with equal numbers allocated to active blood pressure treatment and placebo. Half-way through follow-up, the overall event rates (in active and placebo groups combined) were lower than expected. To enhance the statistical power of the trial to detect plausible treatment e ects, two amendments dated Nov 30, 2005, were made to the study protocol: "rst, analyses of the primary outcomes were extended to include consideration of major macrovascular and microvascular events jointly as well as separately; and second, treatment and follow-up in the blood pressure arm was extended by 12 months.

Thus, the protocol pre-specie"d that the composite of major mascrovascular and microvasular outcomes would be included in the analyses of the primary outcomes. All analyses would also be by intention to treat. The e ects of treatment on the primary and secondary endpoints were estimated from unadjusted Cox proportional hazard models. For participants with more than one outcome event during follow-up, survival time to the "rst 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 visit. Patients with an unknown vital status were censored when they were last known to be alive. Relative risk reductions are described in the text and "gures as percentage reductions ([1…hazard ratio]×100). Di erences between randomised groups during follow-up, in blood pressure and other continuous variables, were estimated from linear mixed models. Numbers needed to treat were calculated as reciprocals of the absolute risk di erences with their normally-approximated 95% CIs.[14] All p values were calculated from two-tailed tests of statistical sig"cance with a Type I error rate of 5%. As is common practice in the analysis of data from large scale trials in which all major outcomes are reported (many of which are correlated), no adjustment for multiple statistical testing was done.[15]

Separate estimates for treatment e ects were obtained among subgroups of participants de"ned by age, sex, history of vascular disease, ancillary treatments, blood pressure, and HbA_{1c} at study entry. No subgroup analyses were pre-specie"d. Homogeneity of treatment e ects for both categorical and continuous variables was tested by adding interaction terms to the relevant Cox models. All analyses were done using SAS version 9.1.

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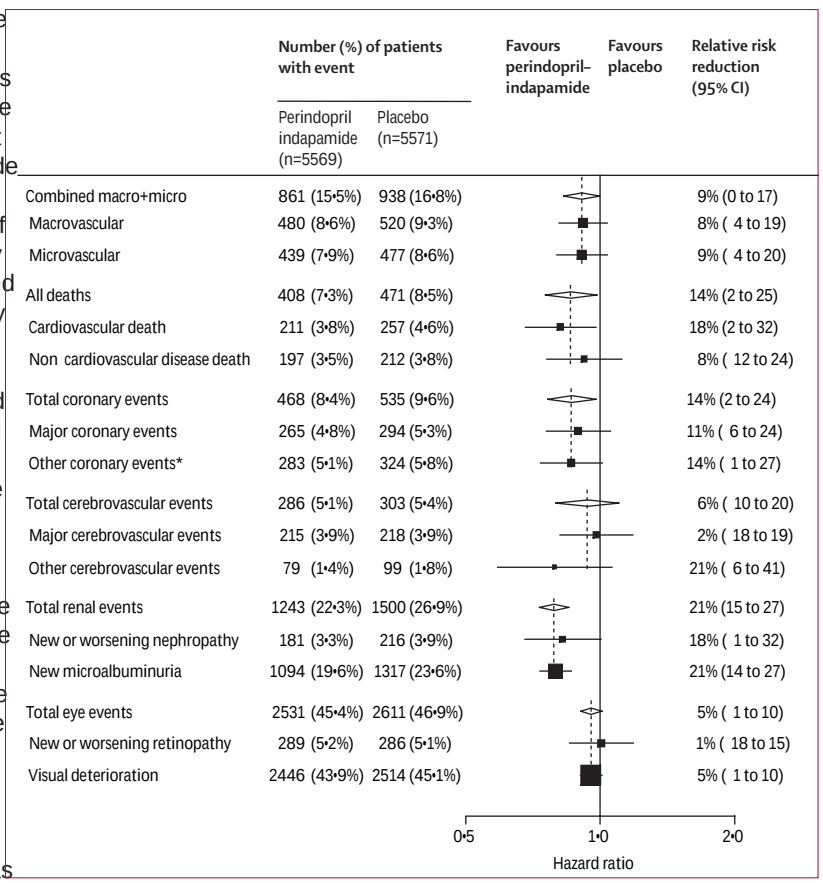

Figure **Effects of study treatment on deaths, coronary events, cerebrovascular events, renal events, and eye events**

*Other coronary events=unstable angina requiring hospitalisation, coronary revascularisation or silent myocardial infarction. Other cerebrovascular events=transient ischaemic attack (including amaurosis fugax) or subarachnoid haemorrhage. Black squares=point estimates (with area proportional to number of events); horizontal lines=95% CI. Diamonds=point estimate and 95% CI for overall e ects. Vertical broken lines=point estimates for overall e ect, within categories.

Results

12 877 potentially eligible participants were registered, 1737 (13·5%) were subsequently withdrawn during the 6-week active run-in period, and 11 140 (86·5%) were randomised ("gure 1). As would be expected in a population of this size, there was good balance between randomised groups across a range of characteristics at entry (tables 1 and 2). Around a third of patients had a history of major macrovascular disease and about 10% had a history of major microvascular disease at baseline (table 1). The mean entry blood pressure of randomised patients was 145/81 mm Hg and 41% had a blood pressure less than 140 mm Hg systolic and 90 mm Hg diastolic. At randomisation, 47% of patients were receiving treatment with open-label perindopril (2…4 mg a day). Additionally, 47% of patients were receiving anti-platelet therapy, 35% were receiving cholesterol lowering drugs, and 91% were receiving oral hypoglycaemic agents at baseline (table 2).

The mean duration of follow-up was 4·3 years (24 005 patient-years in the active treatment group and

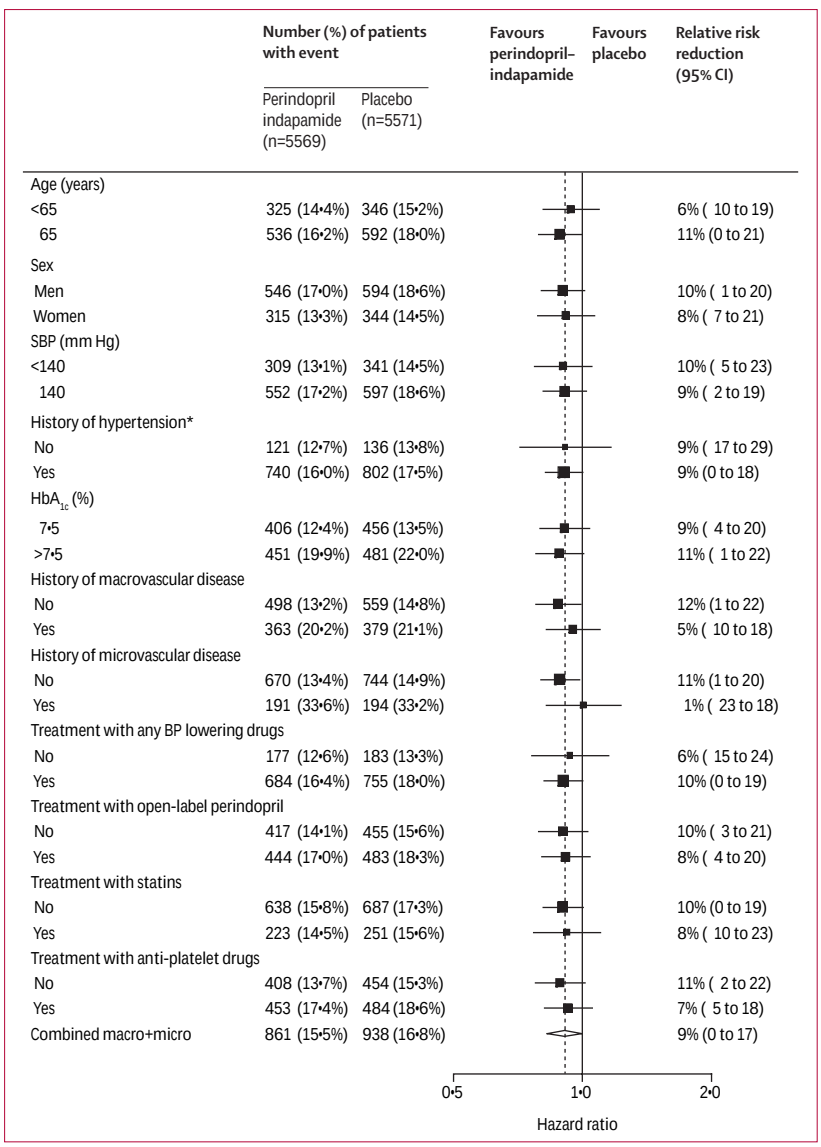

Figure **Effects of study treatment on combined major macrovascular or microvascular events in subgroups of participants defined by characteristics at baseline**
*History of hypertension=blood pressure lowering drugs used at baseline, or systolic pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at study entry. Vertical broken line=point estimate for overall e ect.

23 845 patient-years in the placebo group) and the range was from less than 1 month to 5·6 years. During follow-up, randomised treatment was continued for 20 001 patient-years (83%) in the active treatment group and 20 849 patient-years (87%) in the placebo group. At the end of follow-up, 4081 (73%) patients in the active treatment group and 4143 (74%) patients in the placebo group were adherent to randomised therapy. The main reasons for permanent discontinuation were participant decision or inability to attend clinic visits (active 521 [9·4%], placebo 635 [11·4%]), cough (active 184 [3·3%], placebo 72 [1·3%]) and hypotension or dizziness (active 69 [1·2%], placebo 22 [0·4%]), and serious adverse events (active 67 [1·2%], placebo 66 [1·2%]). Serious suspected adverse drug reactions were reported in 47 (0·8%) patients randomised to active treatment and 31 (0·6%) patients allocated placebo, including five cases of angioedema (three active, two placebo), none of which was fatal.

Over the duration of follow-up, blood pressure was reduced by an average of 5·6 (SE 0·2) mm Hg systolic and 2·2 (SE 0·1) mm Hg diastolic in patients assigned active treatment compared with those assigned placebo (Figure 2).

At the end of follow-up, mean levels of HbA_{1c} (6·9%), fasting plasma glucose (7·2 mmol/L), total cholesterol (5·0 mmol/L) and HDL cholesterol (1·0 mmol/L) were not di erent between randomised groups (all p>0·1). Fewer participants randomised to active treatment were taking other blood pressure lowering therapy (including background perindopril) at the final visit, compared with those allocated placebo (74% vs 83%) but use of lipid modifying therapy, antiplatelet medication, and glucose lowering treatments (including insulin) was similar (table 2). The large increase in insulin use during follow-up in both treatment groups mainly indicates the intensified glucose lowering regimen being studied in the other factorial arm of the trial.

1799 participants had a major macrovascular or a major microvascular event during follow-up: 861 (15·5%) in the active treatment group and 938 (16·8%) in the placebo group (relative risk reduction 9% [95% CI 0…17%; p=0·041]; Figure 3). On this basis, we estimated that one participant in every 66 (95% CI 34…1068) assigned active treatment would avoid at least one major macrovascular or microvascular event over 5 years. The proportional e ects of active treatment on major macrovascular outcomes (relative risk reduction 8% [95% CI …4 to 19%; p=0·16]) and major microvascular outcomes (9% […4 to 20%; p=0·16]) were similar, though not separately significant.

Data for vital status at the end of follow-up were missing for only 15 randomised participants (Figure 1). During the study 879 participants died: 408 (7·3%) in the active treatment group and 471 (8·5%) in the placebo group (relative risk reduction 14% [95% CI 2…25], p=0·025; Figure 3). Over 5 years, one death in every 79 (95% CI 43 to 483) patients assigned active treatment was estimated to have been averted. This reduction in total mortality was mainly due to a reduction in cardiovascular deaths (3·8% vs 4·6%; relative risk reduction 18% [95% CI 2 to 32%], p=0·027) in participants assigned active treatment, with no significant di erence between randomised groups in non-cardiovascular deaths (3·5% vs 3·8%; 8% […12 to 24%], p=0·41).

Significantly fewer total coronary events occurred in participants randomly assigned to active treatment compared with those assigned placebo (8·4% vs 9·6%; 14% [2…24%], p=0·020; Figure 4). Over 5 years, one patient in every 75 (95% CI 41…453) assigned active treatment would have avoided at least one coronary event. There

was no signi“cant di erence between randomised groups in either total cerebrovascular events (relative risk reduction 6% [95% CI …10 to 20%], p=0·42) or heart failure (2% […20 to 19%], p=0·86).

Active treatment was associated with a signi“cant 21% reduction in all renal events (95% CI 15…27%, p<0·0001), with a borderline signi“cant reduction in new or worsening nephropathy (3·3% vs 3·9%; relative risk reduction 18% […1 to 32%], p=0·055) and a signi“cant reduction in the development of microalbuminuria (19·6% vs 23·6%; 21% [14…27%]; p<0·0001). Over 5 years, one patient in every 20 (95% CI 15…30) assigned active treatment would have avoided one renal event (mostly the onset of new microalbuminuria). There was no signi“cant di erence between randomised groups in the rate of new or worsening retinopathy (relative risk reduction …1% […18 to 15%], p=0·94), including the need for retinal photocoagulation (…14% […41 to 8%], p=0·23).

There was also no signi“cant e ect of active treatment on any of the other secondary outcomes of visual deterioration (relative risk reduction 5% [95% CI …1 to 10%]; p=0·10), new or worsening neuropathy (1% […5 to 7%]; p=0·68), cognitive function (2% […9 to 12%], p=0·72), dementia (…4% […64% to 33%], p=0·85), and total hospitalisations (…3% […9% to 3%], p=0·39).

The e ects of study treatment on the combined major macrovascular and microvascular outcome were broadly consistent across a range of participant subgroups de“ned by baseline characteristics (p for heterogeneity all >0·1; “gure 5). Additionally, there was no evidence of an interaction between the eect of treatment and baseline systolic blood pressure considered as a continuous variable (p>0·5). Similarly, there was no evidence of heterogeneity of treatment e ects between the same subgroups for other outcomes including total mortality, cardiovascular death, total coronary events, total cerebrovascular events, and microalbuminuria (data not shown).

Discussion

In ADVANCE, the routine administration of a “xed combination of perindopril and indapamide to a broad range of patients with type 2 diabetes reduced the risk of death and the risk of major macrovascular or microvascular events. The separate reductions in macrovascular and microvascular events were similar but were not independently signi“cant. There were signi“ cant reductions in total coronary and renal events, but not in total cerebrovascular or diabetic eye events. The bene“ts were achieved against a background of medical care that, by the end of follow-up, included non-study drugs for lowering blood pressure for more than three-quarters of participants, and one or more glucose lowering agents for more than 90%, including insulin for a third of patients. The e ects of the study drugs seemed to be independent of the use of ancillary treatments at baseline, including ACE inhibitors, which were provided to about half the study participants. There was no evidence that the e ects of study drugs were independent on initial blood pressure, HbA_{1c}, age, sex, or vascular disease history.

Over an average of 4·3 years of follow-up, the risk of a major macrovascular or microvascular event was reduced from 16·8% to 15·5%, suggesting that for every 66 patients commencing long-term treatment with perindopril and indapamide, one patient would avoid at least one major vascular event in 5 years as a direct consequence of study treatment. The major contributor to the 9% overall reduction in the risk of major macrovascular or microvascular events was an 18% reduction in the risk of death from cardiovascular disease, which largely accounted for the 14% reduction in total mortality. Although e ects of blood pressure lowering agents on total mortality have rarely been seen in individual trials in patients with hypertension[16] or diabetes,[17] meta-analyses have previously con“rmed that drugs for lowering blood pressure can improve survival.[3,18] From the results of ADVANCE, it seemed that over 5 years, one death would be averted in every 79 patients commencing treatment with the study drugs.

ADVANCE was initially designed to detect reductions of about 16% in the relative risk of each of the major macrovascular and microvascular outcomes, assuming yearly event rate of 3% in the placebo group for each. However, the actual event rate for the two outcomes combined was only 4% per year, which is much lower than the event rates seen in previous large trials of blood pressure lowering regimens in type 2 diabetes.[17,19] Although the results suggest that the e ects of treatment are probably smaller than initially anticipated, the upper con“ dence limits remain consistent with true e ects of this size, for both the combined and individual primary outcomes. No adjustments were made for multiple statistical testing,[15] but the results for the primary study outcomes seem to be both internally and externally consistent. The estimates for treatment e ect were mostly in the same direction for other events not included in the primary outcomes (“gure 4) and for the combined primary outcome, were similar in multiple subgroups de“ned by characteristics at baseline (“gure 5).

Additionally, treatment e ects on coronary events, cardiovascular death, and total mortality in ADVANCE were broadly consistent with e ects seen in earlier meta-analyses of placebo-controlled trials of ACE-inhibitor-based regimens in populations including individuals with and without diabetes.[3,20,21] Although there was no signi“cant e ect of study treatment on cerebrovascular events, the CIs for the treatment e ect in ADVANCE overlap with those described in the meta-analyses. Given that previous epidemiological and clinical trial evidence does not predict heterogeneity between diabetic and non-diabetic subgroups in the relative e ects of blood pressure lowering on stroke,[16] ADVANCE results are not likely to indicate any real

differences in the treatment response of those with and without diabetes. The greater use of calcium channel blockers in the placebo group (43% at the end of follow-up) than the active treatment group (32% at the end of follow-up) might be relevant, but the play of chance remains the most likely explanation for the absence of any clear effect of study treatment on cerebrovascular outcomes.

Study treatment in ADVANCE produced a one-fifth reduction in the development of microalbuminuria. This result is consistent with other data indicating that ACE inhibitors, compared with placebo or calcium antagonists, are effective in preventing the development of microalbuminuria.[4] Treatment with ACE inhibitors has also been shown to be effective in reducing progression to macroalbuminuria,[4] and the reduction in the incidence of new or worsening nephropathy in ADVANCE, albeit of borderline statistical significance, is entirely consistent with these data. Such effects of treatment are important in view of the high risk of progression to end stage renal failure and premature death in patients who develop diabetic nephropathy, as well as the emerging evidence of substantial cardiovascular risks associated with progression of renal impairment.[22,23]

There was no evidence that active treatment in ADVANCE reduced the incidence of new or worsening microvascular eye disease, including that defined by retinal photocoagulation. This finding contrasts with those of the United Kingdom Prospective Diabetes Study (UKPDS),[5] in which there was a one-third reduction in microvascular eye disease (largely the result of a reduction in retinal photocoagulation) in patients randomised to more intensive antihypertensive therapy. However, the ADVANCE results are consistent with the findings of the Heart Outcomes Prevention Evaluation (HOPE) study in the subgroup of participants with diabetes,[6] among whom there was no significant reduction in the use of laser photocoagulation after treatment with ramipril. The use of laser photocoagulation is a specific, but insensitive, marker for progression of retinal microvascular disease that is undoubtedly affected by variation in treatment practice and health care access. In ADVANCE, the use of laser photocoagulation was much less frequent (0·6% per year for those assigned placebo) than in previous studies (1·7% per year in UKPDS and 2·2% per year in HOPE). The low rate of laser photocoagulation in ADVANCE limited the power of the study to detect plausibly moderate effects of study treatment on this outcome. Further data for the potential effects of study treatment on retinopathy will be available from analyses of retinal photographs obtained in a subgroup of participants in ADVANCE.[24]

The fixed combination regimen used in ADVANCE was well tolerated. During the pre-randomisation run-in period, in which all potentially eligible patients received active treatment, only 3·6% were withdrawn because of suspected side-effects. After an average of 4·3 years of follow-up post-randomisation, adherence to active treatment was 73%, only 1% less than adherence to placebo. This finding indicates that a short course of active treatment identifies the small proportion of patients who are intolerant. Among all others, treatment can be continued long-term, with adherence comparable to that seen with placebo. This result has important practical implications for health services delivery, since only one follow-up visit is needed to establish a patient's suitability for long-term treatment with this regimen. Thereafter, follow-up visits can be maintained at 3…6-month intervals with minimum requirement for titration. This simple strategy, with its attendant reductions in vascular events and death, should prove practical and affordable in most clinical circumstances, and might have special relevance in those primary health care settings where there are practical barriers to providing individually titrated treatment regimens for patients with diabetes.

The consistency of the relative effects across subgroups indicate that the absolute benefits conferred by treatment will be established mainly by each patient's future risk of vascular complications, rather than their initial level of blood pressure alone. These results support the provision of treatment, not on the basis of arbitrary cutoffs for blood pressure, but rather on assessment of vascular risk, which is raised in patients with type 2 diabetes, even in the absence of hypertension. However, a 9% reduction in combined macrovascular and microvascular events, including an 18% reduction in cardiovascular deaths, represents only partial reversal of the doubling of fatal and non-fatal vascular risks typically conferred by diabetes in both Asian and white populations.[25,26] Further reductions in blood pressure might confer even larger reductions in risk.[3] Considering that less than half of all participants in ADVANCE were treated with a statin, an increase in the use of these agents would be expected to produce substantial additional reductions in macrovascular events.[27,28] Additionally, greater use of antiplatelet drugs might further reduce these risks, although for the primary prevention of vascular events in patients with diabetes, this reduction remains to be proven in randomised trials.[29] Reduction of blood glucose levels with regimens based on sulphonylureas or insulin have been shown to reduce microvascular eye complications, but there remains uncertainty about the effects of such treatment on microvascular renal complications, as well as macrovascular complications of diabetes.[19,30] Follow-up in the glucose lowering arm of ADVANCE will end in December, 2007, and the results will provide further evidence about the effects of intensive glucose control on these and other outcomes.

In summary, the results of ADVANCE indicate that the routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with diabetes reduces the risks of death and major macrovascular or microvascular complications, irre-

spective of initial blood pressure level or ancillary treatment with the many other preventive treatments typically provided to diabetic patients today. The study treatment was well tolerated, needed little monitoring or titration and is, therefore, suitable for use in a wide range of clinical circumstances worldwide. If the benefits seen in ADVANCE were applied to just half the population with diabetes worldwide, more than a million deaths would be avoided over 5 years. For these reasons, there is now a case for considering such treatment routinely for patients with type 2 diabetes.

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