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Received: 20.8.2019; Editorial decision: 17.4.2020

Nephrol Dial Transplant (2020) 35: 1810–1818
doi: 10.1093/ndt/gfaa131

Impact of cardiovascular risk stratification strategies in kidney transplantation over time

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ABSTRACT

Background. Kidney transplant recipients exhibit a dramatically increased cardiovascular (CV) risk. In 2007, Austrian centres implemented a consensus of comprehensive CV screening programme prior to kidney transplantation (KT). The consensus placed a particular emphasis on screening for coronary artery disease (CAD) with cardiac computed tomography (CT) or coronary angiography (CAG) in patients with diabetes mellitus, known CAD or those having multiple conventional CV risk factors. Here, we investigate if this affected risk stratification and post-transplant CV outcomes.

Methods. In a retrospective chart review, we evaluated 551 KTs performed from 2003 to 2015 in our centre. Patients were categorized into three groups: KT before (2003–07), directly after (2008–11) and 5 years after (2012–15) implementation of the consensus. We analysed clinical characteristics, the rate of cardiac CTs and CAGs prior to KT as well as major adverse cardiac events (MACEs) during a 2-year follow-up after KT.

Results. The three study groups showed a homogeneous distribution of comorbidities and age. Significantly more cardiac CTs (13.6% versus 10.2% versus 44.8%; $P = 0.002$) and CAGs (39.6% versus 43.9% versus 56.2%; $P = 0.003$) were performed after the consensus. Coronary interventions were performed during 42 out of 260 CAGs (16.2%), the cumulative 2-year MACE incidence was 8.7%. Regarding MACE occurrence, no significant difference between the three groups was found.

Conclusion. CV risk stratification has become more rigorous and invasive after the implementation of the consensus; however, this was not associated with an improvement in CV outcome.

Keywords: chronic kidney disease, coronary angiography, coronary artery disease, kidney transplantation, major adverse cardiac event

INTRODUCTION

Cardiovascular (CV) disease is the most common cause of death after kidney transplantation (KT) worldwide [1–3]. The annual risk of a fatal or non-fatal CV event may be up to 50-fold higher than in the age-matched general population without kidney disease [4]. Patients are exposed to the highest risk for a major adverse cardiac event (MACE) in the peri-transplant period [5–7]. However, in the long run, transplant recipients have a significant CV risk reduction compared with patients on maintenance dialysis [7, 8]. Occlusive coronary artery disease (CAD) is highly prevalent in KT candidates and accounts for adverse outcomes after KT [9, 10]. Therefore, screening for CAD also in asymptomatic patients is advised in the course of pre-transplant check-up with a series of non-invasive and invasive examinations [11, 12]. The value and accuracy of conventional non-invasive cardiac stress testing in chronic kidney disease (CKD) patients are questionable and are subject to intense discussion [12–14]. The use of cardiac computed tomography (CT) is another widespread non-invasive imaging method to detect coronary artery calcification in the general non-CKD population. However, it is inaccurate in the CKD population, with poor correlations of coronary calcification scores and severity of occlusive coronary lesions [15, 16]. This is most likely due to its inability to anatomically distinguish between intimal and medial calcification. The latter is a typical pathological hallmark of CKD resulting in a high degree of imaging artefacts [17]. The use of cardiac CT angiography allows an appropriate intimal plaque characterization and has a diagnostic accuracy to detect obstructive CAD which rivals that of coronary angiography (CAG) [18]. Unfortunately, its use in advanced CKD patients/KT candidates—especially in those not yet requiring dialysis—is restricted due to the application of iodinated contrast media. Although similar reservations exist concerning the use of invasive CAG, it is still the best predictor of adverse events in renal transplant candidates [19, 20]. Furthermore, it allows for immediate revascularization of critical coronary lesions when indicated. Whether or not KT candidates indeed benefit from pre-transplant coronary intervention is, however, controversial. Two recent retrospective studies showed that kidney transplant recipients who underwent cardiac catheterization with consecutive intervention may experience less angina pectoris (AP) and require less repeated CAG after KT. However, in terms of post-transplant mortality no benefit was shown [21, 22]. On the other hand, a coronary intervention may often be a prerequisite to make the candidates suitable for anaesthesia and surgery. Although the data in this regard are partially controversial, a uniformed CV screening including CAG has been recommended by international guidelines [11, 12].

In line with these recommendations, Austrian KT centres accepted a consensus of a comprehensive CV screening programme in KT candidates with the purpose of improving post-transplant CV outcomes in 2007 [23]. All candidates were subjected to a basic CV screening with physical examination, chest X-ray, electrocardiogram (ECG) and transthoracic echocardiogram. The consensus recommended an intensified CAD screening using coronary CT and/or CAG in candidates with diabetes mellitus (DM), previous CAD and those with multiple conventional CV risk factors (age >50 years, tobacco smoking, hyperlipidaemia, prevalence of peripheral or cerebral vascular disease). The impact of this comprehensive risk stratification on post-transplant CV outcomes has not yet been evaluated. Data regarding CV screening procedures in the European population are scarce. Therefore, we performed a retrospective chart review of KT patients over a 13-year period, divided into three groups (2003–07, 2008–11 and 2012–15). This separation allowed us to compare the rate of cardiac CTs, CAGs, coronary interventions and post-transplant CV outcomes in a time-dependent manner and to analyse the impact of the consensus.

KEY LEARNING POINTS

What is already known about this subject?

- end-stage renal disease is associated with increased cardiovascular (CV) risk, and kidney transplantation (KT) is the optimal therapy. Therefore, KT candidates are typically subjected to an intensive CV screening prior to KT.

What this study adds?

- an aggressive pre-transplant CV screening strategy with up to 50% coronary angiography rate and low count of interventions does not improve short-term post-transplant outcomes.

What impact this may have on practice or policy?

- after 10–15 years of unchanged policy, it may be time to reconsider current pre-transplant CV screening procedures.

MATERIALS AND METHODS

Study population

In our centre (Medical University of Graz), 50–70 KTs are performed annually. We retrospectively evaluated all KT recipients ($n = 676$) transplanted in our centre between 1 January 2003 and 31 December 2015. We included 551 recipients in our analysis as depicted in Figure 1. A total of 125 KTs were excluded due to the following reasons: age <18 years, combined organ transplantation (e.g. pancreas–kidney) or loss to follow-up. Patients were divided into three groups: patients transplanted before (Group I: 2003–07), directly after (Group II: 2008–11) and 5 years after (Group III: 2012–15) the Austrian consensus was published. According to the consensus a basic CV screening with physical examination, chest X-ray, ECG and transthoracic echocardiogram was necessary for all candidates. CAG was indicated in case of pre-existing DM or CAD or, if more than one of the following risk factors was present: age

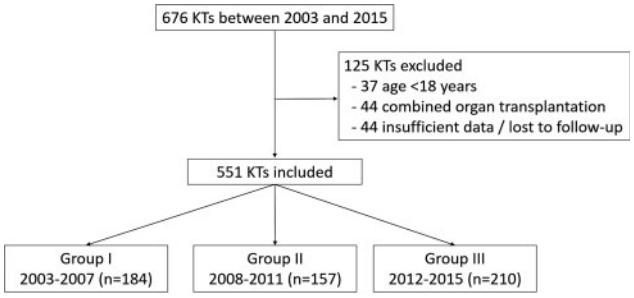

FIGURE 1: Selection of study participants.

>50 years, tobacco smoking, hyperlipidaemia or prevalence of peripheral or cerebral vascular disease. CAG could be skipped if the candidate had a negative coronary CT with a coronary artery calcification score (CACS) <100. At the level of CACS <300, the negative predictive value of CACS to rule out CAD is >90%, at CACS <40 it is 100% [24]. Based on this evidence the national experts of the Austrian Society of Nephrology chose in 2007 a stringent cut-off <100 as a requirement to waive the need of angiography [23]. Re-transplantations during the study period ($n = 21$) were considered in each case as an individual KT, since a comprehensive CV examination was always mandatory before the candidate was waitlisted and transplanted again. In >98% of cases, the ethnicity of the patients was Caucasian, representing the Austrian ethnical background, and was not specified further. From 2000 to 2015, an additional 183 candidates were evaluated for KT, but were not suitable for KT. From these 183 ineligible candidates, 18 died during the evaluation procedure and an additional 18 patients were not listed due to CV reasons. These included mostly symptomatic conditions with non-reparable coronary, valvular or cerebrovascular disease as well as severe chronic heart failure (HF). These are typical CV conditions that mean a candidate is not considered eligible for surgery. Other non-CV reasons for not listing were active malignancy ($n = 16$), chronic infection ($n = 3$), surgical contraindications ($n = 30$), non-adherence ($n = 43$), lost to follow-up/change of centre ($n = 33$) and miscellaneous reasons ($n = 22$).

Ethical approval (EK-Number 29-111 ex 16/17) was provided by the institutional review board of our university. For study participation, no written informed consent was required. Study-related procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Data collection

Medical records were retrieved from the KT records and the electronic medical documentation system of our centre as well as from the Austrian Dialysis and Transplantation Register (OEDTR). The OEDTR is a validated, nationwide database established in 1965 holding records of patients with end-stage renal disease (ESRD) on maintenance dialysis. The database is updated annually, and data are obtained from dialysis and KT centres from Austria on a voluntary basis [25]. For data transfer, a written informed consent from the patients is required. The registry provides information on demographics, primary renal disease (PRD), type and duration of renal replacement therapy (RRT), comorbidities, as well as organ/disease-specific cause of death. The comprehensive annual reports can be obtained from the website of the OEDTR (https://www.nephro.at/JB_all.htm). To ensure consistent documentation, clinical records were collected by the same KT expert and reviewed afterwards by another transplant nephrologist. Unclear cases were discussed in the regular transplant boards.

Baseline characteristics and comorbidities

Baseline clinical characteristics, comorbidities and medication with aspirin, lipid-lowering therapy (e.g. statins, cholesterol absorption inhibitors, bile acid sequesters, etc.), as well as renin–angiotensin–aldosterone system (RAAS) blocking agents were recorded at the time point of KT. Underlying renal disease was categorized according to PRD codes of the ERA-EDTA Registry [26, 27]. Patients with DM included those with Type I or II DM requiring antidiabetic medication and/or dietary restrictions. CAD was defined as >50% stenosis of at least one coronary artery diagnosed by angiography, previous myocardial infarction or previous coronary intervention documented in the records. Peripheral artery disease was defined as stenosis/occlusion of the limb arteries diagnosed by duplex ultrasound or angiography. Patients with cerebrovascular disease had documented transient ischaemic attack (TIA) or ischaemic stroke in their case history. Patients with hyperlipidaemia had age-dependent pathologically elevated levels of cholesterol and/or triglycerides or took lipid-lowering agents. Dialysis vintage was the time period between the initiation of RRT and KT.

Left ventricular ejection fraction, cardiac symptoms and coronary imaging (cardiac CT, CAG) prior to KT

Left ventricular ejection fraction (LVEF) was retrieved from pre-transplant echocardiographic studies and was categorized into preserved (LVEF ≥55%), mild to moderately reduced (LVEF 35–54%) and severely reduced (LVEF ≤34%), respectively. We analysed the rate of cardiac CTs with respective CACS scores as well as the rate of CAGs with or without consecutive coronary intervention (angioplasty, stenting or bypass operation) [28]. Cardiac symptoms—AP or dyspnoea at least Stage II according to the classification system of the New York Heart Association—were also included in candidates subjected to CAG. If the candidate had several CAGs during the course of the pre-transplant check-up, only the latest CAG was considered. The decision regarding the need for cardiac CT or CAG after individual assessment of each KT candidate was made by the same board of transplant experts in our centre. The indication for a consecutive coronary intervention was left to the decision of the interventional cardiologist, who performed the examination.

Post-transplant CV outcome

The primary outcome measure was the rate of MACEs, a composite of all-cause mortality, non-fatal acute coronary syndrome (ACS), non-fatal cerebrovascular event (TIA or ischaemic stroke) and non-fatal HF within 2 years following KT. Registry data regarding mortality were obtained from the OEDTR, which was validated after careful examination of the respective clinical records. Post-transplant ACS was specified as

the occurrence of ST- and non-ST-elevation myocardial infarction or unstable AP according to the definitions and diagnostic criteria of the European Society of Cardiology (ESC) [29]. Patients with HF had a documented rapid onset of new or worsening signs and symptoms typical for HF (e.g. dyspnoea, lower limb oedema, fatigue, elevated jugular venous pressure, pulmonary congestion, fatigue, etc.) and/or an echocardiographic diagnosis of systolic or diastolic dysfunction based on ESC definitions in their medical records after KT [30]. Patients diagnosed with TIA and ischaemic stroke met the imaging and clinical diagnostic criteria of the European Stroke Organization recommendations [31].

Statistical analysis

Numerical variables were presented as median and interquartile range (IQR) and were compared using the Kruskal–Wallis test with adequate *post hoc* tests. Categorical variables were presented as absolute (n) and percentage (%) values within each group and were compared using Chi-squared test. Kaplan–Maier analysis and log-rank tests were performed to assess cumulative MACE probability. The significance level was set to $\alpha = 0.05$. Statistical analysis and figure illustration were performed with SPSS version 25.0 (IBM Inc., Chicago, IL, USA) and GraphPad PRISM version 5.01 (GraphPad Software Inc., La Jolla, CA, USA), respectively.

RESULTS

The three study groups with a median age of 52 years, predominantly male (67.2%), showed a homogeneous distribution of clinical characteristics, underlying kidney diseases, comorbidities and medication (Table 1). The most common underlying renal disease was glomerulonephritis (33.9%). The cumulative prevalence of diabetic kidney disease and renal vascular disease was 7.6% and 12.2%, respectively. The rate of pre-emptive KT ($P = 0.003$) and living kidney donation (LKD) ($P < 0.001$) significantly increased in Group III (2012–15). Dialysis vintage showed a slightly increasing trend, without any significant differences over the years ($P = 0.137$).

LVEF determined by echocardiographic studies, native coronary CTs, cardiac symptoms and CAGs with or without interventions [CAG ± percutaneous transluminal coronary angioplasty (PTCA)/coronary artery bypass grafting (CABG)] performed during pre-transplant check-up are depicted in Table 2. Most patients (94.4%) had a preserved LVEF, a small minority (4.7%) had a mild to moderately reduced and a few (1%) had severely reduced LVEF, without any differences between the three study groups ($P = 0.067$ for 'preserved', $P = 0.062$ for 'mild to moderately reduced' and $P = 0.442$ for 'severely reduced'). The prevalence of cardiac symptoms in candidates undergoing CAG did not significantly differ from each other in the three study groups ($P = 0.702$). Notably, in case of $n = 7$ in Group I, $n = 3$ in Group II and $n = 8$ patients in Group

Table 1. Baseline characteristics, comorbidities and underlying renal disease

Baseline Characteristics	Total 2003–15 ($n = 551$)	Group I 2003–07 ($n = 184$)	Group II 2008–11 ($n = 157$)	Group III 2012–15 ($n = 210$)	P-value
Age, median (IQR), years	52 (42–61)	51 (42–59)	53 (42–65)	51 (40–58)	0.114
Dialysis vintage, median (IQR), months	41 (22–76)	39.5 (21.8–82.8)	45 (27–76)	46 (22–83)	0.137
BMI, median (IQR), kg/m^2	24.6 (22.1–27.7)	24.2 (21.9–26.9)	24.6 (21.7–28.1)	25.0 (22.6–27.9)	0.104
Male sex, *n* (%)	370 (67.2)	116 (63.0)	107 (68.2)	147 (70.0)	0.324
Haemodialysis, *n* (%)	435 (78.9)	153 (83.2)	124 (79.0)	158 (75.2)	0.158
Peritoneal dialysis, *n* (%)	86 (15.6)	24 (13.0)	30 (19.1)	32 (15.2)	0.301
Pre-emptive KT, *n* (%)	30 (5.4)	7 (3.8)	3 (1.9)	20 (9.5)	0.003
LKD, *n* (%)	52 (9.4)	5 (2.7)	10 (6.4)	37 (17.6)	<0.001
Previous KT, *n* (%)	121 (22)	44 (23.9)	29 (18.5)	48 (22.9)	0.444
DM, *n* (%)	75 (13.6)	25 (13.6)	24 (15.3)	26 (12.4)	0.724
Hypertension, *n* (%)	524 (95.1)	174 (95.6)	152 (96.8)	196 (93.3)	0.284
Previous CAD/ACS, *n* (%)	51 (9.3)	13 (7.1)	16 (10.2)	22 (10.5)	0.452
Peripheral artery disease, *n* (%)	71 (12.9)	21 (11.4)	19 (12.1)	31 (14.8)	0.577
Cerebrovascular disease, *n* (%)	76 (13.8)	22 (12.0)	28 (17.8)	26 (12.4)	0.220
Hyperlipidaemia, *n* (%)	289 (52.5)	101 (54.9)	86 (54.8)	102 (48.6)	0.359
Tobacco smoking, *n* (%)	244 (44.3)	83 (45.1)	67 (42.7)	94 (44.8)	0.889
Aspirin, *n* (%)	204 (37.0)	59 (32.1)	58 (36.9)	87 (41.4)	0.158
RAAS blockade, *n* (%)	353 (64.1)	120 (65.2)	105 (66.9)	128 (61.0)	0.465
Lipid lowering therapy, *n* (%)	208 (37.7)	70 (38.0)	59 (37.1)	79 (37.6)	0.995
Underlying renal disease, *n* (%)					
Glomerular disease	187 (33.9)	70 (38.0)	59 (37.6)	58 (27.6)	0.05
Tubulointerstitial disease	78 (14.2)	25 (13.6)	21 (13.4)	32 (15.2)	0.848
Diabetic kidney disease	42 (7.6)	14 (7.6)	11 (7.0)	17 (8.1)	0.927
Renal vascular disease/hypertension	67 (12.2)	21 (11.4)	18 (11.5)	28 (13.3)	0.803
Systemic disease affecting the kidney	38 (6.9)	11 (6.0)	12 (7.6)	15 (7.1)	0.820
Hereditary nephropathies	77 (14.0)	24 (13.0)	20 (12.7)	33 (15.7)	0.650
Miscellaneous renal disorders	62 (11.2)	19 (10.3)	16 (10.2)	27 (12.9)	0.645

Comparison of variables between the study groups (Groups I versus II versus III) was performed using Kruskal–Wallis test for numerical and chi-square tests for categorical variables, respectively; $P < 0.05$ corresponds to statistically significant differences between all three groups. BMI, body mass index.

Table 2. Cardiological screening procedures prior to KT

Screening Procedures	Total 2003–15 ($n = 551$)	Group I 2003–07 ($n = 184$)	Group II 2008–11 ($n = 157$)	Group III 2012–15 ($n = 210$)	P-value
Echocardiography (LVEF), *n* (%)					
≥55 (preserved)	520 (94.4)	172 (93.5)	144 (94.7)	204 (97.1)	0.067
35–54 (mild to moderately reduced)	26 (4.7)	9 (4.9)	12 (7.6)	5 (2.4)	0.062
≤34 (severely reduced)	5 (1.0)	3 (1.7)	1 (0.6)	1 (0.5)	0.442
Cardiac CT, *n* (%)	135 (24.5)	25 (13.6)	16 (10.2)	94 (44.8)	<0.001
CACS <100	87 (15.8)	12 (6.5)	8 (5.1)	67 (31.9)	<0.001
CACS >100	48 (8.7)	13 (7.1)	8 (5.1)	27 (12.9)	0.021
CAG, *n* (%)	260 (47.2)	73 (39.6)	69 (43.9)	118 (56.2)	0.003
Cardiac symptoms before CAG	38/242 (15.7)	11/66 (16.7)	12/66 (18.2)	15/110 (13.6)	0.702
CAG − PTCA	218 (39.5)	58 (31.5)	61 (38.9)	99 (47.1)	0.007
CAG + PTCA	32 (5.8)	12 (6.5)	7 (4.5)	13 (6.2)	0.687
CAG + CABG	10 (1.8)	3 (1.6)	1 (0.6)	6 (2.9)	0.281
Coronary intervention (PTCA + CABG)	42 (7.6)	15(8.1)	8 (5.1)	19 (9.0)	0.349
Coronary intervention (PTCA + CABG) to CAG ratio	42/260 (16.2)	15/73 (20.5)	8/69 (11.6)	19/118 (16.1)	0.350
CAD diagnosis, *n* (%)	103 (18.7)	35 (19.1)	30 (18.9)	38 (18.0)	0.059
CAD I	42 (7.6)	15 (8.2)	16 (10.1)	11 (5.2)	0.198
CAD II	29 (5.3)	14 (7.6)	8 (5)	8 (3.8)	0.210
CAD III	32 (5.8)	7 (3.8)	6 (3.8)	19 (9.0)	0.039

LVEF was categorized into preserved (≥55%), mild to moderately reduced (35–54%) and severely reduced (≤34%). Cardiac symptoms (AP or dyspnoea) were added in those patients, who underwent CAG. In case of $n = 7$ in Group I, $n = 3$ in Group II and $n = 8$ patients in Group III, no documentation was found regarding cardiac symptoms, thus the total number of analysed patients was $n = 242$. Comparison of variables between the study groups (Groups I versus II versus III) was performed using Chi-squared tests; $P < 0.05$ corresponds to statistically significant differences between all three groups.

Table 3. Rate of MACE within 2 years after KT

Outcomes	Total 2003–15 ($n = 551$)	Group I 2003–07 ($n = 184$)	Group II 2008–11 ($n = 157$)	Group III 2012–15 ($n = 210$)	P-value
MACE, *n* (%)	48 (8.7)	17 (9.2)	14 (8.9)	17 (8.1)	0.917
All-cause mortality, *n* (%)	33 (6.0)	12 (6.5)	13 (8.3)	8 (3.8)	0.189
Infection	13 (2.4)	4 (2.2)	6 (3.8)	3 (1.4)	0.800
CV	14 (2.5)	6 (3.3)	4 (2.5)	4 (1.8)	0.132
Malignancy	2 (0.4)	2 (1.1)	0	0	0.155
Other	4 (0.7)	0	3 (1.9)	1 (0.7)	0.210
ACS, *n* (%)	11 (1.9)	6 (3.2)	2 (1.2)	3 (1.5)	0.503
Unstable AP	5 (0.9)	3 (1.6)	1 (0.6)	1 (0.5)	0.442
Non-ST-elevational myocardial infarction	3 (0.5)	2 (1.1)	1 (0.6)	0	0.337
ST-elevational myocardial infarction	3 (0.5)	1 (0.5)	0	2 (1.0)	0.471
Stroke/TIA, *n* (%)	7 (1.3)	3 (1.6)	0	4 (2.0)	0.217
HF, *n* (%)	6 (1.1)	1 (0.5)	0	5 (2.4)	0.064

Comparison of variables between the study groups (Groups I versus II versus III) was performed using multiple Chi-squared tests; $P < 0.05$ corresponds to statistically significant differences between all three groups.

III, no documentation was found regarding cardiac symptoms; therefore, the total number of analysed patients was $n = 242$.

The implementation of the 2007 Consensus did not significantly change the rate of coronary CTs with negative findings (CACS <100) immediately (Group II), but was followed by a marked increase in Group III (2012–15) ($P < 0.001$). Altogether, 260 out of 551 KT recipients underwent CAG prior to KT. The frequency of CAGs increased significantly from 39.6% (Group I) to 43.9% (Group II) and 56.2% (Group III) ($P = 0.003$) over the years. Similarly, there was an increase in CAGs without intervention (CAG − PTCA), which rose from 31.5% through 38.9% to 47.1% ($P = 0.007$). The frequency of coronary interventions (PTCA + CABG) remained unchanged with 8.0% (Group I), 5.1% (Group II) and 9.0% (Group III) ($P = 0.349$). The proportion of CAG with coronary intervention showed the same trend: 20.5% in Group I, 11.5% in Group II and 16.1% in Group III ($P = 0.350$). CAD affecting one or more vessels (CAD I–III) was diagnosed (or confirmed, in case of pre-existing CAD) in 18.0–19.1% of the cases.

The post-transplant composite endpoint was reached in 17 of 184 KTs (9.2%) in Group I (2003–06), 14 of 157 KTs (8.9%) in Group II (2007–11) and 17 of 210 KTs (8.1%) in Group III (2011–15) (Table 3). This represents a 2-year cumulative MACE incidence of 48 out of 551 KTs (8.7%) in the whole study population. The numbers of events for the components of the composite endpoint did not significantly differ in the three groups ($P = 0.189$ for all-cause mortality, $P = 0.503$ for ACS, $P = 0.217$ for stroke/TIA and $P = 0.064$

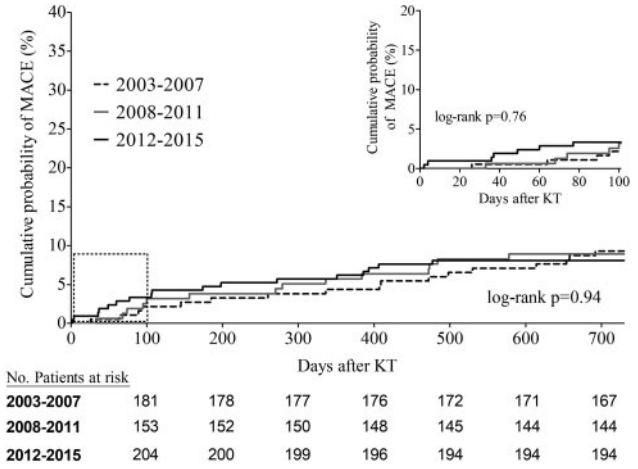

FIGURE 2: Kaplan–Maier analysis for the occurrence of MACE in the three study groups. Curves indicate cumulative probability of MACE (%) in 2 years (large image; P = 0.94) and in the first 100 days (insert; P = 0.76) following KT, respectively.

for HF, respectively). CV death occurred in 14 cases and there were 13 deaths due to infections (Table 3). Kaplan–Maier analysis revealed no significant differences regarding cumulative MACE probability in the study groups either in the early post-transplantation period (P = 0.76) or after 2 years (P = 0.94), respectively (Figure 2).

DISCUSSION

The primary goal of this monocentric study was to analyse the rate of coronary CT, CAGs and CV outcomes of KT recipients between 2003 and 2015 after the introduction of a nationwide screening consensus in 2007. Therefore, we split the population in three groups (Group I 2003–07, Group II 2008–11 and Group III 2012–15) and analysed the impact of consensus on CV outcomes. Our data indicate a stable prevalence of comorbidities and age over a 13-year period in a Central European population. Nevertheless, more intensive and invasive pre-transplant cardiac screening procedures were undertaken as reflected by the increasing numbers of CCTs and CAGs, especially 5 years after the publication of the consensus. Despite the intensified efforts to screen for CV diseases, the overall incidence of MACE and diagnosis of CAD with therapeutic consequences remained unchanged over the years.

Through this 13-year observational period, the median age of KT patients and the prevalence of comorbidities remained unchanged, despite international trends. Registry data from the USA [32] and Europe [33] point towards an ageing transplant recipient population. Single studies from the USA [34], Canada [35], Australia [36] and Europe [37] also report increasing recipient age. It is feasible that current evaluation strategies implemented in Austria promote the exclusion of 'older and sicker' ESRD patients from KT waiting list. The implementation of restrictive recommendations may explain why diabetic patients (with a prevalence of 13.6%) were underrepresented in our study population. Another potential explanation for why fewer diabetics are transplanted is provided by an earlier nationwide Austrian study indicating a decreasing incidence of ESRD caused by diabetes after 2006, despite an increasing overall prevalence of diabetes [38]. In other studies enrolling primarily ESRD patients or KT candidates, the prevalence of DM shows large variations (26–91%) depending on study setting [21, 22, 35, 39]. These large variations are already present on the population level and are attributed to geographical reasons. Registry data of the US Renal Data System from 2012 showed that in ∼50% of the dialysis patients diabetic kidney disease was the underlying renal disease [40], whereas this rate was ∼25% according to Austrian registry data [41]. The prevalence of diabetic kidney disease in our KT collective was surprisingly low (7.6%). Our explanation for this discrepancy is that a 'preselection' of KT candidates may already begin at the level of outpatient dialysis units, who preferably consider undertaking KT evaluation only in younger patients with fewer comorbidities. The most common underlying renal disease was glomerulonephritis, which is comparable to data reported by Lam *et al.* [35].

Previous studies have delineated CAD to be highly prevalent in KT candidates and to account for adverse outcomes after KT [9, 10]. Therefore, pre-transplant screening for CAD—including asymptomatic patients—has been recommended repeatedly by various guidelines [11, 12, 23]. The feasibility of conventional non-invasive cardiac stress-testing and nuclear imaging due to their variable specificity and sensitivity in CKD patients is, however, questionable [12]. Of our KT recipients, 9.3% had a history of CAD or ACS (Table 1) before pre-transplant check-up procedures were begun, which shows that compared with many other retrospective analyses our cohort may have had a lower baseline rate of CAD [21, 22, 35]. The vast majority of our patients had a normal LVEF and ∼15% of the catheterized patients—as far as retrospectively traceable—showed prior cardiac symptoms (AP or dyspnoea) with unchanged prevalence over the years. Nevertheless, our patients were subjected to a more intensive and invasive CV screening as reflected by an increasing number of CCTs and CAGs in Group III (2012–15). During these screening procedures, CAD was diagnosed in 103 out of 551 cases (18.7%). CAGs without coronary intervention (CAG–PTCA, P = 0.007 Group I versus III) increased, while coronary interventions (PTCA or CABG) to CAG ratio remained constantly low over the years [P = 0.350, 42 out of 260 CAGs (16.2%)] (Table 2). The larger proportion of preemptive and living kidney recipients in Group III may partially explain the increased rate of native cardiac CTs. It is, however, more likely that the implementation of the consensus *per se* contributed to the increase of cardiac CTs and CAGs: though with some delay, it led to a heightened awareness of CAD and its adverse sequelae after in KT. Thus, this may have translated into a better adherence to the recommendations and may have lowered the subjective threshold of transplant physicians to subject (especially high risk) KT candidates to CAG. In the entire study population of 551 KT recipients, 42 coronary interventions (7.6%) were performed. These intervention rates are lower than those reported by Felix *et al.* [21] and de Lima *et al.* [22], but comparable with that of a recent trial of elderly (age ≥65 years) haemodialysis patients [42]. Notably, the rate of

CAGs and consecutive interventions may also show large inter-provider variations ranging from 1.0% to 73.6%, as shown by a large observational study of asymptomatic, non-CKD patients from the USA [43]. Whether or not KT candidates indeed benefit from pre-transplant coronary intervention is controversial. The study of Kumar *et al.* report excellent post-transplant outcomes, when a rather permissive strategy of pre-transplant catheterization is followed [44]. In a recent study, de Lima *et al.* confirmed that patients with severe CAD (>70% stenosis) had worse outcome compared with those without CAD [22]. Yet, coronary intervention compared to a conservative medical treatment did not show any benefit regarding mortality. Felix *et al.* principally confirmed these findings, showing a more beneficial outcome for KT recipients without CAD, but the same rate of post-transplant adverse events for patients with CAD irrespective of previous revascularization [21]. Finally, Hage *et al.* found that the prevalence and severity of CAD on angiogram was not predictive of mortality. Coronary revascularization did not impact survival except for patients with three-vessel disease [45]. Clearly, these retrospective analyses are inherently difficult to interpret due to a large risk of bias: interventional cardiologists will be more likely to intervene in high-risk morphology. Thus, a similar outcome in intervened and non-intervened patient patients may already reflect a favourable treatment effect. In our cohort, the overall 2-year rate of MACE was between 8.1% and 9.2% without any significant variations over the study period. In line with the findings of Lam *et al.*, the incidence of adverse cardiac events remained stable over the years [35]. However, a direct comparison with other trials is challenging due to a heterogeneous definition of MACE and observation periods [21, 39, 46–48].

This single-centre experience focused on the CV risk stratification of KT candidates with regard to the guidelines adopted from European recommendations in 2007. As a result of the implementation of the consensus, CV screening prior to KT became more intensive and invasive, yet was not associated with an improved outcome. In our case, nearly 50% of the candidates underwent CAG. It is feasible that current practice causes harm by unnecessarily subjecting patients to invasive cardiac examinations and delaying or excluding them from KT. This is supported by data from the very recent ISCHEMIA-CKD trial. Findings from this large randomized controlled trial demonstrated no benefit regarding CV outcomes when an invasive strategy (CAG and revascularization on top of optimal medical treatment) in patients with advanced CKD was applied [49]. Furthermore, a coronary intervention may preclude the patient from KT for the duration of the consecutive dual antiplatelet therapy and increase bleeding risk in subsequent KT. This raises the question of whether the current approach is still appropriate or whether it is time to consider integrating other CV screening methods in the practice of routine regular pre-transplant check-up procedures. This dilemma may be further supported by findings of the 4D trial or recent American registry data, which actually show that CV mortality in dialysis patients is primarily attributed to sudden cardiac death, caused by malignant arrhythmias and HF, rather than atherosclerotic CV disease [50, 51]. CurrentEuropean Renal Best Practice recommendations (last updated in 2013) are ambiguous and have low evidence grading, partially due to the lack of data especially from Europe [11]. We thus provide retrospective data in KT recipients, which show that a low-threshold to perform invasive CV diagnostics, based on a history of CAD or the presence of classical CV risk factors in the setting of routine pre-transplant evaluation is not associated with improved outcomes.

Limitations

Our study was retrospective and chart-based, and thus has the usual limitations of such studies; however, the number of included patients is reasonable considering the monocentric design. For the retrieval of cardiac symptoms, we had to rely on CAG reports and concomitant physicians' letters. Inquiry of symptoms in a retrospective setting is particularly exposed to bias, thus, these findings need to be interpreted with caution. The low MACE count, as well as a relatively brief period of follow-up (2 years after KT) are also limitations. The preselection of patients with severe comorbidities before undertaking KT evaluation may also limit the utility of screening procedures, but it may provide an explanation for low diabetes prevalence in our KT recipients. Comparison of outcomes to that of patients on the transplant waiting list as well as the consideration of transplant-related factors (e.g. donor organ quality, immunological and infectious complications) was beyond the scope of this study.

FUNDING

The study received no external funding.

AUTHORS' CONTRIBUTIONS

A.T.D. and P.P.R. designed the study; A.T.D., F.I., B.O., M.P.K. and R.K. performed data collection and processing; K.E. and A.B. performed the statistical analysis; A.T.D., A.H.K and A.R.R. wrote the manuscript.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract form. The authors declare no conflict of interest.

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Received: 2.1.2020; Editorial decision: 22.4.2020