

## Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial

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### Abstract

**Objectives** To determine whether data on proteinuria are useful for refining estimates of risk based on kidney function alone, and whether the results of kidney function tests can be a useful adjunct to data on proteinuria.

**Design** Analysis of data from a randomised trial. Impaired kidney function was defined as low glomerular filtration rate ( $<60$  ml/min/1.73 m<sup>2</sup>) and proteinuria ( $\geq 1+$  protein) on dipstick urinalysis.

**Setting** Study of cholesterol and recurrent events: a randomised trial of pravastatin 40 mg daily versus placebo.

**Participants** 4098 men and women with previous myocardial infarction.

**Main outcome measures** All cause mortality and cardiovascular events.

**Results** 371 participants died in nearly 60 months of follow-up. Compared with participants without proteinuria or impaired kidney function, patients with both characteristics were at high risk (hazard ratio 2.39, 95% confidence interval 1.72 to 3.30), and those with only proteinuria or only impaired kidney function were at intermediate risk (1.69, 1.32 to 2.16; 1.41, 1.12 to 1.79, respectively) of dying from any cause. The results were similar for cardiovascular outcomes, including new cases of heart failure, stroke, and coronary death or non-fatal myocardial infarction. A graded increase in the risk of all cause mortality was seen for severity of renal impairment and degree of proteinuria by dipstick.

**Conclusions** The presence or absence of proteinuria on dipstick urinalysis may be used to refine estimates of risk based on kidney function alone.

### Introduction

Chronic kidney disease is an independent risk factor for premature death and cardiovascular morbidity. For example, cardiovascular events are 10-20 times more frequent in patients with end stage renal disease than in age and sex matched controls in the general population.<sup>1</sup> Recent evidence shows that even mild impairment of kidney function is associated with increased mortality and higher risk of first and recurrent cardiovascular events.<sup>2-6</sup>

In people with a normal glomerular filtration rate (such as the general population or people being treated for hypertension), proteinuria is associated with an increase in adverse clinical outcomes, even when excretion of protein in the urine is as

low as 7 mg/day.<sup>7-12</sup> When kidney function is impaired, proteinuria is associated with an increased risk of cardiovascular events, which persists after adjustment for estimated glomerular filtration rate (GFR) and is independent of diabetic status.<sup>13 14</sup>

Although proteinuria is a fundamental manifestation of kidney disease, in the United States only 25% of people with proteinuria have a low GFR ( $<60$  ml/min/1.73 m<sup>2</sup>) and only 25% of people with a low GFR have proteinuria.<sup>15</sup> Therefore, few studies examine the relation between adverse outcomes and these two risk factors in combination. We used data from a randomised trial of people with previous myocardial infarction to test the hypothesis that patients with proteinuria and low GFR have higher mortality than those with one or neither characteristic. We wanted to determine whether information on proteinuria was useful for refining estimates of risk based on kidney function alone, and whether the results of kidney function tests can be a useful adjunct to data on proteinuria.

### Methods

#### Study design and patients

Our study of data from a randomised trial was approved by the institutional review board at the University of Alberta. The cholesterol and recurrent events (CARE) study was a randomised trial of pravastatin versus placebo in 4159 people with hyperlipidaemia and previous myocardial infarction.<sup>16 17</sup> Men and postmenopausal women were eligible if they had had an acute myocardial infarction 3-20 months before the study, low density lipoprotein cholesterol concentrations of 3.0-4.5 mmol/l, fasting glucose concentrations of no more than 12.2 mmol/l, left ventricular ejection fractions of no less than 25%, no symptoms of congestive heart failure, and were 21-75 years old. Participants were stratified according to clinical centre and randomly assigned in a double blinded fashion to receive either 40 mg of pravastatin (Pravachol, Bristol Myers Squibb) or placebo once daily. The allocation of treatment was concealed by using a centrally maintained code.

#### Measuring proteinuria and kidney function

Patients with proteinuria  $\geq 2+$  on routine dipstick testing or serum creatinine concentrations more than 1.5 times the upper limit of normal before randomisation were excluded from the trial. However, some patients with proteinuria  $\geq 2+$  and patients in whom repeat urinalysis gave results of  $<2+$  were enrolled at the discretion of the site investigator. We used the results of the first urinalysis before randomisation to classify patients with

respect to proteinuria. Typical dipstick measures of proteinuria were none, trace, 1+, 2+, and 3+, which corresponds to urinary protein concentrations of <0.1, 0.1-0.3, 0.31-1.0, 1.01-3.0, and more than 3.0 g/l. We defined proteinuria as 1+ or greater protein on baseline dipstick urinalysis (Multistix; Ames Miles Bayer) read automatically. We measured baseline serum creatinine in fasting participants with an alkaline picrate method. We estimated GFR using the equation

$$186 \times \text{SCr}^{-1.154} \times \text{age in years}^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}$$

where SCr is serum creatinine in g/dl. This formula agrees with iothalamate measurements of GFR.<sup>18</sup> In agreement with recent guidelines, we defined overtly impaired kidney function as GFR < 60 ml/min/1.73 m<sup>2</sup> body surface area.<sup>18</sup>

### Study outcomes

The primary outcome was all cause mortality. Secondary outcomes were developing symptomatic congestive heart failure, ischaemic or non-ischaemic stroke, and the composite of fatal coronary disease (fatal myocardial infarction, either definite or probable; sudden death; death during a coronary intervention; and death from other coronary causes) or non-fatal myocardial infarction confirmed by measuring serum creatine kinase. The outcomes committee reviewed deaths without knowing the participant's treatment assignment or laboratory values.

### Statistical analysis

Descriptive statistics are reported as medians and interquartile ranges or percentages where appropriate. We used  $\chi^2$  and Kruskal-Wallis tests to test for differences between four groups defined by the presence and absence of proteinuria and impaired kidney function. We used Cox proportional hazard models to examine the association between proteinuria, kidney dysfunction, and clinical outcomes. On the basis of a priori decisions about potential confounders, we adjusted for the following baseline covariates in all multivariate models: age; ethnic origin (black *v* other); sex; smoking status; diabetic status; waist to hip circumference ratio; fasting glucose; haemoglobin; serum albumin; low density lipoprotein cholesterol; high density lipoprotein cholesterol; triglycerides; systolic and diastolic blood pressure; country of treatment (USA *v* Canada); left ventricular ejection fraction; and use of  $\beta$  adrenergic blockers, angiotensin converting enzyme inhibitors, aspirin, and pravastatin. We used the mean of covariates method to produce adjusted survival curves for these final models.<sup>19</sup> We determined that the proportional hazard assumption was satisfied by examining plots of the log negative log of the within-group survivorship functions versus log-time, the Schoenfeld residuals, and Kaplan-Meier (observed) versus Cox (expected) survival curves. In a sensitivity analysis, we compared the full model results to the parsimonious model fit with a backwards elimination selection method. Results were similar by using this last approach to those obtained using the fully adjusted model, and we report the results of the backwards elimination selection method. We also evaluated whether risk increased with increasing severity of proteinuria (none, trace, 1+, 2+, or >2) and kidney dysfunction (GFR  $\geq$  60, 45-59.9, or < 45 ml/min/1.73 m<sup>2</sup>). All P values are two sided and 95% confidence intervals are provided where appropriate. Analyses were performed with Stata 8 SE software.

## Results

### Baseline characteristics

Of 4159 participants, 4098 (98.5%) had serum creatinine and proteinuria measured at baseline and were eligible for analysis.

Table 1 lists the demographic characteristics of the participants. A total of 2839 (69.3%) participants had neither proteinuria nor impaired kidney function, 707 (17.3%) had only impaired kidney function, 379 (9.3%) had only proteinuria, and 173 (4.2%) had both. Overall, 19.7% (173) of participants with impaired kidney function had proteinuria, and 31.3% (173) of participants with proteinuria had impaired kidney function. The median follow-up was 58.9 months.

### Association with all cause mortality

The unadjusted risk of all cause mortality was significantly higher in patients with both proteinuria and impaired kidney function (27.2%) than in those with neither condition (7.1%;  $P < 0.001$  by using  $\chi^2$ ; table 2). A Cox model that adjusted for age, ethnic origin, and sex, showed that proteinuria (hazard ratio 2.00, 95% confidence interval 1.58 to 2.53) and impaired kidney function (1.41, 1.12 to 1.77) were significantly associated with the risk of all cause mortality. Impaired kidney function and proteinuria were independently associated with all cause mortality when entered separately into the fully adjusted model (1.41, 1.12 to 1.79 and 1.69, 1.32 to 2.16). Participants with both characteristics were at highest risk (2.39, 1.72 to 3.30), and participants with neither characteristic were at lowest risk (1.0) (table 2; fig 1). The risk of all cause mortality increased with the severity of renal impairment ( $P$  for trend 0.003) and degree of proteinuria by dipstick ( $P$  for trend < 0.001) (table 3; fig 2).

After full adjustment, interaction between impaired kidney function and proteinuria on mortality was of borderline significance ( $P = 0.046$ ). The risk associated with concomitant proteinuria and kidney dysfunction (compared with the risk in participants with neither characteristic) was qualitatively similar in models with and without the interaction term (2.78, 1.98 to 3.92; 2.39, 1.72 to 3.30, respectively), indicating that the interaction was of modest clinical importance. Results were similar when participants with diabetes mellitus at baseline were excluded (data not shown).

### Association with other adverse clinical outcomes

Results were similar for other adverse outcomes, including cardiovascular death or non-fatal myocardial infarction, the development of new congestive heart failure, and stroke. For all three outcomes, risk was qualitatively higher for participants with both proteinuria and impaired kidney function than for participants with one or neither characteristic (all  $P < 0.001$  by  $\chi^2$ ; table 2; fig 1), and tests for interaction were non-significant (all  $P > 0.15$ ).

## Discussion

We found that impaired kidney function and proteinuria often exist independently, so that the presence of both these conditions could be used to identify people at high risk of death.<sup>15</sup> Among survivors of myocardial infarction who were clinically stable, patients with proteinuria and impaired kidney function were more than twice as likely to die as patients with one or neither abnormality. These results were consistent for a range of adverse clinical outcomes, including all cause mortality, stroke, new congestive heart failure, and cardiovascular death or non-fatal myocardial infarction. We also found a dose effect for proteinuria and kidney dysfunction: increased risk was associated with greater proteinuria and lower GFR. Thus the presence or absence of proteinuria on routine urinalysis could help refine estimates of risk that are based on kidney function alone.

**Table 1** Baseline characteristics of participants; values are median (interquartile range)

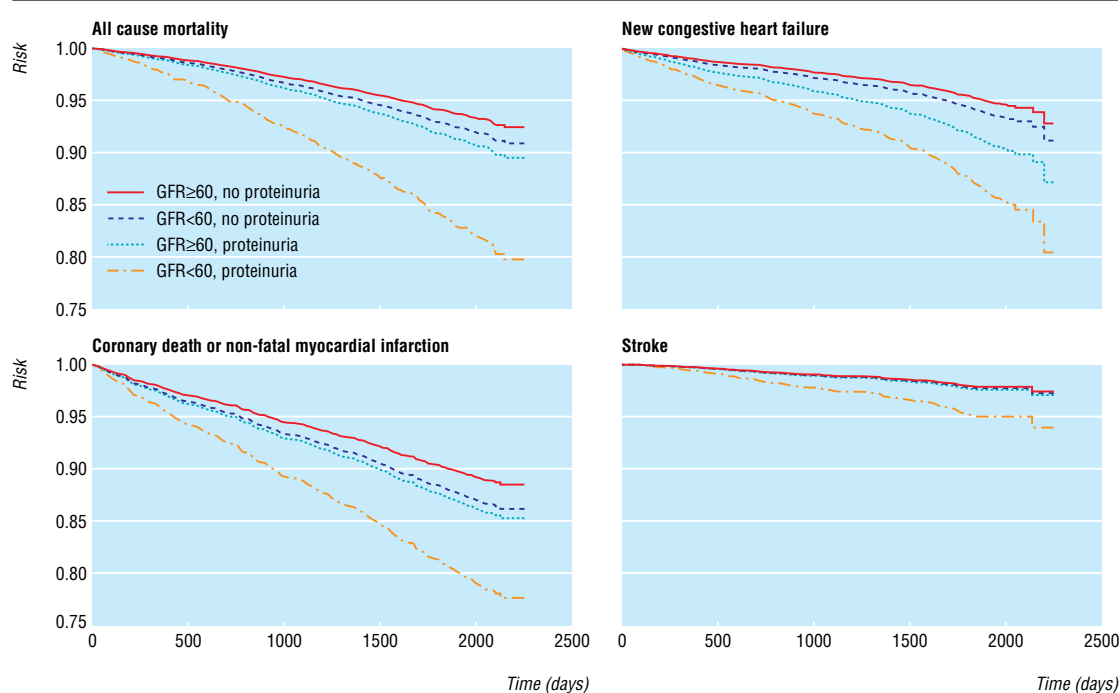
Variable	No proteinuria		Proteinuria		P value
	GFR ≥60 (n=2839)	GFR <60 (n=707)	GFR ≥60 (n=379)	GFR <60 (n=173)	
<b>Demographic variables</b>					
Age (years)	58 (50-64)	65 (59-70)	60 (52-66)	65 (60-70)	<0.001
% female	10.7	25.2	12.9	19.1	<0.001
% black	3.0	1.7	7.9	3.5	<0.001
Body mass index (kg/m <sup>2</sup> )	27 (25-30)	27 (24-30)	28 (25-31)	27 (24-29)	<0.001
% with history of hypertension	37.8	49.7	51.7	70.5	<0.001
% current smokers	17.4	8.9	20.1	15.6	<0.001
% with known diabetes mellitus	11.5	15.3	28.0	22.5	<0.001
% treated in the US (v Canada)	65.5	65.5	71.0	66.5	0.20
<b>Drugs</b>					
Pravastatin	50.3	48.4	48.3	52.6	0.62
β blocker	38.7	41.9	41.2	42.2	0.35
Angiotensin converting enzyme inhibitor	12.5	17.7	15.0	26.0	<0.001
Aspirin	84.6	81.6	79.4	79.2	0.01
<b>Lipid status</b>					
Total cholesterol (mmol/l)	5.4 (5.1-5.8)	5.5 (5.1-5.8)	5.4 (5.1-5.7)	5.4 (5.0-5.8)	0.009
Low density lipoprotein cholesterol (mmol/l)	3.6 (3.3-3.9)	3.6 (3.3-3.9)	3.5 (3.3-3.8)	3.6 (3.3-3.8)	0.05
High density lipoprotein cholesterol (mmol/l)	0.98 (0.85-1.1)	1.0 (0.85-1.2)	0.96 (0.83-1.1)	0.93 (0.83-1.1)	0.003
Triglycerides (mmol/l)	1.6 (1.2-2.1)	1.6 (1.2-2.2)	1.6 (1.3-2.3)	1.7 (1.3-2.3)	0.40
<b>Renal function, blood pressure, and ejection fraction</b>					
GFR (ml/min/1.73m <sup>2</sup> )	75 (68-84)	55 (51-58)	74 (67-84)	53 (47-57)	<0.001
Serum creatinine (μmol/l)	97 (88-106)	123 (115-133)	97 (88-106)	123 (123-141)	<0.001
Systolic blood pressure (mm Hg)	126 (116-140)	130 (120-142)	132 (120-145)	136 (120-150)	<0.001
Diastolic blood pressure (mm Hg)	80 (70-85)	80 (70-85)	80 (72-88)	80 (74-90)	<0.001
Ejection fraction (%)	53 (45-61)	53 (44-62)	54 (45-61)	50 (44-59)	0.04
<b>Laboratory variables</b>					
Haemoglobin (g/l)	150 (140-160)	150 (140-160)	150 (140-160)	150 (140-150)	<0.001
Serum albumin (g/l)	42 (41-44)	42 (40-43)	42 (40-43)	41 (40-43)	<0.001

Proteinuria was ≥1+ on routine dipstick urinalysis; GFR ≥60/<60 is estimated glomerular filtration rate ≥60/<60 ml/min/1.73 m<sup>2</sup>.

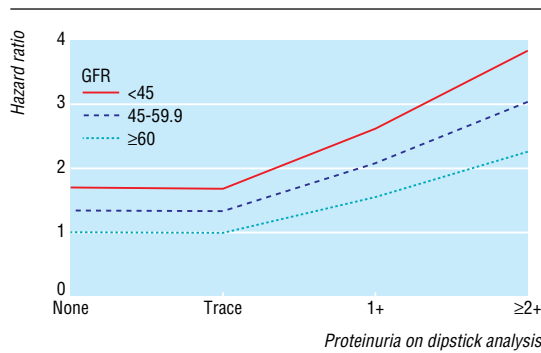
**Comparison with other studies**

Many studies with a wide range of participants have found an association between adverse outcomes and kidney dysfunction.<sup>3, 4, 20-23</sup> Several studies have shown an association between urinary protein excretion (overt proteinuria and micro-

albuminuria) and the risk of death or cardiovascular events.<sup>7-10</sup> Despite this, data on how proteinuria and kidney function together affect prognosis are lacking. Studies have either not reported data on both characteristics, or they have reported that one characteristic is independently associated with risk after



**Fig 1** Time to clinical outcomes by proteinuria and kidney dysfunction



**Fig 2** Adjusted risk of all cause mortality according to proteinuria and kidney dysfunction

controlling for the other. Our findings are consistent with the findings of the heart outcomes prevention evaluation study.<sup>3</sup> However, that analysis excluded participants with proteinuria on dipstick urinalysis and did not report findings for all cause mortality. Given the low cost and ready availability of estimates of kidney function based on urinalyses and serum creatinine, our finding is likely to be clinically useful.

**Implications of the study**

We do not know how concomitant proteinuria and renal insufficiency mediate increased cardiovascular risk, but several possibilities exist. Firstly, proteinuria and impaired kidney function often coexist with other cardiovascular risk factors.<sup>24-27</sup>

**Table 3** Association between proteinuria, kidney dysfunction, and all cause mortality

Grade	No	Fully adjusted hazard ratio (95% CI)	P value
<b>≥2+ proteinuria</b>			
GFR <45	10	3.84 (2.12 to 6.96)	<0.001
GFR 45-59.9	30	3.04 (1.87 to 4.94)	<0.001
GFR ≥60	55	2.26 (1.46 to 3.52)	<0.001
<b>1+ proteinuria</b>			
GFR <45	28	2.62 (1.56 to 4.40)	<0.001
GFR 45-59.9	105	2.08 (1.44 to 3.00)	<0.001
GFR ≥60	324	1.55 (1.17 to 2.05)	0.002
<b>Trace proteinuria</b>			
GFR <45	21	1.68 (0.99 to 2.86)	0.06
GFR 45-59.9	119	1.33 (0.91 to 1.96)	0.15
GFR ≥60	479	0.99 (0.73 to 1.34)	0.95
<b>No proteinuria</b>			
GFR <45	48	1.7 (1.08 to 2.67)	0.02
GFR 45-59.9	519	1.34 (1.05 to 1.72)	0.02
GFR ≥60	2360	1.0	

Adjusted for age, sex, ethnic origin, smoking status, diabetic status, waist to hip circumference ratio, fasting glucose, haemoglobin, serum albumin, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, country of treatment (US v Canada), left ventricular ejection fraction, and use of drugs (β adrenergic blockers, angiotensin converting enzyme inhibitors, aspirin, or pravastatin) (all at baseline).

Secondly, patients with renal disease might be less likely to receive beneficial treatments.<sup>6, 28, 29</sup> Although we controlled for these two factors, we cannot exclude the possibility of residual

**Table 2** Association between proteinuria, kidney dysfunction, and clinical outcomes

Outcome	Unadjusted event rate (%)	Hazard ratio			
		Adjusted for age, ethnic origin, and sex		Fully adjusted*	
		Ratio (95% CI)	P value	Ratio (95% CI)	P value
<b>All cause mortality</b>					
No proteinuria:					
GFR ≥60	201/2839 (7.1)	1.0		1.0	
GFR <60	74/707 (10.5)	1.20 (0.91 to 1.58)	0.203	1.41 (1.12 to 1.79)	0.004
Proteinuria:					
GFR ≥60	49/379 (12.9)	1.61 (1.17 to 2.20)	0.003	1.69 (1.32 to 2.16)	<0.001
GFR <60	47/173 (27.2)	3.31 (2.39 to 4.59)	<0.001	2.39 (1.72 to 3.30)	<0.001
<b>Coronary death or non-fatal myocardial infarction</b>					
No proteinuria:					
GFR ≥60	293/2839 (10.3)	1.0		1.0	
GFR <60	87/707 (12.3)	1.19 (0.93 to 1.53)	0.173	1.28 (1.03 to 1.60)	0.03
Proteinuria:					
GFR ≥60	60/379 (15.8)	1.47 (1.11 to 1.95)	0.007	1.43 (1.14 to 1.81)	0.003
GFR <60	38/173 (22.0)	2.31 (1.63 to 3.26)	<0.001	1.84 (1.35 to 2.50)	<0.001
<b>New symptomatic heart failure</b>					
No proteinuria:					
GFR ≥60	150/2839 (5.3)	1.0		1.0	
GFR <60	65/707 (9.2)	1.28 (0.94 to 1.73)	0.115	1.31 (1.01 to 1.71)	0.04
Proteinuria:					
GFR ≥60	50/379 (13.2)	2.13 (1.54 to 2.95)	<0.001	1.83 (1.40 to 2.40)	<0.001
GFR <60	36/173 (20.8)	3.30 (2.28 to 4.79)	<0.001	2.41 (1.68 to 3.45)	<0.001
<b>Stroke</b>					
No proteinuria:					
GFR ≥60	71/2839 (2.5)	1.0		1.0	
GFR <60	28/707 (4.0)	1.07 (0.68 to 1.69)	0.761	1.25 (0.84 to 1.84)	0.27
Proteinuria:					
GFR ≥60	16/379 (4.2)	1.41 (0.82 to 2.45)	0.216	1.33 (0.87 to 2.03)	0.19
GFR <60	15/173 (8.7)	2.61 (1.48 to 4.61)	0.001	1.66 (0.95 to 2.90)	0.08

Proteinuria was defined by ≥1+ proteinuria on routine dipstick urinalysis; GFR ≥60/<60 means estimated glomerular filtration rate ≥60/<60 ml/min/1.73m<sup>2</sup>. The number of participants in each category was 2839 (no proteinuria, GFR ≥60), 707 (no proteinuria, GFR <60), 379 (proteinuria, GFR ≥60), and 173 (proteinuria, GFR <60).

\*Factors adjusted for: age, sex, ethnic origin, smoking status, diabetic status, waist to hip circumference ratio, fasting glucose, haemoglobin, serum albumin, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, country of treatment (US v Canada), left ventricular ejection fraction, and use of drugs (β adrenergic blockers, angiotensin converting enzyme inhibitors, aspirin, or pravastatin).

confounding. Thirdly, proteinuria and impaired kidney function may be markers of endothelial dysfunction, inflammation, or severity of vascular disease, including atherosclerosis that is not yet clinically evident.<sup>30–35</sup> Finally, patients with proteinuria and impaired kidney function may be more likely to have clinically relevant kidney disease than those with either characteristic alone.

Our findings indicate that studies of the relation between chronic kidney disease and death should consider stratifying patients on the presence or absence of proteinuria (and studies evaluating the risk associated with proteinuria should stratify on kidney function). The proportion of patients with proteinuria may have varied in previous studies examining this issue; this might partly explain the heterogeneity in the reported size of the association between chronic kidney disease and death.<sup>31</sup>

### Strengths and limitations of the study

In the CARE study, outcomes were measured according to pre-specified criteria by people who were unaware of kidney function or the results of urinalysis. We also adjusted for many potential confounders, including comorbidity, use of drugs, left ventricular ejection fraction, and other laboratory results, which reduced the risk of bias. However, our study does have limitations. Firstly, although the analysis was retrospective, the study hypothesis was formulated before starting analyses. Secondly, we analysed a selected population (clinically stable survivors of myocardial infarction) that may not be representative of the general population. Thirdly, we did not determine the cause of renal dysfunction in the participants.

Fourthly, baseline dipstick urinalysis and measurements of serum creatinine were performed only once, but the resulting loss of precision (compared with measuring more than once) would be expected to bias towards the null, so that the true relation between proteinuria, impaired kidney function, and death is probably stronger than our findings indicate. However, the use of dipstick urinalysis probably resulted in a stronger association between proteinuria and adverse outcomes than if a more sensitive marker of urinary protein had been used.

Fifthly, although serum creatinine was measured in a central laboratory, we did not calibrate our GFR assay against the reference laboratory assay used to develop the GFR equation. This may have led to misclassification of some patients with respect to disease status, which again would be expected to bias towards the null. Finally, the number of participants in some groups (especially the group with proteinuria and impaired kidney function) was small.

Natasha Wiebe (research associate, University of Alberta) performed statistical analyses and a detailed statistical review. Thanks to Tim Craven for his assistance. The CARE study was initiated by the investigators and was funded by Bristol-Myers-Squibb. This study was not supported by industry. Contributors: MP had the idea for the analysis, and MT designed the detailed analysis plan, with input from MP and GC. MT wrote the first draft and is guarantor. All authors helped to interpret the data and to revise the article.

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Competing interests: None declared.

Ethical approval: The institutional review board at the University of Alberta, Canada.

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### What is already known on this topic

Many studies have shown that impaired kidney function and proteinuria are risk factors for all cause mortality and cardiovascular events

Data are lacking on how these common laboratory tests can be used together to predict risk

### What this study adds

Higher risk of mortality was associated with heavier proteinuria on dipstick urinalysis and lower kidney function, and the risk associated with these conditions was additive

The results of kidney function tests and urinalysis improve the accuracy of estimates of risk

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