



ORIGINAL ARTICLE

Plasma biomarkers outperform echocardiographic measurements for cardiovascular risk prediction in kidney transplant recipients: results of the HOME ALONE study

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ABSTRACT

Background. Since kidney transplant recipients (KTRs) have a high cardiovascular disease burden, adequate risk prediction is of importance. Whether echocardiographic parameters and plasma biomarkers, natriuretic peptides [N-terminal pro-B-type natriuretic peptide (NT-proBNP)] and troponin T provide complementary or overlapping prognostic information on cardiovascular events remains uncertain.

Methods. The prospective Heterogeneity of Monocytes and Echocardiography Among Allograft Recipients in Nephrology (HOME ALONE) study followed 177 KTRs for 5.4 ± 1.7 years. Predefined endpoints were hospitalization for acute decompensated heart failure or all-cause death (HF/D) and major atherosclerotic cardiovascular events or all-cause death (MACE/D). At baseline, plasma NT-proBNP, plasma troponin T and echocardiographic parameters [left atrial volume index, left ventricular (LV) mass index, LV ejection fraction, and LV filling pressure] were assessed.

Results. Among all echocardiographic and plasma biomarkers measured, only NT-proBNP was consistently associated with HF/D in univariate and multivariate [third versus first tertile: hazard ratio [HR] 4.20 [95% confidence interval (CI) 1.02–17.27]] analysis, and only troponin T was consistently associated with MACE/D in univariate and multivariate [third versus first tertile: HR 8.15 (95% CI 2.75–24.18)] analysis.

Conclusion. Our data suggest that plasma biomarkers are robust and independent predictors of heart failure and atherosclerotic cardiovascular events after kidney transplantation, whereas standard echocardiographic follow-up does not add to risk prediction.

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Keywords: cardiovascular outcomes, echocardiographic parameters, heart failure, kidney transplant recipients, plasma NT-proBNP, plasma troponin T, risk prediction

INTRODUCTION

Kidney transplantation is the preferred kidney replacement therapy (KRT) for suitable patients with advanced chronic kidney disease (CKD). Compared with dialysis treatment, kidney transplantation improves survival [1] and increases quality of life [2, 3]. Still, kidney transplant recipients (KTRs) have a higher cardiovascular event rate and mortality compared with age-matched individuals from the general population [4], although potential KTRs are screened for cardiovascular disease preoperatively. In particular, the incidence of atherosclerotic cardiovascular events [5] and heart failure [6] remains high after kidney transplantation. Risk stratification with subsequent implementation of preventive lifestyle and pharmacologic strategies might reduce cardiovascular events post-transplant.

Several cohort studies have identified plasma natriuretic peptides, plasma troponin T and echocardiographic parameters, such as left ventricular mass index (LVMI), left atrial volume index (LAVI), left ventricular ejection fraction (LVEF) and markers of left ventricular (LV) filling pressure [E/e' ; ratio of early mitral inflow velocity (E) to mitral annular early diastolic velocity (e')], as useful tools for risk prediction in the general population [7–9], in patients with cardiac diseases [10–14] and in CKD patients prior to transplantation [15, 16]. However, less evidence on the prognostic role of plasma biomarkers [17, 18] and echocardiographic parameters [19] is available for KTRs.

We now prospectively aimed to assess the predictive role of N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin T and routine echocardiographic parameters in a cohort of stable KTRs. Moreover, if plasma biomarkers and echocardiographic parameters both predict cardiovascular events in KTRs, we sought to assess whether they provide complementary or redundant information.

This analysis has been inspired by our recent findings among CKD patients not requiring KRT, in whom plasma natriuretic peptides were independent predictors of adverse cardiovascular outcomes, whereas the additional use of echocardiographic parameters did not improve risk stratification [20]. However, these findings should not uncritically be transferred to KTRs, in whom the long-term intake of immunosuppressive medication may induce specific cardiovascular side effects [21].

MATERIALS AND METHODS

The Heterogeneity of Monocytes and Echocardiography Among Allograft Recipients in Nephrology (HOME ALONE) study is a prospective cohort study that recruited 184 kidney allograft recipients between 2012 and 2015. All participants were followed regularly in the renal outpatient clinic of the Saarland University Medical Centre in Homburg, Germany; they were in stable clinical conditions and had received their allograft at least 9 months prior to enrollment.

Exclusion criteria were age <18 years, pregnancy, apparent clinical infections (defined as plasma C-reactive protein levels >50 mg/L and/or the need for systemic antibiotic treatment), acute kidney injury and active malignancy.

The study design was approved by the local ethics committee (54/04), and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was given by

each participant at baseline. At baseline, blood samples were taken under standardized conditions after an overnight fast. All routine laboratory parameters were measured at baseline in the Department of Clinical Chemistry and Laboratory Medicine of the Saarland University Medical Centre. Plasma NT-proBNP was measured by an electrochemiluminescence immunoassay (Cobas System, Elecsys 2010 proBNP II; Roche Diagnostics, Indianapolis, IN, USA). Plasma troponin T was assessed by an electrochemiluminescence immunoassay (Cobas System, Elecsys Troponin T-high sensitive; Roche Diagnostics, Indianapolis, IN, USA). Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease equation. Albuminuria was quantified as the albumin to creatinine ratio from a morning spot urine sample.

All echocardiographic studies were performed by the same sonographer following the American Society of Echocardiography (ASE) guidelines [22]. The sonographer completed the echocardiographic studies directly after the blood samples were taken, so he was generally not aware of the results of the plasma biomarkers. Standard echocardiographic parameters were measured from parasternal and apical views using a Sequoia C512 Ultrasound Unit (Acuson, Thousand Oaks, CA, USA) with a cardiac probe (model 3V2c; 2–3 MHz). LAVI and LVMI were measured and calculated following the ASE guidelines. As a marker of LV filling pressure, E/e' , calculated as the ratio of early diastolic mitral inflow velocity (E), to early diastolic mitral annular velocity (e'), both assessed with pulsed wave Doppler ultrasound, was used; e' was calculated as the mean of septal and lateral mitral annular velocity. LVEF was measured by the biplane Simpson's method. Plasma troponin T, plasma NT-proBNP and echocardiographic data were not blinded to the treating physicians.

Detailed information on cardiovascular risk factors and on other comorbidities was gathered by a standardized questionnaire (provided in the appendix) and by chart review. Generally, participants were invited for revisits at regular intervals at least once yearly. At the end of follow-up, we additionally contacted all participants by telephone.

The participants were followed for the occurrence of two predefined endpoints: hospitalization for acute decompensated heart failure, defined as admission for a clinical syndrome involving symptoms (progressive dyspnea) in conjunction with clinical (peripheral edema, pulmonary rales) or radiologic (cardiomegaly, pulmonary edema, pleural effusions) signs of heart failure or all-cause death, whichever occurred first (HF/D) and major atherosclerotic cardiovascular events or all-cause death, whichever occurred first (MACE/D).

All reported events were verified by independent physicians blinded to echocardiographic parameters and plasma NT-proBNP and plasma troponin T measurement at baseline.

In line with their pathophysiological role, we primarily considered plasma NT-proBNP as a potential marker of HF/D, and plasma troponin T as a potential marker of MACE/D. Major atherosclerotic cardiovascular events included acute myocardial infarction (defined as an increase in troponin T above the 99th percentile of the reference limit accompanied by symptoms of ischemia and/or electrocardiographic changes indicating new ischemia), surgical or interventional coronary/peripheral-arterial/cerebrovascular revascularization, stroke (defined as rapidly developing clinical symptoms or signs of focal, or at

times global, disturbance of cerebral function lasting 24 h, unless interrupted by surgery, or leading to death, with no apparent cause other than of vascular origin) and amputation above the ankle. In post hoc analyses we analyzed plasma NT-proBNP as a potential risk factor for MACE/D and plasma troponin T for HF/D.

Statistical analyses were performed by PASW Statistics 25 (SPSS, Chicago, IL, USA). Continuous data are presented as mean \pm standard deviation (SD) or as median and interquartile range (IQR) in case of skewed deviation. Categorical variables are presented as absolute numbers and percentages of participants. Correlation coefficients were calculated according to Spearman. Correlation (with $r = 0.2$ – 0.4 was considered weak, with $r = 0.4$ – 0.7 moderate and with $r = 0.7$ – 0.9 strong).

After stratifying participants for their LVEF (<50% versus >50%) and for tertiles of NT-proBNP, troponin T, LAVI, LVMI, and E:e', respectively, univariate Kaplan–Meier analyses with subsequent log rank test were performed. In a second step we performed univariate and multivariate Cox regression analyses and considered log-transformed NT-proBNP (for models analyzing HF/D as the endpoint), log-transformed troponin T (for models analyzing MACE/D as the endpoint), LAVI, LVMI, E:e' and LVEF consecutively as exposure variables, both as continuous parameters and after categorization into tertiles (with the single exception of LVEF, which was categorized as impaired at <50% and as preserved at >50%). We predefined four models: sModel 1 represents the univariate analysis; Model 2 adjusts for age and gender; Model 3 additionally adjusts for estimated GFR (eGFR), diabetes mellitus, prevalent atherosclerotic cardiovascular disease (ASCVD; defined as reported earlier [23]), systolic blood pressure, current smoker and total cholesterol; and Model 4 additionally adjusts for log-transformed NT-proBNP (for all models with echocardiographic parameters as exposure variables that analyzed HF/D as the endpoint) or for log-transformed troponin T (for all models with echocardiographic parameters as exposure variables that analyzed MACE/D as the endpoint) or echocardiographic parameters (for analyses with NT-proBNP or with troponin T as the exposure variable). For this analysis, in order to avoid overadjustment, we *a priori* decided to adjust for a single echocardiographic parameter, namely for LVEF (in line with our previous study in non-transplant CKD patients [20]). Exploratory Cox regression analyses that substituted other echocardiographic parameters for LVEF yielded similar results (data not shown).

Finally, we calculated receiver operating characteristic (ROC) analyses for both predefined endpoints that occurred within 5 years after study initiation.

Two-sided P-values <0.05 were considered significant.

RESULTS

Among the 184 HOME ALONE participants, 6 participants had no plasma NT-proBNP/plasma troponin T measurement at baseline and 1 patient did not undergo echocardiography, leaving 177 participants for final analysis. The mean age of the total cohort was 56 ± 13 years, 37.6% of the participants were female and 23.6% had prevalent ASCVD. The mean eGFR was 46 ± 17 mL/min/1.73 m², mean LVEF was $73 \pm 12\%$, median plasma NT-proBNP was 366 ng/L IQR (155–972), and median plasma troponin T was 17 ng/L IQR (11–31) ng/L. LVEF was >50% in 169 participants and <50% in the remaining 8 participants. Further baseline characteristics are summarized in Tables 1 and 2 (patients stratified into tertiles of plasma NT-proBNP) and in Supplementary data, Table S1 (patients stratified into tertiles of plasma troponin T). Primary

Table 1. Baseline characteristics of the total cohort (N = 177)

| | |
|---|-------------------|
| Time since TX (years), mean \pm SD | 6.9 \pm 6.2 |
| Age (years), mean \pm SD | 56 \pm 13 |
| Deceased donor recipients, n (%) | 118 (66.7) |
| Prevalent episode of rejection, n (%) | 23 (13.0) |
| Cold ischemia time (min), median (IQR) | 769 (110–1020) |
| Warm ischemia time (min), mean \pm SD | 48.5 \pm 15.4 |
| Gender (female), n (%) | 67 (37.6) |
| BMI (kg/m ²), mean \pm SD | 27 \pm 6 |
| Prevalent CVD (yes), n (%) | 42 (23.6) |
| Prevalent PCI (yes), n (%) | 20 (11.3) |
| Prevalent AMI (yes), n (%) | 20 (11.3) |
| Prevalent CABG (yes), n (%) | 13 (7.3) |
| Prevalent CTEA (yes), n (%) | 1 (0.6) |
| Prevalent stroke (yes), n (%) | 11 (62.1) |
| Prevalent PAD bypass (yes), n (%) | 1 (0.6) |
| Prevalent PAD stent (yes), n (%) | 1 (0.6) |
| AF (yes), n (%) | 10 (5.6) |
| PM (yes), n (%) | 12 (6.8) |
| Family history of CVD (yes), n (%) | 46 (26.0) |
| DM (yes), n (%) | 52 (29.2) |
| Systolic BP (mmHg), mean \pm SD | 147 \pm 20 |
| Diastolic BP (mmHg), mean \pm SD | 87 \pm 11 |
| Current smoker (yes), n (%) | 24 (13.5) |
| eGFR (mL/min/1.73 m ²), mean \pm SD | 46 \pm 17 |
| Albuminuria (mg/g crea), median (IQR) | 48 (11–191) |
| Triglyceride (mg/dL), median (IQR) | 138 (102–198) |
| LDL-C (mg/dL), mean \pm SD | 115 \pm 34 |
| HDL-C (mg/dL), mean \pm SD | 58 \pm 18 |
| Hemoglobin (g/dL), mean \pm SD | 13.1 \pm 1.6 |
| Calcium (mmol/L), mean \pm SD | 2.4 \pm 0.2 |
| Phosphorus (mg/dL), mean \pm SD | 3.1 \pm 0.7 |
| Ferritin (ng/mL), median (IQR) | 170 (93–357) |
| C-reactive protein (mg/L), median (IQR) | 2.2 (1–5.6) |
| Vitamin D (ng/mL), mean \pm SD | 31 \pm 14 |
| NT-proBNP (ng/L), median (IQR) | 366 (155–972) |
| Troponin T (ng/L), median (IQR) | 17 (11–31) |
| LVMI (g/m ²), mean \pm SD | 101 \pm 28 |
| LVEF (%), mean \pm SD | 73 \pm 12 |
| LAVI (mL/m ²), mean \pm SD | 43 \pm 14 |
| E:e', mean \pm SD | 9 \pm 4 |
| Normal cardiac geometry (yes), n (%) | 62 (37.5) |
| Eccentric cardiac hypertrophy (yes), n (%) | 34 (18.5) |
| Concentric cardiac hypertrophy (yes), n (%) | 33 (17.9) |
| Concentric cardiac remodeling (yes), n (%) | 48 (26.1) |
| Mild-to-moderate aortic valve stenosis (yes), n (%) | 12 (6.8) |
| Severe aortic valve stenosis (yes), n (%) | 0 |
| Mild-to-moderate aortic valve regurgitation (yes), n (%) | 12 (6.8) |
| Severe aortic valve regurgitation (yes), n (%) | 0 |
| Mild-to-moderate mitral valve stenose (yes), n (%) | 3 (1.7) |
| Severe mitral valve stenosis (yes), n (%) | 0 |
| Mild-to-moderate mitral valve regurgitation (yes), n (%) | 7 (4.0) |
| Severe mitral valve regurgitation (yes), n (%) | 5 (2.8) |
| Mild-to-moderate tricuspid valve regurgitation (yes), n (%) | 9 (5.1) |
| Severe tricuspid valve regurgitation (yes), n (%) | 3 (1.7) |
| ACE inhibitors (yes), n (%) | 57 (32.0) |
| ARB (yes), n (%) | 56 (31.5) |
| Beta blockers (yes), n (%) | 137 (77.0) |
| MRA (yes), n (%) | 8 (4.5) |

Table 1. Continued.

| | |
|-----------------------------|------------|
| Cyclosporine A (yes), n (%) | 22 (12.4) |
| Tacrolimus (yes), n (%) | 116 (65.2) |
| Azathioprine (yes), n (%) | 5 (2.8) |
| MMF (yes), n (%) | 109 (61.2) |
| Steroids (yes), n (%) | 135 (75.8) |
| Sirolimus (yes), n (%) | 27 (15.2) |
| Everolimus (yes), n (%) | 2 (1.1) |

TX: transplantation; BMI: body mass index; DM: diabetes mellitus; BP: blood pressure; CVD: cardiovascular disease; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CTEA: carotid thromboendarterectomy; PAD: peripheral artery disease; AF: atrial fibrillation; PM: pacemaker; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; MRA: mineralocorticoid receptor antagonist; MMF: mycophenolate mofetil. Categorical variables are presented as absolute numbers and percentages of participants. Continuous data are expressed as mean \pm SD. In case of skewed distribution, variables are presented as median (IQR).

kidney diseases are summarized in Supplementary data, Table S2.

The majority of participants had undergone deceased donor kidney transplantation ($n = 118$). The median time since transplantation was 6.9 ± 6.2 years. Time since transplantation was <5 years for 85 participants, 5–10 years for 57 participants and >10 years for 42 participants.

When stratifying participants to their NT-proBNP tertiles, participants with higher levels of plasma NT-proBNP were older, had higher systolic blood pressure, lower eGFR and more often had prevalent ASCVD and diabetes mellitus (Table 2).

Plasma NT-proBNP and plasma troponin T were moderately correlated. Moreover, plasma NT-proBNP correlated moderately with LAVI and $E:e'$, and weakly with eGFR and LVMI. Plasma troponin T correlated moderately with eGFR, NT-proBNP and $E:e'$ and weakly with LVMI and LAVI. A very weak correlation was observed between eGFR and $E:e'$ (Table 3).

In the follow-up period of 5.4 ± 1.7 years, HF/D occurred in 42 participants (3 of whom were living donor recipients) and MACE/D occurred in 60 participants (6 of whom were living donor recipients), including 34 participants who died during the follow-up (2 of whom were living donor recipients).

In univariate Kaplan–Meier analyses, higher LAVI, LVMI, $E:e'$, plasma NT-proBNP tertiles and low LVEF were all significantly associated with HF/D (Figure 1). LAVI, $E:e'$ and plasma troponin T tertiles were significantly associated with MACE/D, while tertiles of LVMI and low LVEF were not (Figure 2).

Similarly, in univariate Cox regression analyses, plasma NT-proBNP and all echocardiographic parameters, predicted HF/D, whether regarded as continuous or as categorized variable. They largely remained predictive markers when adjusting for age, gender and traditional cardiovascular risk factors, prevalent ASCVD and eGFR. However, after adjusting for plasma NT-proBNP, echocardiographic parameters were no longer consistently associated with the endpoint, as no echocardiographic parameter predicted HF/D both when considered as a continuous and as a categorized variable. In contrast, after adjusting for LVEF, plasma NT-proBNP predicted HF/D both when considered as a continuous variable as well as a categorized variable (Table 4).

Plasma troponin T and all echocardiographic parameters but LVEF were associated with MACE/D in univariate analysis. High LAVI was no longer associated with the endpoint after adjustment for age and gender; high LVMI lost its predictive power after additionally adjusting for traditional cardiovascular risk fac-

tors, prevalent ASCVD and eGFR, while high $E:e'$ was an independent predictor in the fully adjusted model when considered as a continuous variable, but not when considered as a categorized parameter. However, plasma troponin T was consistently associated with MACE/D in multivariate analysis, whether regarded as a continuous or categorized variable (Table 5).

In post hoc analyses, plasma troponin T was significantly associated with HF/D, even after adjustment for all predefined variables, and plasma NT-proBNP was significantly associated with MACE/D, again after adjustment for all predefined variables.

In subsequent ROC analyses, plasma NT-proBNP and plasma troponin T numerically had the highest area under the curve for predicting HF/D within 5 years (Figure 3) and for predicting MACE/D within 5 years (Figure 4).

DISCUSSION

The present study evaluated whether echocardiographic and plasma biomarkers provide complementary or redundant information on cardiovascular prognosis among 177 stable KTRs. As the high cardiovascular burden is a substantial clinical problem in KTRs, numerous biomarkers for predicting major atherosclerotic cardiovascular events and hospitalization for acute decompensated heart failure have been suggested. Evidence-based selection of essential biomarkers is as important as knowledge about which biomarkers might be dispensable.

Herein, four common echocardiographic parameters were outperformed by plasma NT-proBNP and plasma troponin T for prediction of hospitalization for acute decompensated heart failure and major atherosclerotic cardiovascular events, respectively. These results are in line with earlier findings from the Cardiovascular and Renal Outcome in CKD 2-4 Patients-The Fourth Homburg Evaluation Study, which recruited CKD patients not requiring KRT [20]: among 496 CKD Kidney Disease: Improving Global Outcomes GFR stages G2–G4 patients, plasma NT-proBNP levels were independent predictors of hospitalization for acute decompensated heart failure and major atherosclerotic cardiovascular events, while the additional use of echocardiography did not further improve risk stratification [20]. However, plasma troponin T levels were not analyzed in that study.

In contrast, only a few cohort studies have investigated echocardiographic or plasma cardiac biomarkers individually in patients after kidney transplantation. In 510 US KTRs, plasma natriuretic peptides were generally found to be strong predictors of atherosclerotic cardiovascular events across all stages of allograft function [17], and plasma troponin T predicted total survival among 372 European allograft recipients [18]. Acute decompensated heart failure, which is of high epidemiological and clinical importance among CKD patients, was not assessed in those studies. In HOME ALONE, we *a priori* chose to analyze plasma NT-proBNP as a specific marker of hospitalization for acute decompensated heart failure, and plasma troponin T as a specific marker of major atherosclerotic cardiovascular events, reflecting their individual role in cardiac (patho)physiology. In our study, post hoc analyses additionally revealed a potential prognostic role of troponin T for predicting heart failure events and a potential role of NT-proBNP for predicting atherosclerotic events, even though their pathophysiological implications may appear less obvious. These findings are in line with data from the large epidemiological Chronic Renal Insufficiency Cohort Study, which recruited nearly 4000 CKD patients not on KRT [24–26].

Table 2. Baseline characteristics; participants stratified into tertiles of plasma NT-proBNP

| | NT-proBNP first tertile, 15–228 ng/L (n = 58) | NT-proBNP second tertile, 230–737 ng/L (n = 60) | NT-pro BNP third tertile, 739–15 579 ng/L (n = 59) |
|---|--|--|---|
| Time since TX (years), mean ± SD | 6.2 ± 5.0 | 7.0 ± 6.5 | 7.6 ± 7.2 |
| Age (years), mean ± SD | 48 ± 12 | 57 ± 11 | 62 ± 12 |
| Gender (female), n(%) | 20 (33.9) | 23 (38.3) | 24 (40.7) |
| BMI (kg/m ²), mean ± SD | 28 ± 5 | 27 ± 5 | 27 ± 6 |
| Prevalent CVD (yes), n(%) | 4 (6.8) | 13 (21.7) | 25 (42.4) |
| DM (yes), n(%) | 9 (15.3) | 14 (23.3) | 29 (49.2) |
| Systolic BP (mmHg), mean ± SD | 139 ± 13 | 145 ± 20 | 156 ± 22 |
| Diastolic BP (mmHg), mean ± SD | 88 ± 8 | 86 ± 11 | 86 ± 14 |
| Current smoker (yes), n(%) | 5 (8.5) | 7 (11.7) | 12 (20.3) |
| eGFR (mL/min/1.73 m ²), mean ± SD | 53 ± 16 | 48 ± 17 | 39 ± 14 |
| Albuminuria (mg/g creatinine), median (IQR) | 21 (10–78) | 40 (10–109) | 132 (20–436) |
| Triglycerides (mg/dL), median (IQR) | 126 (93–178) | 152 (106–198) | 145 (110–219) |
| LDL-C (mg/dL), mean ± SD | 115 ± 30 | 119 ± 33 | 114 ± 40 |
| HDL-C (mg/dL), mean ± SD | 58 ± 17 | 60 ± 19 | 57 ± 18 |
| NT-proBNP (ng/L), median (IQR) | 117 (83–154) | 364 (286–516) | 1550 (972–2285) |
| Troponin T (ng/L), median (IQR) | 12 (9–16) | 15 (12–22) | 33 (19–44) |
| LVMi (g/m ²), mean ± SD | 89 ± 21 | 100 ± 26 | 114 ± 30 |
| LVEF (%), mean ± SD | 74 ± 10 | 72 ± 10 | 72 ± 16 |
| LAVI (mL/m ²), mean ± SD | 34 ± 8 | 43 ± 13 | 52 ± 15 |
| E:e' | 7 ± 2 | 8 ± 3 | 11 ± 5 |
| Normal cardiac geometry (yes), n(%) | 32 (54.2) | 23 (38.3) | 11 (18.6) |
| Eccentric cardiac hypertrophy (yes), n(%) | 7 (11.9) | 12 (20.0) | 15 (25.4) |
| Concentric cardiac hypertrophy (yes), n(%) | 3 (5.1) | 8 (13.3) | 20 (33.9) |
| Concentric cardiac remodeling (yes), n(%) | 17 (28.8) | 17 (28.3) | 13 (22.0) |
| ACE inhibitors (yes), n(%) | 12 (20.3) | 21 (35.0) | 24 (40.7) |
| ARB (yes), n(%) | 23 (39.0) | 17 (28.3) | 16 (27.1) |
| Beta blockers (yes), n(%) | 38 (64.4) | 47 (78.3) | 52 (88.1) |
| MRA (yes), n(%) | 1 (1.7) | 2 (3.3) | 5 (8.5) |
| Cyclosporine A (yes), n(%) | 9 (15.3) | 8 (13.3) | 5 (8.5) |
| Tacrolimus (yes), n(%) | 42 (71.2) | 37 (61.7) | 37 (62.7) |
| Azathioprine (yes), n(%) | 2 (3.4) | 1 (1.7) | 2 (3.4) |
| MMF (yes), n(%) | 37 (62.7) | 42 (70.0) | 30 (50.8) |
| Steroids (yes), n(%) | 39 (66.1) | 47 (78.3) | 49 (83.1) |
| Sirolimus (yes), n(%) | 6 (10.2) | 9 (15.0) | 12 (20.3) |
| Everolimus (yes), n(%) | 0 (0) | 1 (1.7) | 1 (1.7) |

TX: transplantation; BMI: body mass index; DM: diabetes mellitus; BP: blood pressure; CVD: cardiovascular disease; PCI: percutaneous coronary intervention; AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CTEA: carotid thromboendarterectomy; PAD: peripheral artery disease; AF: atrial fibrillation; PM: pacemaker; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; MRA: mineralocorticoid receptor antagonist; MMF: mycophenolate mofetil.

While the majority of longitudinal echocardiographic cohort studies among KTRs analyzed parameters from ultrasound studies performed before transplantation [27–29], to the best of our knowledge, only a single prospective outcome study collected echocardiographic parameters after kidney transplantation. In this study, left ventricular hypertrophy was associated with an increased risk for future atherosclerotic cardiovascular events in 68 nondiabetic KTRs [19]. Of note, the authors did not adjust for plasma cardiac biomarkers.

Our study findings now suggest that routine echocardiography in addition to plasma NT-proBNP and troponin T measurements provides only limited prognostic information in KTRs. This may be related in part to the higher intra-observer variability of echocardiographic studies.

A dedicated echocardiography study including core lab analysis might contrast routine clinical echocardiography as used in the current investigation. Furthermore, parameters of diastolic dysfunction are less robust than measuring systolic dysfunction by merely quantifying ejection fraction. This is reflected by the rather complicated definition of diastolic LV function as pro-

vided in the current European Society of Cardiology consensus document [30].

In contrast, measurements of plasma NT-proBNP levels and troponin T levels have been standardized across different laboratories so that measurement variability is limited and results are easily and fast available from a single blood sample.

Often, the accumulation of plasma NT-proBNP and troponin T levels due to decreased kidney function is discussed as a limitation for cardiovascular risk prediction in CKD patients [31]. Nevertheless, both biomarkers were strong outcome predictors in HOME ALONE before and after adjustment for GFR. Similar findings were observed in non-transplant CKD patients [32, 33].

Several limitations should be discussed. Compared with studies that only analyzed plasma biomarkers [17, 18, 34], we have a smaller number of participants and consequently a smaller number of participants who had heart failure events and atherosclerotic cardiovascular disease events. To allow all echocardiographic studies to be performed by a single

Table 3. Correlations between NT-proBNP, troponin T, eGFR and echocardiographic parameters

| Variables | | eGFR | NT-proBNP | Troponin T | LVMI | LVEF | LAVI | E:e' |
|------------|---|------------------|------------------|------------------|------------------|--------------|------------------|------------------|
| eGFR | r | | -0.374 | -0.421 | -0.071 | -0.052 | -0.093 | -0.184 |
| | P | | <0.001 | <0.001 | 0.335 | 0.484 | 0.212 | 0.013 |
| NT-proBNP | r | -0.374 | | 0.553 | 0.399 | -0.025 | 0.509 | 0.549 |
| | P | <0.001 | | <0.001 | <0.001 | 0.739 | <0.001 | <0.001 |
| Troponin T | r | -0.421 | 0.553 | | 0.306 | 0.043 | 0.339 | 0.434 |
| | P | <0.001 | <0.001 | | <0.001 | 0.570 | <0.001 | <0.001 |
| LVMI | r | -0.071 | 0.399 | 0.306 | | -0.172 | 0.455 | 0.257 |
| | P | 0.335 | <0.001 | <0.001 | | 0.020 | <0.001 | <0.001 |
| LVEF | r | -0.052 | -0.025 | 0.043 | -0.172 | | -0.090 | 0.115 |
| | P | 0.484 | 0.739 | 0.570 | 0.020 | | 0.227 | 0.126 |
| LAVI | r | -0.093 | 0.509 | 0.339 | 0.455 | -0.090 | | 0.535 |
| | P | 0.212 | <0.001 | <0.001 | <0.001 | 0.227 | | <0.001 |
| E:e' | r | -0.184 | 0.549 | 0.434 | 0.257 | 0.115 | 0.535 | |
| | P | 0.013 | <0.001 | <0.001 | <0.001 | 0.126 | <0.001 | |

Significant values are in bold.

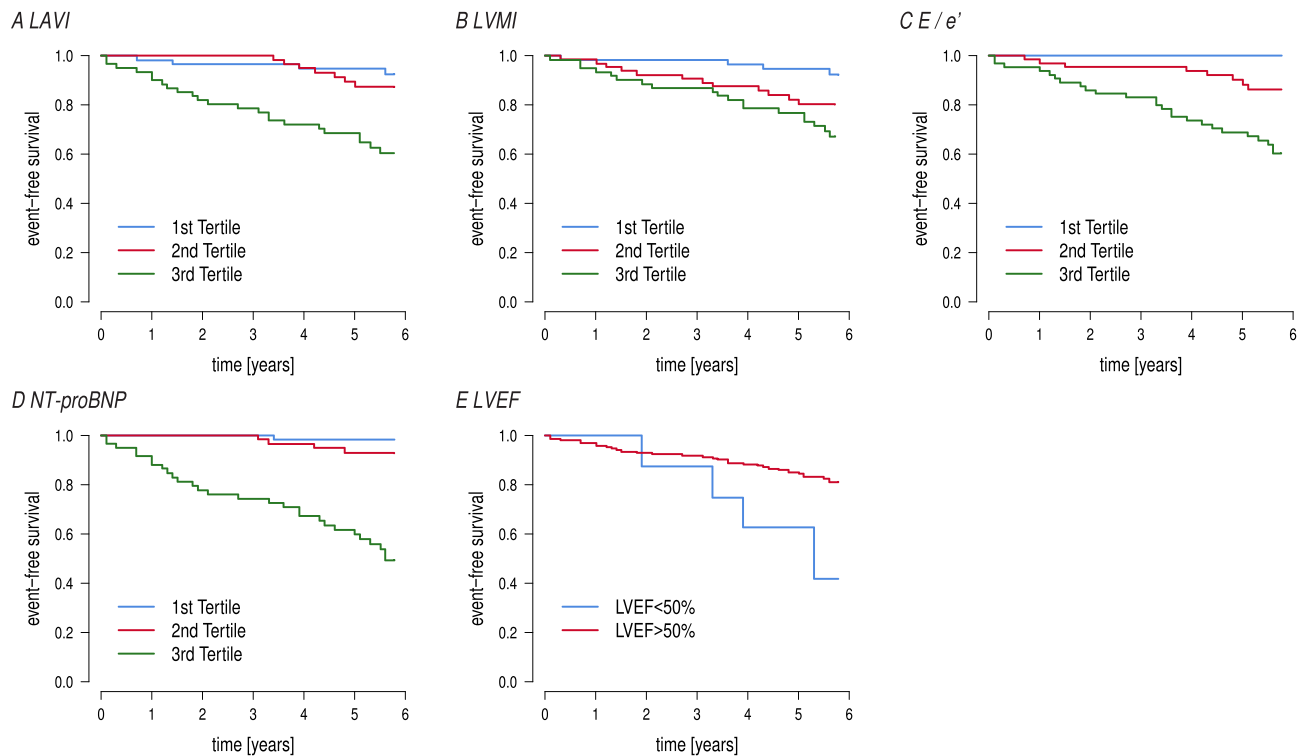


FIGURE 1: Kaplan-Meier analyses with subsequent log rank test. Endpoint: hospitalization for acute decompensated heart failure plus all-cause death (HF/D). Event-free survival of KTRs stratified by their (A) tertiles of LAVI, (B) tertiles of LVMI, (C) tertiles of left ventricular filling pressure (E:e' ratio), (D) tertiles of NT-proBNP and (E) LVEF >50% and LVEF <50%.

sonographer, we deliberately decided to conduct the study at a single center. Due to the observational character of our analysis, underlying pathophysiological mechanisms remain elusive. Only eight participants had an LVEF of <50%, so that the prognostic implication of impaired LV function may have been underestimated. Furthermore, we did not assess New York Heart Association categories at baseline, so that cardiac plasma biomarkers and echocardiographic findings cannot be correlated with symptomatology at baseline. Plasma NT-proBNP levels are volume dependent and we cannot provide solid information on volume status. However, all patients were under regular nephrological care, which generally comprises assess-

ment and, if present, treatment of hypervolemia. Additionally, we did not assess more sophisticated echocardiographic parameters, such as speckle-tracking analysis, which might have provided more detailed information on LV function [35]. Biomarkers were assessed only once, and we cannot provide information on time-averaged levels. Similarly, immunosuppressive medication was only assessed at baseline, but not before study initiation or during follow-up. Thus we deliberately decided not to analyze associations between different immunosuppressive agents and echocardiographic or plasma cardiac biomarkers, which would require information on long-term medication.

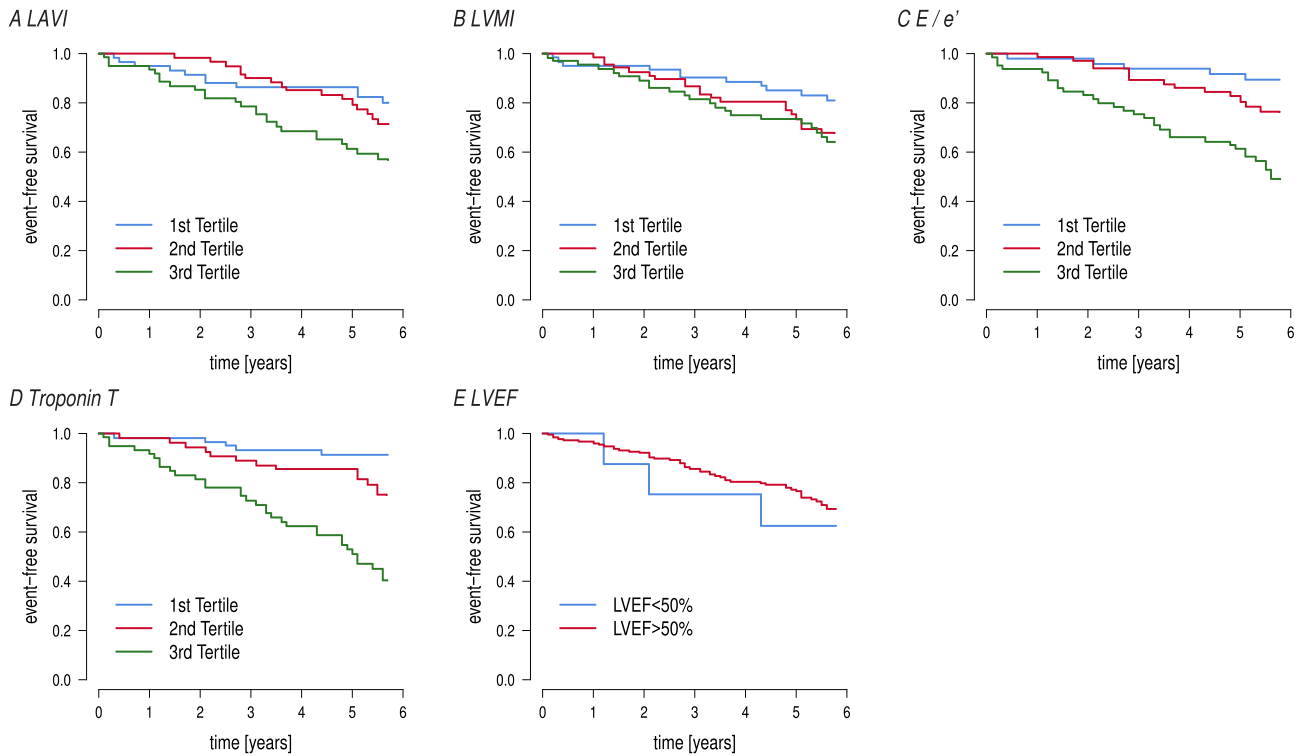


FIGURE 2: Kaplan-Meier analyses with subsequent log rank test. Endpoint: major atherosclerotic cardiovascular events plus all-cause death (MACE/D). Event-free survival of KTRs stratified by their (A) tertiles of LAVI, (B) tertiles of LVMI, (C) tertiles of left ventricular filling pressure (E:e'), (D) tertiles of troponin T and (E) LVEF >50% and LVEF <50%.

Table 4. Cox regression models [endpoint: hospitalization for acute decompensated heart failure + all-cause death (HF/D)]

| Exposure variable | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---------------------------------------|--------------------|------------------|--------------------|------------------|-------------------|------------------|-------------------|--------------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Categorized predictors | | | | | | | | |
| E:e' second tertile ^a | 2.72 (0.73–10.11) | 0.135 | 1.90 (0.47–7.63) | 0.367 | 1.32 (0.31–5.70) | 0.711 | 1.58 (0.33–7.49) | 0.563 |
| E:e' third tertile ^a | 8.66 (2.60–28.87) | <0.001 | 5.00 (1.28–19.58) | 0.021 | 3.77 (0.88–16.22) | 0.074 | 2.77 (0.60–12.91) | 0.193 |
| LAVI second tertile ^a | 1.24 (0.43–3.57) | 0.693 | 1.07 (0.37–3.08) | 0.907 | 1.22 (0.41–3.69) | 0.720 | 1.03 (0.33–3.25) | 0.961 |
| LAVI third tertile ^a | 4.81 (1.96–11.79) | 0.001 | 2.70 (1.04–7.00) | 0.041 | 2.75 (1.01–7.49) | 0.049 | 1.91 (0.66–5.53) | 0.232 |
| LVMI second tertile ^a | 2.66 (0.95–7.47) | 0.063 | 3.27 (1.15–9.33) | 0.027 | 4.02 (1.29–12.54) | 0.017 | 2.50 (0.75–8.30) | 0.136 |
| LVMI third tertile ^a | 4.91 (1.85–13.08) | 0.001 | 4.33 (1.60–11.71) | 0.004 | 4.67 (1.63–13.37) | 0.004 | 3.04 (1.03–9.01) | 0.045 |
| NT-proBNP second tertile ^a | 1.72 (0.41–7.19) | 0.459 | 1.27 (0.29–5.44) | 0.752 | 0.71 (0.15–3.34) | 0.665 | 0.67 (0.15–3.04) | 0.605 |
| NT-proBNP third tertile ^a | 16.65 (5.04–55.04) | <0.001 | 11.48 (3.29–40.02) | <0.001 | 4.70 (1.14–19.29) | 0.032 | 4.20 (1.02–17.27) | 0.047 |
| LVEF <50% ^b | 3.42 (1.20–9.77) | 0.022 | 3.12 (1.08–8.97) | 0.036 | 1.75 (0.43–7.13) | 0.436 | 0.81 (0.18–3.71) | 0.782 |
| Continuous predictors | | | | | | | | |
| E:e' | 1.20 (1.13–1.27) | <0.001 | 1.18 (1.11–1.26) | <0.001 | 1.18 (1.09–1.28) | <0.001 | 1.13 (1.03–1.23) | 0.007 |
| LAVI | 1.05 (1.03–1.08) | <0.001 | 1.04 (1.02–1.07) | <0.001 | 1.04 (1.02–1.07) | 0.001 | 1.03 (1.01–1.06) | 0.014 |
| LVMI | 1.02 (1.01–1.03) | <0.001 | 1.02 (1.01–1.03) | 0.001 | 1.02 (1.01–1.03) | 0.005 | 1.01 (0.99–1.02) | 0.140 |
| Log NT-proBNP | 7.12 (3.88–13.06) | <0.001 | 6.72 (3.50–12.89) | <0.001 | 4.53 (2.01–10.22) | <0.001 | 3.24 (1.31–8.03) | 0.011 |

Model 1 is the univariate analysis. Model 2 is adjusted for age and gender. Model 3 is additionally adjusted for eGFR, diabetes mellitus, prevalent cardiovascular disease, systolic blood pressure, current smoking and total cholesterol. Model 4 is additionally adjusted for log-transformed NT-proBNP (for all analyses with echocardiographic parameters as exposure variable) or LVEF (analyses with NT-proBNP as exposure variable). ^aReference is the first tertile for LVMI LAVI NT-proBNP and E:e' ratio. ^bReference is LVEF >50%. Significant values are in bold.

Finally, adjustment for nine different variables in Model 4 may have led to statistical overfitting.

CONCLUSION

In conclusion, among 177 KTRs we found plasma NT-proBNP and troponin T to be independent predictors of hospitalization

for acute decompensated heart failure and major atherosclerotic cardiovascular events, respectively. Their predictive implications persist after adjustment for multiple confounders, including echocardiographic parameters. In contrast, echocardiographic parameters were not consistently associated with the predefined endpoints. Their routine assessment in allograft recipients for cardiovascular outcome prediction appears dispensable.

Table 5. Cox regression models [endpoint: major atherosclerotic cardiovascular events + all-cause death (MACE/D)]

| Exposure variable | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|--|--------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Categorized predictors | | | | | | | | |
| E:e' second tertile ^a | 1.64 (0.66–4.06) | 0.287 | 1.10 (0.41–2.90) | 0.855 | 0.95 (0.34–2.63) | 0.922 | 0.95 (0.35–2.57) | 0.919 |
| E:e' third tertile ^a | 4.72 (2.09–10.66) | <0.001 | 2.53 (0.98–6.56) | 0.056 | 2.10 (0.80–5.53) | 0.133 | 1.85 (0.70–4.93) | 0.217 |
| LAVI second tertile ^a | 1.37 (0.66–2.84) | 0.400 | 1.16 (0.56–2.42) | 0.688 | 1.08 (0.50–2.32) | 0.697 | 1.65 (0.75–3.65) | 0.213 |
| LAVI third tertile ^a | 2.40 (1.21–4.77) | 0.012 | 1.25 (0.60–2.59) | 0.555 | 1.24 (0.59–2.62) | 0.569 | 1.36 (0.63–2.92) | 0.436 |
| LVMl second tertile ^a | 2.02 (0.98–4.17) | 0.057 | 2.64 (1.25–5.61) | 0.011 | 2.34 (1.07–5.10) | 0.033 | 2.28 (1.03–5.02) | 0.042 |
| LVMl third tertile | 2.35 (1.15–4.81) | 0.019 | 2.14 (1.03–4.44) | 0.042 | 1.87 (0.88–3.97) | 0.104 | 1.61 (0.75–3.44) | 0.222 |
| Troponin T second tertile ^a | 3.31 (1.21–9.04) | 0.020 | 3.07 (1.09–8.63) | 0.034 | 3.14 (1.11–8.87) | 0.031 | 3.15 (1.11–8.90) | 0.031 |
| Troponin T third tertile ^a | 10.14 (3.97–25.89) | <0.001 | 7.86 (2.89–21.38) | <0.001 | 8.13 (2.74–24.09) | <0.001 | 8.15 (2.75–24.18) | <0.001 |
| LVEF <50% ^b | 1.47 (0.46–4.71) | 0.517 | 1.25 (0.39–4.05) | 0.707 | 0.97 (0.26–3.54) | 0.959 | 1.05 (0.30–3.67) | 0.935 |
| Continuous predictors | | | | | | | | |
| E:e' | 1.15 (1.10–1.21) | <0.001 | 1.14 (1.07–1.20) | <0.001 | 1.12 (1.07–1.22) | 0.001 | 1.11 (1.03–1.19) | 0.003 |
| LAVI | 1.03 (1.01–1.05) | 0.001 | 1.01 (0.99–1.03) | 0.179 | 1.01 (0.99–1.03) | 0.227 | 1.01 (0.99–1.03) | 0.279 |
| LVMl | 1.01 (1.00–1.02) | 0.017 | 1.01 (1.00–1.02) | 0.029 | 1.01 (1.00–1.02) | 0.063 | 1.01 (0.99–1.02) | 0.213 |
| Log troponin T | 13.26 (6.18–28.42) | <0.001 | 9.22 (3.89–21.83) | <0.001 | 7.71 (2.65–22.40) | <0.001 | 8.05 (2.75–23.53) | <0.001 |

Model 1 is the univariate analysis. Model 2 is adjusted for age and gender. Model 3 is additionally adjusted for eGFR, diabetes mellitus, prevalent cardiovascular disease, systolic blood pressure, current smoking and total cholesterol. Model 4 is additionally adjusted for log-transformed troponin T (for all analyses with echocardiographic parameters as exposure variable) or LVEF (analyses with troponin T as exposure variable). ^aReference is the first tertile for LVMl LAVI troponin T and E:e' ratio. ^bReference is LVEF >50%. Significant values are in bold.

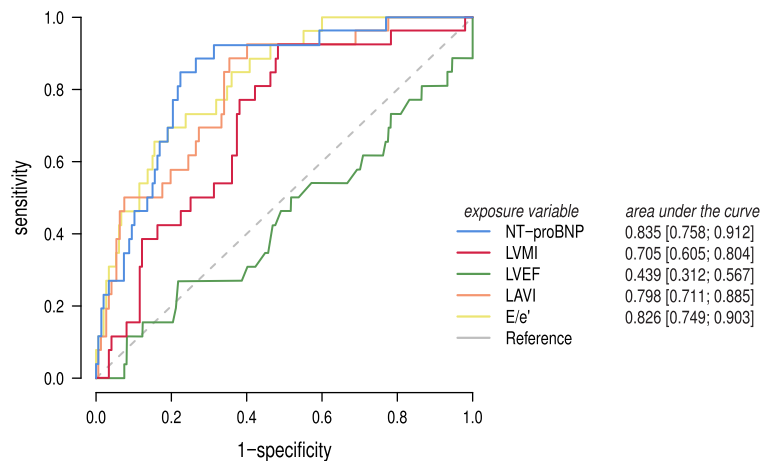


FIGURE 3: ROC analysis for hospitalization for acute decompensated heart failure plus all-cause death (HF/D).

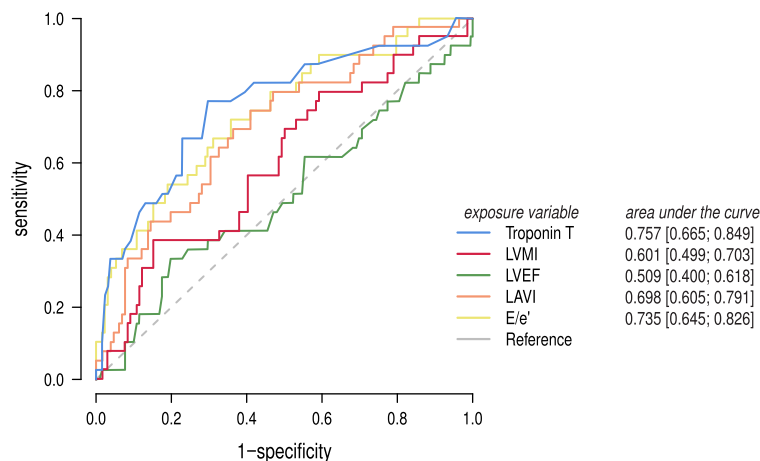


FIGURE 4: ROC analysis for major atherosclerotic cardiovascular events plus all-cause death (MACE/D).

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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AUTHORS' CONTRIBUTIONS

I.E.E., G.H.H., S.H.S. and D.F. designed the research. K.R., F.M., M.B. and I.E.E. conducted the research. I.E.E., G.H.H. and S.W. analyzed the data and performed the statistical analysis. I.E.E., A.L.S. and G.H.H. wrote the article. All the authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interests. The results presented in this article have not been published previously in whole or part, except in abstract format.

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