Comparison of interventional and surgical myocardial revascularization in kidney transplant recipients – A single-centre retrospective analysis

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A B S T R A C T

Background: Kidney transplant recipients (KTR) reflect a high-risk population for coronary artery disease (CAD). CAD is the most common cause for morbidity and mortality in this population. However, only few data are available on the favourable revascularization strategy for these patients as they were often excluded from studies and not mentioned in guidelines.

Methods: This retrospective single-centre study includes patients with a history of kidney transplantation undergoing myocardial revascularization for multivessel or left main CAD by either percutaneous coronary intervention (PCI, n = 27 patients) or coronary artery bypass grafting (CABG, n = 24 patients) at University Hospital Frankfurt, Germany, between 2005 and 2015.

Results: In-hospital mortality was higher in the CABG group (20.8% vs. 14.8% PCI group; p = 0.45). In Kaplan-Meier analysis, one-year-survival showed better outcome in the PCI group (85.2% vs. 75%). After four years, outcome was comparable between both strategies (PCI 66.5% vs. CABG 70.8%; log-rank p = 0.94).

Conclusions: This retrospective single-centre study of KTR requiring myocardial revascularization, PCI seems to be superior to CABG with regard to in-hospital mortality, acute kidney injury and one-year-survival. To optimise treatment of these high-risk patients, larger-scaled studies are urgently warranted.

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1. Introduction

Patients suffering from chronic kidney disease (CKD) display a higher incidence of coronary artery disease (CAD) compared with the general population [1,2]. I patients with end-stage renal disease (ESRD), cardiovascular events are the most common cause for morbidity and mortality [3].

CKD is an important and independent predictor of CAD and MACCE (major adverse cardiac and cerebrovascular events) [2], with poorest outcome for patients with diabetic nephropathy or with a history of stroke or myocardial infarction [4].

Kidney transplantation provides long-term survival benefit compared to patients requiring chronic renal replacement therapy (RRT) [3] However, even after kidney transplantation, the incidence of CAD remains high [5,6], and cardiovascular events are the most common cause for death in KTR [2].

Consequently, a substantial number of KTR have to undergo coronary angiography (CA), which can be performed safely in these patients [6]. Recommendations for an optimised revascularisation strategy do not exist, since KTR are often excluded from studies and not addressed in current guidelines.

Both, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are routine procedures improving symptoms and prognosis of CAD. Both strategies are associated with the risk of acute kidney injury (AKI). Exposure to contrast dye during PCI is an often discussed risk factor for AKI, as well as surgery “on-pump” demanding extracorporeal circulation (ECC) and potential transient organ hypoperfusion [7,8]. Postoperative AKI reflects a risk factor for bleeding complications, in-hospital mortality and lower one-year survival [9].

Patients with ESRD undergoing CABG are at high risk for prolonged hospitalisation and higher mortality [10]. Similar findings were made...
for patients treated with PCI, irrespective of the stent type used [11], and patients suffering from contrast-induced nephropathy [8].

In ESRD patients undergoing CABG, a higher in-hospital mortality was observed while patients treated with PCI showed repeated revascularization procedures more often [12]. In CKD patients suffering from diabetes mellitus (DM), even asymptomatic patients benefit from revascularisation: the incidence of MACCE is reduced [13]. CABG showed higher initial mortality whereas long-term survival comparing both strategies displayed similar results in various studies [12,14].

For KTR, only a limited number of determinant reports of coronary revascularization is available. The aim of the present study is to describe short- and long-term prognosis, differences in the postoperative course and the impact on renal graft function in KTR patients treated either with PCI or CABG.

2. Methods

2.1. Patient population

The purpose of this retrospective single-centre study was to investigate the outcome of KTR undergoing myocardial revascularization for multivessel or left main CAD by either PCI or CABG. We reviewed all patients who had previously received kidney transplantation and underwent myocardial revascularization for multivessel or left main CAD from 2005 to 2015 at University Hospital Frankfurt, Germany. A total of 51 patients were included and analysed: 27 patients were treated with PCI and 24 patients with CABG. Individual treatment decisions were based on contemporary guidelines for CAD. A consensus of the interdisciplinary heart team, consisting of cardiologists, cardiothoracic surgeons and anaesthesiologists, was obtained if needed. In one patient, revascularization was performed with staged PCI. Approval for this study was obtained from the institutional ethics committee of Goethe University, Frankfurt, Germany (reference number 312/16).

Primary endpoint was in-hospital mortality. Secondary endpoints were bleeding complications, acute kidney injury and renal graft failure. Further, long-term follow-up was observed.

2.2. Data collection and follow-up

Patients matching the inclusion criteria were identified by screening the diagnosis-related groups and procedural codes for renal transplantation, CABG and PCI. Demographic, clinical, laboratory and periprocedural data were retrieved from the electronic medical case files for every patient.

Follow-up data were collected by investigating the electronic patient files, the affiliated outpatient clinic (KfH Schleusenweg, Kuratorium für Dialyse und Nierentransplantation e.V., Schleusenweg 22, 60528 Frankfurt am Main, Germany) and the patients’ general practitioners. Patients were followed up from the day of index procedure until 48 months after, all-cause death or until the end of June 2017.

2.3. SYNTAX Score I, II and EuroSCORE II

SYNTAX Score I was calculated by using the SYNTAX Score Calculator Tool on the official website (www.syntaxscore.com, accessed 03/16–07/16). This tool is based on the SYNTAX Trial (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) [15] which investigated the differences between PCI and cardiac surgery in high-risk patients with left main and multivessel CAD. The score illustrates the complexity of coronary anatomy and CAD lesions in order to classify high- and low-risk patients.

SYNTAX Score II [16] is a development of SYNTAX Score I and supports the clinicians’ decision-making by giving individual treatment recommendations. It includes the anatomical conditions but also clinical parameters like age, sex, glomerular filtration rate (GFR) and comorbidities such as diabetes mellitus and peripheral artery disease (PAD). All clinical parameters were analysed by screening the laboratory findings and comorbidities. The online calculator was used for estimation of SYNTAX Score II (www.syntaxscore.com, accessed 03/16–07/16).

EuroSCORE II™ (European System for Cardiac Operative Risk Evaluation) is used as a risk model to estimate the probable mortality after cardiac surgery. The score was calculated by using the online calculator tool (www.euroscore.org/calc.html, accessed 03/16–07/16) [17].

2.4. BARC bleeding criteria

Bleeding complications were defined by BARC criteria (Bleeding Academic Research Consortium) [18]. Patients are classified as type 0 if no signs of bleeding are apparent. Type 1 bleedings do not require treatment. Overt signs of hemorrhage without need for action are defined as type 2 bleedings. Type 3 bleedings are defined as following: type 3a overt bleeding with haemoglobin drop of 3–5 g/dl and transfusion; type 3b haemoglobin drop >5 g/dl, cardiac tamponade, need for surgical intervention or IV vasoactive agents; type 3c intracranial bleeding. CABG-related bleeding is classified as type 4 and type 5 as fatal bleeding.

2.5. AKIN classification

Baseline kidney function was estimated at admission based on the first creatinine value and the corresponding estimated glomerular filtration rate (eGFR) using the 4-variable MDRD formula. AKI was defined according to the Acute Kidney Injury Network (AKIN) classification [19], which defines AKIN 1 as a creatinine increase of <0.3 mg/dl or an 1.5 to 2 fold increase from baseline, AKIN 2 as a creatinine increase >2 to 3 fold increase from baseline and AKIN 3 as a creatinine increase above 3 fold or creatinine >4 mg/dl with an acute increase ≥0.5 mg/dl.

2.6. Statistical analysis

Continuous variables are shown as median and interquartile range (IQR). Categorical variables are reported as frequencies and percentages. Differences between patient cohorts were determined using the Fisher’s exact test for categorical variables; for quantitative variables the Mann-Whitney-U test was used. All p-values reported are two-sided, the level of significance was set p < 0.05. The Kaplan-Meier estimator was used for survival analysis. Statistical analyses and figures were performed using Prism 7 (GraphPad Software Inc.: San Diego, USA).

2.7. Compliance with ethical standards

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted (Ethics Committee approval number 312/16) and within the 1975 Helsinki declaration.

3. Results

3.1. Baseline characteristics

As depicted in Table 1, baseline characteristics of both groups (PCI and CABG) were similar, with patients in the PCI group tending to be older (64 years (IQR 55–73) vs. 62 years (IQR 54–68); p = 0.40) and more often of male gender (77.8% vs. 54.2%; p = 0.14).

Parameters of renal function are presented for patients with sufficient graft function only. Creatinine and GFR were 1.7 mg/dl (IQR 1.3–2.1) and 37.4 ml/min (IQR 31.9–48) in the PCI group and 1.6 mg/dl (IQR 1.3–2.2) and 34.5 ml/min (IQR 25–46.7) in the CABG group (p = 0.51 and p = 0.51).

One third of the PCI patients (33.3%) suffered from DM while only 25% patients of the CABG group had DM (p = 0.55). PAD was found more often in der PCI group (33.3% vs. 20.8%; p = 0.36). Chronic
respiratory disease showed lower incidence in this population. Only 11.1% of the PCI patients and 25.0% of the CABG patients suffered from this disease (p = 0.97). Median left ventricular ejection fraction (LVEF) was 60% (IQR 48.8–65) in the PCI group and 55% (IQR 50–65) in the CABG group (p = 0.97).

The majority of both groups suffered from a three-vessel disease, 55.6% in the PCI group and 66.7% in the CABG group (p = 0.57), respectively. The remaining 44.4% of the PCI group showed a two-vessel disease. Three patients (12.5%) of the CABG group showed only one-vessel disease. These three patients received CABG in addition to surgical aortic valve replacement (SAVR). Another 20.8% of the bypass group suffered from two-vessel disease, 55.6% of the PCI patients and 62.5% of the CABG patients had a history of prior PCI (p = 0.78).

The most common cause for ESRD and reason for kidney transplantation was chronic glomerulonephritis, 51.9% of the PCI group and 41.7% of the CABG patients suffered from this disease. Diabetic nephropathy was found in 7.4% of the patients undergoing PCI and none of the CABG patients.

Immunosuppressive maintenance therapy was performed using a combined regimen including corticoids in all patients. Tacrolimus was the calcineurin inhibitor of choice in 37.0% of the PCI group and 41.7% of the CABG group.

### 3.2. Indications and procedures

The majority of revascularizations were performed electively. In 40.7% of the PCI group and 37.5% of the CABG group, urgent revascularization due to an acute coronary syndrome was necessary (p = ns). A total of 12 patients in the CABG group underwent combined surgery. In most of these cases, patients received aortic valve replacement. In 25.0% of the surgical patients, the operation was performed as off-pump coronary artery bypass (OPCAB) (see Table 3).

A median amount of three stents were implanted during PCI in this disease (p = 0.97). Only one procedure was performed as drug eluting stents (DES). DES were used more often in the second half of the study period. Only one procedure was performed as staged PCI. Median amount of contrast dye used for PCI was 210 ml (IQR 144–293) and 18 min of fluoroscopy time (IQR 10–29) were needed. All patients received intravenous hydration with crystalloids to the operators’ discretion according to contemporary PCI guidelines and stratified by the level of heart failure in the individual patient during the peri-PCI period. A median amount of three grafts per patient were performed in this cohort, and 154 min of ECC (IQR 89–177) were needed. An anastomosis of LIMA to LAD was performed 18 times (75.0%).

### 3.3. Mortality and follow-up

In-hospital mortality was higher in the CABG group: five patients of the CABG group died during hospitalisation (20.8%; p = 0.45), whereas only three patients of the PCI group (11.1%) died in hospital (see Table 2). Follow-up was analysed for one and four years after treatment. Median follow-up was 41 (PCI) and 37 months (CABG).

After one year, the PCI group showed higher survival. 75.0% of the CABG patients and 85.2% of the PCI patients completed one-year follow-up.

### Table 2

Primary and secondary endpoints: in-hospital mortality, acute kidney injury, perioperative complications.

| Death [in-hospital], n (%) | PCI (n = 27) | CABG (n = 24) | p-Value |
|---------------------------|-------------|---------------|---------|
| - All, n (%)              | 3 (11.1)    | 5 (20.8)      | 0.45    |
| - AKIN\(^a\), n (%)       | 1 (3.7)     | 1 (4.2)       | 0.47    |
| - AKIN 2, n (%)           | 1 (2.0)     | 0 (0.0)       | <0.01   |
| - Myocardial infarction, n (%) | 2 (3.9) | 1 (3.7) | 1.42 | 0.09 |
| - Stroke, n (%)           | 0 (0.0)     | 0 (0.0)       | <0.09   |
| - Operation, n (%)        | 1 (2.0)     | 0 (0.0)       | 0.09    |
| - Wound healing deficit, n (%) | 2 (7.4) | 2 (8.3) | <0.05  |

\(^a\) Acute Kidney Injury Network.
\(^b\) Cardiopulmonary resuscitation.
Follow-up (see Fig. 1). After four years, comparable survival rates were observed: four-year survival was 70.0% for the surgical patients and 66.5% in the PCI group (p = 0.94) (see Fig. 2).

In comparison to CABG-only patients, patients with combined surgery displayed reduced 1-year and 4-year survival (1 year survival: 83.3 versus 58.3%, p = 0.13; 4 year survival: 83.3 versus 48.6%, p = 0.06).

In the long term follow up, the predominant cause of mortality was sepsis (CABG and PCI group: both n = 4 patients), followed by cardiovascular disease (CABG and PCI group: both n = 3 patients), 2 deaths of unknown cause in the CABG group and 1 patient with lethal accident in the PCI group.

Predicted survival differed from the observed survival after four years in this cohort. As calculated by SYNTAX Score II, predicted four-year survival was 92.5% for CABG and 83.0% for PCI (see Fig. 3).

3.4. Acute kidney injury

AKI occurred more often after CABG. Only 18.5% of the PCI patients suffered from this complication, while 58.3% of the patients undergoing cardiac surgery suffered from AKI (p < 0.01). Furthermore, AKI was more distinct in the CABG group. Only mild extent of AKI was observed in the PCI group; all patients suffered from AKIN 1. Patients after cardiac surgery showed all forms of AKI: 29.2% AKIN 1, 4.1% AKIN 2, and 25.0% AKIN 3. Since PCI patients only developed mild AKI, no acute hemodialysis was needed. 20.8% of the CABG group underwent RRT due to severe AKI. One patient did not recover graft function and returned to chronic renal replacement therapy during the hospital stay.

3.5. Perioperative complications and repeated PCI

Compared to the PCI group, the incidence of bleeding complications, as defined by BARC bleeding criteria, was about twice as high following CABG (37.5% vs. 14.8%; p = 0.11). One patient of each group suffered from acute myocardial infarction during the postoperative period (p > 0.99). Ischemic or hemorrhagic stroke did not occur in this patient population. In the CABG group, 11 patients (45.8%) underwent 12 reoperations, predominantly driven by bleeding complications (n = 5) and wound infections (n = 5). One patient experienced compartment syndrome of the forearm after harvesting the radial artery as bypass graft. No access site infection was observed in the PCI group.

During follow up, 13 patients of the PCI group (48.1%) underwent repeated PCI due to in-stent restenosis (n = 8) and de novo lesions (n = 5).

3.6. On-pump versus off-pump CABG

The distribution between on-pump and off-pump CABG was 3:1 in this study population. In-hospital mortality was 27.8% in the group of patients undergoing on-pump CABG whereas no patient of the OPCAB
group died during hospitalisation. Bleeding was observed in 44.4% of the CABG cases performed with ECC while only 16.7% of the OPCAB patients showed this complication (see Table 3). 50.0% of the on-pump patients underwent reoperation in comparison to only 33.3% of the OPCAB patients needed reoperation. AKI was observed much more often in the on-pump group: 72.2% suffered from this complication versus 16.7% in the off-pump group (p = 0.05). In 38.5% of the cases, RRT was needed.

3.7. Transplant survival

One person suffered from graft loss after cardiac surgery in a short time after operation. No periprocedural graft loss was observed in the PCI group. Graft survival was analysed as death censored graft survival. One-year graft survival was 95.7% in the PCI group and 94.1% in the PCI group. Graft survival after four years showed similar graft survival in both groups (76.8% PCI and 77.0% CABG, p = 0.71) (see Fig. 4). One-year graft survival was better for PCI; however, long-term follow-up showed no differences between both revascularisation strategies.

CABG patients experienced a remarkably high number of reoperations (45.8%). This is explained by reduced platelet function in CKD patients and well described in other reports [20,21]. Our data stand in line with Reine et al. - 25% of their patients needed surgical revision because of wound healing deficiency [22]. Further, impaired wound healing in kidney transplant recipients is influenced by comorbidities such as peripheral artery disease or diabetes mellitus and the use of immunosuppressive agents. Moreover, uremic toxins may affect wound healing [23].

In our cohort, the leading causes of mortality in the long term follow up were sepsis and cardiovascular disease. This finding stands in line with Hayer et al. who analysed a cohort of almost 20,000 kidney transplant recipients. Most common cause for mortality was cardiovascular events, followed by infections and malignancy [24]. Death by infection in this high risk collective is often caused by urinary tract infections [25,26].

Contemporary reports of KTR and revascularization are characterised by either a) large number of patients with less detailed reports or b) small number of patients with more precise results concerning AKI and graft loss. Our data stand in line with Charytan et al. [27] and Lenihan et al. [14] who compared PCI and CABG in a large number of KTR. Their studies showed higher periprocedural risk for CABG with a higher in-hospital mortality of the CABG patients similar to our findings. No survival benefit was found regarding the type of revascularisation; long-term survival was comparable for both revascularization strategies. Herzog et al. [12] reported comparable long-term outcome for about 2000 KTR undergoing PCI or CABG between 1995 and 1999.

Furthermore, our data stand in line with Taduro et al. [28]. Their study revealed higher incidence for AKI and RRT for KTR receiving CABG compared to PCI in a large study cohort. The small study of Basic-Jukic et al. [29] in 2015 included 13 patients undergoing CABG or combined surgery with a higher incidence of RRT (30%) and graft loss compared to our study. A comparably high amount of RRT was found by Zhang et al. [30]; they included 57 KTR undergoing cardiac surgery of which 29% suffered from AKI requiring RRT. Yet, long-term survival was comparable to the survival in our study.

Rocha et al. [31] reported combined surgery as an important risk factor for morbidity and mortality. They analysed 92 patients undergoing CABG, valve replacement and combined surgery. Their findings are from postoperative complications, compared to patients undergoing PCI. The incidence and extent of AKI was higher in the CABG group, as well as perioperative graft loss and the need for RRT. Patients treated with OPCAB showed less AKI and less bleeding complications. Survival after one year was better for PCI; however, long-term follow-up showed no differences between both revascularisation strategies.

4. Discussion

In this single centre retrospective study, KTRs undergoing CABG showed higher in-hospital mortality and suffered more frequently

### Table 3

|                          | All  (n = 24) | On-pump (n = 18) | Off-pump (n = 6) | p-Value |
|--------------------------|--------------|-----------------|-----------------|---------|
| **Acute kidney injury**   |              |                 |                 |         |
| - Death [in-hospital], n | 5 (20.8)     | 5 (27.8)        | 0 (0)           | 0.28    |
| - All, n (%)             | 14 (58.4)    | 13 (72.2)       | 1 (16.7)        | 0.05    |
| - AKIN 1, n (%)          | 7 (29.2)     | 6 (33.3)        | 1 (16.7)        | 0.63    |
| - AKIN 2, n (%)          | 1 (4.2)      | 1 (5.6)         | 0 (0)           | <0.001  |
| - AKIN 3, n (%)          | 6 (25.0)     | 6 (33.3)        | 0 (0)           | 0.28    |
| - Need for acute        | 5 (20.8)     | 5 (28.5)        | 0 (0)           | 0.28    |
| haemodialysis, n (%)     |              |                 |                 |         |
| - Graft loss, n (%)      | 1 (4.2)      | 1 (5.6)         | 0 (0)           | <0.001  |
| **Perioperative complications** |          |                 |                 |         |
| - Bleeding [BARC], n (%) | 9 (37.5)     | 8 (44.4)        | 1 (16.7)        | 0.35    |
| - Myocardial infarction, |              |                 |                 |         |
| n (%)                    | 1 (4.2)      | 1 (5.6)         | 0 (0)           | <0.001  |
| - Stroke, n (%)          | 0 (0.0)      | 0 (0.0)         | 0 (0)           | <0.001  |
| - Operation, n (%)       | 11           | 9 (50.0)        | 2 (33.3)        | 0.65    |
|                          |              |                 |                 |         |
| - CPR, n (%)             | 2 (8.3)      | 2 (11.1)        | 0 (0)           | <0.001  |
| - Wound healing deficit, |              |                 |                 |         |
| n (%)                    | 7 (29.2)     | 5 (27.8)        | 2 (33.3)        | <0.001  |

Fig. 3. Four-year survival PCI vs. CABG – predicted 4-year survival by SYNTAX Score II.
Concordant to the high in-hospital mortality and the low one-year survival of our CAGB group consisting of patients with combined surgery, Shayan et al. [32] analysed 21 patients undergoing on-pump and 22 patients undergoing off-pump CAGB. OPCAB patients showed better long-term survival, but the graft loss was higher in both groups than in our cohort (28% on-pump, 22% off-pump). KTR in need for cardiac surgery might benefit from less invasive procedures as preliminary data from our centre indicate for aortic valve replacement [33,34].

The clinical relevance of these findings is high, since guidelines addressing myocardial revascularization in KTR suffering from CAD do not exist. This patient collective is an issue of enormous interest all over the world due to the large numbers of ESRD awaiting kidney transplantation and the increasing long-term survival of KTR. This study does not only provide long-term survival follow-up (median follow-up 41 and 37 months) but also long-term information about graft function and graft loss.

4.1. Limitations

This study is limited by the small number of patients and its retrospective design as a single-centre study. We analysed patients with combined surgery together with patients undergoing CAGB only. The SYNTAX Score could not be calculated on the basis of original angiographies in all patients but by reviewing angiography reports and estimation of the score. Due to the retrospective design, we cannot provide information about the ratio and prognostic impact of complete and incomplete revascularization, which might be of particular interest in the majority of KTR with diffuse multivessel disease. Moreover, this KTR-cohort consisting of relatively few patients suffering from diabetic nephropathy might not represent the majority of present and upcoming KTR.

Further, the present study cannot supply sufficient information about differences in prognosis after PCI or CAGB in KTR on RRT before revascularization.

To opt for the optimal treatment strategy, estimation of perioperative morbidity and mortality is mandatory. Interestingly, the SYNTAX Score II overestimated four-year survival for this cohort. It seems not to be suitable as a prognostic tool for mortality for patients after kidney transplantation and remains to be evaluated in larger patient cohorts. KTR represent a high-risk population for CAD and are at higher risk of death, AKI and graft loss related to CAGB and PCI. Moreover, long-term survival in KTR patients with concomitant CAD appears reduced regardless of the revascularisation type used.

5. Conclusions

In KTR, the optimal revascularization strategy should focus less on improved long-term survival but choose approaches with reduced invasivity such as off-pump CAGB and PCI in order to shorten hospitalisation and reduce risk of AKI and graft loss. Finally, in order to improve revascularization strategy in KTR with CAD, we encourage KTR units to investigate and report outcomes of their patients after PCI and/or CAGB.

Contributorship

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Conflict of interest

None.

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