Inflammation in Renal Transplantation

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Background and objectives: Renal transplant recipients experience premature cardiovascular disease and death. The association of inflammation, all-cause mortality, and cardiovascular events in renal transplant recipients has not been examined in a large prospective controlled trial.

Design, setting, participants, & measurements: ALERT was a randomized, double-blind, placebo-controlled study of the effect of fluvastatin on cardiovascular and renal outcomes in 2102 renal transplant recipients. Patients initially randomized to fluvastatin or placebo in the 5- to 6-yr trial were offered open-label fluvastatin in a 2-yr extension to the original study. The association between inflammation markers, high-sensitivity C-reactive protein (hsCRP), and IL-6 on cardiovascular events and all-cause mortality was investigated.

Results: The baseline IL-6 value was 2.9 ± 1.9 pg/ml (n = 1751) and that of hsCRP was 3.8 ± 6.7 mg/L (n = 1910). After adjustment for baseline values for established risk factors, the hazard ratios for a major cardiac event and all-cause mortality for IL-6 were 1.08 [95% confidence interval (CI), 1.01 to 1.15, P = 0.018] and 1.11 (95% CI, 1.05 to 1.18, P < 0.001), respectively. The adjusted hazard ratio for hsCRP for a cardiovascular event was 1.10 (95% CI, 1.01 to 1.20, P = 0.027) and for all-cause mortality was 1.15 (95% CI, 1.06 to 1.1.25, P = 0.049).

Conclusions: The inflammation markers IL-6 and hsCRP are independently associated with major cardiovascular events and all-cause mortality in renal transplant recipients.

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Although cholesterol lowering therapy with statins has reduced the incidence of cardiac events in renal transplant recipients, premature cardiovascular events and premature death is still a major concern in this population (1,2). The prevalence of traditional cardiovascular risk factors cannot fully explain the increased incidence of cardiovascular events, and several reports have emphasized the role of nontraditional cardiovascular risk factors (3,4).

Inflammation and activation of the immune system may play important roles in atherogenesis (5,6). Cytokines induce production of IL-6 from various tissues, including the liver, and increase downstream mediators such as C-reactive protein (CRP) (7). Renal transplant recipients, by the process of receiving an allograft, have an additional activation of their immune system (8–11).

In the general population, CRP is regarded as a risk factor for cardiovascular events and all-cause mortality (12,13). In patients without hyperlipidemia but with elevated high-sensitivity CRP (hsCRP), it was recently demonstrated that rosuvastatin significantly reduced the incidence of major cardiovascular events (14).

In patients with chronic renal failure, an association between malnutrition, inflammation, and atherosclerosis has been demonstrated (15). In dialysis patients CRP has been shown to be a marker of all-cause and cardiovascular death (16). It has also been speculated that the better graft survival achieved with preemptive transplantation might be due to less exposure to inflammation markers associated with dialysis (17,18). In renal transplant recipients there are few studies examining the association between inflammatory markers and all-cause mortality,

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cardiac events, or cerebrovascular events. A small cross-sectional study indicated that renal transplant patients with cardiovascular disease (CVD) had higher CRP than patients without CVD (19). Another retrospective study indicated that elevated pretransplant CRP was associated with all-cause and cardiovascular mortality (20). Ducloux *et al.* followed a small cohort of renal transplant patients and reported that elevated CRP predicted coronary events (21). In a prospective registry-based study, Winkelmayer and colleagues showed that kidney transplant patients with a CRP above 5 mg/dl had an increased mortality compared with patients below that threshold (22), and in a subsequent follow-up paper the authors demonstrated a J-shaped association between hsCRP (below 5 mg/L) and mortality (23). There are no reports of assessment of an association between hsCRP and/or IL-6 and major cardiovascular events or all-cause mortality in prospectively controlled trials in renal transplant patients. We therefore performed a *post hoc* analysis of the ALERT trial examining the predictive value of the inflammation markers hsCRP and IL-6 for cardiovascular events and all-cause mortality in renal transplant recipients.

Materials and Methods

Study Design

The ALERT study design and baseline data have been described previously (1). Briefly, ALERT was a randomized, double-blind, placebo-controlled study of the effect of fluvastatin, 40 to 80 mg daily, on cardiovascular and renal outcomes in renal transplant recipients over a follow-up period of 5 to 6 yr. Eligible patients were men and women aged 30 to 75 yr who had received a renal transplant more than 6 mo before enrolment and with a total serum cholesterol concentration between 4.0 and 9.0 mmol/L (155 to 348 mg/dl). Patients with a history of myocardial infarction more than 6 mo before randomization could be enrolled if their total cholesterol levels ranged from 4.0 to 7.0 mmol/L (155 to 270 mg/dl). Of 1787 patients who completed ALERT, 1652 (92%) accepted open-label fluvastatin, 80 mg daily, in a 2-yr extension of the original study. Mean total follow-up time in the extension study was 6.7 yr. The study adhered to the International Conference on Harmonization guidelines for Good Clinical Practice and in accordance with the Declaration of Helsinki. All participants provided written informed consent, and the ethics committee at each participating center approved the trial.

Study patients were seen at 1.5 mo after randomization and at 6-mo intervals thereafter. Clinical status was assessed at each visit. Laboratory measurements of lipids, serum creatinine, creatine kinase, and hepatic enzymes were performed at a central laboratory (CRL, Medinet, Breda, The Netherlands).

IL-6 was measured by a human IL-6 immunoassay (R&D Systems, Inc., Minneapolis, MN, USA) and hsCRP by using an immunoturbometric analysis (Roche Diagnostics GmbH, Mannheim, Germany). Measurements of IL-6 and hsCRP were performed on blood samples at baseline and were not followed longitudinally during the study.

An independent critical events committee blinded to treatment assignment reviewed all primary and secondary endpoints for adjudication. All analyses were based on the committee's classification of endpoints, which was agreed on by consensus or by majority.

Statistical Analyses

SPSS version 16.0 (SPSS, Inc.) was used for statistical analyses. For normally distributed variables, mean, and SD are presented. hsCRP and IL-6 values were not normally distributed and showed a marked tail to the right. Logarithmic transformation showed a strictly bell shaped distribution of both variables and these transformed values were used for the statistical analysis. A Cox proportional hazard model was used to analyze the relationship between risk factors and time to event for all endpoints. All covariates were carefully examined and fulfilled assumptions of proportionality of hazard ratios in the Cox hazard models. Univariate and multivariate analysis were then carried out to study how risk factors associated with the risk of all-cause mortality, major cardiac events (MACE), and cerebrovascular (CBV) events. Corresponding hazard ratios for group comparisons were calculated with 95% confidence limits.

Results

Baseline Characteristics

Basic patient and demographic data in ALERT and the ALERT extension have been previously published (2). Patients were transplanted at a mean of 4.5 yr before randomization into the trial. Both treatments groups in the ALERT trial were well balanced with regard to baseline demographics and renal characteristics.

In this *post hoc* analysis, we separated the patients into those with available baseline hsCRP and IL-6 values. The patients' demographic characteristics based on this separation are summarized in Table 1.

The number of patients with hsCRP ($n = 1910$) and IL-6 ($n = 1751$) at baseline differed, and baseline data are therefore shown separately for each cohort. However, baseline characteristics between the two cohorts were practically identical. There were no differences in proportion of patients with diabetes, coronary heart disease, current smokers, and transplant type between the groups (Table 1). hsCRP and IL-6 were correlated ($r = 0.332$, $P < 0.001$).

Endpoints

hsCRP and IL-6 increased with increasing body mass index (BMI) and both were significantly correlated with BMI ($r = 0.18$, $P < 0.001$). However, BMI was not a significant risk factor for all-cause death and MACE in univariate analysis.

Further analysis by Kaplan–Meier survival method did not show any significant differences in occurrence of all-cause death or MACE by stratifying patients by BMI (normal BMI 18.5 to 25, $n = 890$, 46%; overweight BMI 25 to 30, $n = 684$, 35%; obese BMI ≥ 30, $n = 268$, 14%).

In the hsCRP cohorts, there were 176 CBV events, 287 cardiac events, and 354 deaths. Corresponding numbers for the IL-6 cohort were 166, 255, and 308, respectively. The prevalence of the study endpoints within the quartiles of hsCRP and IL-6 are summarized in Table 2 a and b, and demonstrate a comparable incidence of all-cause mortality and MACE.

In both cohorts of patients there were significantly more cardiovascular events and all-cause death in the fourth quartile compared with the first quartile, with the exception of CBV events in the hsCRP cohort. We also performed separate analyses for deaths in patients with a baseline hsCRP below 5 mg/L (23), and we divided this population in quartiles (Figure 1d). Also in this subset of patients there was a successive increase in deaths by increasing hsCRP quartiles. There was a consistent increase in all endpoints from first to fourth quartile.

Table 1. Patients demographic and baseline characteristics in patients with available baseline hsCRP and IL-6[a]

Baseline Variables[b]	Patients with hsCRP Data (n = 1910)	Patients with IL-6 Data (n = 1751)
Cholesterol (mmol/L)	6.48 (1.13)	6.52 (1.13)
HDL cholesterol (mmol/L)	1.34 (0.45)	1.34 (0.45)
LDL cholesterol (mmol/L)	4.18 (1.02)	4.19 (1.01)
Apolipoprotein B (mg/dl)	117.97 (25.88)	117.08 (25.63)
Triglycerides (mmol/L)	2.22 (1.39)	2.21 (1.39)
Age at baseline (yr)	49.7 (10.0)	49.5 (11.0)
Total time on RRT (mo)	89.0 (57.9)	89.2 (57.8)
Systolic BP (mmHg)	144.0 (19.0)	145.0 (19.0)
Diastolic BP (mmHg)	86.0 (10.0)	86.0 (10.0)
Diabetes mellitus	361 (19.0)	327 (18.7)
Body mass index (kg/m^2)	25.7 (4.3)	25.6 (4.18)
Serum creatinine (μmol/L)	145.0 (53.0)	145.0 (53.0)
Serum glucose (mg/dl)	93.4 (51.5)	93.0 (51.0)
PTH (pg/ml)	51.65 (66.6)	50.72 (65.07)
hsCRP (mg/L)	3.82 (6.71)	–
IL-6 pg/ml	–	2.92 (1.87)
Coronary heart disease *N* (%)	175 (9.2)	145 (8.3)
Diabetes mellitus *N* (%)	361 (19)	327 (18.7)
Smoking (current) *N* (%)	358 (18.8)	326 (18.6)
Living donor transplant *N* (%)	427 (22.4)	400 (22.8)
Cadaveric donor transplant *N* (%)	1477 (77.5)	1351 (77.2)
MACE *N* (%)	287 (15.1)	256 (14.6)
All-cause death *N* (%)	354 (18.6)	309 (17.6)

[a]Data are expressed as mean (SD) unless otherwise indicated.
[b]hsCRP, high-sensitivity C-reactive protein; RRT, renal replacement therapy; BP, blood pressure; PTH, parathyroid hormone; MACE, major adverse cardiovascular events.

Table 2a. Occurrence of all-cause death, MACE, and CBV events by quartiles of hsCRP[a]

Occurrence	Quartile 1 (<0.63)	Quartile 2 (0.63 to 1.53)	Quartile 3 (1.54 to 3.68)	Quartile 4 (≥3.69)
All-cause death	476/60 (12.3)	479/79 (16.5)	479/93 (19.4)	476/122 (25.6)
patients/events (%)	–	$P = 0.088$	$P = 0.006$	$P < 0.001$
MACE	476/52 (10.9)	479/71 (14.8)	479/74 (15.4)	476/90 (18.9)
patients/events (%)	–	$P = 0.056$	$P = 0.035$	$P < 0.001$
CBV events	476/33 (6.9)	479/49 (10.2)	479/52 (10.9)	476/42 (8.8)
patients/events (%)	–	$P = 0.052$	$P = 0.025$	$P = 0.153$

[a]Data expressed as number of patients in quartile/number of events (%). Significance *versus* first quartile.
CBV events, cerebrovascular events.

Table 2b. Occurrence of all-cause death, MACE, and CBV events by quartiles of IL-6[a]

Occurrence	Quartile 1 (<1.57)	Quartile 2 (1.57 to 2.38)	Quartile 3 (2.39 to 3.74)	Quartile 4 (≥3.75)
All-cause death	444/46 (10.4)	428/60 (14.0)	437/70 (16.0)	440/132 (30.0)
patients/events (%)	–	$P = 0.117$	$P = 0.012$	$P < 0.001$
MACE	444/45 (10.1)	428/58 (13.6)	437/65 (14.9)	440/87 (19.8)
patients/events (%)	–	$P = 0.134$	$P = 0.028$	$P < 0.001$
CBV events	444/25 (5.6)	428/34 (7.9)	437/46 (10.5)	440/58 (13.2)
patients/events	–	$P = 0.172$	$P = 0.005$	$P < 0.000$

[a]Data expressed as number of patients in quartile/number of events (%). Significance *versus* first quartile.

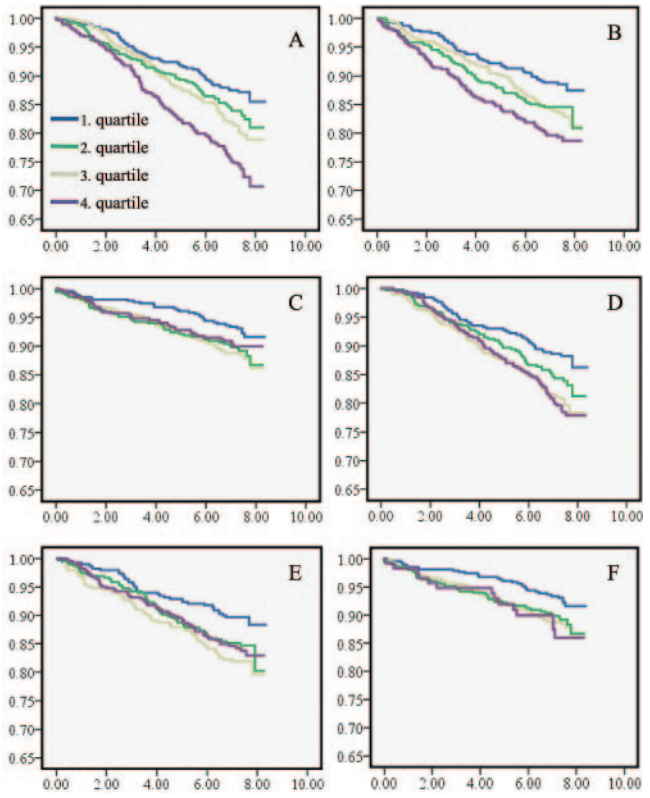

Figure 1. Association between (A) all-cause death, (B) major cardiovascular events, and (C) cerebrovascular events for quartiles of high-sensitivity C-reactive protein (hsCRP) over the whole range of hsCRP. (D) Association between all-cause death, (E) major cardiovascular events, and (F) cerebrovascular events for quartiles of hsCRP below 5 mg/dl. *x*-axis represents follow-up time in years. *y*-axis represents cumulative survival.

Risk Factor Analyses

Exploratory risk factor analysis was carried out on many potentially important risk factors for all-cause death, MACE, and CBV events (Tables 3 and 4).

On the basis of univariate analysis using Cox regression, diabetes mellitus, smoking, previous coronary heart disease, hsCRP, age, serum creatinine, and systolic blood pressure (BP), were significant risk factors for all causes of death and MACE in the hsCRP cohort. Gender and LDL cholesterol were significant univariate risk factors for MACE but not for all-cause death in the hsCRP cohort.

For all types of CBV events, diabetes mellitus, previous coronary heart disease, age, and systolic BP were significant univariate risk factors.

On the basis of multivariate Cox regression including all of the above risk factors, diabetes mellitus, smoking, age, previous coronary heart disease, hsCRP, and serum creatinine were significant for all causes of death and MACE in the hsCRP cohort, but LDL cholesterol was only a significant risk factor for MACE in the hsCRP cohort. Smoking was a significant risk factor for CBV events in multivariate analysis, but IL-6 and systolic BP were no longer significant risk factors for CBV events. Risk factors for all-cause death, MACE, and CBV events in the IL-6 cohort were very much the same as in the hsCRP cohort, with small differences in the size of the hazard ratios.

Hazard ratios for the different univariate and multivariate risk factors for all-cause death, MACE, and CBV events did not differ substantially for the two cohorts (Tables 3 and 4).

Kaplan–Meier survival curves show associations between all-cause death, MACE, and CBV events and hsCRP values within the hsCRP quartiles (Figures 1A through 1C). Risk of death, MACE, and CBV events increased significantly with increasing hsCRP quartiles not only in the continuous range of hsCRP values but also in the increasing quartile for hsCRP values below 5.0 mg/L (Figures 1D through 1F).

The Kaplan–Meier survival curves by quartiles of IL-6 (Figures 2A through 2C) were comparable to the hsCRP curves in Figures 1A through 1C.

Discussion

In this *post hoc* analysis, we have shown that the inflammatory markers hsCRP and IL-6, adjusted for traditional risk factors, are predictive for future cardiovascular events and all-cause mortality in renal graft recipients. Although hsCRP and IL-6 are correlated, the observation that both markers were predictive for outcome parameters strengthens the notion that inflammation is an important risk factor for cardiovascular events and all-cause mortality in renal transplant patients.

Our data support previous observational and/or registry data that have indicated that CRP is associated with cardiovascular events and/or all-cause mortality in renal transplant recipients (19–23) and in the general population (5,6,12,13)

In hemodialysis and peritoneal dialysis patients (24–26) and also in the general population, an association between IL-6 and cardiovascular morbidity and mortality has been established (13,27). No trial has examined the association of IL-6 with all-cause mortality or cardiovascular events in renal transplant patients. The data from this analysis demonstrate that the association of IL-6 with cardiovascular events and all-cause mortality also extends to renal transplant patients.

Vascular inflammation is an important factor in the pathogenesis of atherosclerosis in renal transplant recipients (8–11), whereas genetically based elevation in CRP is not associated with posttransplant morbidity and mortality (28), as also shown for the general population (29,30).

In the adult nontransplanted population, the American Heart Association and the Centers for Disease Control and Prevention have endorsed three cutoff points for CRP: <1 mg/dl, low risk; 1 to 3 mg/dl, average risk; and >3 mg/L, high risk (31). By this definition, the overall population in ALERT is in the moderate to high-risk end. The IL-6 data are more difficult to assess across diverse populations because of lack of standardized methods (31). However, in the posttransplant recipients, the inflammatory markers CRP and IL-6 have been reported to be elevated in most studies on renal transplant recipients (19,21–23,32–36), although they are lower than pretransplant values (37).

By dichotomizing the CRP at 0.5 mg/dl, Winkelmayer *et al.* showed that renal transplant patients above that level had a 53% increased mortality risk compared with patients with a

Table 3a. Hazard ratios for all-cause mortality by univariate and multivariate Cox regression in the hsCRP cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)[b]	*P* Value	Multivariate Hazard Ratio (95% CI)	*P* Value
Diabetes mellitus	2.12 (1.69 to 2.65)	0.000	2.03 (1.60 to 2.58)	0.000
Smoking current	1.87 (1.43 to 2.46)	0.000	1.98 (1.49 to 2.64)	0.000
CHD	2.49 (1.90 to 3.27)	0.000	1.48 (1.11 to 1.99)	0.008
hsCRP (mg/L)	1.36 (1.21 to 1.52)	0.000	1.15 (1.06 to 1.25)	0.001
Age (yr)	1.07 (1.06 to 1.07)	0.000	1.07 (1.06 to 1.07)	0.000
Creatinine (μmol/L)	1.00 (1.00 to 1.01)	0.000	1.01 (1.00 to 1.01)	0.000
Systolic BP (mmHg)	1.02 (1.01 to 1.02)	0.000	1.00 (0.99 to 1.01)	0.149
Gender	1.08 (1.86 to 1.34)	0.512	1.04 (0.82 to 1.33)	0.740
LDL cholesterol (mmol/L)	1.01 (098 to 1.21)	0.980	1.02 (0.91 to 1.13)	0.788

[a]n = 1910.
[b]CHD, coronary heart disease; CI, confidence interval.

Table 3b. Hazard ratios for MACE by univariate and multivariate Cox regression in the hsCRP cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio (95% CI)	*P* Value
CHD	3.35 (2.53 to 4.44)	0.000	2.28 (1.69 to 3.08)	0.000
Diabetes mellitus	2.06 (1.59 to 2.64)	0.000	2.08 (1.59 to 2.73)	0.000
LDL cholesterol (mmol/L)	1.38 (1.23 to 1.54)	0.000	1.35 (1.20 to 1.51)	0.000
Smoking current	1.54 (1.11 to 2.14)	0.010	1.43 (1.02 to 2.02)	0.041
hsCRP (mg/L)	1.25 (1.10 to 1.43)	0.001	1.10 (1.01 to 1.20)	0.027
Age (yr)	1.04 (1.03 to 1.05)	0.000	1.03 (1.02 to 1.04)	0.000
Systolic BP (mmHg)	1.01 (1.01 to 1.08)	0.000	1.00 (0.99 to 1.00)	0.560
Creatinine (μmol/L)	1.00 (1.00 to 1.01)	0.000	1.01 (1.00 to 1.00)	0.000
Gender	0.72 (0.55 to 0.93)	0.012	0.86 (0.66 to 1.13)	0.287

[a]n = 1910.

Table 3c. Hazard ratios for CBV events by univariate and multivariate Cox regression in the hsCRP cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio (95% CI)	*P* Value
CHD	2.35 (1.58 to 3.51)	0.000	1.46 (0.96 to 2.22)	0.080
Diabetes mellitus	3.36 (2.49 to 4.54)	0.000	3.17 (2.30 to 4.37)	0.000
LDL cholesterol (mmol/L)	1.10 (0.95 to 1.28)	0.215	1.07 (0.92 to 1.25)	0.401
Smoking current	1.44 (0.97 to 2.14)	0.071	1.61 (1.06 to 2.43)	0.024
hsCRP (mg/L)	1.09 (0.98 to 1.20)	0.109	1.02 (0.92 to 1.14)	0.727
Age (yr)	1.06 (1.04 to 1.07)	0.000	1.06 (1.04 to 1.08)	0.000
Systolic BP (mmHg)	1.02 (1.02 to 1.03)	0.000	1.01 (1.00 to 1.01)	0.059
Creatinine (μmol/L)	1.00 (1.00 to 1.00)	0.314	1.00 (1.00 to 1.01)	0.057
Gender	1.05 (0.90 to 1.23)	0.515	0.49 (0.63 to 1.24)	0.489

[a]n = 1910.

CRP below the threshold (22). In a subsequent paper, Winkelmayer and colleagues demonstrated a J-shaped association between hsCRP and mortality in kidney transplant recipients when dividing hsCRP values into quartiles for values below 5 mg/L. Patients in the lowest quartile (quartile 1) had an increased mortality risk of about two-fold compared with the chosen reference of quartile 2. There is a linear relationship between CRP and mortality in the general population (12,38) and in the dialysis population (15,16). No J-shaped curves for mortality have been demonstrated in nonrenal (39) or in dialysis patients (40) for the companion inflammation marker IL-6.

We performed detailed statistical analyses over the whole range of hsCRP values and a separate analysis for hsCRP below 5 mg/L. None of these analyses revealed a J-shaped curve for

Table 4a. Hazard ratios for all-cause death by univariate and multivariate Cox regression in the IL-6 cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio 95% (95% CI)	*P* Value
Diabetes mellitus	2.11 (1.65 to 2.70)	0.000	1.96 (1.52 to 2.54)	0.000
Smoking current	1.85 (1.38 to 2.45)	0.000	1.96 (1.44 to 2.67)	0.000
CHD	2.56 (1.89 to 3.46)	0.000	1.52 (1.11 to 2.10)	0.010
IL-6 (pg/ml)	1.24 (1.18 to 1.30)	0.000	1.11 (1.05 to 1.18)	0.000
Age (yr)	1.07 (1.05 to 1.08)	0.000	1.07 (1.05 to 1.08)	0.000
Creatinine (μmol/L)	1.00 (1.00 to 1.01)	0.000	1.01 (1.00 to 1.01)	0.000
Systolic BP (mmHg)	1.02 (1.01 to 1.03)	0.000	1.01 (0.99 to 1.01)	0.080
LDL cholesterol (mmol/L)	1.11 (0.99 to 1.24)	0.075	1.03 (0.92 to 1.16)	0.621
Gender	0.94 (0.75 to 1.20)	0.637	1.07 (0.82 to 1.39)	0.615

[a]$n = 1751$.

Table 4b. Hazard ratios for MACE by univariate and multivariate Cox regression in the IL-6 cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio 95% (95% CI)	*P* Value
Diabetes mellitus	215 (1.65 to 2.80)	0.000	2.22 (1.66 to 2.95)	0.000
CHD	3.10 (2.27 to 4.25)	0.000	2.04 (1.45 to 2.85)	0.000
Smoking current	1.55 (1.09 to 2.20)	0.014	1.45 (1.00 to 2.08)	0.048
LDL cholesterol (mmol/L)	1.34 (1.24 to 1.58)	0.000	1.38 (1.22 to 1.55)	0.000
IL-6 (pg/ml)	1.15 (1.08 to 1.22)	0.000	1.08 (1.01 to 1.15)	0.018
Age (yr)	1.04 (1.03 to 1.02)	0.000	1.03 (1.01 to 1.04)	0.000
Creatinine (μmol/L)	1.00 (1.00 to 1.01)	0.000	1.01 (1.00 to 1.01)	0.000
Systolic BP (mmHg)	1.01 (1.00 to 1.02)	0.000	1.00 (0.99 to 1.01)	0.385
Gender	0.75 (0.57 to 0.99)	0.038	0.94 (0.73 to 1.25)	0.653

[a]$n = 1751$.

Table 4c. Hazard ratios for all type of CBV events by univariate and multivariate Cox regression in the IL-6 cohort[a]

Parameter	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio 95% (95% CI)	*P* Value
CHD	2.67 (1.77 to 4.04)	0.000	1.65 (1.06 to 2.55)	0.026
Diabetes mellitus	3.34 (2.44 to 4.56)	0.000	3.10 (2.23 to 4.33)	0.000
LDL cholesterol (mmol/L)	1.08 (0.92 to 1.26)	0.345	1.05 (0.89 to 1.23)	0.572
Smoking current	1.48 (0.98 to 2.22)	0.061	1.62 (1.05 to 2.45)	0.028
IL-6 (pg/ml)	1.81 (1.41 to 2.33)	0.000	1.24 (0.94 to 1.63)	0.123
Age (yr)	1.06 (1.04 to 1.07)	0.000	1.06 (1.04 to 1.07)	0.000
Systolic BP (mmHg)	1.02 (1.02 to 1.03)	0.000	1.01 (1.00 to 1.02)	0.075
Creatinine (μmol/L)	1.00 (1.00 to 1.00)	0.632	1.00 (1.00 to 1.01)	0.288
Gender	0.87 (0.63 to 1.19)	0.369	0.88 (0.62 to 1.24)	0.464

[a]$n = 1751$.

the association of mortality and hsCRP. Repeating these analyses using IL-6 also indicated no J-shaped curve for mortality. The reason for the difference in results is unclear; however, we believe that the data from our trial are more robust because we do have 354 fatal events with a follow-up time of 6.7 yr within the hsCRP cohort.

Inflammatory markers CRP and IL-6 are associated with diabetes mellitus, insulin resistance, obesity, and adipose tissue (41). Our findings also suggest that higher BMI is associated with increased values of inflammatory markers in transplant patients, but BMI was not a significant risk factor for all-cause death or MACE.

The dialysis population is characterized by a status of high inflammation, and an inverse relationship between cholesterol

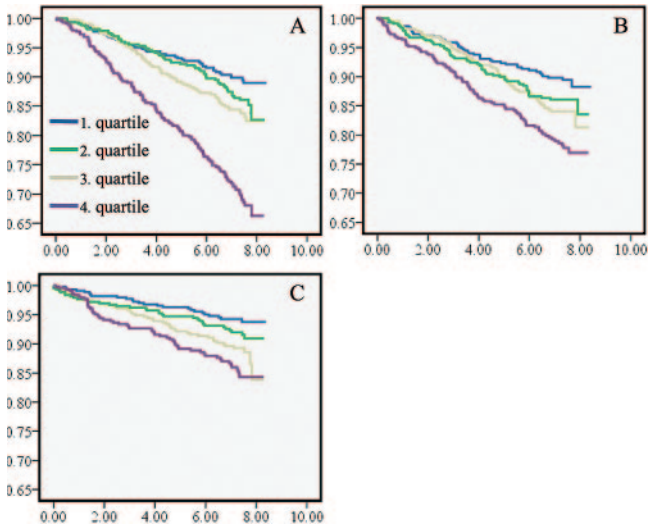

Figure 2. Association between (A) all-cause death, (B) major cardiovascular events, and (C) cerebrovascular events with IL-6 for quartiles of IL-6. *x*-axis represents follow-up time in years. *y*-axis represents cumulative survival.

and all-cause mortality has been shown (15,42). However, when corrected for inflammation the usual association for cholesterol and cardiovascular outcome is evident (43). In two recent trials in hemodialysis patients, 4D and Aurora, the inflammation marker hsCRP was significantly associated with increased risk for cardiovascular endpoints (44,45). However, although statin treatment in both trials significantly reduced in LDL cholesterol and hsCRP, the trials failed to show a reduction in the primary cardiovascular endpoints. The findings from these two trials might indicate that inflammation markers in patients receiving hemodialysis differ from other populations, including the renal transplant patients (44,46)

Potential limitations of our study merit consideration. First, this analysis was a *post hoc* analysis of the ALERT extension trial. IL-6 and hsCRP were not available for all patients at baseline, but baseline demographic data of those with or without inflammation analyzed were not different. The strengths of the study are the many patients followed for an extended period and the independent adjudication of predefined outcome parameters.

Renal transplant recipients are at high risk of for premature CVD, which is the leading cause of death in patients with a functional renal graft (3,47). We have previously shown that long-term statin treatment reduces MACE in this population (1,2). However, despite lipid-lowering there is considerable residual risk for cardiovascular events in renal transplant recipients. This might indicate that current management of kidney transplant recipients fails to utilize optimal cardiovascular risk reduction strategies. There is a pressing need to explore the role of other classical and novel cardiovascular risk factors in this population. Adding markers of inflammation such as hsCRP might be helpful to identify high-risk patients.

In conclusion, the inflammatory markers hsCRP and IL-6 may be predictive for future cardiovascular events and all-cause mortality in renal transplant recipients. These parameters should be considered in the design of future intervention trials.

Disclosures

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