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Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease

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Aims Individuals with diabetes and chronic kidney disease (CKD) are at high risk for cardiovascular disease. In these analyses of the ADVANCE trial, we assessed the effects of a fixed combination of perindopril–indapamide on renal and cardiovascular outcomes in patients with type 2 diabetes according to baseline CKD stage.

Methods and results Patients with type 2 diabetes were randomized to perindopril–indapamide (4 mg/1.25 mg) or placebo. Treatment effects on cardiovascular (cardiovascular death, myocardial infarction, or stroke) and renal outcomes were compared in subgroups defined by baseline Kidney Disease Outcome Quality Initiative CKD stage. Homogeneity in treatment effect was tested by adding interaction terms to the relevant Cox models. The study included 10 640 participants with known CKD status, of whom 6125 did not have CKD, 2482 were classified as CKD stage 1 or 2, and 2033 as CKD stage $\geq$3. The relative treatment effects on major cardiovascular events were similar across all stages of CKD, with no heterogeneity in the magnitude of the effects for any outcome. In contrast, the absolute treatment effects approximately doubled in those with CKD stage $\geq$3 when compared to those with no CKD. For every 1000 patients with CKD stage $\geq$3 treated for 5 years, active treatment prevented 12 cardiovascular events when compared with six events per 1000 patients with no CKD.

Conclusion The treatment benefits of a routine administration of a fixed combination of perindopril–indapamide to patients with type 2 diabetes on cardiovascular and renal outcomes, and death, are consistent across all stages of CKD at baseline. Absolute risk reductions are larger in patients with CKD highlighting the importance of blood pressure-lowering in this population.

Keywords ACE-inhibitor • type 2 diabetes • chronic kidney disease

Introduction

Blood pressure-lowering prevents cardiovascular events in a broad range of high-risk individuals,[1] and most guidelines recommend the prescription of blood pressure-lowering medications for people at high cardiovascular risk. Angiotensin-converting enzyme (ACE)-inhibitors and diuretics are among the most widely used blood pressure-lowering drugs and have been demonstrated to

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improve clinical outcome in a broad range of populations including those with type 2 diabetes, vascular disease, heart failure, and chronic kidney disease (CKD).[2–7]

In populations with and without diabetes, ACE-inhibitors and diuretics have been shown to reduce blood pressure and albuminuria, two important risk factors for renal and cardiovascular disease progression.[7–9] Since people with type 2 diabetes and CKD (defined as decreased estimated glomerular filtration rate (eGFR) or elevated albuminuria levels) are at substantially increased risk for renal and cardiovascular events,[10] the benefits of these agents in this population could be greater than in people without renal disease. Previous studies have reported that individuals with CKD are more likely to obtain renal benefit from inhibitors of the renin–angiotensin system.[7,11] It has also been suggested that they may obtain greater cardiovascular benefits.[12,13] Whether this is also true for patients with type 2 diabetes and CKD is unclear as few data are available on the effects of combination ACE inhibitor-diuretic therapy in this population.

The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial investigated effects of routine administration of a fixed combination of perindopril and indapamide on cardiovascular and renal outcomes in patients with type 2 diabetes at elevated cardiovascular risk. The trial included a broad range of participants with different degrees of CKD, as defined by the Kidney Disease Outcome Quality Initiative (KDOQI) using eGFR and/or albuminuria thresholds.[14] In this *post hoc* analysis of the ADVANCE trial,[6] we investigated whether the stage of CKD modified the efficacy of perindopril–indapamide treatment on renal and cardiovascular outcomes.

Methods

Study design and participants

ADVANCE is a factorial randomized controlled trial evaluating the effects of blood pressure-lowering and intensive blood glucose control on vascular outcomes. The design has previously been published,[15] and is described here in brief. Patients were potentially eligible if they had been diagnosed with type 2 diabetes at the age of 30 years or older, were 55 years of age or older at study entry and had evidence of elevated risk of cardiovascular disease. Patients were not selected

Table 1 Baseline characteristics of the overall study population and according to eGFR and UACR at study entry

	No CKD (eGFR ≥ 60 and UACR < 30) *n* = 6125	CKD stage 1/2 (eGFR ≥ 60 and UACR ≥ 30) *n* = 2482	CKD stage ≥3 (eGFR < 60) *n* = 2033
Age (years), mean (SD)	65.3 (6.2)	65.0 (6.4)	68.3 (6.4)[a]
Female, *n* (%)	2382 (38.9)	972 (39.2)	1168 (57.5)[a]
Previous vascular disease			
History of major macrovascular disease, *n* (%)	1827 (29.8)	814 (32.8)[a]	753 (37.0)[a]
History of myocardial infarction, *n* (%)	673 (11.0)	274 (11.0)	303 (14.9)[a]
History of stroke, *n* (%)	484 (7.9)	265 (10.7)[a]	222 (10.9)[a]
Blood pressure control			
Systolic blood pressure (mm Hg), mean (SD)	143.0 (20.3)	148.3 (22.1)[a]	146.8 (23.0)[a]
Diastolic blood pressure (mm Hg), mean (SD)	80.4 (10.7)	82.1 (11.2)[a]	79.7 (11.3)[a]
History of currently treated hypertension, *n* (%)	3920 (64.0)	1775 (71.5)[a]	1594 (78.4)[a]
Other major risk factors			
Current smokers, n (%)	970 (15.8)	412 (16.6)	212 (10.4)[a]
Serum haemoglobin A_{1c} concentration (%), mean (SD)	7.4 (1.4)	7.8 (1.7)[a]	7.5 (1.6)
Serum LDL cholesterol (mmol/L), mean (SD)	3.1 (1.0)	3.1 (1.1)	3.2 (1.0)
Serum HDL cholesterol (mmol/L), mean (SD)	1.3 (0.4)	1.3 (0.3)	1.2 (0.4)
Urinary albumin:creatinine ratio (μg/mg), median (IQR)	9.0 (5.3–15.9)	71.6 (42.4–146.2)[a]	19.4 (8.0–64.5)[a]
Estimated glomerular filtration rate (mL/min)	84.1 (19.8)	86.9 (29.3)[a]	51.0 (7.8)[a]
Body mass index (kg/m^2), mean (SD)	28.2 (5.1)	28.2 (5.4)	28.7 (5.3)[a]
Blood pressure-lowering drugs			
Perindopril, *n* (%)	492 (8.0)	224 (9.0)	180 (8.9)
Other angiotensin-converting enzyme inhibitor, *n* (%)	1954 (31.9)	851 (34.3)	856 (42.1)[a]
Angiotensin receptor-blocker, *n* (%)	291 (4.8)	138 (5.6)	144 (7.1)[a]
Diuretics, *n* (%)	1272 (20.8)	510 (20.6)	725 (35.7)[a]
β-blockers, *n* (%)	1432 (23.4)	533 (21.5)	607 (29.9)[a]
Calcium antagonists, *n* (%)	1670 (27.3)	889 (35.8)[a]	706 (34.7)[a]
Other blood pressure-lowering drugs, *n* (%)	691 (11.3)	365 (14.7)[a]	275 (13.5)[a]

[a]Indicates whether baseline characteristics are significantly different ($P < 0.05$) when compared to participants with no CKD, adjusted for multiple comparisons.

based on levels of blood pressure or eGFR, but the presence of albuminuria was one of a number of potential criteria for inclusion. Approval for the study was obtained from each centre's institutional ethics committee and all participants gave written informed consent.

All potentially eligible participants entered a six-week run-in period during which they received perindopril 2 mg and indapamide 0.625 mg in a fixed combination. All other treatments were continued at the discretion of the responsible physician, except that ACE inhibitors other than perindopril were substituted with open-label perindopril at a dose of 2 mg or 4 mg daily. Those who were tolerant and adherent to the study drugs were subsequently randomized to perindopril–indapamide (2 mg/0.625 mg) or matching placebo. The doses were doubled after 3 months, so that participants were receiving either perindopril–indapamide 4 mg/1.25 mg or matching placebo. Use of concomitant treatment during follow-up remained at the discretion of the responsible physician, except that open-label perindopril to a

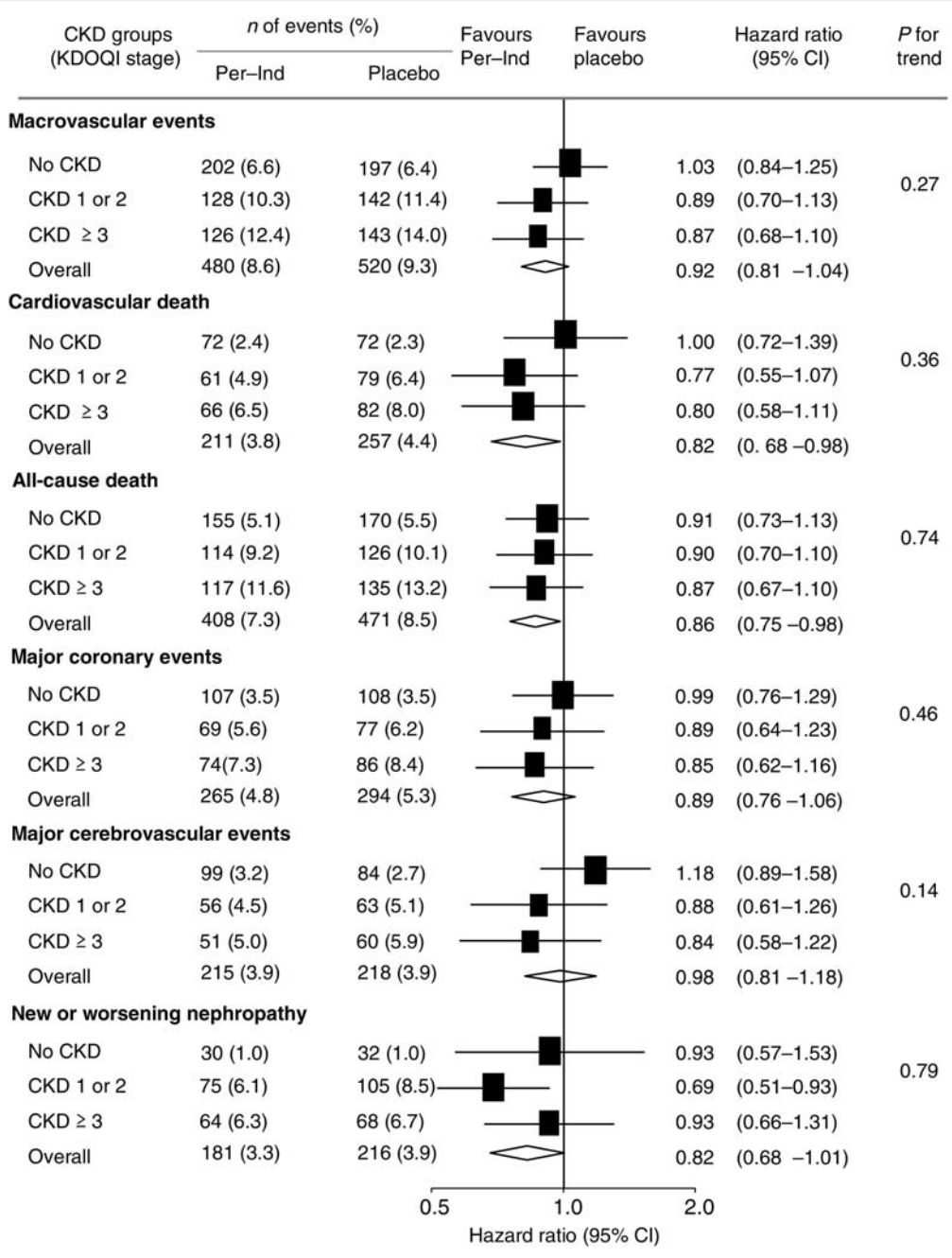

Figure 1 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline KDOQI CKD stage. The centre of the diamond represents the overall estimate and the width its 95% confidence interval (CI) as previously reported by Patel *et al.*[6] Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI. The '*P* for trend' tested the consistency of treatment effect in subgoups.

maximum of 4 mg daily was the only ACE inhibitor allowed, and that thiazide (-like) diuretics were not permitted.

Follow-up and assessments

Participants were seen at two pre-randomization visits, at 3, 4, and 6 months after randomization, and subsequently at 6-month intervals. Blood pressure was measured as the mean of two measurements made in the seated position using an automated sphygmomanometer (Omron HEM-705 CP, Tokyo Japan) at each study visit. Serum creatinine and electrolyte levels were measured at registration and randomization, at 4- and 12-month visits, and yearly thereafter. Measurement of urinary albumin creatinine ratio (UACR) was performed on spot urine samples at the registration visit, 24 months, 48 months, and 60 months after randomization and at the end of follow-up. The abbreviated Modification of Diet in Renal Disease

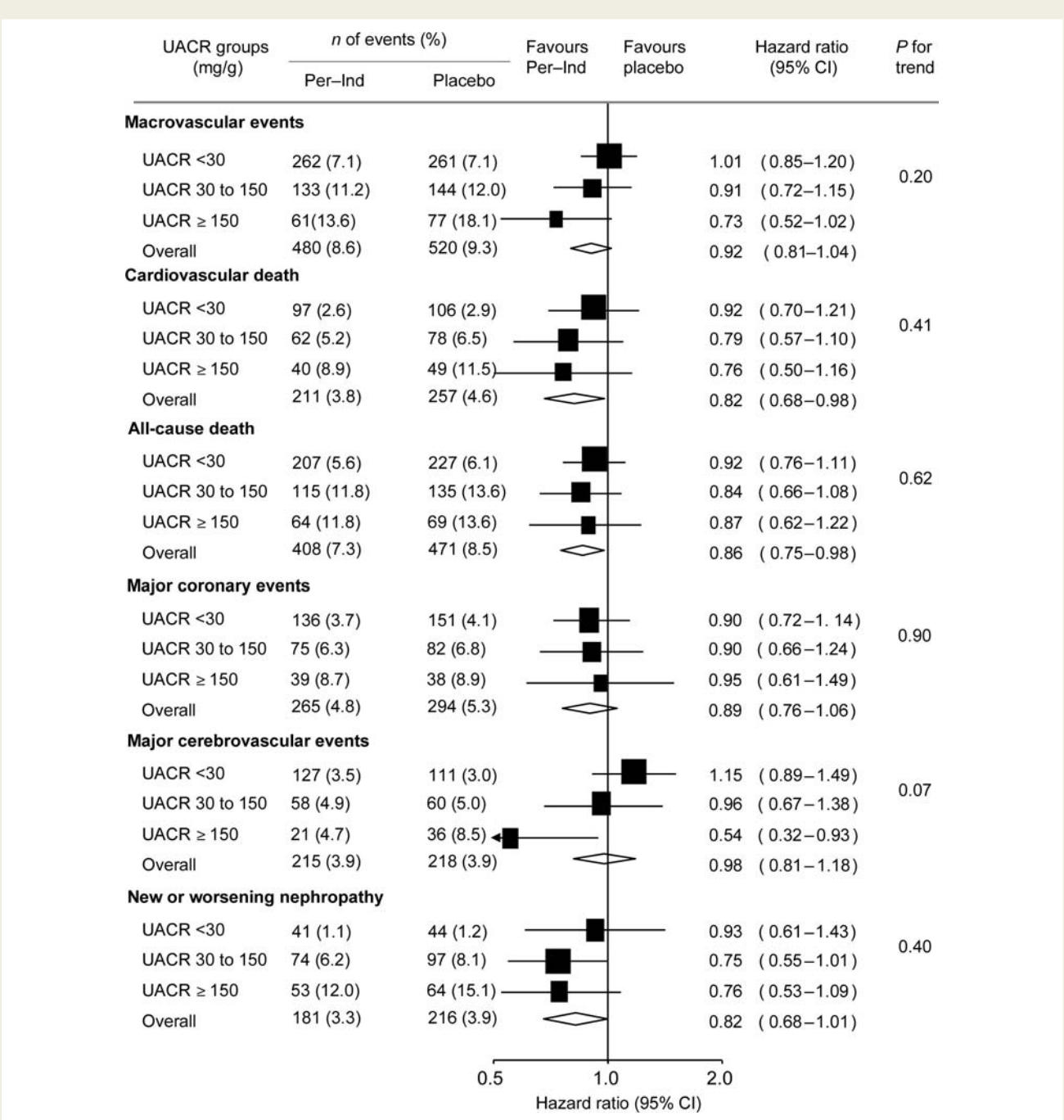

Figure 2 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline UACR. The centre of the diamond represents the overall estimate and the width its 95% CI as previously reported by Patel *et al.*[6] Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI. The '*P* for trend' tested the consistency of treatment effect in subgoups.

(MDRD) equation was used to estimate eGFR.[16] To assess the safety and tolerability of a perindopril–indapamide regimen, we assessed the frequency of suspected adverse drug reactions leading to permanent treatment discontinuation by CKD stage.

Outcomes

The primary outcome for this analysis was the composite of major macrovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Secondary outcomes included cardiovascular death, all-cause mortality, coronary events, cerebrovascular events, and new or worsening nephropathy [development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL (200 μmol/L), need for renal replacement therapy, or death due to renal disease]. All outcomes were pre-specified endpoints in the ADVANCE trial.

Statistics

The effects of randomized treatment on all endpoints were estimated from unadjusted Cox proportional hazard models, based on the intention-to-treat principle. For participants who experienced more than one primary event during follow-up, survival time to the first relevant endpoint was used in each analysis. Participants were censored at their date of death or, for those still alive at the end of follow-up, the date of their last clinic visit before the termination of this study arm. Patients with unknown vital status were censored when they were last known to be alive. A total of 500 patients had missing UACR values at baseline. These patients were excluded in the primary analysis, and then included in sensitivity analyses. Treatment effects on all cardiovascular and renal endpoints were calculated according to baseline KDOQI defined CKD stage, as defined in the Supplementary material online, table S1.[14] Few individuals had CKD stage 1 ($n = 811$) or 4 ($n = 51$). For the purpose of analysis, we combined individuals with CKD stage 1 or 2 and CKD stage 3 or 4. Differences in baseline characteristics between subjects with no CKD and CKD stage 1 or 2 or CKD stage ≥ 3 were tested with one-way analysis of variance or Kruskal–Wallis, where appropriate. In additional analyses, participants with CKD stage ≥ 3 were sub-classified into two further categories according to the level of albuminuria at baseline; UACR < 30 mg/g or UACR ≥ 30 mg/g. We also calculated treatment effects at different cut-off points for UACR (UACR < 30 mg/g; $30 \leq$ UACR < 150 mg/g, UACR ≥ 150 mg/g) and eGFR (eGFR > 90 mL/min; $60 <$ eGFR ≤ 90 mL/min and eGFR ≤ 60 mL/min). The upper threshold level for UACR of 150 mg/g was chosen, as only few patients in the ADVANCE trial met the definition of having macroalbuminuria, that is UACR ≥ 300 mg/g. Test for trends in treatment effects across CKD stages, UACR, and eGFR levels, as categorical and continuous variables, were performed by adding interaction terms to the relevant Cox models. Relative risk reductions are described in the text as percentage reductions ([1 − hazard ratio] × 100). Absolute risk reductions (ARRs) were calculated as the difference in cumulative incidence between active treatment and placebo treatment. For calculation of the ARRs, we used the overall relative risk reduction as treatment effects were consistent among CKD subgroups. Suspected adverse drug reactions leading to permanent drug discontinuations according to the stage of CKD are reported as odds ratios. Hazard ratios could not be calculated for this analysis, as patients were often unable to exactly pin-point the date of discontinuation so that the time interval from randomization to the onset of the suspected adverse drug reactions could not always be accurately estimated. Differences between randomized groups in blood pressure during follow-up were estimated from linear mixed models. Consistency of blood pressure reductions across CKD subgroups were tested by adding an interaction term between CKD subgroups and treatment assignment in the linear mixed models. A P-value ≤ 0.05 (two-sided) was considered to indicate a statistically significant difference. Analyses were performed using SAS 9.1 for Windows (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 10 640 participants from whom baseline UACR and eGFR levels were available. Of these participants, 6125 had no CKD at entry into the trial, 2482 had CKD stage 1 or 2, and 2033 had CKD stage ≥ 3. Participants with CKD stage 3 or greater at study entry were older, more likely to be female, more likely to have pre-existing cardiovascular disease, and higher systolic and diastolic blood pressure as well as more likely to be treated with blood pressure-lowering drugs.

Effects of perindopril–indapamide therapy on blood pressure during follow-up

After a mean duration of 4.3 (SD 0.7) years of follow-up, active treatment compared with placebo-reduced mean systolic and diastolic blood pressure levels by 6.1/2.4 mmHg, 5.3/2.1 mmHg, and 4.5/1.8 mmHg in individuals with no CKD, CKD stage 1 or 2, or CKD stage ≥ 3, respectively (P for heterogeneity in systolic and diastolic blood pressure of 0.023 and 0.073, respectively).

Relative effects of perindopril–indapamide therapy on the risk for cardiovascular events according to clinical stage of CKD

The administration of a fixed perindopril–indapamide regimen resulted in similar relative effects on major cardiovascular events irrespective of the stage of CKD (P for trend across CKD subgroups 0.27, *Figure 1*). Participants had similar reductions in the risk for cardiovascular deaths, all-cause mortality, and renal events irrespective of the stage of CKD (*Figure 1*). Essentially similar results were obtained when the relative treatment effects were adjusted for the differences in systolic blood pressure reduction among CKD groups (Supplementary material online, figure S1). When the effects of a fixed perindopril–indapamide regimen were analysed according to baseline UACR or eGFR, no significant interaction, both in categorical and continuous analyses, was observed between either baseline UACR or eGFR and treatment effect (*Figures 2* and *3*). A trend towards a greater relative risk reduction for major macrovascular events was observed in participants with lower eGFR, but this was of borderline statistical significance ($P = 0.07$). An additional analysis that sub-classified individuals into two categories of UACR < 30 mg/g or ≥ 30 mg/g provided similar results (see Supplementary material online, figure S2). Sensitivity analyses that sub-classified CKD stage 3 into two categories of UACR < 30 mg/g or UACR ≥ 30 mg/g, which imputed missing UACR values, or that excluded patients

using an angiotensin-receptor blocker (ARB) at the end of the trial also obtained similar results.

Absolute effects of perindopril–indapamide by CKD stage

ARRs for major cardiovascular events, cardiovascular mortality, and all-cause mortality were greater in participants with CKD stage ≥3 compared to those with no CKD or CKD stage 1 or 2 (*Table 2*). When individuals were grouped according to the level of albuminuria in CKD stage 3, the greatest ARRs were observed for individuals with CKD stage ≥3 and UACR ≥ 30 mg/g. For every 1000 patients with CKD stage ≥3 and UACR ≥ 30 mg/g treated for 5 years, active treatment prevented 18 cardiovascular events, 26 cardiovascular deaths, and 30 all-cause deaths, when compared with six cardiovascular events, six cardiovascular deaths, and 10 deaths per 1000 patients with no CKD.

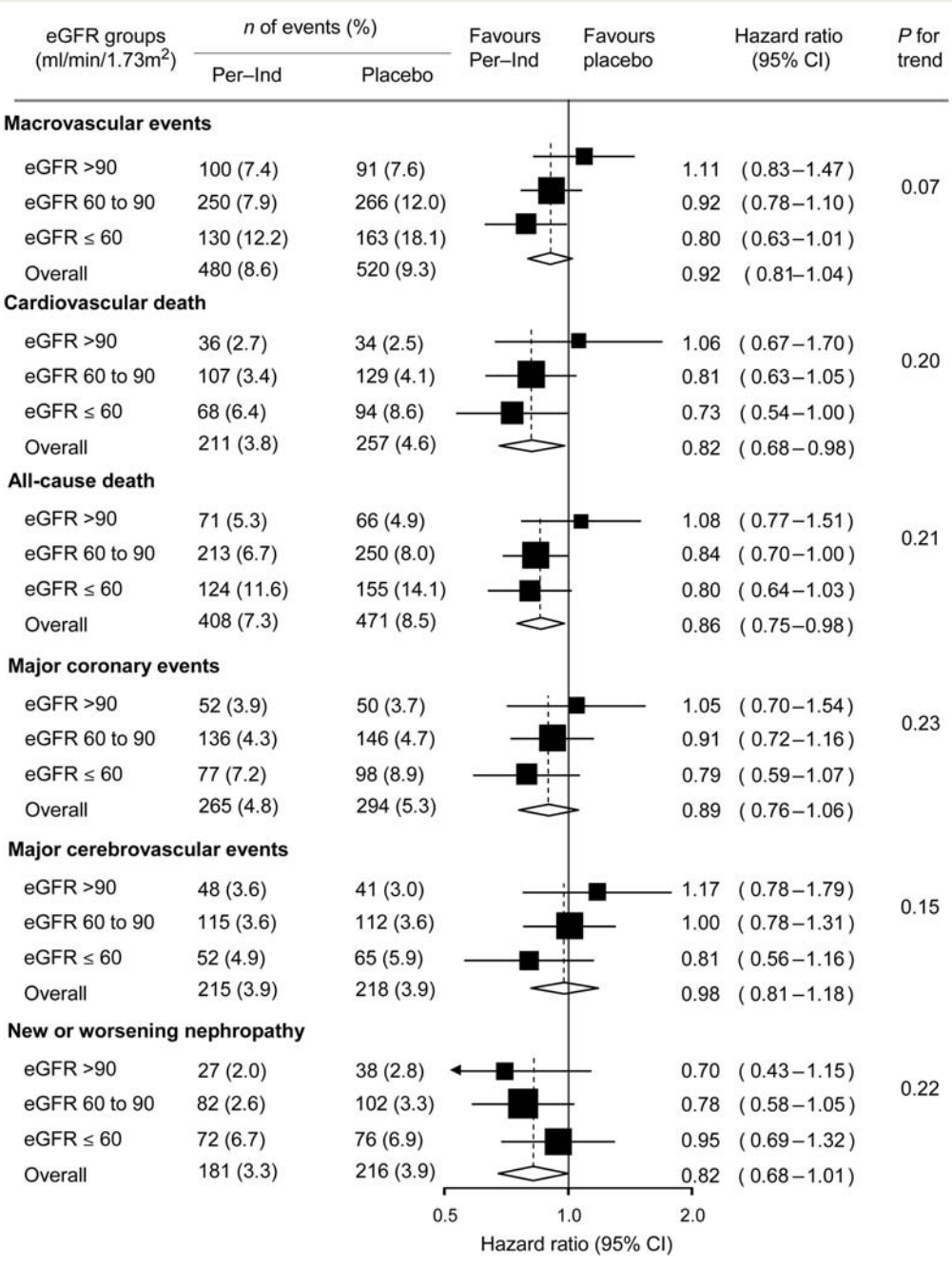

Figure 3 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline eGFR. The centre of the diamond represents the overall estimate and the width its 95% CI as previously reported by Patel *et al.*[6] Solid boxes represent estimates of treatment effects in subgroups, and the horizontal line represents the 95% CI. The '*P* for trend' tested the consistency of treatment effect in subgoups.

Table 2 Incidence rate and ARR for major cardiovascular events, cardiovascular deaths or all-cause deaths according the stage of CKD. Since the reductions in relative risk for each outcome were consistent across CKD subgroups, the ARRs were calculated on the basis of the relative risk reductions for the overall population

Parameter	5-year Cumulative incidence rate; perindopil–indapamide vs. placebo	ARR over 5 year (95% CI) per 1000 patients
Major cardiovascular outcomes		
No CKD	0.069/0.074	5.7 (−7.2 to 18.6)
Stage 1 or 2	0.122/0.132	10.0 (−16.2 to 36.2)
Stage 3	0.149/0.161	12.2 (−19.3 to 43.7)
UACR < 30 in stage 3	0.107/0.116	8.8 (−26.1 to 43.7)
UACR ≥ 30 in stage 3	0.218/0.236	17.7 (−41.0 to 76.5)
Cardiovascular death		
No CKD	0.021/0.025	4.5 (−2.7 to 11.7)
Stage 1 or 2	0.060/0.074	13.1 (−6.6 to 32.8)
Stage 3	0.076/0.093	16.5 (−7.7 to 40.7)
UACR < 30 in stage 3	0.051/0.062	11.0 (−14.5 to 36.5)
UACR ≥ 30 in stage 3	0.119/0.144	25.5 (−21.9 to 72.9)
All-cause death		
No CKD	0.052/0.059	7.9 (−3.1 to 18.9)
Stage 1 or 2	0.101/0.117	15.5 (−9.0 to 40.0)
Stage 3	0.132/0.152	19.2 (−10.2 to 50.4)
UACR < 30 in stage 3	0.090/0.103	5.7 (−19.0 to 46.4)
UACR ≥ 30 in stage 3	0.202/0.233	45.4 (−27.3 to 88.4)

Adverse drug reactions according to the clinical stage of CKD

The rate of adverse drug reactions was similar in subgroups defined by CKD stage, with no evidence that drug-related side effects were more or less common in people with CKD. A trend towards a higher overall rate of serious adverse events was observed in individuals with CKD, but this was similar in the active treatment group. Cough and hypotension or dizziness leading to permanent discontinuation were more frequently observed in the active treatment group but did not differ according to the stage of CKD (*Table 3*).

Discussion

The results of this study demonstrate that the reductions in relative risk of cardiovascular and renal events achieved with a fixed ACE-inhibitor diuretic combination are consistent among subgroups of patients with diabetes defined by the stage of CKD. As a result of their substantially increased cardiovascular risk, the ARRs obtained with a fixed combination of the ACE-inhibitor-diuretic regimen were greater in patients with CKD stage ≥3, underlining the importance of early recognition of CKD in patients with diabetes and the value of this preventative therapy.

Previous studies have reported cardiovascular benefits of ACE inhibitors regardless of kidney function in patients with coronary artery disease, cerebrovascular disease, or vascular disease.[13,17,18] Some evidence for larger relative treatment benefits for ACE inhibitors in individuals with reduced kidney function has been reported in *post hoc* analyses of other trials.[12,13,19] In patients with type 2 diabetes participating in the ADVANCE trial, there was no clear evidence of differences in relative risk reductions by the stage of kidney function. However, some non-significant trends towards larger benefit in patients with stage 3 CKD compared to those without CKD were observed, despite slightly less effective blood pressure reductions. As individual clinical trials have limited statistical power to detect statistical interaction in the treatment effects, even when the trial itself is relatively large,[20] future meta-analyses will be important for providing more reliable and accurate analyses of the relative benefits of ACE inhibitors and their combination with diuretic therapy in patients with CKD.

The ARRs in people with CKD stage ≥3 were greater than those in people without CKD, reflecting their underlying increased cardiovascular risk. In the present study, urinary albumin was used as an additional marker to select people with CKD, whereas many previous studies solely used creatinine clearances or eGFR measurements to differentiate between individuals with and without renal insufficiency.[13,17,18] By doing this, we found that the large ARRs observed in individuals with CKD stage ≥3 were principally driven by the benefits of treatment attained among individuals with microalbuminuria. In this CKD population with diabetes, the magnitude of the ARRs achieved over 5 years with active therapy for cardiovascular events and all-cause mortality were three- and six-fold higher, respectively, compared to those without CKD. As a result, the number of patients needed to treat to prevent one fatal event over a 5-year period was significantly reduced. These data highlight the importance of blood pressure reduction in individuals with diabetes and CKD particularly in those with albuminuria.

There is a plausible explanation for expecting greater risk reductions in people with kidney disease, and especially those with albuminuria. High urinary albumin excretion is assumed to be a reflection of endothelial dysfunction and microvascular disease,[21,22] which has been shown to contribute to a worsening of cardiovascular risk factors and may also play a role in the pathophysiological process that leads to accelerated cardiovascular disease.[22,23] ACE inhibitors reduce albuminuria as well as blood pressure, and this dual effect might result in greater benefit than that achieved by blood pressure-lowering alone in people without albuminuria. In addition, the combination of an ACE inhibitor with a diuretic has been shown to further lower blood pressure and albuminuria, as shown by the PREMIER study.[22] Recent studies even demonstrate that uptitration of a diuretic in combination with half-dose ACE inhibitor or ARB is more effective in reducing albuminuria than uptitrating to full dose of combined

Table 3 Suspected adverse drug reactions leading to permanent discontinuation according to CKD stage (*n*, %). The absolute numbers (%) of suspected adverse drug reactions across CKD subgroups as well as the odds ratio are reported (95% CI)

CKD subgroups	Number of events (%)			
Cough	Perl–Ind	Placebo	Odds ratio (95% CI)	*P* for trend
No CKD	98 (3.2)	33 (1.1)	3.04 (2.04–4.52)	
CKD 1 or 2	38 (3.1)	17 (1.4)	2.28 (1.28–4.06)	0.36
CKD ≥ 3	40 (3.9)	18 (1.8)	2.29 (1.50–4.02)	
Overall[a]	184 (3.3)	72 (1.3)	2.61 (1.98–3.44)	
Hypotension/dizziness				
No CKD	42 (1.4)	12 (0.4)	3.53 (1.86–6.74)	
CKD 1 or 2	9 (0.7)	6 (0.5)	1.51 (0.53–4.24)	0.99
CKD ≥ 3	14 (1.4)	3 (0.3)	4.75 (1.36–16.58)	
Overall[a]	69 (1.2)	22 (0.4)	3.16 (1.96–5.12)	
SAE				
No CKD	21 (0.7)	22 (0.7)	0.96 (0.53–1.74)	
CKD 1 or 2	17 (1.4)	20 (1.6)	0.85 (0.44–1.63)	0.66
CKD ≥ 3	22 (2.2)	19 (1.9)	1.17 (0.63–2.17)	
Overall[a]	67 (1.2)	66 (1.2)	1.02 (0.72–1.43)	

SAE, serious adverse event. The number (%) of SAEs leading to permanent treatment discontinuation, irrespective of whether they were considered to be drug related, are reported in the table.
[a]The overall number of adverse events is presented as previously reported by Patel *et al.*[6]

ACE-inhibitor and ARB.[24] These enhanced surrogate organ protective effects of the combination of an ACE inhibitor and diuretic may result in further renal and cardiovascular risk reduction. Whether this is true remains to be demonstrated by future prospective randomized controlled trials.

The strengths of this study include the large sample size, the availability of both eGFR and urinary albumin data, and the large numbers of individuals with CKD of different stages. In addition, the rigorous methods of data collection, recording, and analysing allowed precise estimation of the effect sizes. The limitations include the relatively few participants in the ADVANCE trial meeting the definition of having macroalbuminuria (UACR > 300 mg/g), which limited our ability to examine the effects of treatment in this particular group of individuals. Furthermore, UACR and eGFR were only assessed at some of the visits during the course of the trial so that we could not assess the time course of changes in albuminuria and eGFR and their interaction with ACE-inhibitor-based therapy.

In conclusion, the relative treatment benefits of routine administration of a fixed combination of perindopril–indapamide in patients with type 2 diabetes on renal and cardiovascular outcomes are consistent and not materially modified by the stage of CKD at baseline. The absolute benefits of treatment are, however, greater in people with CKD. This highlights the importance of blood pressure-lowering therapy in preventing renal and cardiovascular complications in this high-risk population.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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