in the placebo group), 187 nonfatal major bleeding events, and 208 minor bleeding events.

Cardiovascular events and bleeding in subjects with kidney disease. Patients with lower eGFR levels experienced greater rates of cardiovascular events, bleeding events, and death: major cardiovascular event rates were 32.2, 46.4, and 80.2 per 1,000 patients with eGFR ≥60, 45 to 59, and <45 ml/min/1.73 m^2, respectively; myocardial infarction rates were 17.2, 22.7, and 39.2 per 1,000 patients; stroke rates were 13.3, 23.4, and 31.7 per 1,000 patients; cardiovascular mortality rates were 12.6, 18.5, and 42.9 per 1,000 patients; major bleeding event rates were 10.8, 7.8, and 28.0 per 1,000 patients; and total mortality rates were 29.1, 32.8, and 84.0 per 1,000 patients. Event rates were increased by 70% to 100% for every halving of eGFR: major cardiovascular events (HR: 1.84, 95% CI: 1.37 to 2.46), myocardial infarctions (HR: 1.84, 95% CI: 1.09 to 3.11), stroke (HR: 1.87, 95% CI: 1.28 to 2.73), cardiovascular mortality (HR: 1.99, 95% CI: 1.32 to 2.99), bleeding events (HR: 1.77, 95% CI: 1.09 to 2.86), and total mortality (HR: 1.69, 95% CI: 0.82 to 3.49) (Fig. 1).

Effect of aspirin according to categories of reduced kidney function. MAJOR CARDIOVASCULAR EVENTS. As previously reported (19), aspirin significantly reduced the risk of major cardiovascular events for the overall study population for whom creatinine measurements were available (event rates for active and placebo groups were 3.32% and 3.90%, respectively; HR: 0.85, 95% CI: 0.73 to 0.98). The benefit provided by aspirin was significantly greater for

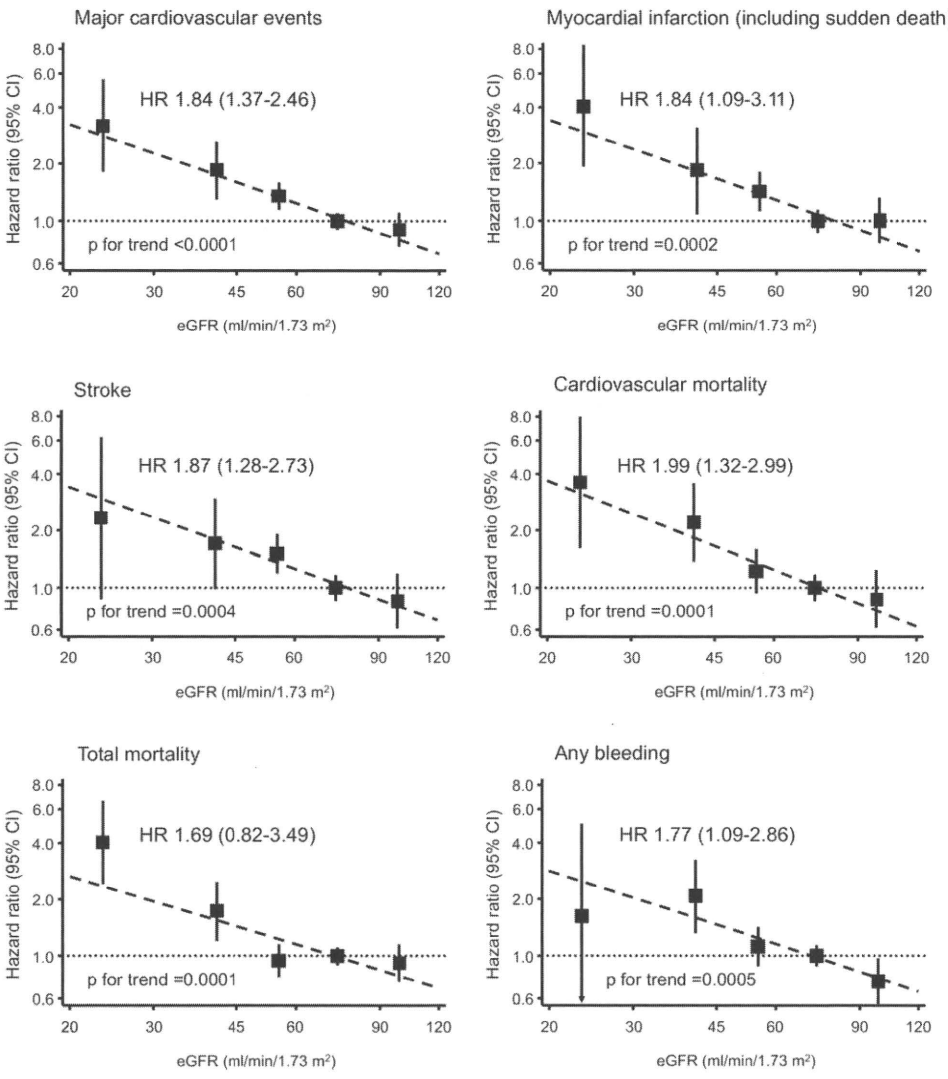

Figure 1 Increase in HR With Decline in eGFR

Hazard ratio (HR) for any cardiovascular event, myocardial infarctions, strokes, cardiovascular mortality, total mortality, and bleeding incidence increases as estimated glomerular filtration rate (eGFR) declines, according to Kidney Disease Outcomes Quality Initiative categories of eGFR (median eGFR for Stage 0/1, 2, 3a, 3b, and 4 depicted). CI = confidence interval.

subjects with low eGFR: risk reductions of 9% (HR: 0.91, 95% CI: 0.76 to 1.09), 15% (HR: 0.85, 95% CI: 0.61 to 1.17), and 66% (HR: 0.34, 95% CI: 0.17 to 0.67) were observed for patients with eGFR ≥60, 45 to 60, and <45 ml/min/1.73 m^2, respectively (p for interaction = 0.03) (Fig. 1). Event rates for subjects treated with aspirin fell from 3.38% to 3.10% for those with eGFR ≥60 ml/min/1.73 m^2, from 5.01% to 4.26% for those with eGFR 45 to 60 ml/min/1.73 m^2, and from 11.76% to 4.17% for those with eGFR <45 ml/min/1.73 m^2 over the mean 3.8 follow-up years in the study. There was no interaction between assignment to different diastolic blood pressure targets and assignment to aspirin (all p values for interaction > 0.2; data not shown).

SECONDARY END POINTS. The protection afforded by aspirin for myocardial infarction increased as kidney function declined (Fig. 2), although the interaction was of borderline statistical significance (p = 0.08). Subjects with the highest eGFR (≥60 ml/min/1.73 m^2) had a borderline significant risk reduction of 22% (HR: 0.78, 95% CI: 0.61 to 1.00), subjects with an eGFR of 45 to 59 ml/min/1.73 m^2 had a risk reduction of 36% (HR: 0.64, 95% CI: 0.39 to 1.03), and subjects with eGFR <45 ml/min/1.73 m^2 had a risk reduction of 69% (HR: 0.31, 95% CI: 0.11 to 0.85). Event rates for subjects treated with aspirin fell from 1.93% to 1.52% for those with eGFR ≥60 ml/min/1.73 m^2, from 2.76% to 1.77% for those with eGFR 45 to 60 ml/min/1.73 m^2, and from 5.88% to 1.89% for those with eGFR <45 ml/min/1.73 m^2 over the mean 3.8 follow-up years in the study.

There was no significant benefit in the total study population from aspirin therapy for total mortality, cardiovascular mortality, or stroke (Fig. 2). However, aspirin did confer significant protection for subjects with an eGFR <45 ml/min/1.73 m^2 for whom total mortality was reduced

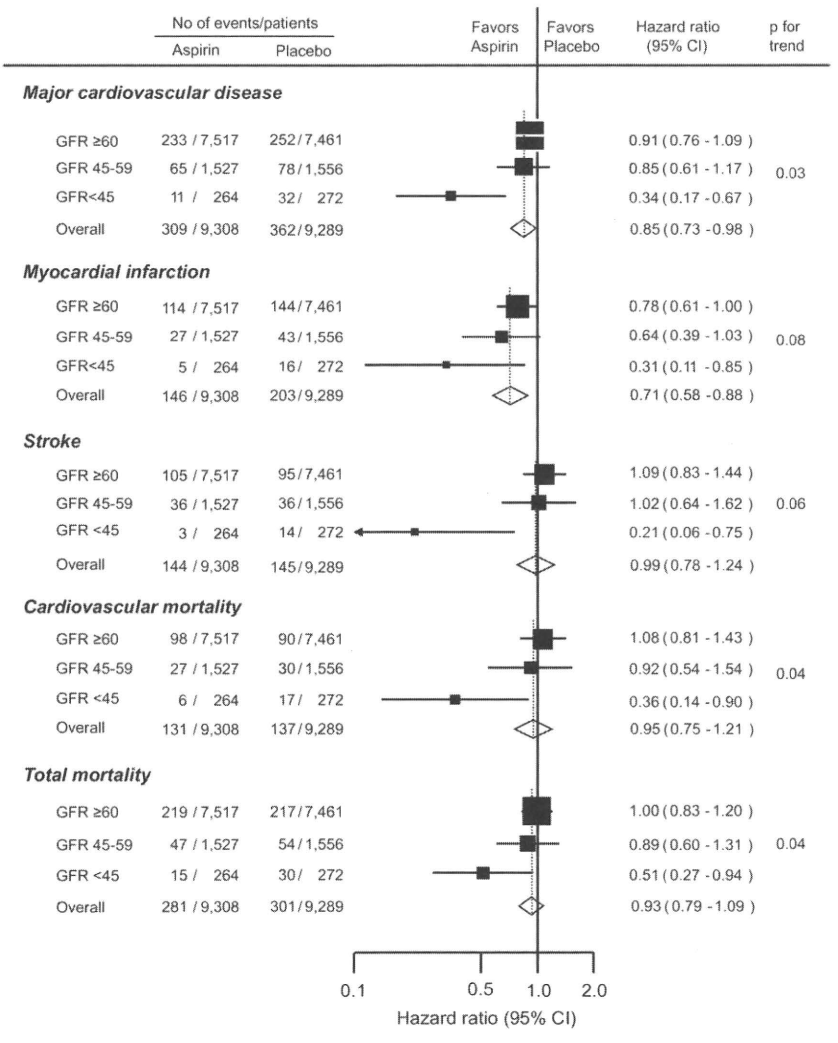

Figure 2 **Effect of Aspirin According to eGFR Category**

Effect of randomized aspirin on outcomes according to estimated glomerular filtration rate (eGFR) category. CI = confidence interval.

by roughly one-half (event rates for active and placebo groups 11.03% and 5.68%, respectively; HR: 0.51, 95% CI: 0.27 to 0.94), cardiovascular mortality by nearly two-thirds (event rates for active and placebo groups 6.25% and 2.27%, respectively; HR: 0.36, 95% CI: 0.14 to 0.90), and stroke by nearly four-fifths (event rates for active and placebo groups 5.15% and 1.14%, respectively; HR: 0.21, 95% CI: 0.06 to 0.75). The benefit for cardiovascular mortality and total mortality was significantly greater for patients with reduced kidney function than for subjects with normal kidney function (p for both interactions = 0.04) and was nearly significantly greater for stroke (p for interaction = 0.06).

KIDNEY FUNCTION DEFINES THRESHOLD OF ASPIRIN BENEFIT. We performed sensitivity analyses to identify any eGFR threshold level below which the benefit associated with aspirin therapy changed and to confirm that our analyses did not appear vulnerable to adjustments in the cut-off between the eGFR categories. The benefit from aspirin therapy progressively, but not linearly, increased (declining risk ratio among subjects randomly assigned to aspirin therapy) as eGFR declined for all end points (Fig. 3). However, the risk reduction of aspirin therapy for cardiovascular mortality, total mortality, and stroke became large and significant when baseline eGFR was <45 ml/min/1.73 m^2.

HARMS OF ASPIRIN ACCORDING TO eGFR CATEGORY. In the overall study population, aspirin increased the risk of major bleeding by 61% (HR: 1.61, 95% CI: 1.21 to 2.14) (Fig. 4). The risk of major bleeding associated with aspirin was nonsignificantly greater with categories of lower eGFR (HR: 2.81, 95% CI: 0.90 to 8.84 for eGFR <45 ml/min/1.73 m^2; HR: 1.70, 95% CI: 0.74 to 3.88 for eGFR 45 to 59 ml/min/1.73 m^2; and HR: 1.52, 95% CI: 1.11 to 2.08 for eGFR ≥60 ml/min/1.73 m^2; p trend = 0.30). There were 15 fatal bleeds in the study, 7 among subjects assigned aspirin therapy and 8 among subjects assigned placebo. All fatal bleeds were in subjects with an eGFR ≥60 ml/min/1.73 m^2. There was a trend toward an increased risk of any bleeding as categories of eGFR declined, although the absolute numbers of events in subjects with reduced kidney function were few (p for interaction = 0.08). There was no interaction between assignment to different diastolic blood pressure targets and assignment to aspirin (all p values for interaction > 0.2; data not shown).

Net absolute effect. Overall, 6 major cardiovascular events will be prevented for every 1,000 participants treated for 3.8 years, while there will be 6 major bleeds and 6 minor bleeds (Table 2). Both the benefits and risks increase as kidney function declines, with the net benefit appearing to increase. For every 1,000 people with eGFR <45 ml/min/1.73 m^2 treated with aspirin for 3.8 years, 76 people will avoid a major cardiovascular event, and 40 myocardial infarctions, 40 strokes, 40 cardiovascular deaths, and 54 all-cause deaths will be prevented. Conversely, 27 major bleeding episodes and 12 minor bleeding episodes would be caused by aspirin therapy for persons with an eGFR <45 ml/min/1.73 m^2.

Effect of aspirin on kidney function. Aspirin therapy did not affect renal function in the overall study population nor within any eGFR category (Table 3).

Discussion

Safe treatments to reduce the high risk of cardiovascular disease for patients with CKD are urgently required. In this analysis, we confirm that aspirin therapy prevented significantly more cardiovascular events, cardiovascular deaths, and all-cause deaths in patients with CKD than in subjects with normal kidney function. Aspirin therapy had no detrimental effect on renal function. Although the absolute risk of bleeding was greater for subjects with CKD, the overall cardiovascular benefits appear to outweigh bleeding risks. These results suggest that primary prevention with aspirin reduces the burden of cardiovascular disease and has an overall net benefit among high-risk patients with CKD.

Our analysis confirms previous findings in the HOT study population and in other studies that cardiovascular risk increases with declining CKD stage (5–7,28,29). Overall, the HOT study participants were at low risk, with a 5-year rate of myocardial infarction of 2.9% and of major cardiovascular events of 5.1%, observed in the control arm. However, the HOT study participants with stage 3b CKD randomly assigned to placebo had a 5-year myocardial infarction rate of 7.7%, with a 5-year major cardiovascular event rate of 15.5%. These high event rates underscore the need for a clear understanding of the risks and benefits of potentially effective preventative therapies.

Aspirin appears to produce greater absolute benefits for patients with CKD. The explanation for this greater benefit lies partly in the high baseline risk of these patients, translating a similar proportional benefit into a greater absolute benefit. In addition, the current analysis demonstrates greater proportional benefits with progressively lower eGFR. The explanation for this difference in proportional benefit is unclear. Patients with advanced CKD are known to have abnormal platelet function and evidence of a predisposition to both thrombotic and bleeding events. Patients with all stages of CKD (30–33) have higher rates of thromboembolism than the general population. Conversely, patients with kidney disease appear to have an increased bleeding risk, with evidence in advanced kidney disease of decreased platelet aggregation and of a range of platelet abnormalities (34–37). Observational and randomized clinical studies in dialysis patients sometimes (38), but not always, report increased bleeding rates with antiplatelet therapy (39–41), although some of these studies excluded those at high bleeding risk.

There are few other randomized trials describing the effects of antiplatelet therapy involving substantial numbers of subjects with CKD. The Antithrombotic Trialists' Collaborative Group reported the results of an individual

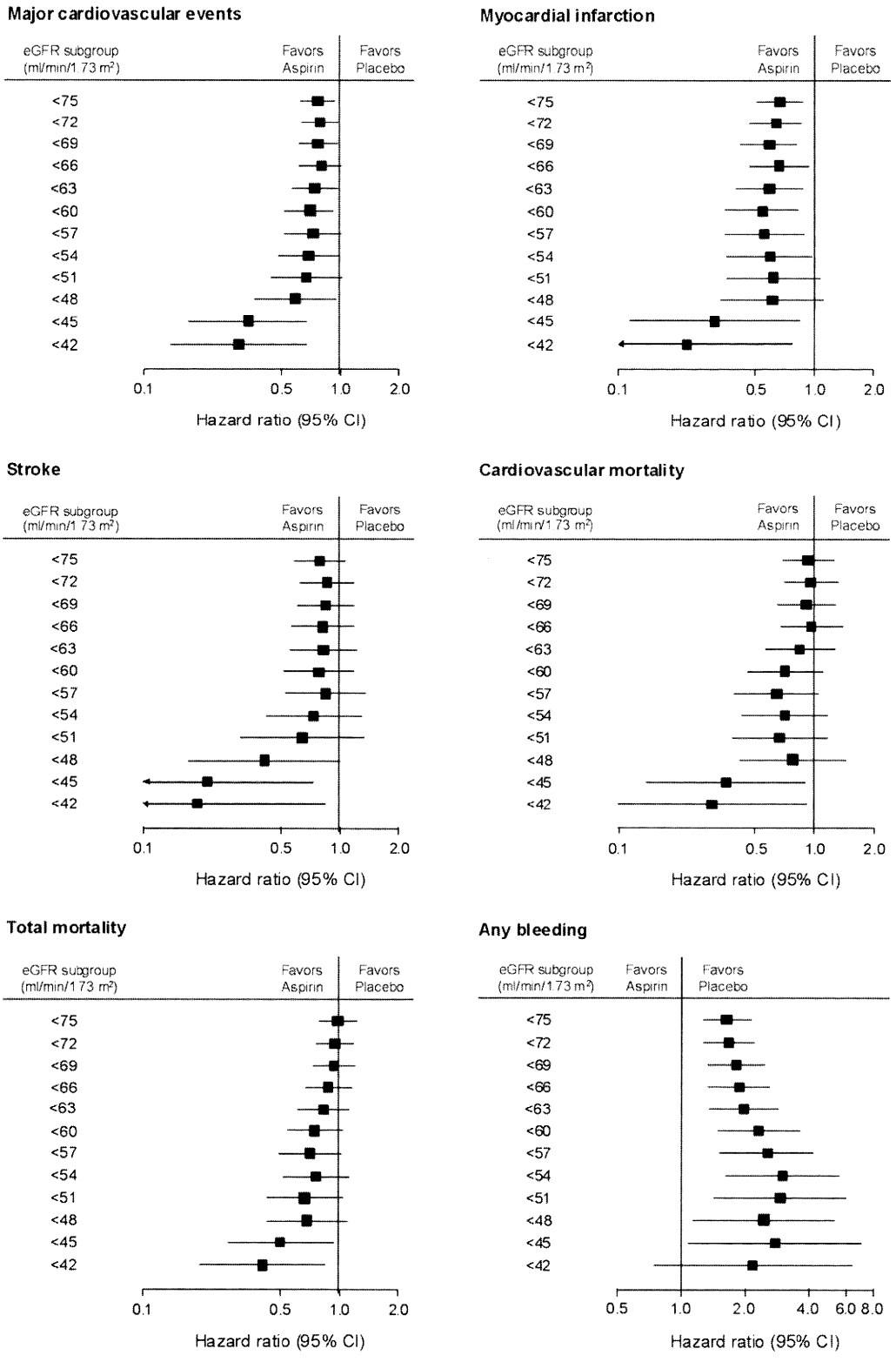

Figure 3 **Effect of Aspirin on End Points**

The effects of aspirin treatment on end points in the subgroup below each cut-off value of estimated glomerular filtration rate (eGFR). CI = confidence interval.

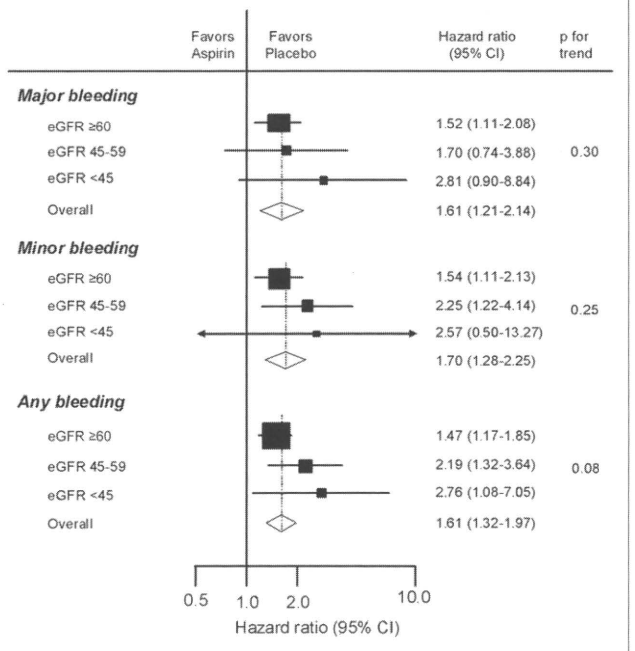

Figure 4 Effect of Aspirin on Bleeding Rates

Effect of randomization to aspirin on bleeding rates according to estimated glomerular filtration rate (eGFR) category. CI = confidence interval.

patient data meta-analysis of antiplatelet therapy that included 99 cardiovascular events in 2,632 hemodialysis patients. They found a 41% odds reduction (SE 16%) in the risk of cardiovascular events among hemodialysis patients (40), compared with a 22% odds reduction (SE 2%) seen in the overall study population, although the difference was not statistically significant. The efficacy and harm of aspirin and other antiplatelet agents may not be homogeneous. Post-hoc analyses of the effect of additional clopidogrel over standard therapy according to GFR categories has shown a benefit consistent with that in the population with normal renal function in some (42) but not all (29) studies. For patients with diabetes and albuminuria, the addition of clopidogrel to aspirin was associated with increased mortality not seen in nonalbuminuric diabetic patients or nondiabetic patients in a post-hoc analysis (43).

This analysis has some important limitations. Only 2.9% of the study population had an eGFR <45 ml/min/1.73 m^2, limiting our power to estimate bleeding risk in this group. The small number of participants with CKD stage 4 and above (98 had an eGFR <30 ml/min/1.73 m^2) mean the findings cannot be extrapolated to patients with severe CKD or end-stage kidney disease. In addition, the HOT study, as in many randomized trials of aspirin administration, did not report bleeding episodes with the same precision as cardiovascular outcomes, and bleeding episodes were not validated by an expert committee. Furthermore, this is a post-hoc analysis of a trial that was not designed (or powered) to examine the effects of aspirin according to categories of kidney function. Finally, the participants in this trial were at increased cardiovascular risk due to the blood pressure–based entry criteria, meaning extrapolation to persons with normal blood pressure levels is not possible.

Our results indicate that CKD predicts increased cardiovascular risk and greater net benefit with aspirin therapy.

Table 3 Difference in Change in Renal Function During Follow-Up Between Group Randomized to Aspirin and Group Randomized to Placebo, According to eGFR Categories

eGFR Levels at Baseline (ml/min/1.73 m^2)	Annual Change in eGFR During Follow-Up for Aspirin Group Versus Placebo Group (ml/min/1.73 m^2 yr)	
	Mean (95% Confidence Interval)*	p Value
eGFR ≥60	−0.16 (−0.33 to 0.01)	0.06
eGFR 45–59	−0.08 (−0.37 to 0.21)	0.57
eGFR <45	0.30 (−0.74 to 1.34)	0.57
Overall	−0.15 (−0.30 to 0.00)	0.06

*The difference in the annual changing rate of estimated glomerular filtration rate (eGFR) during follow-up was estimated by subtracting the mean annual changing rate of eGFR in the placebo group from that in the aspirin group. Negative value indicates greater reduction in eGFR during follow-up in the aspirin group than the placebo group.

Table 2 Events Prevented and Caused by Aspirin Therapy for Every 1,000 Patients Treated According to eGFR Category

	eGFR, ml/min/1.73 m^2			
	≥60	45–59	<45	Overall
Events prevented by aspirin therapy				
Major cardiovascular events	3 (−3 to 8)	8 (−7 to 22)	76 (31 to 121)	6 (0 to 11)
Myocardial infarctions	4 (0 to 8)	10 (−1 to 20)	40 (7 to 72)	6 (2 to 10)
Stroke	−1 (−5 to 2)	0 (−11 to 10)	40 (11 to 69)	0 (−3 to 4)
Cardiovascular mortality	−1 (−5 to 3)	2 (−8 to 11)	40 (6 to 74)	1 (−3 to 4)
Total mortality	0 (−5 to 5)	4 (−9 to 17)	54 (7 to 100)	2 (−3 to 7)
Events caused by aspirin therapy				
Major bleeding	4 (1 to 8)	4 (−2 to 10)	27 (−1 to 55)	6 (3 to 8)
Minor bleeding	4 (1 to 8)	12 (3 to 21)	12 (−8 to 31)	6 (2 to 9)
Any bleeding	8 (3 to 12)	16 (5 to 27)	39 (5 to 72)	10 (6 to 14)

Values are absolute risk change (95% confidence interval) per 1,000 patients treated for an average of 3.8 years.
eGFR = estimated glomerular filtration rate.

This finding reinforces calls to consider CKD when making decisions regarding treatment to mitigate cardiovascular risk. These results suggest that aspirin might be used more widely as primary prevention for high-risk patients with CKD.

Acknowledgment

The authors gratefully acknowledge the kind assistance of Ingrid Warnold, PhD, AstraZeneca, Mölndal, Sweden.

Reprint requests and correspondence: Dr. Vlado Perkovic, The George Institute for Global Health, KGV Building, RPAH, Missenden Road, Camperdown, New South Wales 2050, Australia. E-mail: vperkovic@george.org.au.

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Key Words: aspirin ■ bleeding ■ cardiovascular risk ■ chronic kidney disease ■ mortality ■ primary prevention ■ risk-benefit analysis.

European Heart Journal (2010) **31**, 2888–2896
doi:10.1093/eurheartj/ehq139

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

Hiddo J. Lambers Heerspink[1,2], Toshiharu Ninomiya[1], Vlado Perkovic[1]*, Mark Woodward[3], Sophia Zoungas[1,4], Alan Cass[1], Mark Cooper[5], Diederick E. Grobbee[6], Giuseppe Mancia[7], Carl Eric Mogensen[8], Bruce Neal[1], and John Chalmers[1], for the ADVANCE Collaborative Group†

[1]The George Institute for International Health, University of Sydney, Missenden Road, Camperdown, Sydney, NSW 2050, Australia; [2]Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Mount Sinai School of Medicine, New York, NY, USA; [4]School of Public Health, Monash University, Melbourne, Australia; [5]Baker IDI Heart Research Institute, Melbourne, Australia; [6]Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [7]University of Milan_Bicocca and San Gerardo Hospital, Milan, Italy; and [8]Medical Department M, Aarhus, University Hospital, Aarhus Sygehus, Aarhus C, Denmark

Received 15 December 2009; revised 30 March 2010; accepted 9 April 2010; online publish-ahead-of-print 25 May 2010

See page 2837 for the editorial comment on this article (doi:10.1093/eurheartj/ehq281)

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

* Corresponding author. Tel: +61 2 9993 4500, Fax: +61 2 9993 4502, Email: vperkovic@george.org.au

† See online Supplementary material appendix for additional authors.

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

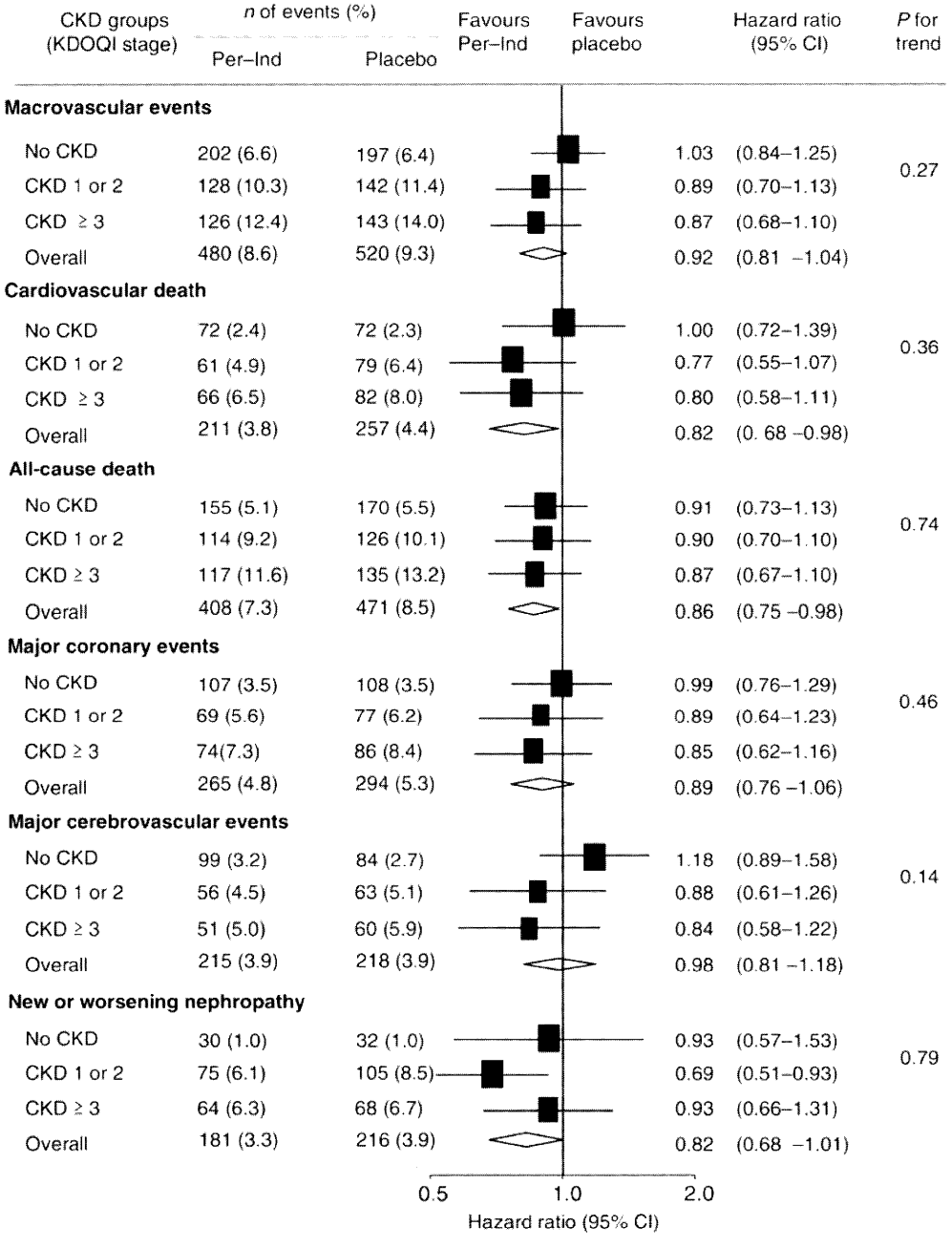

Figure 1 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline KDOQI CKD stage. The centre of the diamond represents the overall estimate and the width its 95% confidence interval (CI) as previously reported by Patel *et al.*[6] Solid boxes 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

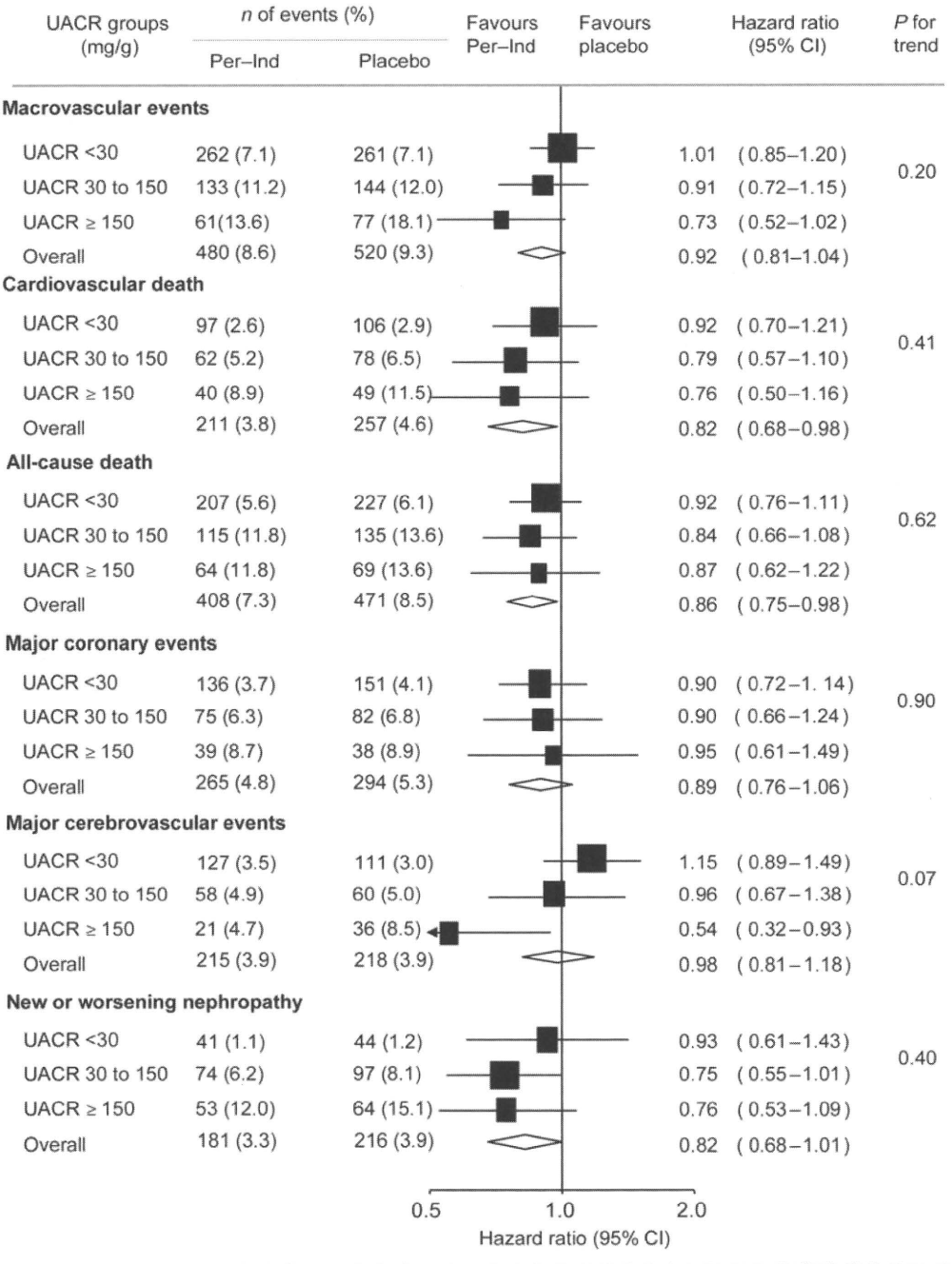

Figure 2 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline UACR. The centre of the diamond represents the overall estimate and the width its 95% CI as previously reported by Patel *et al.*[6] Solid boxes represent estimates of treatment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

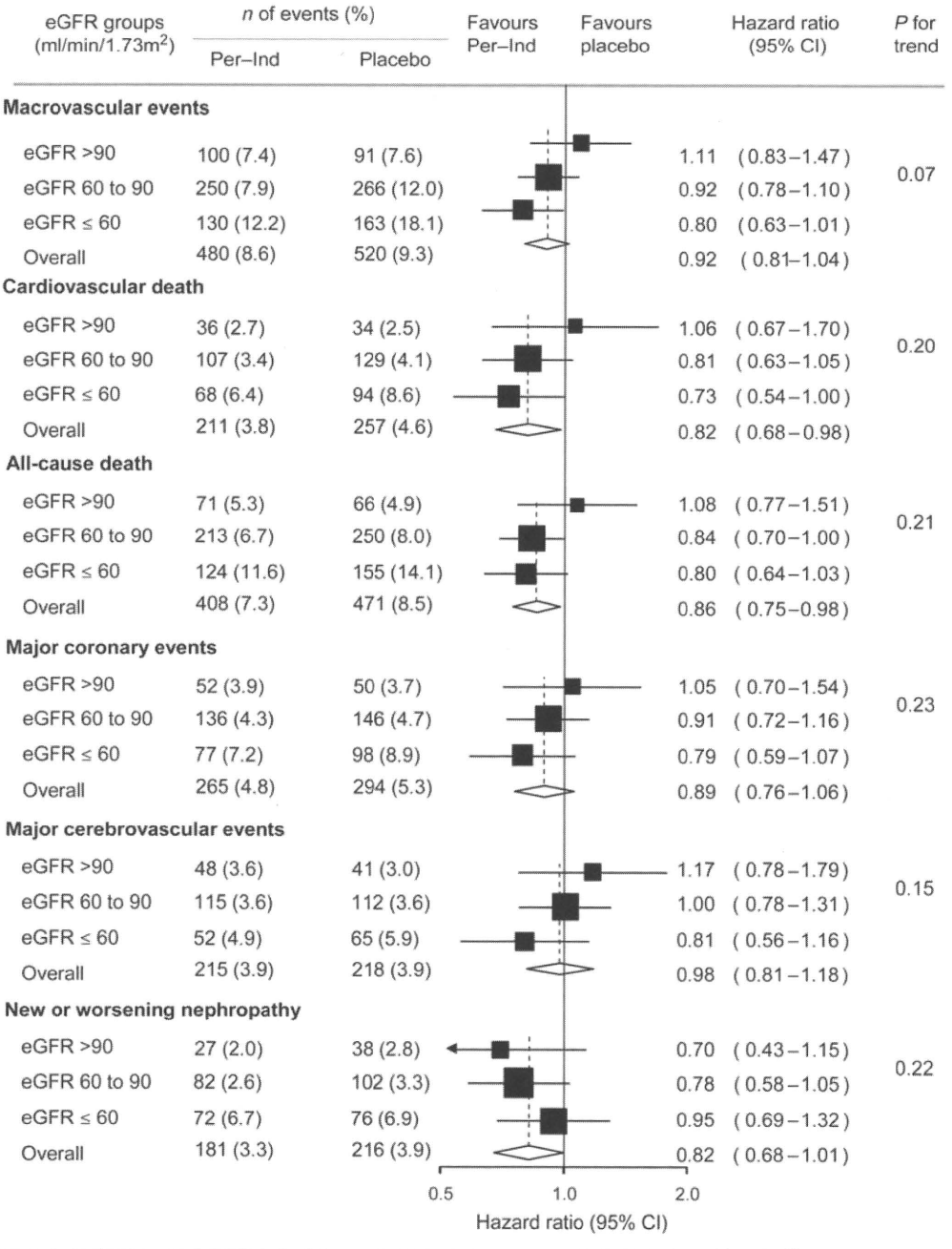

Figure 3 Effect of randomized treatment on the risk for cardiovascular or renal outcomes in patients according to baseline eGFR. The centre of the diamond represents the overall estimate and the width its 95% CI as previously reported by Patel *et al.*[6] Solid boxes represent estimates of treatment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

Acknowledgements

All members of the ADVANCE collaborative study group have been listed in full in the appendix provided as Supplementary material online. We thank the patients and all of the investigators at the participating centres. H.J. Lambers Heerspink was supported by a Fellowship from the Dutch Kidney Foundation and International Society of Hypertension Visiting Postdoctoral Fellowship awarded by the Foundation for High Blood Pressure Research Council of Australia.

Funding

The ADVANCE trial was supported by grants from Servier and the National Health and Medical Research Council Australia (211086 and 358395).

Conflict of interest. J.C. hold research grants from Servier as principal investigator for ADVANCE. J.C., V.P., M.W., S.Z., A. Patel, A.C., M.C., D.E.G., S. Harrap, G.M., C.E.M. and B.N. have received lecturing fees from Servier.

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Efficacy and safety of routine blood pressure lowering in older patients with diabetes: results from the ADVANCE trial

Toshiharu Ninomiya[a], Sophia Zoungas[a,b], Bruce Neal[a], Mark Woodward[a,c], Anushka Patel[a], Vlado Perkovic[a], Alan Cass[a], Mark Cooper[d], Diederick Grobbee[e], Pavel Hamet[f], Stephen Harrap[g], Lisheng Liu[h], Giuseppe Mancia[i], Carl-Erik Mogensen[j], Neil Poulter[k], Anthony Rodgers[a], Bryan Williams[l], Stephen MacMahon[a], John Chalmers[a], on behalf of the ADVANCE Collaborative Group

Objective **The efficacy and safety of blood pressure lowering in elderly patients have not been sufficiently investigated in patients with diabetes. Using data from the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation study, we assessed the efficacy and safety of routine blood pressure lowering to prevent major clinical outcomes in elderly patients with type 2 diabetes.**

Methods **Eleven thousand one hundred and forty patients aged at least 55 years with type 2 diabetes (mean 66 ± 6 years) were randomly assigned to perindopril–indapamide or placebo. The primary endpoint was a composite of major macrovascular and microvascular disease. The effects of active treatment on outcomes were estimated in subgroups according to age: below 65, 65–74 and at least 75 years.**

Results **During a mean 4.3-year follow-up, 1799 (16.1%) patients experienced a major event. Active treatment produced similar relative risk reductions for the primary outcome, major macrovascular disease, death and renal events across age groups (all *P* heterogeneity >0.3). Over 5 years, active treatment was estimated to prevent one primary outcome in every 21, 71 and 118 patients of at least75, 65–74 and below 65 years, respectively. Similar patterns of benefits were observed for secondary outcomes. There were no differences in the tolerability between randomized allocations across age groups (all *P* heterogeneity >0.6)**

Conclusion **Routine administration of perindopril–indapamide lowers blood pressure safely and reduces the risk of major clinical outcomes in patients of at least 75 years with type 2 diabetes. The greater absolute benefits in older patients in this age group were not offset by an increased risk of side effects. *J Hypertens* 28:1141–1149**

Journal of Hypertension 2010, 28:1141–1149

Keywords: age, blood pressure, blood pressure lowering, cardiovascular disease, elderly, perindopril–indapamide

Abbreviation: eGFR, estimated glomerular filtration rate

[a]The George Institute for International Health, University of Sydney, Sydney, New South Wales, [b]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [c]Mount Sinai School of Medicine, New York, New York, USA, [d]Baker Heart Research Institute, Melbourne, New South Wales, Australia, [e]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands, [f]Centre hospitalier de l'Université de Montréal (CHUM), Montreal, Canada, [g]University of Melbourne and Royal Melbourne Hospital, Melbourne, New South Wales, Australia, [h]Chinese Hypertension League Institute, Beijing, China, [i]University of Milan–Bicocca and San Gerardo Hospital, Milan, Italy, [j]Medical Department M, Aarhus University Hospital, Aarhus Sygehus, Aarhus, Denmark, [k]Imperial College London, London and [l]University of Leicester School of Medicine and Leicester Royal Infirmary, Leicester, UK

Correspondence to Sophia Zoungas, MD, PhD, The George Institute for International Health, University of Sydney, Level 10, King George V Building, Royal Prince Alfred Hospital, Missenden Road Camperdown, Sydney NSW 2050, Australia
Tel: +61 2 9993 4589; fax: +61 2 9993 4502; e-mail: szoungas@george.org.au

Received 15 September 2009 **Revised** 10 February 2010
Accepted 11 February 2010

Introduction

The proportion of older people is increasing rapidly in most countries, and cardiovascular disease is a leading cause of death and disability among the elderly [1–4]. Blood pressure (BP) rises steadily with age in industrialized societies, so that BP lowering becomes increasingly important for the prevention of cardiovascular disease in the elderly [5].

Current guidelines for the management of hypertension recommend a target BP level of less than 140/90 mmHg in older people, as well as in younger people [6–9]. Although a number of observational studies [10–12] have shown that BP levels are strongly and directly related to the risk of cardiovascular disease at all ages, the strength of the association appears to change with age (declining in proportional terms but increasing in absolute terms). To date, there are very few studies addressing these relationships in patients with type 2 diabetes [13]. Nevertheless, a number of randomized trials [14–26] have demonstrated substantial benefits of BP-lowering therapy in older people with hypertension. In addition, a large overview [27] of data from randomized trials concluded that the proportional effects of antihypertensive therapy

0263-6352 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e328338a89c

were not significantly different for people aged above and below 65 years. In older people with type 2 diabetes, the safety and efficacy of this approach has not been sufficiently examined [28].

The BP-lowering arm of the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study recently reported that the routine administration of a fixed combination of the angiotensin-converting enzyme inhibitor, perindopril, and the diuretic, indapamide, to a broad cross-section of patients with type 2 diabetes reduced the risk of death, cardiovascular and kidney outcomes, irrespective of initial levels of BP [29,30]. The aims of the current analyses were to examine the association between age and the risk of cardiovascular disease and to compare the efficacy and safety of routine BP lowering with the fixed combination of perindopril and indapamide for the prevention of major clinical outcomes in subgroups of patients aged below 65, 65–74 and at least 75 years with type 2 diabetes.

Methods

Study design and patients

ADVANCE is a factorial randomized controlled trial evaluating the effects of BP lowering and intensive blood glucose control on vascular outcomes. A detailed description of the design has been published previously [31]. In brief, 11 140 individuals with type 2 diabetes aged 55 years and older, with at least one additional risk factor for cardiovascular disease, were enrolled from 215 centres in 20 countries. There were no participant inclusion or exclusion criteria based on levels of BP. Eligible patients were randomly assigned to either a fixed combination of perindopril and indapamide (4 mg/1.25 mg) or matching placebo and to either a gliclazide (modified release)-based intensive glucose control regimen or to standard glucose control based on local guidelines of participating countries, after a 6-week active run-in period with perindopril–indapamide. Approval for the trial was obtained from each centre's institutional review board, and all patients provided written informed consent.

Follow-up and assessments

Patients were seen at 3, 4 and 6 months after randomization, and subsequently every 6 months. At study visits, information on adherence to, and tolerability of, study treatments, BP, blood glucose, haemoglobin (Hb)A1c, lipid levels, urinary albumin–creatinine ratio, serum creatinine and occurrence of study outcomes was obtained. The measurement of biochemistry was conducted at local laboratories. BP was recorded as the mean of two measurements made in the seated position using an automated sphygmomanometer (Omron HEM-705 CP, Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated by the four-variable Modification of Diet in Renal Disease equation [32].

Outcomes

The primary study outcome was a composite of major macrovascular and microvascular disease, as defined previously [29]. Secondary outcomes included major macrovascular disease (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke), all-cause mortality, cardiovascular death and total renal events (development of micro or macroalbuminuria, doubling of serum creatinine to a level of at least 200 μmol/l, need for renal replacement therapy and death due to renal disease). Only the first event of the relevant outcome type was included in each analysis. All these events, except for new-onset microalbuminuria, were reviewed and validated by an independent end point adjudication committee.

Data analysis

For the purpose of these analyses, follow-up was restricted to the perindopril–indapamide versus placebo arm of ADVANCE, which terminated after a median follow-up of 4.3 years. Patients 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 prior to termination of this arm of the study.

Observational analyses of the effects of aging on the risks of major clinical outcomes

The hazard ratios for each outcome in each baseline age group categorized into equal fifths were estimated using a univariate Cox proprotional hazard regression model. Multivariate-adjusted analyses were also conducted by using Cox model including potential confounding baseline covariates, including sex, duration of diabetes, urinary albumin–creatinine ratio, eGFR, SBP, history of currently treated hypertension, history of macrovascular disease, HbA1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, BMI, ECG abnormalities, current smoking, current drinking, randomized BP treatment and randomized glucose treatment. Only patients without missing data for all these variables were included in these analyses; this led to the exclusion of only 4.5% of the participants. The linear relationships between age as a categorical variable and the log hazard ratio of outcomes were tested by using Cox models including the median value of age for each category. The variances of each log hazard ratio were calculated by using the floating absolute risk method [33,34]. The regression lines for the log hazard ratio according to age groups were fitted using regression analysis with inverse variance weighting [34].

Effects of randomized blood pressure-lowering treatment on major clinical outcomes or the tolerability to study treatment according to age

Trial participants were subdivided into three age groups (<65, 65–74 and ≥75 years). Differences between

randomized groups in BP during follow-up were estimated from linear mixed models after adjusting for BP levels at baseline. The effects of randomized BP-lowering treatment on primary and secondary outcomes were estimated from univariate Cox proportional hazard regression models, according to the intention-to-treat principle. The odds of discontinuation were estimated for active treatment compared with placebo with univariate logistic regression models. The heterogeneity in the effects between age groups was tested by adding interaction terms to the relevant model. The absolute risk reduction over 5 years for major clinical outcomes were calculated as the differences in the incidence rates of the outcome over 5 years between randomized treatment groups, in which the incidence rates over 5 years were estimated under the assumption of constant probability of the event each year [34]. Absolute risk reduction for major clinical outcome without causing side effects were estimated as the difference in absolute risk reduction on major clinical outcomes and the absolute risk increments of relevant side effects.

The SAS software package for Windows, version 9.1 (SAS Institute, Inc., Cary, North Carolina, USA) was used to perform statistical analyses. All *P* values were calculated from two-tailed tests of statistical significance with a type I error rate of 5%.

Results

Baseline characteristics

Of 11 140 randomized patients, there were 4527 (40.6%) participants aged below 65 years, 5605 (50.3%) participants aged 65–74 years and 1008 (9.1%) participants aged at least 75 years. The characteristics according to age group are summarized in Table 1. Compared with patients below 65 years of age, patients of 65–74 and at

Table 1 Baseline characteristics of patients according to age group

Variables	Age groups (years)			*P* for trend
	<65 (*n* = 4527)	65–74 (*n* = 5605)	≥75 (*n* = 1008)	
Age [years, median (IQR)]	60 (57–62)	68 (66–71)	77 (76–79)	<0.0001
Women, *n* (%)	1953 (43)	2379 (42)	403 (40)	0.09
Duration of diabetes [years, median (IQR)]	7 (3–11)	7 (3–11)	7 (3–12)	0.002
BP				
SBP [mmHg, mean (SD)]	142 (21)	146 (22)	151 (22)	<0.0001
DBP [mmHg, mean (SD)]	82 (11)	80 (11)	78 (11)	<0.0001
BP level of ≥140/90 mmHg, *n* (%)	2494 (55)	3440 (61)	678 (67)	<0.0001
Kidney factors				
Urinary albumin–creatinine ratio [mg/g, median (IQR)]	15.0 (7.0–42.4)	14.5 (7.1–35.4)	16.8 (7.5–45.1)	0.74
Serum creatinine [μmol/l, median (IQR)]	80 (69–94)	86 (72–99)	91 (80–107)	<0.0001
eGFR [ml/min per 1.73 m^2, median (IQR)]	80 (68–94)	73 (62–87)	66 (55–76)	<0.0001
Previous vascular disease				
History of macrovascular disease, *n* (%)	1574 (35)	1646 (29)	370 (37)	0.05
History of MI, *n* (%)	547 (12)	624 (11)	163 (16)	0.06
History of stroke, *n* (%)	425 (9)	476 (8)	121 (12)	0.26
Other major risk factors				
HbA1c [%, mean (SD)]	7.7 (1.7)	7.4 (1.5)	7.3 (1.4)	<0.0001
Serum total cholesterol [mmol/l, mean (SD)]	5.3 (1.3)	5.1 (1.1)	5.0 (1.1)	<0.0001
Serum LDL-cholesterol [mmol/l, mean (SD)]	3.2 (1.1)	3.1 (1.0)	3.0 (1.0)	<0.0001
Serum HDL-cholesterol [mmol/l, mean (SD)]	1.2 (0.4)	1.3 (0.4)	1.3 (0.3)	<0.0001
Serum triglycerides [mmol/l, median (IQR)]	1.8 (1.3–2.5)	1.6 (1.1–2.2)	1.5 (1.1–2.1)	<0.0001
BMI [kg/m^2, mean (SD)]	28.8 (5.6)	28.1 (4.9)	27.8 (4.6)	<0.0001
ECG abnormalities[a], *n* (%)	727 (16)	989 (18)	263 (26)	<0.0001
Current smoker, *n* (%)	1073 (24)	549 (10)	60 (6)	<0.0001
Current drinker, *n* (%)	1325 (29)	1703 (30)	368 (37)	0.0001
BP-lowering drugs				
Any BP-lowering drug, *n* (%)	3350 (74)	4223 (75)	793 (79)	0.003
ACE-I, *n* (%)	1958 (43)	2349 (42)	483 (48)	0.19
ARB, *n* (%)	202 (4)	329 (6)	78 (8)	<0.0001
Calcium antagonists, *n* (%)	1342 (30)	1769 (32)	316 (31)	0.07
β-blockers, *n* (%)	1179 (26)	1317 (23)	233 (23)	0.004
Diuretics, *n* (%)	1039 (23)	1290 (23)	311 (31)	<0.0001
Other BP-lowering drug, *n* (%)	554 (12)	735 (13)	94 (9)	0.24
Other drug				
Aspirin, *n* (%)	1990 (44)	2452 (44)	452 (45)	0.79
Statins, *n* (%)	1283 (28)	1596 (28)	267 (26)	0.43
Any oral hypoglycaemic drug, *n* (%)	4170 (92)	5076 (91)	883 (88)	<0.0001
Insulin, *n* (%)	68 (2)	74 (1)	17 (2)	0.96
Randomized treatment				
Perindopril–indapamide, *n* (%)	2251 (50)	2835 (51)	483 (48)	0.74
Intensive glucose lowering, *n* (%)	2275 (50)	2805 (50)	491 (49)	0.45

ACE-I, angiotnesin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; SD, standard deviation; IQR, interquartile range. [a]ECG abnormalities were defined as presence of Q waves consistent with prior MI, left ventricular hypertrophy and atrial fibrillation.

least 75 years had progressively higher BP and serum creatinine levels, and lower eGFR, HbA1c levels, cholesterol and triglyceride levels, and BMI. Patients of at least 75 years of age were also more likely to have ECG abnormalities or consume alcohol, but were less likely to be smokers. BP levels of at least 140/90 mmHg were more frequent in patients of at least 75 years as was the use of BP-lowering agents. Patients of at least 75 years were more likely to be prescribed angiotensin-II receptor blockers and diuretics, and less likely to be prescribed a β-blocker.

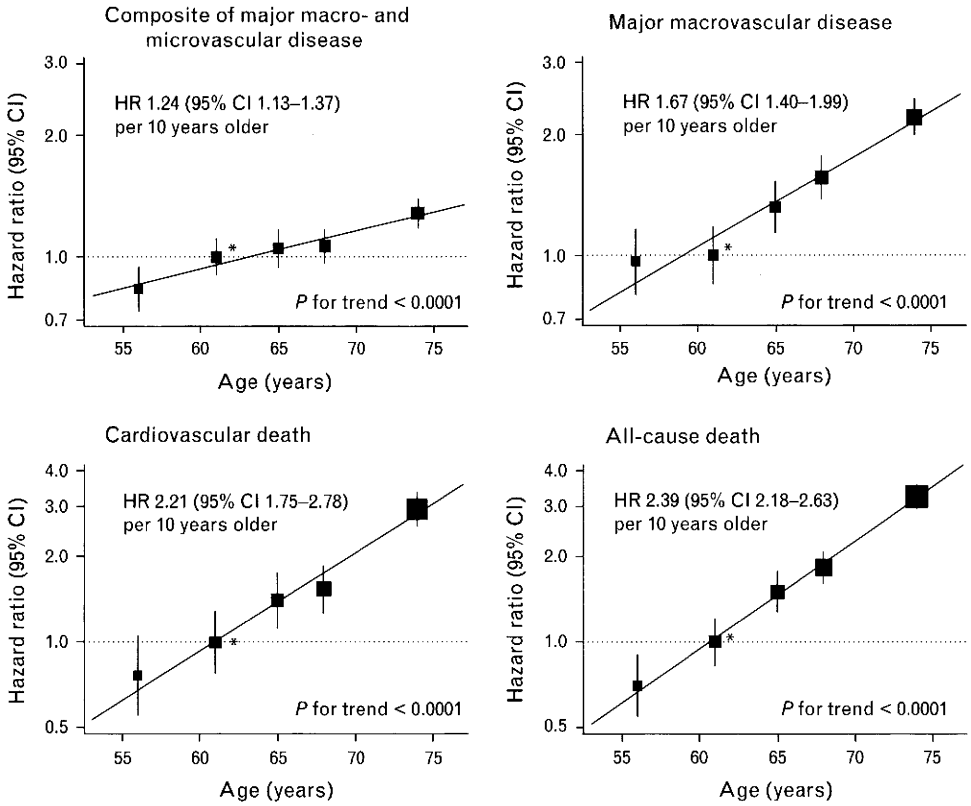
Observational analyses of the effects of aging on the risks of major clinical outcomes

During an average of 4.3 years of follow-up, a total of 1799 patients (16.1%) experienced a major macrovascular or microvascular event, 1000 experienced (9.0%) a major macrovascular event and 2683 experienced (24.1%) a renal event. Moreover, 879 patients (7.9%) died, 468 due to cardiovascular causes. Every 10-year increase in age was associated with a 24% [95% confidence interval (CI) 13–37] greater risk of a major macrovascular or microvascular event (Fig. 1). Likewise, the risk of major cardiovascular events, cardiovascular death and all-cause death increased by 67% (95% CI 40–99), 121% (95% CI 75–178) and 139% (95% CI 118–163) for every 10-year increase in age, respectively. These log–linear associations were observed even after adjustment for potential confounding factors (all P for trend <0.008). These relationships were similar irrespective of treatment allocation (all P for heterogeneity >0.16) There was a modest effect of aging on the risk of total renal events [hazard ratio 1.05 (95% CI 1.01–1.10) for every 10-year increase in age].

Effects of randomized blood pressure-lowering treatment on major clinical outcomes in older compared with younger people

During follow-up, active treatment with perindopril–indapamide compared with placebo reduced BP by 5.5/2.2 mmHg (SE 0.3/0.2), by 5.5/2.2 mmHg (SE 0.3/0.2) and by 6.9/2.3 mmHg (SE 0.8/0.4) in patients aged below 65, 65–74 and at least 75 years, respectively (P for heterogeneity = 0.21 for SBP and P for

Fig. 1



The relationship between age and the risk of major clinical outcomes. The centres of the square are placed at the point estimates and vertical lines represent the corresponding 95% CIs. The area of each square is proportional to the inverse variance of each estimate. The cutoff values of quintiles of age were 59, 64, 67 and 71 years and the median values of age were 56, 61, 65, 68 and 74 years, respectively. Asterisk indicates the reference group. CI, confidence interval; HR hazard ratio.