Cardiovascular disease: Risk factors and applicability of a risk model in a Greek cohort of renal transplant recipients

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AIM
To investigate the incidence and the determinants of cardiovascular morbidity in Greek renal transplant recipients (RTRs) expressed as major advance cardiac event (MACE) rate.

METHODS
Two hundred and forty-two adult patients with a functioning graft for at least three months and available the presented data are anonymized and risk of identification is low.

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Abstract

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METHODS
Two hundred and forty-two adult patients with a functioning graft for at least three months and available...
data that were followed up on the August 31, 2015 at two transplant centers of Western Greece were included in this study. Baseline recipients’ data elements included demographics, clinical characteristics, history of comorbid conditions and laboratory parameters. Follow-up data regarding MACE occurrence were collected retrospectively from the patients’ records and MACE risk score was calculated for each patient.

RESULTS
The mean age was 53 years (63.6% males) and 47 patients (19.4%) had a pre-existing cardiovascular disease (CVD) before transplantation. The mean estimated glomerular filtration rate was 52 ± 17 mL/min per 1.73 m². During follow-up 36 patients (14.9%) suffered a MACE with a median time to MACE 5 years (interquartile range: 2.2-10 years). Recipients with a MACE compared to recipients without a MACE had a significantly higher mean age (59 years vs 52 years, P < 0.001) and a higher prevalence of pre-existing CVD (44.4% vs 15%, P < 0.001). The 7-year predicted mean risk for MACE was 14.6% ± 12.5% overall. In RTRs who experienced a MACE, the predicted risk was 22.3% ± 17.1% and was significantly higher than in RTRs without an event 13.3% ± 11.1% (P = 0.003). The discrimination ability of the model in the Greek database of RTRs was good with an area under the receiver operating characteristics curve of 0.68 (95%CI: 0.58-0.78).

CONCLUSION
In this Greek cohort of RTRs, MACE occurred in 14.9% of the patients, pre-existing CVD was the main risk factor, while MACE risk model was proved a dependable utility in predicting CVD post RT.

Key words: Cardiovascular disease; Major advance cardiac event; Risk factors; Risk model; Kidney; Transplantation

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INTRODUCTION
Renal transplantation is the treatment of choice for patients with end stage renal disease (ESRD), as it enhances survival and quality of life and is also cost-effective. Nevertheless, cardiovascular disease (CVD) is the leading cause of death with functioning graft in renal transplant recipients (RTRs) [1-2]. Cardiovascular mortality rates in RTRs are significant lower than in an age stratified dialysis population but remain at least twice as high as in an age-stratified sample of the general population [3-5]. Although, successful renal transplantation results in the removal of the hemodynamic and uremic abnormalities associated with dialysis along with the improvement of cardiovascular indices such as left ventricular hypertrophy [6-7], by the time of renal transplantation, the majority of patients already have a heavy burden of atherosclerosis [8].

Knowledge of responsible cardiovascular risk factors has improved in RTRs but precise risk calculation and realistic prediction of a subsequent cardiovascular fatal or non-fatal event still remains a challenge among transplant physicians. In this direction, risk prediction models for cardiovascular events, based on traditional cardiovascular risk factors, have been validated and applied in the general population but their validity remains controversial in RTRs. Accordingly, the Framingham risk score which is a simple and easily accessible tool for the prediction of the risk of a coronary event within the following 10 years has been shown to underestimate cardiovascular risk in RTRs [9]. Given this gap in prediction, transplant-related risk factors have been investigated in large multicenter databases of RTRs, showing that cardiovascular comorbid conditions and risk factors linked to graft function explain much of the variation in coronary heart disease after kidney transplantation [10].

More recently, Soveri et al. [11] developed and internally validated major adverse cardiac event (MACE) and mortality risk calculators for prevalent RTRs by using Assessment of Lescol in Renal Transplantation (ALERT) data from the extension trial. The same group of investigators subsequently externally validated the risk equation in an international transplant database using RTRs from the patient outcomes in renal transplantation (PORT) cohort and successfully applied the risk estimator in the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-EXT ended criteria donors trial (BENEFIT-EXT) [12].

In our study, we sought to investigate the incidence and the determinants of cardiovascular morbidity in Greek RTRs expressed as MACE rate. Additionally, we examined the applicability of a validated risk prediction model for MACE in our population.
MATERIALS AND METHODS

Patient characteristics
The full database consisted of 293 RTRs. Adult patients with a functioning graft for at least three months and available data that were followed up on the August 31, 2015 at the two transplant centers of the 6th District Health (Renal Transplant Units of the University Hospital of Patras and University General Hospital of Ioannina), were included in this study. The final analysis included 242 RTRs as for the rest of the patients detailed data regarding coronary heart events and potential CVD risk factors were insufficient.

Recipients’ data elements included demographics, clinical characteristics, time on dialysis prior to transplant, history of comorbid conditions such as diabetes (including new onset diabetes after transplantation (NODAT)), hypertension, cardiac ischemic heart disease [myocardial infarction (MI) based on electrocardiography or troponin rise, coronary angioplasty or artery bypass grafting], congestive heart failure, cerebrovascular accident, transient ischemic attack and peripheral artery disease, pre- and post-transplant smoking status and immunosuppression therapy. Laboratory parameters included renal function markers [serum creatinine, 24 h urine protein content (UPR, mg/24 h)], glucose, hemoglobin, lipid profile [total cholesterol (TChol) and low density lipoprotein-(LDL)], C-reactive protein (CRP) and mineral bone disease markers [calcium, phosphate, parathyroid hormone (PTH)]. Estimated glomerular filtration rate (eGFR) was calculated using the four variable modification of diet in renal disease study equation (MDRD)[13]. Clinical characteristics, laboratory parameters, cardiovascular disease and immunosuppressive medications recorded closest to 3 mo post-transplant were used in the analysis. All data were collected retrospectively and were obtained from the patients’ medical files.

MACE definition and risk calculation
Major adverse cardiac event was strictly defined as one or more of nonfatal MI and/or invasive coronary artery revascularization (angioplasty or coronary artery bypass grafting), that occurred 3 mo post-transplant in a RTR with a functioning allograft on the cross-sectional database review as of August 31, 2015. Follow-up data regarding MACE occurrence were collected retrospectively from the patients’ records. Time to event was defined as time from transplant to the earliest date of MACE.

For prediction of a subsequent MACE, the MACE risk calculator, recently described by Soveri et al[11], was applied in the study. It is a seven variable calculator using age, previous cardiac event, history of diabetes mellitus (DM) including NODAT, pre- and post-transplantation smoking habits, number of renal grafts received, serum creatinine and LDL levels to predict 7-year risk of MACE. The area under the receiver operator curve (ROC) in the original study was 0.738[11]. The MACE risk was calculated for all 242 participants (http://www.medsci.uu.se/forskning/Inflammation_och_autoimmunitet/).

This study was approved by the Institutional Scientific Committee and the Review Board of the University General Hospital of Ioannina, 6th District Health (Peloponnesse, Ionian Islands, Epirus and Western Greece), Greece.

Statistical analysis
Data are expressed as mean and standard deviation (for normally distributed data), median and interquartile range (IQR) (for not-normally distributed data), or as percentage frequency (for binary variables). Differences in baseline characteristics of RTRs without (group A) and with MACE (group B) were compared by using the Mann Whitney U test for continuous variables and the chi-square test for categorical variables.

Univariate and multivariate Cox proportional hazards models were used to assess effects of potential risk factors on the primary outcome, first MACE. Tested covariates in the univariate analysis included, age, sex, pre- and post-transplant smoking status, hypertension, systolic blood pressure (BP), DM, pre-existing CVD, total time on dialysis and transplantation, number of grafts, serum creatinine, UPR, TChol, LDL, PTH, CRP and calculated MACE risk. Risk factors with a P value ≤ 0.1 in the univariate analysis were included in the multivariate model. In the Cox analysis data were expressed as hazard ratio (b), 95%CI and P value.

The validation for discrimination was performed externally using the Greek cohort of RTRs. The discriminative power of MACE risk model for identifying patients with from those without the primary outcome was assessed by calculating the area under the ROC curve (c-statistics). A value of AUC of 50% is considered as the threshold of prognostic usefulness.

All the statistical analyses were performed by using a standard statistical package (IBM SPSS Statistics for Windows, version 22.0).

RESULTS

Characteristics of RTRs
Demographics, clinical characteristics and laboratory parameters of the 242 RTRs overall and classified in the two groups are shown in Table 1. In the whole group, the mean age was 53 years and 63.6% were males. The vast majority of RTRs were hypertensive patients (87.6%), 29.4% of them were diabetics (including NODAT) and 47 patients (19.4%) had a positive history of CVD before transplantation. The percentage of active smokers in the whole cohort was almost halved after transplantation (previous smokers 35.1% vs current smokers 17.8%, P < 0.001). The mean time on dialysis before transplantation was 4.8 ± 3.9 years. Most of the patients received one renal graft (90%), while 23 patients received two grafts and one patient three grafts. The mean eGFR of the functioning graft was 52 ± 17 mL/min per 1.73 m² and the median UPR level was 309 mg/24 h (IQR, 167-600 mg/24 h). Immunosuppression regimen was effectively recorded in 209 patients (Table
In RTRs who experienced a MACE the predicted risk was 22.3% ± 17.1% and was significantly higher than in RTRs without a subsequent event 13.3% ± 11.1% (P = 0.003) (Figure 1).

Table 3 provides the results of the univariate and multivariate analysis with MACE as the dependent variable of interest. In the univariate Cox regression analysis we found that the calculated MACE risk (HR = 1.04, 95%CI: 1.02-1.06) was associated with a higher risk of a subsequent event. When the risk factors of the model and other factors were tested separately, older age (HR = 1.05, 95%CI: 1.02-1.08) was associated with an increased risk of MACE. In the multivariate model, pre-existing CVD was the main independent predictor for the occurrence of MACE (HR = 2.86, 95%CI: 1.45-5.62), while older age (HR = 1.05, 95%CI: 1.01-1.08) was associated with an increased risk of MACE as well.

The discrimination ability of the model in the Greek cohort of RTRs was good with an area under the ROC curve of 0.68 (95%CI: 0.58-0.78) (Figure 2).

**DISCUSSION**

The incidence of MACE before graft loss in our clinical database of RTRs was 14.9% with a median time to event 5 years. Recipients who suffered a MACE were older and had higher prevalence of pre-existing CVD. The first attempt to apply an externally validated risk MACE model in a Greek cohort of RTRs showed that the model can be used for risk stratification in this...
Table 2  Immunosuppression and cardiovascular disease therapy in all renal transplant recipients and differences between the two groups

|                      | Total RTRs | Group A | Group B | P     |
|----------------------|------------|---------|---------|-------|
| Steroids             | 199 (95.2) | 167 (95)| 32 (97) | 0.61  |
| Mycophenolate mofetil| 207 (99)   | 175 (99.4)| 32 (97) | 0.18  |
| Tacrolimus           | 56 (26.8)  | 49 (27.8)| 7 (21.2) | 0.43  |
| Cyclosporine         | 146 (69.9) | 122 (69.3)| 24 (72.7) | 0.69  |
| Everolimus           | 6 (2.9)    | 4 (2.3)  | 2 (6.1)  | 0.23  |
| CCB                  | 134 (55.4) | 116 (56.3)| 18 (50)  | 0.65  |
| Beta-adrenergic blockers | 151 (62.4) | 128 (62.1)| 23 (63.9) | 0.86  |
| ARBs/ACEi            | 131 (54.1) | 117 (56.7)| 14 (38.9) | 0.35  |
| Diuretics            | 56 (23.1)  | 46 (21.8) | 10 (27.8) | 0.58  |
| Other antihypertensive drugs | 53 (21.9) | 48 (23.3) | 5 (13.9) | 0.46  |
| Hypolipidemic drugs  | 154 (63.6) | 134 (65) | 20 (55.6) | 0.49  |

Immunosuppression therapy was recorded for 209 RTRs. Cardiovascular disease therapy was recorded in all 242 RTRs. Data are expressed as absolute frequency and percentage. Hypolipidemic drugs included statins, fibrates, ezetimibe or combinations of the aforementioned. Group A: With MACE; Group B: Without MACE. MACE: Major advance cardiac event; CCB: Calcium channel blockers; ARBs: Angiotensin receptor blockers; ACEi: Angiotensin converting enzyme inhibitors; RTRs: Renal transplant recipients.

Figure 1  Calculated major advance cardiac event risk score in the 242 renal transplant recipients and in the two groups. MACE score for all the RTRs, group A, defined as RTRs without MACE and group B, defined as RTRs with MACE, is respectively 14.6% ± 12.5%, 13.3% ± 11.1% and 22.3% ± 17.1%. MACE: Major advance cardiac event; RTRs: Renal transplant recipients.

Population.

Disproportionate increased cardiovascular burden is true since the early stages of chronic kidney disease, further increases during dialysis and although renal transplantation removes hemodynamic and uremic abnormalities associated with dialysis, the vast majority of RTRs with a functioning graft die due to a MACE. In our study, RTRs with a functioning graft who suffered a MACE had higher prevalence of CVD before transplantation, with pre-existing CVD being the most significant risk factor for MACE in this cohort. As regards traditional cardiovascular risk factors such as smoking, hypertension, diabetes and lipid profile their prevalence did not significantly differ between the two groups in our database of RTRs and separately each one could not predict the occurrence of a MACE. Our findings are in accordance with the results of an early study by Kasiske et al.[14] showing that the strongest risk factors were pre-existing coronary heart disease, cerebrovascular and peripheral vascular, which were associated with an increase of three to nine times in cardiovascular risk. In this study, there was not a relation between traditional risk factors (smoking, hypertension, or dyslipidemia) and CVD in 1000 RTRs. In the more recent PORT study, a large scale clinical database of 23575 RTRs, it was found that among the significant predicting factors for MACE were age, male sex and pre-existing CVD, whereas traditional modifiable cardiovascular risk factors were very poor predictors of cardiac events[10]. On the other hand, the investigators of the ALERT study used post-hoc analyses and identified the determinants of specific cardiovascular endpoints such as MI being associated with age, hyperlipidemia and diabetes[18].

Unconventional and transplant-related risk factors, including immunological and non-immunological ones further increase the risk of CVD after transplantation[16,15]. In particular, the large multicentre PORT study found that a number of transplant-specific variables, such as delayed graft function, acute rejection and eGFR could predict cardiac events[10,16,17]. However, interventional studies which tried to normalize unconventional modifiable risk factors, such as haemoglobin and homocysteine, failed to reduce occurrence of CVD in RTRs[16,17]. Moreover, immunosuppressive drugs prescribed to RTRs, mainly corticosteroids and calcineurin inhibitors (cyclosporine, tacrolimus), which possess diabetogenic and atherogenic side effects exacerbate established cardiovascular risk factors such as dyslipidemia, hypertension, and diabetes[18]. Given the fact that traditional, non-traditional and transplant-related risk factors separately only partly can explain the increased burden of CVD and that the interplay between all these factors seems to be the core of the increased cardiovascular risk in RTRs many groups of investigators have tried to apply established risk models or to create new risk calculators in order to accurately predict a subsequent cardiovascular event in this population. In particular, the use of the Framingham risk score in RTRs underestimates cardiovascular risk,
although the addition of renal function in the Framingham equation was shown to improve the prediction of MACE\(^9,19\). More recently, Soveri et al\(^{11}\) used data from the ALERT trial\(^8\), a large scale multicenter trial and constructed a seven year, seven variable MACE risk equation with an area under the ROC curve of 0.738\(^{11}\). Subsequently they externally validated the 7-year risk calculator for discrimination and calibration in the PORT study database, which was an observational study\(^10\).

Although the calculator was derived from the ALERT trial, a transplant population with moderate CVD risk, it was validated in the high risk RTRs of the PORT study and found suitable for this population with an area under the ROC curve of 0.740\(^{12}\).

In this study we applied the MACE risk calculator in our cohort of RTRs from two transplant centers in Western Greece. According to the results the predicted risk was significantly higher in RTRs who experienced a MACE than in RTRs without a subsequent event and the calculator by preserving the discrimination ability is suitable for risk stratification in our population. The incidence of MACE in our database was 14.9%, while the incidence of MACE in ALERT trial was 11.8%. It should be noted that there were important differences in the composition of populations among the two studies as ALERT trial included moderate CVD risk RTRs from North Europe and Canada.

Nevertheless, our study has potential limitations which should be taken into consideration. First of all, this is a retrospective study conducted in a small sample population. Additionally, we did not report on data about graft survival and patients’ cardiovascular and total mortality as we included only RTRs with a functioning kidney graft at the time of the cross-sectional database review. Finally, we did not assess the possible effect of transplant-related risk factors, such as delayed graft function, acute rejection, on the occurrence of MACE.

In conclusion, pre-existing CVD was found to be the most important risk factor of a subsequent MACE, which necessitates holistic approach prevention strategies of CVD starting early in the course of chronic kidney disease. In our study, a validated MACE risk calculator was successfully tested in a Greek cohort of RTRs and was found to be suitable for the prediction of MACE in this patient group. Considering the fact that RTRs are a heterogeneous population as well as the identification of new emerging transplant related risk factors, patient approach should always be individualized. Nevertheless, the application of cardiovascular risk prediction equations potentiates increased level of alertness among caregivers as well as improved interventional strategies in high risk

### Table 3  Univariate and multivariate analysis of risk factors for major advance cardiac event in renal transplant recipients

| Variables (units of increase) | Univariate | Multivariate |
|------------------------------|------------|-------------|
|                              | b (95%CI)  | P           |
| MACE risk (1%)               | 1.04 (1.02-1.06) | < 0.001 |
| Age (1 yr)                   | 1.05 (1.02-1.10) | 0.001 |
| Sex (male reference)         | 0.45 (0.20-0.99) | 0.05 |
| Previous smoker              | 1.51 (0.73-2.92) | 0.21 |
| Current smoker               | 1.0 (0.44-2.29) | 0.99 |
| Systolic BP (1 mmHg)         | 1.01 (0.99-1.02) | 0.61 |
| DM                           | 1.53 (0.78-2.98) | 0.21 |
| Previous CVD                 | 3.63 (1.86-7.01) | < 0.001 |
| Number of grafts (first graft reference) | 0.50 (0.12-2.02) | 0.33 |
| Total time on dialysis and transplantation (1 yr) | 0.99 (0.92-1.01) | 0.33 |
| Creatinine (1 mg/dL)         | 0.90 (0.48-1.68) | 0.74 |
| Urine protein (1 mg/24 h)    | 0.99 (0.99-1.00) | 0.28 |
| Total cholesterol (1 mg/dL)  | 0.99 (0.99-1.00) | 0.3 |
| LDL (1 mg/dL)                | 0.99 (0.98-1.01) | 0.46 |
| Hemoglobin (1 g/dL)          | 1.14 (0.95-1.40) | 0.21 |
| PTH (1 pg/mL)                | 1.00 (0.99-1.00) | 0.25 |
| CRP (1 mg/l)                 | 1.01 (0.92-1.09) | 0.88 |

MACE: Major advance cardiac event; BP: Blood pressure; DM: Diabetes mellitus; CVD: Cardiovascular disease; LDL: Low density lipoprotein; PTH: Parathyroid hormone; CRP: C-reactive protein.

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![ROC curve](image.png)

**Figure 2  Discrimination.** Receiver operating characteristics for major adverse cardiac event in the cohort of RTRs. Area under the curve is 0.68 (95%CI: 0.58-0.78). RTRs: Renal transplant recipients; ROC: Receiver operator curve.
patients.

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COMMENTS

Background
Kidney transplantation offers a significant improvement in all the cardiovascular parameters of end stage renal disease (ESRD) patients, reduces mortality risk and boosts quality of life.

Research frontiers
To determine the risk factors for cardiovascular disease after kidney transplantation and validate a major advance cardiac event (MACE) risk model to a Greek renal transplant recipients (RTRs) cohort.

Innovations and breakthroughs
In this study, the authors found that older age, pre-existing cardiovascular disease (CVD) and MACE risk score, were significant predictors of post-transplant cardiovascular risk. So long as, there are modifiable components to the risk factors/scores, it is the belief that prevention of CVD early in chronic kidney disease along with control of these factors in ESRD patients and RTRs, could possibly reduced cardiovascular burden to some degree.

Applications
The externally validated equation can be used in any appropriate RTR population to calculate MACE risk.

Terminology
MACE was defined as one or more of nonfatal myocardial infarction and/or invasive coronary artery revascularization (angioplasty or coronary artery bypass grafting).

Peer-review
It is a well-written study about the event of cardiovascular disease after renal transplantation.

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