

# 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

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> 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, 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>

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.

## Methods

### Study design and patients

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>15 16</sup> See [bmj.com](http://bmj.com).

### 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 measured baseline serum creatinine in fasting participants and estimated GFR (see [bmj.com](http://bmj.com) for equation).

### Study outcomes

The primary outcome was all cause mortality. Secondary outcomes were developing symptomatic congestive heart failure, ischaemic or non-ischaemic stroke, the composite of fatal coronary disease, or non-fatal myocardial infarction confirmed by measuring serum creatine kinase.

### 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. See [bmj.com](http://bmj.com) for a priori decisions about potential confounders adjusted for all multivariate models. We used the mean of covariates method to produce adjusted survival curves for these final models. We also evaluated whether risk increased with increasing severity of proteinuria. See [bmj.com](http://bmj.com) for full details.



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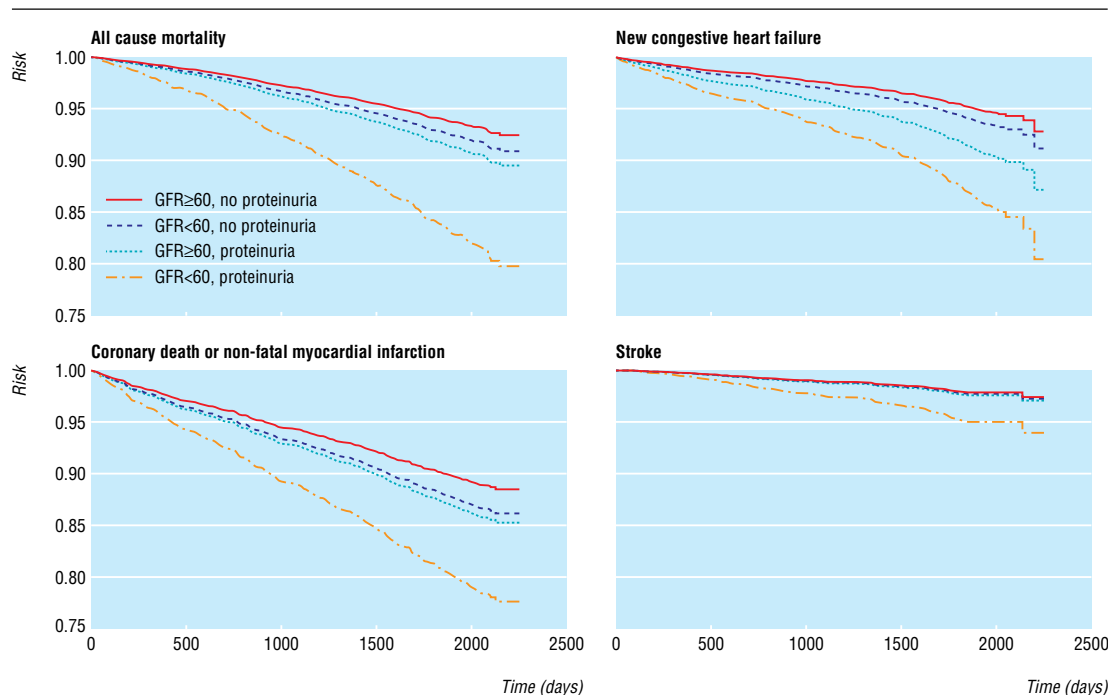


Fig 1 Time to clinical outcomes by proteinuria and kidney dysfunction

## Results

### Baseline characteristics

Of 4159 participants, 4098 (98.5%) had serum creatinine and proteinuria measured at baseline and were eligible for analysis. See [bmj.com](http://bmj.com) for 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 1). Impaired kidney function and proteinuria

were independently associated with all cause mortality when entered separately into the fully adjusted model. Participants with both characteristics were at highest risk, and participants with neither characteristic were at lowest risk (table 1; 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  $< 0.001$ ) (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.

### Association with other adverse clinical outcomes

Results were similar for other adverse outcomes (table 1; fig 1). 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  $\chi^2$ ), and tests for interaction were non-significant (all  $P > 0.15$ ).

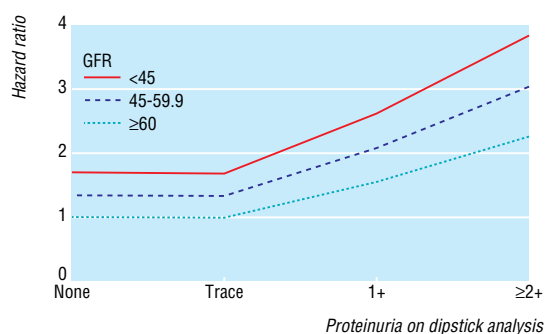


Fig 2 Adjusted risk of all cause mortality according to proteinuria and kidney dysfunction

## 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. 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. We also found a dose effect for proteinuria and kidney dysfunction. Thus the

presence or absence of proteinuria on routine urinalysis could help refine estimates of risk that are based on kidney function alone.

### Comparison with other studies

Many studies with a wide range of participants have found an association between adverse outcomes and kidney dysfunction. Several studies have shown an association between urinary protein excretion (overt proteinuria and microalbuminuria) 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. 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. Secondly, patients with renal disease might be less likely to receive beneficial treatments. Although we controlled for these two factors, we cannot exclude the possibility of residual 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. 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.

### Strengths and limitations of the study

Outcomes were measured according to prespecified criteria by people who were unaware of kidney function or the results of urinalysis. We also adjusted for many potential confounders. 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.

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).

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.

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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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## Double trouble

A middle aged woman was admitted late in the night with diarrhoea and vomiting. Just a few hours previously she had lost her husband due to a massive myocardial infarction. Before she could digest this unexpected and shocking event, she had fallen sick. She was severely dehydrated and had intermittent colicky pain. In spite of adequate intravenous fluids and antibiotics, she did not recover much and became drowsy. Meanwhile, her son, who had recently arrived at the parental home from afar to attend the funeral, was brought to the hospital with the same complaint.

I could not explain this situation on the basis of infection or food poisoning; mother and son lived apart, and neither had taken any food together except fresh lime juice. Then, a relative told me that their lime juice had been prepared in a copper utensil. Now, I could corroborate an earlier suspicion about heavy metal poisoning.

Copper itself is not poisonous, but weak acids such as vinegar or certain fruit juices may react with copper to produce copper acetate (verdigris). Food contaminated with verdigris from dirty copper vessels is poisonous. The inside of copper utensils is normally lined with a thin layer of tin to prevent food coming in contact with the copper. Accidental poisoning can be avoided by regularly checking for erosion of the tin layer and by avoiding drinking fruit juice or wine kept in copper utensils. In the light of the fashion to decorate kitchens with antique copper utensils, awareness of this relatively rare form of poisoning is perhaps increasingly relevant.

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