Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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Abstract

Aims/hypothesis We investigated effects of renal function and albuminuria on cardiovascular outcomes in 9,795 low-risk patients with diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.

Methods Baseline and year 2 renal status were examined in relation to clinical and biochemical characteristics. Out-

comes included total cardiovascular disease (CVD), cardiac and non-cardiac death over 5 years.

Results Lower estimated GFR (eGFR) vs eGFR ≥ 90 ml min⁻¹ 1.73 m⁻² was a risk factor for total CVD events: (HR [95% CI] 1.14 [1.01–1.29] for eGFR 60–89 ml min⁻¹ 1.73 m⁻²; 1.59 [1.28–1.98] for eGFR 30–59 ml min⁻¹ 1.73 m⁻²; $p < 0.001$; adjusted for other characteristics). Albuminuria in-

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creased CVD risk, with microalbuminuria and macroalbuminuria increasing total CVD (HR 1.25 [1.01–1.54] and 1.19 [0.76–1.85], respectively; $p=0.001$ for trend) when eGFR ≥ 90 ml min⁻¹ 1.73 m⁻². CVD risk was further modified by renal status changes over the first 2 years. In multivariable analysis, 77% of the effect of eGFR and 81% of the effect of albumin:creatinine ratio were accounted for by other variables, principally low HDL-cholesterol and elevated blood pressure.

Conclusions/interpretation Reduced eGFR and albuminuria are independent risk factors for cardiovascular events and mortality rates in a low-risk population of mainly European ancestry. While their independent contributions to CVD risk appear small when other risk factors are considered, they remain excellent surrogate markers in clinical practice because they capture risk related to a number of other characteristics. Therefore, both should be considered when assessing prognosis and treatment strategies in patients with diabetes, and both should be included in risk models.

Keywords Albuminuria · Cardiovascular risk · Diabetes · Diabetic nephropathy · Fenofibrate · Glomerular filtration rate · Risk factors

Abbreviations

ACR	Albumin:creatinine ratio
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated GFR
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
MDRD	Modification of Diet in Renal Disease
UKPDS	UK Prospective Diabetes Study

Introduction

Chronic kidney disease (CKD), based on estimated GFR (eGFR), predicts cardiovascular events in the general population [1, 2]. Several studies of type 2 diabetes have shown an association between CKD, proteinuria and cardiovascular disease (CVD) prevalence [3] and risk [4–11]. However, many of these studies were small and did not examine the independent effects of microalbuminuria, macroalbuminuria and eGFR. They were also performed in different patient populations for a variety of outcomes. Recent reports suggest that reduced renal function in people with diabetes, based on eGFR, is more common than

previously recognised [12] and that CKD is often not associated with albuminuria, as was previously assumed [13].

Because there have been few investigations of large prospective series of patients with type 2 diabetes, we examined the predictive value of eGFR and albuminuria in the Fenofibrate Intervention and Event Lowering in Diabetes study (FIELD), which was conducted in Australia, New Zealand and Finland [14, 15]. Patients were largely recruited from the community, did not have severe renal impairment and were at relatively low CVD risk. We examined the relationships of baseline renal function and albuminuria with all-cause mortality rates, CVD and non-CVD endpoints and death in this large population of predominantly European origin. Follow-up exceeded 99% over a median of 5 years. Biochemical analyses were done at central laboratories and an Outcomes Committee using pre-specified definitions adjudicated all endpoints.

Methods

Study design FIELD was a double-blind placebo-controlled trial of 200 mg once-daily micronised fenofibrate or placebo in 9,795 patients. Details of the design and main outcome measures have been published [14, 15]. In brief, patients were aged 50 to 75 years old, had type 2 diabetes according to the WHO criteria and mild dyslipidaemia with no immediate indication at study entry for lipid-modifying therapy (inclusion criteria).

Exclusion criteria included elevated plasma creatinine >130 μ mol/l, chronic liver or gallbladder disease or a CVD event within the 3 months before recruitment. All patients with National Kidney Foundation CKD stage 5 (eGFR <15 ml min⁻¹ 1.73 m⁻²) and stage 4 (eGFR 15 – 29 ml min⁻¹ 1.73 m⁻²), and some with stage 3 (GFR 30 – 59 ml min⁻¹ 1.73 m⁻²) of the disease were therefore excluded [16]; only one patient had an entry eGFR below 40 ml min⁻¹ 1.73 m⁻² (Fig. 1). For the purposes of classification, patients were placed in one of three groups, with groups 1, 2 and 3 having eGFR ranges of ≥ 90 , 60–89 and 30–59 ml min⁻¹ 1.73 m⁻² respectively. The entry criteria led to a group with low CVD risk, in which the total mortality rate over 5 years was only 6.9%, an average rate of 1.4% per year. In a cohort with a mean age of 62 years, this was substantially less than predicted on the basis of other studies [17–19]. Although fenofibrate lowered total cardiovascular events (by 11%, $p=0.035$) and various microvascular outcomes [14], there were no significant differences in the primary endpoint (total coronary events) or death (total or cardiovascular related) between the placebo and active treatment groups.

Primary responsibility for all other aspects of patient care, such as control of glycaemia, blood pressure and eye

Fig. 1 Enrolment and progress of patients in the FIELD study, grouped by renal function

care, remained with the existing healthcare provider. No central targets were set for these measures.

All patients gave written informed consent to the protocol, which was approved by local and national ethics committees in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (clinical trials registration no. ISRCTN 64783481).

Outcome ascertainment An outcomes assessment committee, unaware of treatment allocation, adjudicated all deaths and major cardiovascular events (myocardial infarction and stroke). Detailed criteria for these assessments have been published [14]. At study close, mortality status was confirmed for 99.7% and the primary outcome status for 99.1% of participants in both groups.

Laboratory measurements Plasma creatinine and urinary albumin:creatinine ratio (ACR) (first morning urine specimen) were recorded as the average of two baseline measurements before the active treatment run-in phase (visits 1 and 3). Estimated GFR was calculated using the 4-variable Modification of Diet in Renal Disease study (MDRD) equation: $\text{eGFR (ml min}^{-1} \text{ 1.73 m}^{-2}) = 186 \times (\text{plasma creatinine } [\mu\text{mol/l}] \text{ divided by } 88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$ [20]. All blood and urine samples were

analysed in one of two central laboratories in Adelaide, Australia and Helsinki, Finland, both of which participated in a joint quality assurance scheme to ensure consistency between laboratories.

Blood and urinary creatinine measurements were made with alkaline picrate (Hitachi 917; Roche, Mannheim, Germany) in Australia and using Jaffe's photometric method (Cobas Mira; Roche, Basel, Switzerland) in Finland. Urinary albumin was measured by immunoturbidimetric methods (Beckman Array, Beckman-Coulter, Fullerton, CA, USA [in Australia]; Cobas Mira, Roche [in Finland]). The between-run coefficients of variation for plasma creatinine and urinary creatinine were <3% and <1.5%, respectively. The between-run coefficients of variation for urinary albumin were <3% across the quality control range.

For the purposes of this report, microalbuminuria was defined as >2.5 mg/mmol for men and >3.5 mg/mmol for women; equivalent values for macroalbuminuria were >25 and >35 mg/mmol, respectively [21].

Statistical analysis All analyses used SAS statistical software (version 9.1, SAS Institute; Cary, NC, USA) or ACCORD (version 2; Boffin Software, Eastwood, NSW, Australia). Contrast and trend tests for baseline characteristics were analysed using χ^2 tests for binary variables, and t tests and ANOVA for continuous variables. If the distribution of the data was not normal, log-transformation was applied to achieve normality. Cox proportional hazards analysis was used to compute hazard ratios and 95% CIs to assess the effect of albuminuria on mortality outcomes. Although study treatment did not significantly reduce the primary endpoint of CHD events (non-fatal myocardial infarction and coronary death) or death, total CVD events, revascularisation, hospitalisation for acute coronary syndrome and major microvascular outcomes were significantly lowered. For consistency, we analysed all associations between clinical endpoints and baseline data (before the 6-week active fenofibrate run-in phase) from all 9,795 patients with adjustment for study treatment group. In adjusted analyses, the log of ACR was used as a continuous covariate and age was included as there was little collinearity between age and eGFR, despite age being part of the MDRD calculation. Cumulative risk curves of the time to first event were calculated using the Kaplan–Meier method. In analyses involving only the placebo group, Kaplan–Meier curves were constructed on the basis of baseline renal status up until 2 years, after which a landmark analysis from this point using updated renal status (remained normal/abnormal or changed) was performed. Additionally, the Harrell–Lee c-index [22] was used to quantify the global performance of the various risk models for CVD that were identified by an exhaustive search Cox regression analysis [23]. This allowed identifi-

cation of the contribution of other risk variables to the improvement in global performance that was attributable to either eGFR or albuminuria. All statistical inferences use a two-sided *p* value of 0.05 and are presented unadjusted for multiple comparisons.

Results

Clinical and metabolic characteristics at baseline The mean age in FIELD was 62 years, with mean diabetes duration of 5 years and 37% women participants. The median urinary ACR was 1.1 mg/mmol, with 95% of

patients having an eGFR $>60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ [14]. Mean glycaemic control at baseline was near standard target level (HbA_{1c} 6.9%) and blood pressure averaged 140/84 mmHg.

The 519 group 3 patients (eGFR 30–59 $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) were more likely than the 9,276 group 1 and 2 patients (eGFR $\geq 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) to be women and older, and to have longer diabetes duration and higher blood pressure (Table 1). They also had significantly higher incidences of retinopathy, microalbuminuria and macroalbuminuria. Compared with groups 1 and 2, group 3 participants had significantly lower fasting serum glucose levels, whereas total cholesterol, triacylglycerol and urine ACR were significantly higher. The rate of ACE inhibitor

Table 1 Clinical and metabolic characteristics of the FIELD population at baseline, by eGFR group

Variable	Group 1 eGFR ≥ 90 ^a	Group 2 eGFR 60–89 ^a	Group 3 eGFR 30–59 ^a	All	<i>p</i> value ^b
<i>n</i>	4,058	5,218	519	9,795	
Men (%)	66	62	41	63	<0.001 ^c
Age (years)	60.2 (6.7)	63.4 (6.7)	66.5 (5.9)	62.2 (6.9)	<0.001 ^c
Duration of diabetes (years) ^c	4.8 (4.7–5.0)	5.1 (4.9–5.2)	6.0 (5.5–6.5)	5.0 (4.9–5.1)	<0.001 ^c
BMI (kg/m^2) ^c					
Women	32.2 (31.9–32.5)	31.2 (31.0–31.5)	31.5 (30.9–32.2)	31.6 (31.4–31.8)	0.7
Men	29.7 (29.5–29.9)	29.1 (29.0–29.3)	29.2 (28.6–29.8)	29.4 (29.3–29.5)	0.6
Systolic BP (mmHg)	139 (15)	141 (15)	144 (17)	141 (15)	<0.001 ^c
Current smoker (%)	12	8	7	9	0.05 ^c
Ex-smoker (%)	52	50	42	50	<0.001 ^c
Retinopathy (%)	7	9	13	8	<0.001 ^c
Prior cancers (%)	6	8	12	7	<0.001 ^c
Laboratory data					
Fasting PG (mmol/l) ^c	8.8 (8.7–8.8)	8.5 (8.4–8.5)	8.2 (8.0–8.4)	8.6 (8.5–8.6)	<0.001 ^c
Total cholesterol (mmol/l)	5.02 (5.00–5.04)	5.04 (5.02–5.06)	5.11 (5.05–5.17)	5.04 (5.02–5.05)	0.02 ^d
HDL-cholesterol (mmol/l) ^c	1.07 (1.06–1.07)	1.07 (1.06–1.08)	1.06 (1.03–1.08)	1.07 (1.06–1.07)	0.2
LDL-cholesterol (mmol/l)	3.06 (3.04–3.08)	3.07 (3.05–3.09)	3.07 (3.02–3.13)	3.07 (3.05–3.08)	0.8
Triacylglycerol (mmol/l) ^c	1.76 (1.74–1.78)	1.79 (1.77–1.81)	1.91 (1.85–1.98)	1.78 (1.77–1.80)	<0.001 ^c
HbA _{1c} (%) ^c	7.0 (6.9–7.0)	6.9 (6.9–6.9)	7.0 (6.9–7.1)	6.9 (6.9–7.0)	0.2
Urine ACR (mg/mmol)	1.1 [0.6–2.8]	1.1 [0.6–2.8]	1.9 [0.8–8.7]	1.1 [0.6–3.0]	<0.001 ^c
Normal ACR, <i>n</i> (%) ^f	3,026 (75)	3,927 (75)	307 (59)	7,260 (74)	<0.001 ^c
Microalbuminuria, <i>n</i> (%)	890 (22)	1,068 (21)	146 (28)	2,104 (22)	<0.001 ^c
Macroalbuminuria, <i>n</i> (%)	126 (3)	213 (4)	65 (13)	404 (4)	<0.001 ^c
Baseline medication					
Use of RAAS inhibitors (%)	37	38	55	39	<0.001 ^c

Values are mean (SD), mean (95% CI) or median [interquartile range] unless otherwise indicated

^a In $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$

^b Compares eGFR 30–59 group (stage 3) with other two combined

^c Distribution skewed, so analyses used log-transformed data, reported as geometric means (95% CI)

^d $p < 0.05$ for trend; ^e $p < 0.001$ for trend

^f Baseline albuminuria levels not available for 27 (0.3%) patients

PG, plasma glucose; RAAS, renin–angiotensin–aldosterone system

or angiotensin-receptor blocker use was also higher in this group. At baseline, 2,508 (26%) patients had albuminuria and 5,737 (59%) had eGFR $30\text{--}89\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$. Only a small number had macroalbuminuria (404, 4%) or eGFR $30\text{--}59\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ (519, 5%), and no patients had eGFR $<30\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$. These measures of kidney disease were largely independent, with almost 80% of those with renal impairment being normoalbuminuric and 40% of those with abnormal albuminuria having eGFR $>90\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ (Correlation coefficient $r=-0.05$; $p<0.001$) (Table 1).

Clinical outcomes for participants with a reduced eGFR Total CVD and coronary event rates during the study were progressively higher with greater baseline renal impairment, as were non-fatal stroke and myocardial infarction (Table 2). Death rates due to CVD, CHD, stroke, non-CHD causes, non-CVD causes, cancer and all causes also followed the same trend. When adjusted for age, sex and allocated study treatment, the higher risk remained significant for CVD and CHD events, CVD or non-CHD death, and death from all causes (Table 3). Adjusted for the six outcomes, there was no evidence of any treatment $\times$ subgroup interaction. When risk in a multivariable model was adjusted additionally for a range of clinical and biochemical baseline characteristics, rates of total CVD

events, CVD death, non-coronary death and death from all causes remained significantly higher with greater renal impairment (Table 3). These patterns were similar within each level of urinary albumin group (Tables 4 and 5, Fig. 2a). The hazard ratio for eGFR $<60\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ vs eGFR $\geq 60\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ was 1.44 (95% CI 1.18–1.76; $p<0.001$) for total CVD, 2.00 (95% CI 1.41–2.84; $p<0.001$) for CVD death and 1.66 (95% CI 1.30–2.11; $p<0.001$) for overall mortality. No eGFR group had significantly greater CVD risk reduction than any other group from treatment with fenofibrate.

In multivariable analysis (placebo group), eGFR remained an independent risk factor for CVD, exclusive of age and sex ($p=0.0006$). Nevertheless, 77% of its univariable association with CVD risk was accounted for by the other variables in the full model, most importantly, HDL-cholesterol alone (about 39%), and together with systolic blood pressure (about 71%).

Analysed continuously, for each $10\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ lower baseline eGFR, the risk of a CVD event, CVD death or death from all causes was inversely linearly related, being 6%, 10% and 4% higher over the subsequent 5 years ($p<0.001$, $p=0.01$ and $p=0.08$, respectively).

Among placebo patients, those with eGFR $<60\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ at baseline and year 2 had the greatest total CVD risk, while those with eGFR $\geq 60\text{ ml min}^{-1}\text{ }1.73\text{ m}^{-2}$ over

Table 2 Cardiovascular outcomes, by eGFR group, in patients in the FIELD study

Variable	Group 1 $\geq 90^a$	Group 2 $60\text{--}89^a$	Group 3 $30\text{--}59^a$	All
<i>n</i>	4,058	5,218	519	9,795
Cardiovascular events ($n=1,295$)				
Any	10.8 (9.9–11.8)	14.1 (13.2–15.1)	22.5 (18.9–26.1)	13.2 (12.6–13.9)
CHD event	4.4 (3.8–5.1)	6.0 (5.4–6.7)	9.3 (7.1–12.2)	5.5 (5.1–6.0)
Any stroke	2.7 (2.2–3.2)	3.4 (3.0–3.9)	8.3 (5.9–10.7)	3.4 (3.0–3.8)
Deaths ($n=679$)				
Cardiovascular	2.0 (1.5–2.4)	2.7 (2.3–3.2)	8.5 (6.1–10.9)	2.7 (2.4–3.0)
CHD	1.5 (1.2–2.0)	2.3 (1.9–2.7)	3.9 (2.5–6.0)	2.1 (1.8–2.4)
Stroke	0.2 (0.1–0.4)	0.2 (0.1–0.4)	3.0 (1.8–4.9)	0.4 (0.3–0.5)
Non-CHD	3.8 (3.2–4.4)	5.0 (4.4–5.6)	12.1 (9.3–14.9)	4.9 (4.4–5.3)
Non-cardiovascular	3.4 (2.8–4.0)	4.5 (3.9–5.0)	7.5 (5.5–10.2)	4.2 (3.8–4.6)
Cancer	2.7 (2.2–3.2)	3.4 (2.9–3.9)	5.5 (3.8–7.8)	3.2 (2.9–3.6)
Non-cardiovascular, non-cancer	0.7 (0.4–0.9)	1.1 (0.8–1.4)	2.1 (0.9–3.4)	1.0 (0.8–1.2)
Any cause	5.4 (4.7–6.1)	7.2 (6.5–7.9)	16.4 (13.4–19.8)	6.9 (6.4–7.4)
Non-fatal events ($n=633$)				
Stroke	2.5 (2.0–3.0)	3.2 (2.8–3.7)	5.5 (3.8–7.8)	3.1 (2.7–3.4)
Myocardial infarction	2.9 (2.4–3.5)	4.1 (3.6–4.7)	5.8 (3.8–7.8)	3.7 (3.4–4.1)

Values are per cent (95% CI) of participants experiencing an event, unless otherwise indicated

$p\leq 0.002$ for all outcomes in trend tests across levels of eGFR; $p\leq 0.01$ for all outcomes in comparisons of eGFR $30\text{--}59$ (group 3) with the other two groups combined

^a In $\text{ml min}^{-1}\text{ }1.73\text{ m}^{-2}$

Table 3 Hazard ratios (95% CI) for outcomes, by eGFR group^a, in patients in the FIELD study^b

Variable	Group 1 ≥90 ^c	Group 2 60–89 ^d	Group 3 30–59 ^e	<i>p</i> value
<i>n</i>	4,058	5,218	519	
Cardiovascular event				
Adjusted for age, sex and treatment	1.00	1.15 (1.02–1.30)	2.01 (1.62–2.48)	<0.001
Multivariable model ^f	1.00	1.14 (1.01–1.29)	1.59 (1.28–1.98)	<0.001
CHD event				
Adjusted for age, sex and treatment	1.00	1.14 (0.94–1.38)	1.76 (1.26–2.45)	0.004
Multivariable model ^f	1.00	1.13 (0.94–1.37)	1.27 (0.90–1.79)	0.3
Cardiovascular death				
Adjusted for age, sex and treatment	1.00	1.08 (0.81–1.42)	3.09 (2.09–4.57)	<0.001
Multivariable model ^f	1.00	1.05 (0.79–1.40)	2.08 (1.39–3.12)	<0.001
Non-coronary death				
Adjusted for age, sex and treatment	1.00	0.99 (0.81–1.22)	2.20 (1.62–3.00)	<0.001
Multivariable model ^f	1.00	1.01 (0.82–1.24)	1.97 (1.43–2.70)	<0.001
Cancer death				
Adjusted for age, sex and treatment	1.00	0.95 (0.74–1.21)	1.41 (0.92–2.16)	0.15
Multivariable model ^f	1.00	0.96 (0.75–1.23)	1.28 (0.83–1.98)	0.4
Death from any cause				
Adjusted for age, sex and treatment	1.00	1.02 (0.86–1.21)	2.08 (1.60–2.71)	<0.001
Multivariable model ^f	1.00	1.03 (0.86–1.22)	1.69 (1.29–2.22)	<0.001

^a Group with eGFR ≥90 ml min⁻¹ 1.73 m⁻² is the reference group

^b Tests of interaction between eGFR group and treatment were non-significant except for CVD death

^c Median eGFR (ml min⁻¹ 1.73 m⁻²): 101.7 (95.3–111.2)

^d Median eGFR (ml min⁻¹ 1.73 m⁻²): 78.4 (72.0–84.2)

^e Median eGFR (ml min⁻¹ 1.73 m⁻²): 55.5 (51.6–58.0)

^f Multivariable model adjusted for age, sex, duration of diabetes, smoking status, BMI, systolic BP, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, triacylglycerol, diabetic retinopathy, treatment with ACE inhibitors or angiotensin-receptor blockers, treatment group and log of the ACR (as a continuous covariate)

the same timeframe had the least ($p<0.001$). In participants whose eGFR status changed between the two time-points, CVD risk appeared to be intermediate, with a change in eGFR from ≥60 ml min⁻¹ 1.73 m⁻² at baseline to <60 ml min⁻¹ 1.73 m⁻² at year 2 showing greater risk than the converse, although this was not statistically significant ($p=0.76$) (Fig. 3a). The risk of a CVD event after progressing to eGFR <30 ml min⁻¹ 1.73 m⁻² vs maintaining eGFR ≥30 ml min⁻¹ 1.73 m⁻² was not significantly different (13.0% vs 13.7%, respectively), but only 69 placebo participants deteriorated to this level at any time, and only seven prior to their first CVD event.

Clinical outcomes for participants with albuminuria The effect of albuminuria was examined before and after adjustment for a variety of baseline characteristics. Across all three eGFR groups, hazard ratios for patients with albuminuria were consistently higher than for those without (Fig. 2a, Table 4). Even after adjustment for multiple known risk factors, there were significant, graded hazard

ratios for microalbuminuria and macroalbuminuria across almost all levels of eGFR (Tables 4 and 5), except for cancer death. For example, group 3 patients with microalbuminuria or macroalbuminuria had a higher risk of a coronary event, CVD death, death from all causes or a CVD event than group 3 normoalbuminuric patients ($p<0.05$ for trend for all) (Table 4). The CVD risk for patients with eGFR >90 ml min⁻¹ 1.73 m⁻² and albuminuria was almost the same as for those who were normoalbuminuric with eGFR 30–59 ml min⁻¹ 1.73 m⁻² and was significantly higher than for those who were normoalbuminuric without renal impairment. The highest risk category was group 3 patients with co-existent albuminuria (Fig. 2a, b). Subgroup analyses according to albuminuria level overall failed to show any significant treatment × subgroup interactions.

The pooled hazard ratio for all albuminuria vs normoalbuminuria was 1.31 (95% CI 1.16–1.48; $p<0.001$) for total CVD and 1.46 (95% CI 1.24–1.72; $p<0.001$) for death, both after baseline adjustment. Analysed continuously, for each 5 mg/mmol higher urinary ACR, the risk of a CVD

Table 4 Adjusted hazard ratios (95% CI) for primary and secondary outcomes, by eGFR and albuminuria^{a,b}

Variable	Total (<i>n</i>)	Group 1 ≥90 ^c	Group 2 60–89 ^c	Group 3 30–59 ^c	<i>p</i> value for trend ^d	
					Albuminuria	eGFR
<i>n</i>		4,042	5,208	518		
Cardiovascular events	1,290					
No albuminuria	800	1.00	1.11 (0.95–1.29)	1.63 (1.20–2.20)	0.001	<0.001
Microalbuminuria	382	1.25 (1.01–1.54)	1.43 (1.18–1.72)	1.94 (1.37–2.73)		
Macroalbuminuria	108	1.19 (0.76–1.85)	1.77 (1.33–2.36)	2.30 (1.48–3.55)		
CHD events	541					
No albuminuria	311	1.00	1.07 (0.84–1.36)	1.20 (0.72–2.01)	<0.001	0.13
Microalbuminuria	163	1.26 (0.91–1.76)	1.47 (1.10–1.96)	1.87 (1.12–3.13)		
Macroalbuminuria	67	2.00 (1.15–3.47)	2.65 (1.81–3.89)	2.43 (1.28–4.59)		
Cardiovascular deaths	266					
No albuminuria	137	1.00	1.17 (0.80–1.72)	2.36 (1.29–4.31)	<0.001	0.004
Microalbuminuria	87	1.73 (1.08–2.77)	1.38 (0.88–2.15)	2.96 (1.59–5.51)		
Macroalbuminuria	42	1.89 (0.83–4.27)	2.59 (1.49–4.50)	5.26 (2.73–10.15)		
Non-CHD deaths	475					
No albuminuria	292	1.00	1.08 (0.83–1.40)	2.40 (1.58–3.64)	0.02	0.004
Microalbuminuria	145	1.63 (1.15–2.29)	1.42 (1.04–1.96)	2.19 (1.29–3.73)		
Macroalbuminuria	38	1.52 (0.70–3.31)	1.52 (0.90–2.57)	3.83 (2.11–6.98)		
Cancer deaths	315					
No albuminuria	202	1.00	1.01 (0.75–1.36)	1.44 (0.81–2.57)	0.32	0.55
Microalbuminuria	93	1.42 (0.94–2.15)	1.26 (0.86–1.84)	1.71 (0.87–3.38)		
Macroalbuminuria	20	1.54 (0.61–3.87)	1.24 (0.64–2.40)	1.58 (0.57–4.40)		
Death from any cause	677					
No albuminuria	397	1.00	1.10 (0.88–1.37)	1.93 (1.32–2.82)	<0.001	0.005
Microalbuminuria	209	1.60 (1.20–2.14)	1.36 (1.04–1.78)	2.25 (1.46–3.46)		
Macroalbuminuria	71	1.71 (0.96–3.06)	2.10 (1.44–3.05)	3.48 (2.12–5.73)		

^a Group with eGFR ≥90 and no albuminuria is the reference group; baseline albuminuria levels not available for 27 (0.3%) patients

^b Baseline adjustment for age, sex, duration of diabetes, smoking, BMI, systolic BP, HbA_{1c}, HDL-cholesterol, LDL-cholesterol, triacylglycerol, retinopathy, renin–angiotensin–aldosterone inhibition and treatment group

^c In ml min⁻¹ 1.73 m⁻²

^d Trend tests across increasing levels of albuminuria are stratified by eGFR group and vice versa

event, CVD death or death from all causes was inversely linearly related, being 1%, 3% and 3% higher over the subsequent 5 years, respectively (all $p < 0.002$).

Among placebo patients, those with albuminuria at baseline and year 2 had the greatest total CVD risk, while those who were normoalbuminuric over the same time-frame had the least risk (Fig. 3b). In participants whose albuminuria status changed between these two time-points, the CVD risk was also modified. In them, the development of albuminuria from baseline to year 2 increased risk compared with those who remained normoalbuminuric ($p = 0.006$), whereas regression from albuminuria to normoalbuminuria carried significantly lower CVD risk compared with its persistence ($p = 0.01$).

In multivariable analysis, albuminuria remained an independent risk factor for CVD ($p = 0.0008$). Similar to eGFR, about 81% of its univariate association with CVD

risk was accounted for by the other variables in the full model. Again, the most important of these was HDL-cholesterol alone (about 37%) and together with systolic blood pressure (about 70%).

Discussion

This study confirms and extends previous findings of independent relationships between reduced baseline eGFR, albuminuria and subsequent CVD event rates to a large low-risk, mainly Europid population with type 2 diabetes. The FIELD cohort was between CKD stages 1 to 3 at baseline, with few having prior myocardial infarction, yet there was a strong progressive relationship between lower GFR and death from all causes, particularly CVD-related. This persisted despite correction for

Table 5 Counts and percentages of events per eGFR group

Type of event (no. of events)	Total (<i>n</i>)	Group 1		Group 2		Group 3	
		$\geq 90^a$		60–89 ^a		30–59 ^a	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Cardiovascular event	1,290						
No albuminuria	800	284	9.4	463	11.8	53	17.3
Microalbuminuria	382	131	14.7	211	19.8	40	27.4
Macroalbuminuria	108	22	17.5	63	29.6	23	35.4
CHD event	541						
No albuminuria	311	112	3.7	181	4.6	18	5.9
Microalbuminuria	163	53	6.0	92	8.6	18	12.3
Macroalbuminuria	67	15	11.9	41	19.2	11	16.9
Cardiovascular death	266						
No albuminuria	137	42	1.4	79	2.0	16	5.2
Microalbuminuria	87	31	3.5	41	3.8	15	10.3
Macroalbuminuria	42	7	5.6	22	10.3	13	20.0
Non-CHD death	475						
No albuminuria	292	94	3.1	165	4.2	33	10.7
Microalbuminuria	145	53	6.0	75	7.0	17	11.6
Macroalbuminuria	38	7	5.6	18	8.5	13	20.0
Cancer death	315						
No albuminuria	202	71	2.3	116	3.0	15	4.9
Microalbuminuria	93	34	3.8	49	4.6	10	6.8
Macroalbuminuria	20	5	4.0	11	5.2	4	6.2
Death from any cause	677						
No albuminuria	397	129	4.3	230	5.9	38	12.4
Microalbuminuria	209	76	8.5	106	9.9	27	18.5
Macroalbuminuria	71	13	10.3	39	18.3	19	29.2

Percentages are of the number of people as defined by eGFR and albuminuria grouping as listed in Table 1

^a In ml min⁻¹ 1.73 m⁻²

age and multiple known related factors, with large variations in associated risk. The correlation of the same outcomes with albuminuria within each eGFR group confirmed its independent value as a CVD risk marker, even as a categorical variable.

The FIELD results also demonstrate that changing renal status over several years further modifies subsequent CVD risk. These novel findings underscore the clinical importance of early initiation of treatments known to prevent the renal complications of diabetes in patients considered to be at risk, as well as initiation of efforts to reverse existing renal disease.

Although eGFR and albuminuria are significant independent CVD risk predictors, their contribution to overall risk, when other cardiovascular risk factors are taken into account, is diminished. However, as simple risk markers in clinical practice, they are highly predictive with a doubling of CVD risk in patients with eGFR 30–59 ml min⁻¹ 1.73 m⁻² or macroalbuminuria compared with normal renal status. Thus, eGFR and albuminuria remain excellent surrogate markers of CVD risk because they capture risk related to a number of other characteristics. It is well

documented that much of their association with CVD might be explained by differences in HDL-cholesterol and systolic blood pressure, with low HDL-cholesterol and raised blood pressure being both causes and effects of worsening renal disease [24–26].

A reduced GFR may be associated with an increased level of non-traditional CVD risk factors that are frequently not assessed in many studies. Non-traditional factors such as hyperhomocysteinaemia, oxidant stress and elevated inflammatory markers are associated with atherosclerosis and may be additional contributors to the high incidence of CVD in CKD [27, 28]. Reduced GFR may also be a marker of severity or of undiagnosed vascular disease, and may itself be a risk factor for progression of ventricular remodelling and cardiac dysfunction beyond its direct effects on blood pressure [29]. Furthermore, recent studies suggest that participants with reduced GFR are less likely to receive medications or therapies including cardio-protective ones, compared with those with preserved GFR [30–32].

Albuminuria may reflect generalised endothelial dysfunction and increased vascular permeability, or abnormal-

Fig. 2 **a** Cardiovascular risk for eGFR groups, according to presence of baseline albuminuria. Continuous lines indicate albuminuria present, dotted lines indicate no albuminuria. Red, eGFR 30–59 ml min⁻¹ 1.73 m⁻²; blue, eGFR 60–89 ml min⁻¹ 1.73 m⁻²; green, eGFR ≥90 ml min⁻¹ 1.73 m⁻². **b** Cardiovascular risk of eGFR groups, according to presence or not of baseline micro- and macroalbuminuria

ities in the coagulation and fibrinolytic systems. It is also associated with elevated inflammatory markers and may denote greater severity of end-organ damage [33–35]. Therefore, even after adjusting for the presence of CVD, patients with albuminuria are likely to have more severe disease [29].

In CKD atherosclerosis and large-vessel remodelling (arteriosclerosis) are common. Atherosclerosis can lead to ischaemic heart disease, while arteriosclerosis results in pressure overload leading to cardiomyopathy. Furthermore, anaemia, fluid overload and medical arterio-venous fistulas associated with CKD result in volume overload leading to left ventricular dilatation [29]. Most of the traditional CVD risk factors, such as older age, hypertension and low HDL-cholesterol [36], are highly prevalent in CKD and may have a qualitatively and quantitatively different risk relationship with CVD in CKD compared with the general population [37].

In recent years, three large studies have identified eGFR and albuminuria as baseline risk factors for death in type 2 diabetes in a variety of racial and ethnic groups. Each of

Fig. 3 Proportion of patients in the placebo group with CVD events by status at baseline and after year 2 for **(a)** eGFR defined as normal (N: ≥60 ml min⁻¹ 1.73 m⁻²) and impaired (I: <60 ml min⁻¹ 1.73 m⁻²) (solid lines, N–N; dashed line, N–I; dotted line, I–N; dotted-dashed line, I–I); and **(b)** albuminuria, defined as albuminuric, i.e. micro- or macroalbuminuric (A), and normoalbuminuric (N) (solid lines, N–N; dashed line, N–A; dotted line, A–N; dotted-dashed line, A–A). *eGFR and albuminuria data at year 2 were not available for 250 and 236 patients, respectively. Curve annotations (see the Methods) denote: status at baseline and status at year 2. For example I–N: eGFR <60 ml min⁻¹ 1.73 m⁻² at baseline and ≥60 ml min⁻¹ 1.73 m⁻² at year 2; A–A: albuminuric at baseline and year 2. **a** †*p*=0.33 for I–I vs I–N, logrank test; *p*=0.07 for N–I vs N–N, logrank test. **b** †*p*=0.01 for A–A vs A–N, logrank test; *p*=0.006 for N–A vs N–N, logrank test

these studies relied on local measures of eGFR and albuminuria at each clinical site [38–41]; in contrast, our report used centrally measured laboratory values.

A Hong Kong study by Yang et al [40, 41] and, among broader populations, the Framingham Offspring study [42] and the recent Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study [38] all had similar findings to FIELD. Yang et al investigated a Chinese population with type 2 diabetes, using registry data and non-centralised outpatient laboratory measurements. However, many had CKD at baseline, and Asians with type 2 diabetes may have almost double the risk of developing end-stage kidney disease than their Europid counterparts [43]. In ADVANCE, a large trial of ACE inhibitors and intensive glucose lowering, baseline eGFR and urinary ACR were independently related to cardiovascular death, and to cardiovascular and renal events [38]. ADVANCE recruited patients from Asia, Europe, Oceania and North America, who had a history of CVD or at least one CVD risk factor. Biochemical measurements took place in non-centralised, local laboratories. In comparison, the FIELD population was predominantly Europid, and had generally lower CVD risk, and well-controlled diabetes, blood pressure and lipid levels. Furthermore, measurements were based on averaging two baseline ACR and creatinine measurements, and confirm the findings of independent effects of eGFR and albuminuria on CVD death and death from all causes.

Recently, a large observational study of Canadian outpatients also associated increased all-cause mortality rates, first hospitalisation for myocardial infarction and end-stage renal disease with worsening categories of eGFR and proteinuria [39]. The FIELD trial not only confirms these findings in the context of a randomised trial of well characterised patients, but also provides greater insight, having a longer follow-up period and a greater range of endpoints, as well as using standardised measures of renal function and accounting for concurrent use of renin–angiotensin system blockers. Other studies with fewer participants or more limited outcomes have also produced similar findings in type 2 diabetes. These include a South Tees, UK study of 3,288 participants [8], an Italian study of 1,538 participants [6] and the Hoorn study in the Netherlands with 631 participants [7]. In the larger Prospective Pioglitazone Clinical Trial in Macrovascular Events (PRO-ACTIVE) study ($n=5,154$), a post-hoc comparison of participants with eGFR more or less than $60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ showed a hazard ratio of 1.25 for a composite endpoint on multivariable analysis [44]. The QRISK2 study found that CKD as a categorical variable added 70% to 75% cardiovascular risk [10]. In contrast, the Casale Monferrato Study did not confirm an independent association of eGFR with CVD outcomes after correction for

albuminuria, possibly because of the small sample size or limited follow-up duration [5, 6]. In some of the above studies, albuminuria was not included in the analysis [8, 10] or not analysed as an independent variable [7, 44], and some had smaller samples than FIELD [6–8]. The independent nature of the contributions of eGFR and albuminuria in FIELD highlights that they almost certainly represent different pathological processes in type 2 diabetes [38, 39, 45].

Recent reports suggest substantial secular changes in mortality rates among patients with type 2 diabetes, as well as suggesting that CVD risk factor intervention has been extremely effective in reducing mortality and morbidity rates [46]. FIELD was a large multinational, community-based cohort of people who had relatively uncomplicated type 2 diabetes, representing 50,169 patient-years of follow-up, and who would be estimated to lose 4 to 8 years of life expectancy [47]. By excluding most patients with pre-existing renal dysfunction and all those with CKD stages 4 and 5, the impact of renal disease as assessed in FIELD will have underestimated its overall contribution to CVD risk in the general population. Among those allocated to placebo, only a minority progressed to eGFR $<30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. With too few participants deteriorating to this level prior to their first event, it was not possible to draw reliable conclusions on CVD risk in participants progressing to severe renal impairment. Furthermore, excellent control of HbA_{1c} throughout the study would have further reduced risk in comparison with more poorly controlled populations. The mortality rate for this cohort, around 1.4% per year at a mean entry age of 62, was low and lower than the rates in the UK Prospective Diabetes Study (UKPDS) [18] or the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study [17]. In UKPDS, the myocardial infarction risk per 1,000 patient-years was 14.7 compared with 11.7 in FIELD. Other recent trials of type 2 diabetes with high usage rates of antihypertensive and lipid-lowering therapies (predominantly statins), such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, have also reported fewer CVD events than expected [48]. In ADVANCE, the CVD event and CVD death rates were approximately 2% and 0.9% per annum, while the acute myocardial infarction rate in an observational study of Canadian outpatients (not limited to diabetes) was 0.2% per annum [39, 49]. The CVD, CVD death and coronary event rates of the placebo group in FIELD were 3.0%, 0.5% and 1.2% per annum, respectively [14]. When using the same composite endpoints for CVD as ADVANCE, the annual rate in FIELD was also 2.0%.

A limitation of FIELD was that albuminuria data were only available at baseline, year 2 and study close. More frequent measures might have allowed greater accuracy in risk estimation, although the trends observed would probably have been similar. Measures of renal function

display within-individual variation. Nevertheless, the averaging of two baseline samples would have improved the precision and also reflects real-life scenarios of risk assessment in typical clinical practice. Although we acknowledge that calculated eGFR values greater than $60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ are somewhat imprecise when using the MDRD 4-variable formula compared with directly measured GFR and are not recommended for clinical use, our results suggest that they have group validity in a large study: any categorical misclassification could only have weakened our conclusions. While FIELD was a selected cohort compared with community or clinic-based surveys, the latter rely on hospital discharge summaries or death certificates for outcome classification, whereas FIELD offered consistent data collection, centralised laboratory measurements and detailed central assessment and adjudication of all CVD events and deaths using extensive supporting documentation and pre-specified definitions. Furthermore, over 70% of participants screened for inclusion were recruited into the trial.

We conclude that even early stages of kidney disease in type 2 diabetes, evident from either a reduced eGFR or albuminuria, are important determinants of CVD risk and mortality rates. Additionally, renal status changes further modify CVD risk. Despite plasma creatinine and urinary ACR measurements now being part of routine care of patients with diabetes, moderate falls in eGFR are often not clinically recognised or acted upon, despite routine laboratory reporting of eGFR based on creatinine. Estimated GFR and ACR may be potentially important in redefining CVD risk and should therefore influence the clinical management of patients, especially in the assessment of CVD and renal risk, as well as in the choice, timing and evaluation of interventions to reduce those risks.

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