

Prognostic utility of estimated albumin excretion rate in chronic kidney disease: results from the Study of Heart and Renal Protection

Marion M. Mafham^{1,*}, Natalie Staplin^{1,*}, Jonathan Emberson¹, Richard Haynes¹, William Herrington¹, Christina Reith¹, Christoph Wanner², Robert Walker³, Alan Cass⁴, Adeera Levin⁵, Bengt Fellström⁶, Lixin Jiang⁷, Hallvard Holdaas⁸, Bertram Kasiske⁹, David C. Wheeler¹⁰, Martin J. Landray¹ and Colin Baigent¹
on behalf of the SHARP Collaborative Group

¹Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, Oxford, UK, ²Department of Medicine 1, Division of Nephrology, University of Wuerzburg, Wuerzburg, Germany, ³Dunedin School of Medicine, University of Otago, Otago, New Zealand, ⁴Menzies School of Health Research, Charles Darwin University, Darwin, Australia, ⁵University of British Columbia, Vancouver, British Columbia, Canada, ⁶University Hospital, Uppsala, Sweden, ⁷National Clinical Research Centre of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China, ⁸Renal Section, Department of Transplant Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway, ⁹Hennepin County Medical Centre and the University of Minnesota, Minneapolis, MN, USA and ¹⁰University College London, London, UK

*These authors share joint first authorship.

Correspondence and offprint requests to: Marion M. Mafham; E-mail: marion.mafham@ndph.ox.ac.uk

ABSTRACT

Background. Estimated albumin excretion rate (eAER) provides a better estimate of 24-h albuminuria than albumin:creatinine ratio (ACR). However, whether eAER is superior to ACR in predicting end-stage renal disease (ESRD), vascular events (VEs) or death is uncertain.

Methods. The prognostic utility of ACR and eAER (estimated from ACR, sex, age and race) to predict mortality, ESRD and VEs was compared using Cox proportional hazards regression among 5552 participants with chronic kidney disease in the Study of Heart and Renal Protection, who were not on dialysis at baseline.

Results. During a median follow-up of 4.8 years, 1959 participants developed ESRD, 1204 had a VE and 1130 died (641 from a non-vascular, 369 from a vascular and 120 from an unknown cause). After adjustment for age, sex and eGFR, both ACR and eAER were strongly and similarly associated with ESRD risk. The average relative risk (RR) per 10-fold higher level was 2.70 (95% confidence interval 2.45–2.98) for ACR and 2.67 (2.43–2.94) for eAER. Neither ACR nor eAER provided any additional prognostic information for ESRD risk over and above the other.

For VEs, there were modest positive associations between both ACR and eAER and risk [adjusted RR per 10-fold higher level 1.37 (1.22–1.53) for ACR and 1.36 (1.22–1.52) for eAER]. Again, neither measure added prognostic information over and above the other. Similar results were observed when ACR and eAER were related to vascular mortality [RR per 10-fold higher level: 1.64 (1.33–2.03) and 1.62 (1.32–2.00), respectively] or to non-vascular mortality [1.53 (1.31–1.79) and 1.50 (1.29–1.76), respectively].

Conclusions. In this study, eAER did not improve risk prediction of ESRD, VEs or mortality.

Keywords: albuminuria, cardiovascular, chronic kidney disease, ESRD, mortality

INTRODUCTION

People with chronic kidney disease (CKD) face two major hazards: premature morbidity and mortality (in particular from cardiovascular disease) and progression to end-stage renal disease (ESRD) [1]. Measures of kidney function [e.g. estimated glomerular filtration rate (eGFR)] and markers of kidney damage (e.g. albuminuria) are associated with the risk of ESRD,

vascular disease and death, both in the general population [2] and among those with CKD [3], although both are more strongly associated with ESRD than with vascular events (VEs) and death [4, 5].

Albuminuria is traditionally measured by timed urine collection but current guidelines recommend the measurement of albumin: creatinine ratio (ACR) in a spot urine sample, because ACR provides a reasonably accurate indication of albuminuria and is more convenient for patients [6, 7]. The ACR uses urine creatinine concentration as the denominator to account for urine concentration, but, since urine creatinine concentration is also affected by muscle mass, ACR may not reflect albuminuria accurately in some individuals [8].

Recently, equations have been developed to estimate the urine creatinine excretion rate (eCER) from age, sex and race (and weight in some cases) so that the ACR can be adjusted for factors related to muscle mass by calculating the estimated albumin excretion rate (eAER). Studies have shown that eAER estimates 24-h albumin excretion more accurately than ACR alone [9–11]. However, whether these measures provide additional prognostic information (i.e. improved ability to predict the risk of a future outcome) over ACR for ESRD, VEs or mortality is not known. Using data from 5552 participants with CKD in the Study of Heart of Renal Protection (SHARP) who were not on dialysis at study entry [12], we assessed whether eAER provides superior prognostic information to ACR alone.

MATERIALS AND METHODS

The SHARP trial investigated the efficacy of lowering low-density lipoprotein cholesterol (LDL-C) with simvastatin/ezetimibe in 9270 participants with CKD (of whom 6245 were not on dialysis at randomization) [12]. The trial methods have been published in detail elsewhere and are summarized below [12, 13]. Ethics committee approval was obtained from all sites prior to enrolment and the study was conducted in accordance with the Declaration of Helsinki. SHARP was registered at ClinicalTrials.gov (NCT00125593) on 29 July 2005.

Study participants

Individuals aged 40 years or over were eligible to participate in SHARP if they had CKD with more than one previous measurement of serum or plasma creatinine of at least 1.7 mg/dL in men or 1.5 mg/dL in women. Participants with prior myocardial infarction or coronary revascularization were excluded. All participants provided informed consent prior to enrolment in the trial. Among the 6245 individuals not on dialysis at baseline, no baseline urine ACR was available for 673 participants and a further 20 had missing baseline central eGFR, leaving 5552 participants for analysis in this report (Figure 1).

Baseline assessment

Self-reported history of prior vascular disease, diabetes, smoking status, race, co-medication and cause of kidney disease were recorded by trained study staff. The recorded cause of kidney disease was based on the clinical diagnosis of the managing physician and subsequently categorized into four groups:

glomerulonephritis, diabetic nephropathy, cystic kidney disease and other causes (including unknown) [14]. Blood pressure, height and weight were measured by the study staff.

Laboratory methods

Samples of non-fasting blood and urine (whenever in the day the visit occurred) were collected from all participants. Blood samples were cooled, centrifuged and separated, before being stored locally at -40°C . Samples were then shipped on dry ice to the central laboratory in Oxford where assays of plasma creatinine and urine ACR were conducted. Creatinine and albumin were measured using a Synchron LX20 or DXC800 analyser (Beckman Coulter, Brea, CA, USA). Creatinine was assayed using a kinetic alkaline picrate method, calibrated using material traceable to National Institute of Standards and Technology Standard Reference Material 914a, with a mean expanded uncertainty of 13.4% (7.3% excluding biological variation). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [15]. eAER was calculated by:

$$\text{eAER (mg/day)} = \text{ACR (mg/g)} \times \text{eCER (g/day)}.$$

The eCER was calculated using the formula developed from the Modification of Diet in Renal Disease (MDRD) study as this did not require knowledge of the individual's weight and so is more likely to be used in clinical practice (eAER_{Ellam}) [9]. Sensitivity analyses were conducted using other eCER formulae (eAER_{Lx} and eAER_{Walser}) [10, 11], restricted to the 5522 participants with information on weight at baseline. The eCER formulae are provided in the [Supplementary data](#).

Follow-up

Participants were to be seen at 2 and 6 months after randomization, and then every 6 months until final follow-up.

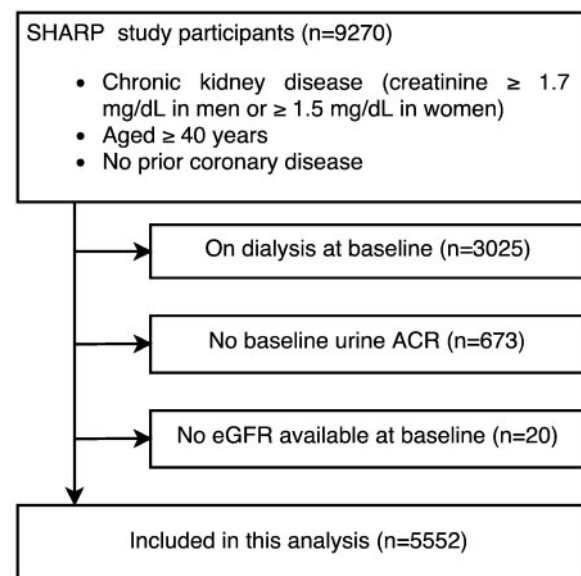


FIGURE 1: Eligibly criteria and participant selection. ACR, albumin creatinine ratio; eGFR, estimated glomerular filtration rate; SHARP, Study of Heart and Renal Protection.

Information on all serious adverse events was sought at each visit and further documentation collected on events of interest (including initiation of renal replacement therapy and possible VEs) by study staff. This information was sent to the international coordinating centre, in Oxford, for central adjudication. A non-fasting blood and urine sample for central laboratory analysis was requested from all participants known to be alive at 2.5 years after randomization.

The main outcomes of interest for these analyses were ESRD, VEs, vascular mortality and non-vascular mortality. The outcome of VEs used in this analysis includes a broader range of events than the pre-specified outcome used for the main trial results [12]. For this analysis, VEs include any cardiovascular death, non-fatal myocardial infarction, hospitalization with angina, any stroke, arterial revascularization, heart failure, arrhythmia or valvular heart disease (see [Supplementary data](#)). ESRD was defined as initiation of maintenance dialysis or renal transplantation.

Statistical analysis

Cox proportional hazards regression was used to compare the relevance of ACR and eAER to the risk of ESRD, VEs and mortality over the period studied. The proportional hazard assumption was tested through examination of the time-dependency of the Schoenfeld partial residuals. The analyses were adjusted for baseline age, sex and eGFR. Analyses of VEs and mortality were also adjusted for other established cardiovascular risk factors [ethnicity, country, systolic and diastolic blood pressure, LDL-C, high-density lipoprotein cholesterol (HDL-C), smoking status, prior diabetes and prior vascular disease]. There were complete data on all these variables with the exception of systolic and diastolic blood pressure, LDL-C and HDL-C, for which 17 (0.3%) participants were missing at least one measurement. Median values were imputed for these participants.

The analyses relate risk to the estimated 'usual' ACR or eAER to correct for the regression dilution bias that would be introduced if only the baseline values were used [16]. In the figures, relative risks (RRs: approximated by the hazard ratio estimates from the Cox models) for each fifth of 'usual' albuminuria measure, including that for the reference group, are accompanied by a confidence interval (CI) derived from the variance of the log risk in that group. These group-specific CIs can be thought of as reflecting the amount of data only in that one group, thereby allowing appropriate statistical comparisons to be made between any two groups [17]. For ESRD, the top fifth is further divided into two equally sized groups, giving six comparison groups. The association between each measure of albuminuria with the outcomes of interest is summarized as the RR per 10-fold increase in albuminuria marker, as this allows comparison with other studies [18] and roughly equates to an increase in albuminuria stage [6]. The magnitude of improvement in risk prediction (over and above other baseline characteristics in the model) was estimated by the difference in twice the log-likelihood statistic between the two "nested" models [which, under the null hypothesis of no improvement, gives a chi-squared (χ^2) statistic with 1 degree of freedom]. This provides not only a test for improvement in fit, but also a quantitative measure of the extent to which the added term improves risk prediction [19] and is the uniformly most powerful test of

the incremental value of a biomarker [20]. A statistically significant improvement is indicated by a change in χ^2 of at least 3.84 (for 1 degree of freedom). As a sensitivity analysis, analyses for ESRD were repeated using Fine and Gray regression, which yields sub-distribution hazard ratios [21], to account for the competing risk of death before ESRD.

RESULTS

Average baseline characteristics in five groups defined by the quintiles of baseline urine ACR are shown in Table 1. Compared with participants with lower urine ACR, individuals with higher urine ACR were younger, had lower eGFR and higher blood pressure at baseline and were more likely to have a diabetic nephropathy or glomerulonephritis recorded as the cause of their renal disease (Table 1). The correlation between ACR or eAER measured at baseline and a repeat measurement (collected around 2.5 years later) was 0.75.

Measures of albuminuria and the risk of ESRD

After a median follow-up of 4.8 years among survivors, 1959 participants had reached ESRD. Both measures of albuminuria displayed strong associations with the risk of ESRD after adjustment for age, sex and eGFR (Figure 2). For both measures curvilinear relationships with ESRD were seen when plotted on a log-log scale, with stronger relationships observed among those with more albuminuria (Figure 2). The average RR throughout the range of values studied was nearly identical for the two measures: RR per 10-fold higher ACR 2.70 (95% CI 2.45–2.98); and per 10-fold higher eAER 2.67 (95% CI 2.43–2.94) (Table 2). Neither ACR nor eAER provided any additional prognostic information for ESRD risk over and above each other [improvement in risk prediction for eAER over and above ACR $\chi^2_1 = 0.3$; for ACR over and above eAER ($\chi^2_1 = 0.0$); [Supplementary Table S1](#)].

The predictive power of ACR and eAER for ESRD was also similar in various subgroups; in men and women; among White and Asian participants; among those with an eGFR ≥ 30 mL/min/1.73 m² and eGFR < 30 mL/min/1.73 m² at baseline; and when the population was separated into groups by age, weight or blood pressure ([Supplementary Table S2](#)). The prognostic utility of eAER was tested separately in the four groups of cause of kidney disease (glomerulonephritis, diabetic nephropathy, cystic kidney disease and other causes; [Supplementary Table S2](#)). In each category of renal disease, a model including either ACR or eAER, along with age, sex and eGFR, was just as informative as one using both measures (χ^2 with either ACR or eAER was 98–99% of the χ^2 for both) although in those with cystic kidney disease neither measure of albuminuria was particularly predictive ($\chi^2 = 4.6$ for the model including ACR and eAER).

In a model without adjustment for age, sex or eGFR, eAER did not add any additional prognostic information for ESRD risk over and above ACR ($\chi^2_1 = 3.8$), but ACR did add prognostic information over and above eAER ($\chi^2_1 = 38.3$) ([Supplementary Table S1](#)). The overall results were similar when eAER was calculated using formulae that include weight as well as age, sex and race ([Supplementary Table S1](#)) [10, 11]. Additionally, neither ACR nor eAER provided any additional

Table 1. Baseline demographic characteristics and physical/laboratory measurements among 5552 patients not on dialysis at randomization, by ACR group defined by the quintiles of the distribution

	ACR (mg/g)					P-value for differences between groups
	<30 n = 1109	≥30 to <118 n = 1109	≥118 to <347 n = 1120	≥347 to <1012 n = 1102	≥1012 n = 1112	
Age at randomization (years)	66 (12)	64 (12)	62 (11)	61 (12)	60 (12)	<0.0001
Men	693 (62%)	688 (62%)	693 (62%)	712 (65%)	678 (61%)	0.48
Race						
White	909 (82%)	872 (79%)	788 (70%)	731 (66%)	625 (56%)	<0.0001
Black	18 (2%)	21 (2%)	16 (1%)	18 (2%)	17 (2%)	0.93
Asian	164 (15%)	195 (18%)	298 (27%)	319 (29%)	450 (40%)	<0.0001
Other/not specified	18 (2%)	21 (2%)	18 (2%)	34 (3%)	20 (2%)	0.07
Prior vascular disease	153 (14%)	179 (16%)	134 (12%)	141 (13%)	201 (18%)	0.0002
Diabetes	197 (18%)	176 (16%)	233 (21%)	249 (23%)	407 (37%)	<0.0001
Current smoker	89 (8%)	125 (11%)	139 (12%)	155 (14%)	181 (16%)	<0.0001
Systolic blood pressure (mmHg)	134 (20)	136 (19)	138 (20)	143 (20)	148 (22)	<0.0001
Diastolic blood pressure (mmHg)	77 (12)	79 (11)	79 (12)	82 (12)	83 (13)	<0.0001
Body mass index (kg/m ²)	27.9 (5.3)	27.3 (5.1)	27.0 (5.2)	27.0 (5.3)	27.1 (5.7)	0.0003
Renal diagnosis						
Glomerulonephritis	92 (8%)	130 (12%)	211 (19%)	278 (25%)	262 (24%)	<0.0001
Diabetic nephropathy	91 (8%)	86 (8%)	135 (12%)	161 (15%)	319 (29%)	<0.0001
Cystic kidney disease	128 (12%)	203 (18%)	160 (14%)	87 (8%)	36 (3%)	<0.0001
Other diagnoses	744 (67%)	624 (56%)	584 (52%)	541 (49%)	466 (42%)	<0.0001
CKD-EPI eGFR (mL/min/1.73 m²)						
Mean (SD)	31.7 (13.4)	26.6 (12.3)	23.7 (11.9)	22.6 (11.6)	20.9 (12.0)	<0.0001
≥60	34 (3%)	16 (1%)	7 (1%)	5 (0%)	12 (1%)	<0.0001
≥30 to <60	540 (49%)	373 (34%)	300 (27%)	267 (24%)	221 (20%)	<0.0001
≥15 to <30	466 (42%)	534 (48%)	510 (46%)	502 (46%)	451 (41%)	0.0022
<15	69 (6%)	186 (17%)	303 (27%)	328 (30%)	428 (38%)	<0.0001
Urinary ACR (mg/g)	11 (6–19)	63 (44–88)	208 (155–265)	601 (457–764)	1866 (1325–3002)	<0.0001
eCER (mg/day) ^a	1329 (1007–1556)	1354 (1031–1578)	1370 (1038–1614)	1422 (1057–1630)	1416 (1057–1640)	<0.0001
eAER (mg/day) ^a	14 (8–24)	80 (54–114)	265 (201–352)	781 (589–1057)	2513 (1819–3983)	<0.0001

Data are n (%), mean (standard deviation) or median (interquartile range). ACR, albumin:creatinine ratio; eCER, estimated creatinine excretion rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eAER, estimated albumin excretion rate; eGFR, estimated glomerular filtration rate.

^aCalculated using the Ellam equation for estimated creatinine excretion rate.

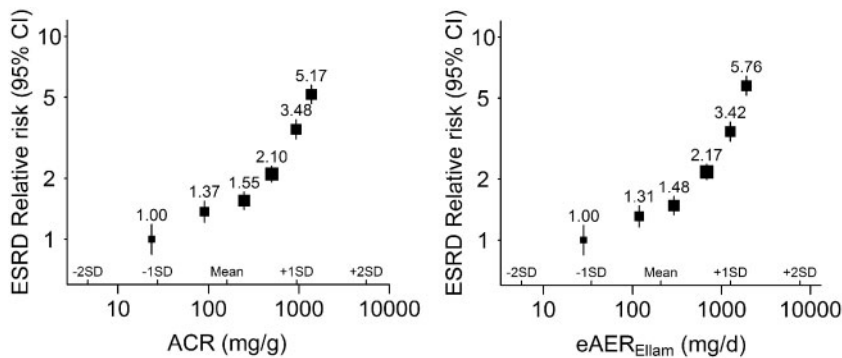


FIGURE 2: Relative risk of ESRD at different levels of ACR and eAER. ACR, albumin:creatinine ratio; eAER, estimated albumin excretion rate; ESRD, end-stage renal disease; SD, standard deviation. The relative risks (adjusted for age, sex and eGFR) and 95% confidence intervals are plotted against the mean usual value (i.e. the medium-term average value). Participants are split into five equally sized groups with the top fifth further divided equally in two.

prognostic information for ESRD risk over and above each other when accounting for the competing risk of death before ESRD (Supplementary Table S3).

Measures of albuminuria and the risk of VEs

During follow-up 1204 participants suffered a fatal or non-fatal VE. Baseline urine ACR and eAER_{Ellam} had modest positive associations with the risk of VEs after adjustment for

established cardiovascular risk factors and eGFR (Figure 3), with almost identical RRs: RR per 10-fold higher ACR 1.37 (95% CI 1.22–1.53); and per 10-fold higher eAER 1.36 (1.22–1.52) (Table 2). Again, neither ACR or eAER provided any additional prognostic information for VE risk over and above each other [improvement in risk prediction for eAER over and above ACR ($\chi^2_1 = 0.8$); for ACR over and above eAER ($\chi^2_1 = 0.5$); Supplementary Table S4].

Findings were similar when eAER was calculated using the formulae that included weight (Supplementary Table S4) [10, 11].

Measures of albuminuria and mortality

In total, 1130 participants died during follow-up, 369 from a vascular cause and 641 from a non-vascular cause. The cause of death was not known in 120 participants. After adjustment for established risk factors and eGFR, both ACR and eAER_{Ellam} showed modest associations with both vascular and non-vascular mortality, and consequently all-cause mortality (Figure 4). After adjustment for known cardiovascular risk factors and eGFR, a 10-fold higher ACR or eAER_{Ellam} was associated with almost identical RRs for vascular mortality [1.64 (1.33–2.03) and 1.63 (1.32–2.00), respectively], for non-vascular mortality [1.52 (1.30–1.78) and 1.50 (1.29–1.76), respectively] and hence for all-cause

Table 2. Age- and sex-adjusted relevance of each marker of albuminuria to ESRD, vascular events and mortality risk before and after additional adjustment for eGFR

Albuminuria marker	Relative risk per 10-fold increase in marker of albuminuria (95% CI)	
	Adjusted for age and sex	Adjusted for age, sex and eGFR
ESRD		
ACR	3.52 (3.22, 3.85)	2.70 (2.45, 2.98)
eAER _{Ellam}	3.46 (3.17, 3.78)	2.67 (2.43, 2.94)
Vascular events		
ACR	1.53 (1.38, 1.70)	1.37 (1.22, 1.53)
eAER _{Ellam}	1.53 (1.38, 1.69)	1.36 (1.22, 1.52)
Vascular mortality		
ACR	1.97 (1.63, 2.40)	1.64 (1.33, 2.03)
eAER _{Ellam}	1.95 (1.61, 2.36)	1.63 (1.32, 2.00)
Non-vascular mortality		
ACR	1.88 (1.63, 2.18)	1.52 (1.30, 1.78)
eAER _{Ellam}	1.86 (1.61, 2.15)	1.50 (1.29, 1.76)
All-cause mortality		
ACR	1.88 (1.69, 2.10)	1.56 (1.38, 1.75)
eAER _{Ellam}	1.86 (1.67, 2.07)	1.54 (1.37, 1.73)

ACR, albumin:creatinine ratio; eAER, estimated albumin excretion rate; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; CI, confidence interval.

mortality [1.56 (1.38–1.75) and 1.54 (1.37–1.73), respectively] (Table 2).

For vascular mortality, neither measure significantly improved model fit over and above the other ($\chi^2_1 = 2.0$ for eAER over and above ACR and $\chi^2_1 = 2.3$ for ACR over and above eAER; Supplementary Table S5). For non-vascular mortality, however, knowledge of both albuminuria measures resulted in small, but significant, improvements in risk prediction compared with knowledge of either one in isolation ($\chi^2_1 = 8.2$ for eAER over and above ACR and $\chi^2_1 = 9.1$ for ACR over and above eAER; Supplementary Table S5). Again, findings were similar when alternative equations that included weight [10, 11] were used to estimate eAER (Supplementary Table S5).

DISCUSSION

Albuminuria is recognized as a strong predictor of the risk of ESRD and of VEs [2, 4]. This report confirms these associations but shows that eAER (a more accurate estimate of 24-h urine albumin excretion than ACR) does not provide more prognostic information than ACR in terms of ESRD or vascular risk. The likely explanation for this finding lies in relationships between ACR and eAER and measured albuminuria.

The eAER_{Ellam} formula was derived from measurements of 24-h urinary excretion of albumin and creatinine in the MDRD study [9]. One of the key findings from the derivation of this formula was that almost all of the MDRD participants, with the exception of White women, excreted substantially more than 1 g of creatinine per day. Thus, estimates of 24-h albuminuria based on ACR, which assumes the amount of albumin per gram of creatinine to be equivalent to the 24-h albumin excretion, are likely to systematically underestimate measured albuminuria in most individuals. This is consistent with the authors' finding that ACR underestimated albuminuria in both validation cohorts, whereas eAER produced a relatively unbiased estimate (assessed by the median difference between ACR or eAER and measured 24-h albuminuria) [9]. However, in the validation cohorts, eAER was not more precise than ACR, meaning that, after accounting for the bias, for any individual in the study the difference between the

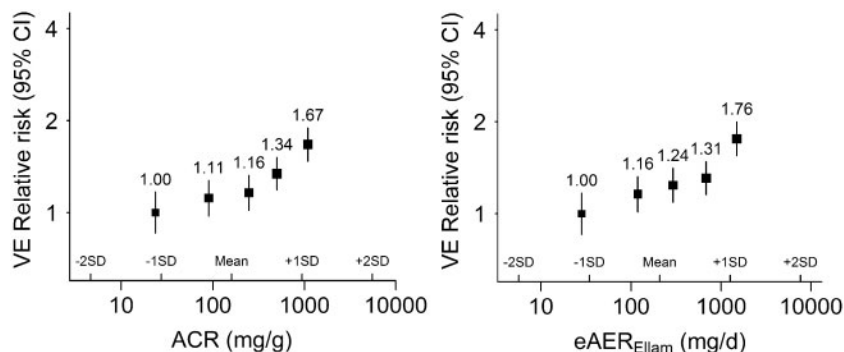


FIGURE 3: Relative risk of vascular events at different levels of ACR and eAER. ACR, albumin:creatinine ratio; eAER, estimated albumin excretion rate; VE, vascular events; SD, standard deviation. The relative risks (adjusted for established risk factors and eGFR) and 95% confidence intervals are plotted against the mean usual value (i.e. the medium-term average value). The established risk factors included are: age, sex, ethnicity, country, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking status, prior diabetes and prior vascular disease.

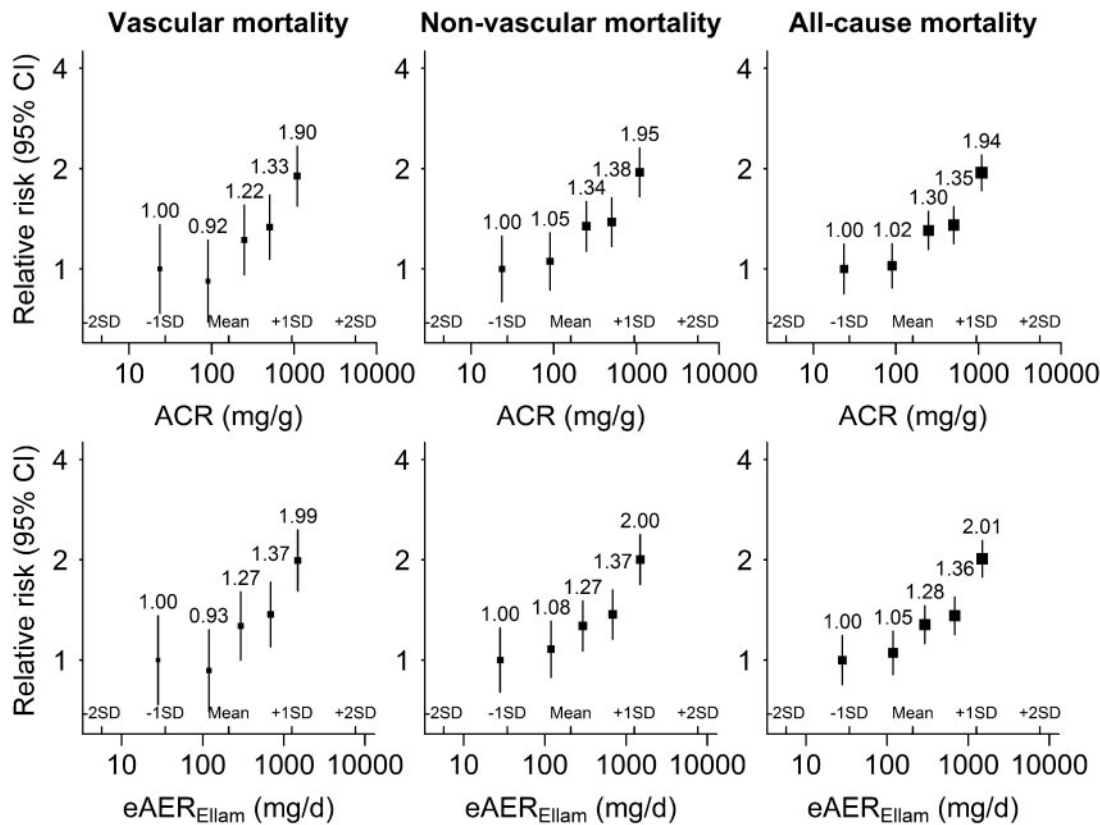


FIGURE 4: Relative risk of mortality at different levels of ACR and eAER_{Ellam}, after adjustment for established risk factors and estimated glomerular filtration rate. ACR, albumin:creatinine ratio; eAER, estimated albumin excretion rate; SD, standard deviation. The relative risks and 95% confidence intervals are plotted against the mean usual value (i.e. the medium-term average value). The established risk factors included are: age, sex, ethnicity, country, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking status, prior diabetes and prior vascular disease.

ACR or eAER estimate and measured 24-h albuminuria was similar (assessed by the interquartile range of the differences between ACR or eAER and measured albuminuria). Because accuracy (assessed as the proportion of individuals in whom ACR or eAER was within 30% or 50% of the measured albuminuria) is heavily dependent on the bias, eAER is substantially more accurate in predicting 24-h albuminuria than ACR [9]. In predicting events in a prospective study, however, the bias is less important than discrimination (i.e. the measure's ability to order individuals according to their level of risk).

Since eAER aims to account for differences in creatinine excretion between individuals it might be expected to perform better than ACR in predicting ESRD without adjustment for other factors, including age and sex. However, in this study, eAER did not provide any additional prognostic information over ACR in predicting ESRD risk in either the null or the adjusted model. Furthermore, knowledge of eAER and ACR was no more informative than ACR alone in predicting ESRD in subgroups expected to have lower creatinine excretion (e.g. women, those aged over 70 years, Asian participants, those weighing under 70 kg) or higher creatinine excretion (e.g. men, those aged under 50 years, White participants and those weighing over 85 kg). It is also interesting that the formulae that included weight in the calculation of CER (eAER_{Ix} or eAER_{Walser}), and therefore eAER, also did not provide additional prognostic information over ACR. However, similar to

the eAER_{Ellam} equation, in the Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort neither the eAER_{Ix} or the eAER_{Walser} formulae were more precise than ACR in predicting measured albuminuria, although they both produced a less biased estimate of albuminuria than ACR [10].

This current study has several important strengths. First, the large number of ESRD events mean that we were able to not only estimate the risks associated with higher albuminuria very precisely, but also compare the predictive performance of measures of albuminuria separately in a number of important subgroups. Second, the measurement of urine and blood biochemistries was conducted in a central laboratory using standard methods. Third, the study population had a wide range of albuminuria including over 1000 individuals with an ACR of >1 g/g.

A number of limitations require consideration. First, albuminuria was measured using a sample collected at only a single time-point. Within individuals, day-to-day variability of albuminuria is substantial [22] and the use of albuminuria measured at just a single time point would underestimate the strength of the true association between usual albuminuria and risk [16]. We were, to some extent, able to overcome this problem by correcting for the regression dilution bias [16]. The regression dilution ratio (the correlation between baseline ACR or eAER and a repeat measurement collected around 2.5 years later) was 0.75 for both albuminuria measures and therefore correction for this

within-individual variation resulted in an association between usual ACR or eAER and risk of ESRD, VEs and mortality (reported here) that was approximately one-third stronger than would have been observed without correction [16]. Second, measures of 24-h albuminuria were not available and so we were not able to assess the prognostic ability of eAER compared with a 'gold standard'. However, the aim of these analyses was to assess whether eAER is superior in terms of predicting ESRD or VEs to ACR, the albuminuria measure used in clinical practice [6]. Third, the study included only individuals with moderate to severe CKD and therefore it is possible that eAER might be more useful than ACR in predicting ESRD or VEs in the general population.

As a major use of ACR in clinical practice is to predict risk of progression of CKD (and to a lesser extent, risk of vascular disease), an important question is whether eAER provides superior prognostic information to ACR alone. These analyses show that if ACR is already known (as it would be in clinical practice), eAER provides no extra predictive prognostic information.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

ACKNOWLEDGEMENTS

SHARP was initiated, conducted and interpreted independently of the principal funder (Merck & Co. and Schering Plough Corporation, which merged in 2009). Additional support was provided from the Australian National Health Medical Research Council, the British Heart Foundation and the Medical Research Council. We thank the SHARP participants and the local centre staff, regional and national coordinators, steering committee and data monitoring committee. Steering committee: Colin Baigent, Martin J. Landray, Christina Reith, Jonathan Emberson, David C. Wheeler, Charles Tomson, Christoph Wanner, Vera Krane, Alan Cass, Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawrence Agodoa, Mike Gaziano, Bertram Kasiske, Robert Walker, Ziad A. Massy, Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Bengt Fellström, Hallvard Holdaas, Vladimir Tesar, Andrzej Wiecek, Diederick Grobbee, Dick de Zeeuw, Carola Grönghagen-Riska, Tanaji Dasgupta, David Lewis, William Herrington, Marion Mafham, William Majoni, Karl Wallendszus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Armitage, Alex Baxter, Christopher Bray, Yiping Chen, Zhengming Chen, Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Young and Rory Collins.

CONFLICT OF INTEREST STATEMENT

The Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) has a staff policy of not accepting honoraria

or consultancy fees. None of the authors has any conflict of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract form.

REFERENCES

1. Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012; 379: 165–180
2. Perkovic V, Verdon C, Ninomiya T *et al*. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med* 2008; 5: e207
3. Landray MJ, Emberson JR, Blackwell L *et al*. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis* 2010; 56: 1082–1094
4. Gansevoort RT, Matsushita K, van der Velde M *et al*. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2011; 80: 93–104
5. Matsushita K, van der Velde M, Astor BC *et al*. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–2081
6. Levin A, Stevens PE *et al*. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter Suppl* 2013; 3: 1–150
7. Hutchison AS, O'Reilly DS, MacCuish AC. Albumin excretion rate, albumin concentration, and albumin/creatinine ratio compared for screening diabetics for slight albuminuria. *Clin Chem* 1988; 34: 2019–2021
8. Ellam TJ. Albumin : creatinine ratio—a flawed measure? The merits of estimated albuminuria reporting. *Nephron Clin Pract* 2011; 118: c324–c330
9. Fotheringham J, Campbell MJ, Fogarty DG *et al*. Estimated albumin excretion rate versus urine albumin-creatinine ratio for the estimation of measured albumin excretion rate: derivation and validation of an estimated albumin excretion rate equation. *Am J Kidney Dis* 2014; 63: 405–414
10. Abdelmalek JA, Gansevoort RT, Lambers Heerspink HJ *et al*. Estimated albumin excretion rate versus urine albumin-creatinine ratio for the assessment of albuminuria: a diagnostic test study from the Prevention of Renal and Vascular Endstage Disease (PREVEND) Study. *Am J Kidney Dis* 2014; 63: 415–421
11. Walser M. Creatinine excretion as a measure of protein nutrition in adults of varying age. *J Parenter Enteral Nutr* 1987; 11 (5 Suppl): 73S–78S
12. Baigent C, Landray MJ, Reith C *et al*. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; 377: 2181–2192
13. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J* 2010; 160: 785–794
14. Haynes R, Staplin N, Emberson J *et al*. Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the study of heart and renal protection (SHARP). *Am J Kidney Dis* 2014; 64: 40–48
15. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
16. Clarke R, Shipley M, Lewington S *et al*. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; 150: 341–353
17. Plummer M. Improved estimates of floating absolute risk. *Stat Med* 2004; 23: 93–104
18. Astor BC, Matsushita K, Gansevoort RT *et al*. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011; 79: 1331–1340
19. Collett D. *Modelling Survival Data in Medical Research*, 2nd edn. London: Chapman and Hall, 2003

20. Kerr KF, McClelland RL, Brown ER *et al.* Evaluating the incremental value of new biomarkers with integrated discrimination improvement. *Am J Epidemiol* 2011; 174: 364–374
21. Noordzij M, Leffondré K, van Stralen KJ *et al.* When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant* 2013; 28: 2670–2677

22. Naresh CN, Hayen A, Weening A *et al.* Day-to-day variability in spot urine albumin-creatinine ratio. *Am J Kidney Dis* 2013; 62: 1095–1101

Received: 1.7.2016; Editorial decision: 10.10.2016

Nephrol Dial Transplant (2018) 33: 264–273
doi: 10.1093/ndt/gfw412
Advance Access publication 7 January 2017

Prognostic significance of pre-end-stage renal disease serum alkaline phosphatase for post-end-stage renal disease mortality in late-stage chronic kidney disease patients transitioning to dialysis

Keiichi Sumida^{1,2,3}, Miklos Z. Molnar⁴, Praveen K. Potukuchi¹, Fridtjof Thomas⁵, Jun Ling Lu¹, Yoshitsugu Obi⁶, Connie M. Rhee⁶, Elani Streja⁶, Kunihiro Yamagata³, Kamyar Kalantar-Zadeh⁶ and Csaba P. Kovesdy^{1,7}

¹Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, ²Nephrology Center, Toranomon Hospital Kajigaya, Kanagawa, Japan, ³Department of Nephrology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan, ⁴Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary, ⁵Division of Biostatistics, Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, ⁶Harold Simmons Center for Chronic Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California-Irvine, Orange, CA, USA and ⁷Nephrology Section, Memphis VA Medical Center, Memphis, TN, USA

Correspondence and offprint requests to: Csaba P. Kovesdy; E-mail: ckovesdy@uthsc.edu

ABSTRACT

Background. Higher serum alkaline phosphatase (ALP) levels have been associated with excess mortality in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) and end-stage renal disease (ESRD). However, little is known about the impact of late-stage NDD-CKD ALP levels on outcomes after dialysis initiation.

Methods. Among 17 732 US veterans who transitioned to dialysis between October 2007 and September 2011, we examined the association of serum ALP levels averaged over the last 6 months of the pre-ESRD transition period ('prelude period') with all-cause, cardiovascular and infection-related mortality following dialysis initiation, using Cox (for all-cause mortality) and competing risk (for cause-specific mortality) regressions adjusted for demographics, comorbidities, medications, estimated glomerular filtration rate and serum albumin levels over the 6-month prelude period, and vascular access type at dialysis initiation.

Results. During a median follow-up of 2.0 (interquartile range, 1.1–3.2) years following dialysis initiation, a total of 9196 all-cause deaths occurred. Higher ALP levels were incrementally associated with higher all-cause, cardiovascular and infection-related mortality. Compared with patients in the lowest ALP quartile (<66.0 U/L), those in the highest quartile (≥111.1 U/L) had multivariable-adjusted hazard/subhazard ratios (95% confidence interval) of 1.42 (1.34–1.51), 1.43 (1.09–1.88) and 1.39 (1.09–1.78) for all-cause, cardiovascular and infection-related mortality, respectively. The associations remained consistent in various subgroups and after further adjustment for liver enzymes, serum phosphorus and intact parathyroid hormone levels.

Conclusions. Higher pre-ESRD serum ALP levels are independently associated with higher post-ESRD mortality risk. Further studies are warranted to determine if interventions that lower pre-ESRD ALP levels reduce mortality in incident dialysis patients.

Keywords: alkaline phosphatase, chronic kidney disease, end-stage renal disease, mortality, transition