR und Mortalität (p=0,0008). Es zeigte sich außerdem, dass es erhebliche Unterschiede bezüglich der Mortalität zwischen den Gruppen A, B und C gab. Die 30-Tages-Mortalität bei Patienten der Gruppe A (GFR ≥ 60 ml/min) lag bei 5,4%, bei Gruppe B (GFR 30-59 ml/min) bei 9% und bei Gruppe C (GFR ≤ 29 ml/min) bei 25%. Die 12-Monats-Mortalität lag bei Gruppe A bei 15%, bei Gruppe B bei 32% und bei Gruppe C bei 49%. Obwohl Patienten aus Gruppe C einen größeren Benefit bezüglich der Verbesserung der Nierenfunktion im Vergleich zu Gruppe A und B zu haben scheinen, zeigte sich, dass diese Patienten eine deutlich höhere 30-Tages- und 12-Monats-Mortalität aufwiesen. Die Indikationsstellung zur TAVI sollte aus diesem Grunde bei dieser Patientengruppe behutsam abgewogen werden. Dumonteil et al. zeigten ebenfalls in ihrer Studie, dass es deutliche Unterschiede zwischen der 12-Monats-Mortalität bei Patienten mit präprozedural stark eingeschränkter Nierenfunktion und den Patienten mit guter Nierenfunktion (37,8% vs. 8,6%) gab (Dumonteil et al., 2013). Patienten mit ANV nach TAVI hatten eine sehr hohe Mortalität, die 30-Tages-Mortalität lag bei 53% und die 12-Monats-Mortalität bei 73% (Abbildung 5). Auch die ROC-Analyse zeigte einen signifikanten Zusammenhang zwischen GFR-Veränderung nach TAVI und 12-Monats-Mortalität. Patienten mit einem GFR-Anstieg ≥ 22,2% hatten eine niedrigere Mortalität (p = 0,0068), im Gegensatz dazu hatten Patienten, bei denen sich die GFR nach TAVI um mehr als 14,9% verschlechterte eine erhöhte Mortalität (p=0,0051). Diese Ergebnisse zeigen zum einen, welch starken Einfluss die präprozedurale Nierenfunktion auf die Prognose der Patienten einnimmt und zum anderen, wie die Veränderung der Nierenfunktion nach TAVI (im Extremfall ein ANV) die Überlebenswahrscheinlichkeit der Patienten moduliert.

2.4 Zusammenfassung

Zusammenfassend lässt sich sagen, dass die präprozedurale Nierenfunktion einen starken Einfluss auf die Mortalität der Patienten nach TAVI besitzt. Auch Nierenfunktionsveränderungen wirken sich stark auf die Prognose der Patienten aus. Insbesondere Patienten mit ANV nach TAVI hatten eine sehr schlechte Prognose. Vor allem Patienten mit präprozedural mittelgradig eingeschränkter Nierenfunktion waren von einem ANV nach TAVI betroffen, so dass eine Prophylaxe (intravenöse Hydratation) auch bei dieser Patientengruppe erwogen werden sollte. Es zeigte sich, dass sich eine Verbesserung der Nierenfunktion positiv auf die Prognose der Patienten auswirkt. Obwohl sich die Nierenfunktion bei Patienten aus Gruppe C am stärksten verbesserte, hatte diese Patientengruppe dennoch die höchste Sterblichkeit nach TAVI. Benefit und Risiko eines TAVI Eingriffes sollten aus diesem Grund in der Indikationsstellung bei dieser Patientengruppe kritisch abgewogen werden.

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3. Erklärung des Eigenanteils an der Promotion

Hiermit versichere ich, Lisa Voigtländer, dass ich die folgenden Anteile der Promotionspublikation „Impact of kidney function on mortality after transcatheter valve
implantation in patients with severe aortic valvular stenosis“ selbstständig erarbeitet habe:

- Datenerhebung und -auswertung
- Literaturrecherche
- Erstentwurf und Bearbeitung des Manuskripts
- Statistische Auswertung in Zusammenarbeit mit Dr. Peter Wohlmuth

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Wissenschaftliche Beiträge

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D. Schewel, J. Schewel, J. Martin, **L.Voigtländer**, C. Frerker, P.Wohlmuth, T. Thielsen, K.H. Kuck, U.Schäfer
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Postervorträge:

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L.Voigtländer, J. Schewel, J. Martin, D. Schewel, C. Frerker, P.Wohlmuth, T.Thielsen, K.H. Kuck, U. Schäfer
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L. Voigtländer, J. Schewel, J. Martin, D. Schewel, C. Frerker, K.-H. Kuck, U. Schäfer
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J. Martin, J. Schewel, **L. Voigtländer**, D. Schewel, C. Frerker, F. Kreidel, K.-H. Kuck, U. Schäfer
Impact of pulmonary hypertension on outcome after transcatheter valve implantation in patients with severe aortic valvular stenosis
Jahrestagung der Deutschen Gesellschaft für Kardiologie
Mannheim, 05.04.2013

6. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....