Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial

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Summary

Background Blood pressure is an important determinant of the risks of macrovascular and microvascular complications of type 2 diabetes, and guidelines recommend intensive lowering of blood pressure for diabetic patients with hypertension. We assessed the effects of the routine administration of an angiotensin converting enzyme (ACE) inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.

Methods The trial was done by 215 collaborating centres in 20 countries. After a 6-week active run-in period, 11 140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease, and analysis was by intention-to-treat. The macrovascular and microvascular composites were analysed jointly and separately. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Findings After a mean of 4·3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomised treatment. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in systolic blood pressure of 5·6 mm Hg and diastolic blood pressure of 2·2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15·5%] active *vs* 938 [16·8%] placebo; hazard ratio 0·91, 95% CI 0·83–1·00, p=0·04). The separate reductions in macrovascular and microvascular events were similar but were not independently significant (macrovascular 0·92; 0·81–1·04, p=0·16; microvascular 0·91; 0·80–1·04, p=0·16). The relative risk of death from cardiovascular disease was reduced by 18% (211 [3·8%] active *vs* 257 [4·6%] placebo; 0·82, 0·68–0·98, p=0·03) and death from any cause was reduced by 14% (408 [7·3%] active *vs* 471 [8·5%] placebo; 0·86, 0·75–0·98, p=0·03). There was no evidence that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline.

Interpretation Routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy.

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Introduction

Prevention of the vascular complications of type 2 diabetes mellitus is a global health priority. By 2030, an estimated 350 million people will be living with diabetes worldwide.[1] Most people with this condition will die or be disabled as a consequence of vascular complications. In patients with diabetes and hypertension, all the main classes of antihypertensive drugs seem to reduce the risks of stroke and coronary heart disease.[2] Moreover, there is evidence that more intensive treatment, targeting lower blood pressure values, confers greater protection against these macrovascular outcomes.[3] Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers have also been shown to reduce the risk of development or progression of diabetic nephropathy.[4] Additionally, there is some evidence that more intensive therapy, targeting lower blood pressure values, confers greater protection against diabetic eye disease.[5]

These findings suggest that prevention strategies designed to increase the use of treatments for lowering blood pressure, and to improve levels of blood pressure control, could produce worthwhile reductions in the risks of macrovascular and microvascular complications of diabetes. Traditional strategies set arbitrary blood pressure levels at which treatment is initiated and arbitrary goals against which treatment should be titrated. This strategy neglects those diabetic patients without what is typically defined as hypertension, and yet for whom blood pressure remains an important determinant of their risk of vascular disease.[6] Additionally, this strategy is usually resource-intensive, needing multiple patient

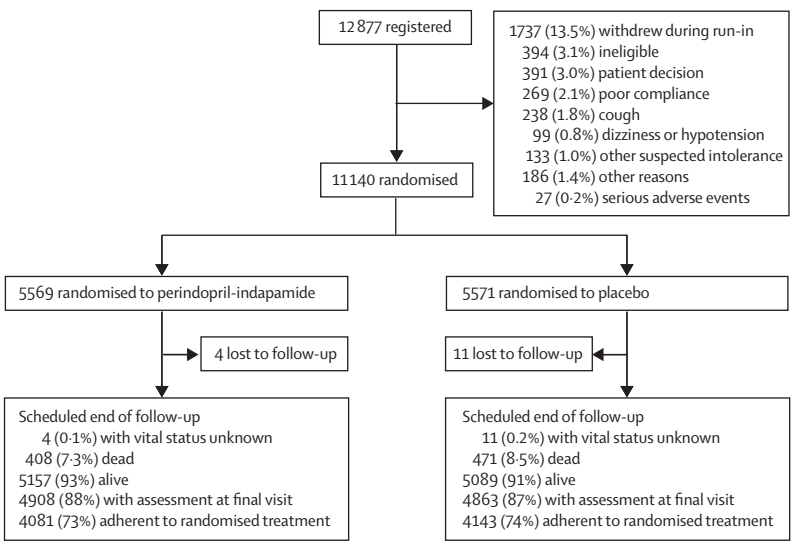

Figure 1: **Trial profile**

	Randomised treatment	
	Active (n=5569)	Placebo (n=5571)
Age (years), mean (SD)	66 (6)	66 (7)
Female, n (%)	2366 (43%)	2369 (43%)
Age when diabetes first diagnosed (years), mean (SD)	58 (9)	58 (9)
Previous vascular disease		
History of major macrovascular disease, n (%)	1798 (32%)	1792 (32%)
History of myocardial infarction, n (%)	678 (12%)	656 (12%)
History of stroke, n (%)	502 (9%)	520 (9%)
History of major microvascular disease, n (%)	568 (10%)	584 (10%)
History of macroalbuminuria†, n (%)	197 (4%)	204 (4%)
History of microvascular eye disease‡, n (%)	389 (7%)	404 (7%)
Blood pressure control		
Systolic blood pressure (mm Hg), mean (SD)	145 (22)	145 (21)
Diastolic blood pressure (mm Hg), mean (SD)	81 (11)	81 (11)
History of currently treated hypertension, n (%)	3802 (68%)	3853 (69%)
Other major risk factors		
Current smokers, n (%)	804 (14%)	878 (16%)
Serum total cholesterol (mmol/L), mean (SD)	5·2 (1·2)	5·2 (1·2)
Serum HDL cholesterol (mmol/L), mean (SD)	1·3 (0·3)	1·3 (0·4)
Urinary albumin:creatinine ratio (µg/mg), median (IQR)	15 (7 to 40)	15 (7 to 40)
Microalbuminuria, n (%)	1441 (26%)	1421 (26%)
Serum creatinine (µmol/L), mean (SD)	87 (23)	87 (26)
Serum haemoglobin A_{1c} concentration (%), mean (SD)	7·5 (1·6)	7·5 (1·6)
Body-mass index (kg/m²), mean (SD)	28 (5)	28 (5)

*Characteristics of participants recorded at the first (registration) visit, before active run-in. †Urinary albumin-creatinine ratio>300 µg/mg. ‡Proliferative diabetic retinopathy, retinal photocoagulation therapy, macular oedema, or blindness in one eye thought to be caused by diabetes.

Table 1: **Baseline* characteristics of randomised participants**

visits, careful monitoring of both blood pressure and side-effects, and the coordination of complex drug regimens. Perhaps partly as a consequence of such complexity, surveys of blood pressure control indicate that few patients receiving antihypertensive drugs achieve recommended goals for blood pressure.[7–10]

An alternative approach, to increase the use and effectiveness of treatment for lowering blood pressure in patients with diabetes, is to add a fixed-dose combination of blood pressure lowering drugs irrespective of initial blood pressure level or the use of other antihypertensive drugs.[11] This approach is more inclusive and less resource-intensive than the target-setting strategy. Although this approach might not produce the largest blood pressure reductions possible, it will shift the entire distribution of blood pressure values down in patients with diabetes, with minimum requirements for titration and, potentially, with fewer side-effects.[12]

The Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial was designed to assess the effects on vascular disease of such an approach using a fixed combination of the ACE inhibitor, perindopril, and the diuretic, indapamide, in a diverse population of patients with type 2 diabetes and a broad range of blood pressure values. Using a factorial design, the study will also assess the effects on the same outcomes of an intensive gliclazide MR-based glucose lowering regimen (aiming for a haemoglobin A_{1c} [HbA_{1c}] level of 6·5% or lower) compared with standard glucose control. Follow-up in the glucose arm of the study will be completed in December, 2007. Here we report the principal results from the blood pressure lowering arm of the study, completed in June, 2007.

Methods

ADVANCE is a randomised controlled trial done by 215 collaborating centres in 20 countries from Asia, Australasia, Europe, and North America. Approval for the trial was obtained from the institutional ethics committee of each centre and all participants provided written informed consent. Detailed study methods are published elsewhere[13] and are described here in brief. This trial is registered with ClinicalTrials.gov, number NCT00145925.

Participants

Patients were potentially eligible if they had been diagnosed with type 2 diabetes mellitus at the age of 30 years or older and were aged 55 years or older at entry to the study. Potentially eligible patients also needed to have at least one of the following: a history of major cardiovascular disease (stroke, myocardial infarction, hospital admission for transient ischaemic attack, hospital admission for unstable angina, coronary revascularisation, peripheral revascularisation, or amputation secondary to vascular disease), or at least one other risk factor for cardiovascular disease. Such risk factors were defined by the presence of at least one of the following: a history of major microvascular disease (macroalbuminuria [urinary albumin-creatinine ratio

>300 μg/mg], proliferative diabetic retinopathy, retinal photocoagulation therapy, macular oedema, or blindness in one eye thought to be caused by diabetes), current cigarette smoking, total cholesterol more than 6·0 mmol/L, HDL cholesterol less than 1·0 mmol/L, microalbuminuria (urinary albumin-creatinine ratio 30–300 μg/mg), diagnosis of type 2 diabetes mellitus made 10 years or more before entry, or age 65 years or older at entry. Patients with an indication for an ACE inhibitor were eligible for inclusion, unless they had a specific indication for an ACE inhibitor other than perindopril at a maximum dose of 4 mg a day. There were no blood pressure criteria for inclusion.

Patients were ineligible if, in the opinion of the investigator, they met any of the following exclusion criteria: a definite indication for, or contraindication to, any of the study treatments or the HbA_{1c} target (≤6·5%); a definite indication for long-term insulin therapy at study entry; or current participation in another clinical trial.

Procedures

Potentially eligible participants entered a 6-week pre-randomisation run-in period during which they received a fixed combination tablet consisting of perindopril (2 mg) and indapamide (0·625 mg). All other treatments were continued at the discretion of the responsible physician, with the exception of ACE-inhibitors; participants taking an ACE-inhibitor other than perindopril had this treatment withdrawn and were offered substitution with open-label perindopril at a dose of 2 mg or 4 mg a day. Those who adhered to, and tolerated, the run-in study drugs were randomly assigned, in a double-blind fashion, to combined perindopril (2 mg) and indapamide (0·625 mg) or matching placebo. After 3 months, the doses of randomised therapy were doubled to 4 mg for perindopril and 1·25 mg for indapamide, or matching placebo. Study treatments were allocated using a central, computer-based, randomisation service accessible by internet, telephone, and facsimile. Randomisation was stratified by study centre, history of macrovascular disease, history of microvascular disease, and background use of perindopril at baseline. The use of concomitant treatments during follow-up, including blood pressure lowering therapy, remained at the discretion of the responsible physician with two exceptions—the use of thiazide diuretics was not allowed, and open-label perindopril, to a maximum of 4 mg a day, was the only ACE-inhibitor allowed, thus ensuring that the maximum recommended dose of 8 mg for perindopril could not be exceeded by patients randomly assigned to active treatment. However, if at any time another ACE inhibitor or a thiazide diuretic was thought to be definitely indicated, study treatment could be withdrawn and alternate open-label treatment provided.

Participants were seen 3, 4, and 6 months after randomisation, and subsequently, every 6 months. At study

	Registration visit		End of follow-up	
	Active	Placebo	Active	Placebo
Blood pressure lowering drugs				
Perindopril, n (%)	490 (9%)†	449 (8%)†	2128 (45%)	2591 (55%)
Other ACE-I, n (%)	1914 (34%)	1969 (35%)	232 (5%)	213 (5%)
ARB, n (%)	289 (5%)	320 (6%)	453 (10%)	618 (13%)
β blockers, n (%)	1344 (24%)	1385 (25%)	1492 (31%)	1671 (35%)
Calcium antagonists, n (%)	1669 (30%)	1758 (32%)	1531 (32%)	2040 (43%)
Thiazides, n (%)	786 (14%)	808 (15%)	158 (3%)	217 (5%)
Other diuretics, n (%)	596 (11%)	577 (10%)	673 (14%)	749 (16%)
Other BP lowering drug, n (%)	700 (13%)	683 (12%)	463 (10%)	638 (14%)
Any BP lowering drug, n (%)	4166 (75%)	4200 (75%)	3634 (74%)	4024 (83)%
Other drugs				
Aspirin, n (%)	2445 (44%)	2449 (44%)	2680 (56%)	2574 (55%)
Other antiplatelets, n (%)	236 (4%)	269 (5%)	292 (6%)	269 (6%)
Statins, n (%)	1538 (28%)	1608 (29%)	2126 (44%)	2132 (45%)
Other lipid modifying drugs, n (%)	472 (9%)	464 (8%)	394 (8%)	309 (7%)
Gliclazide-MR, n (%)	433 (8%)‡	432 (8%)‡	2228 (47%)	2189 (46%)
Other sulphonylurea, n (%)	3570 (64%)	3520 (63%)	1467 (31%)	1491 (32%)
Metformin, n (%)	3399 (61%)	3352 (60%)	3321 (69%)	3390 (72%)
Any oral hypoglycaemic drug (%)	5082 (91%)	5047 (91%)	4438 (90%)	4422 (91%)
Insulin, n (%)	80 (1%)	79 (1%)	1581 (33%)	1431 (30%)

ACE-I=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. BP=blood pressure. *Treatments at the first (registration) visit; participants entered the active run-in phase after this visit. †Percentage taking perindopril at the first (registration) visit; by the randomisation visit 47% were taking open-label perindopril in both groups. ‡Percentage taking gliclazide-MR at the first (registration) visit; by randomisation visit 49% were taking gliclazide-MR in both groups.

Table 2: **Concomitant treatments at baseline* and during follow-up**

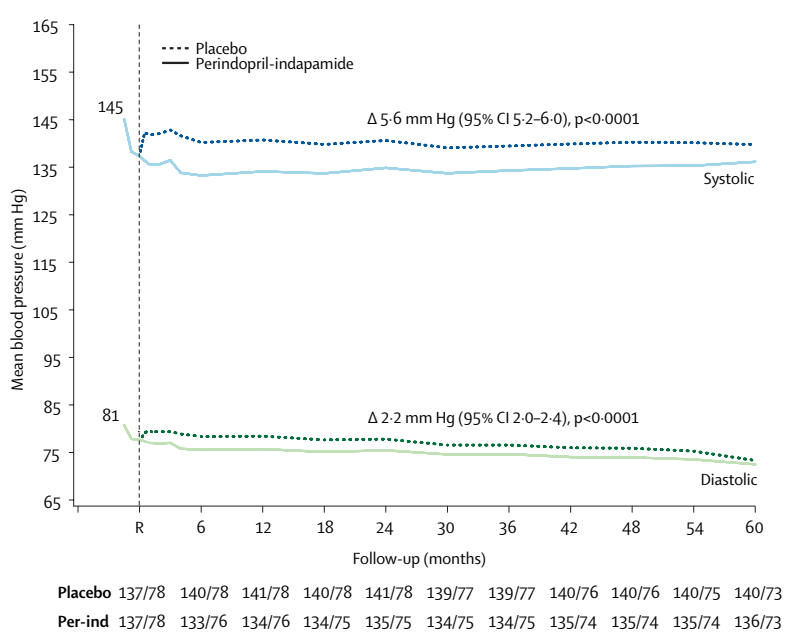

Figure 2: **Mean systolic and diastolic blood pressure during run-in on active treatment and after randomisation to active treatment or placebo**

Δ=average difference between randomised groups during follow-up. R=randomisation. Per-ind=perindopril-indapamide.

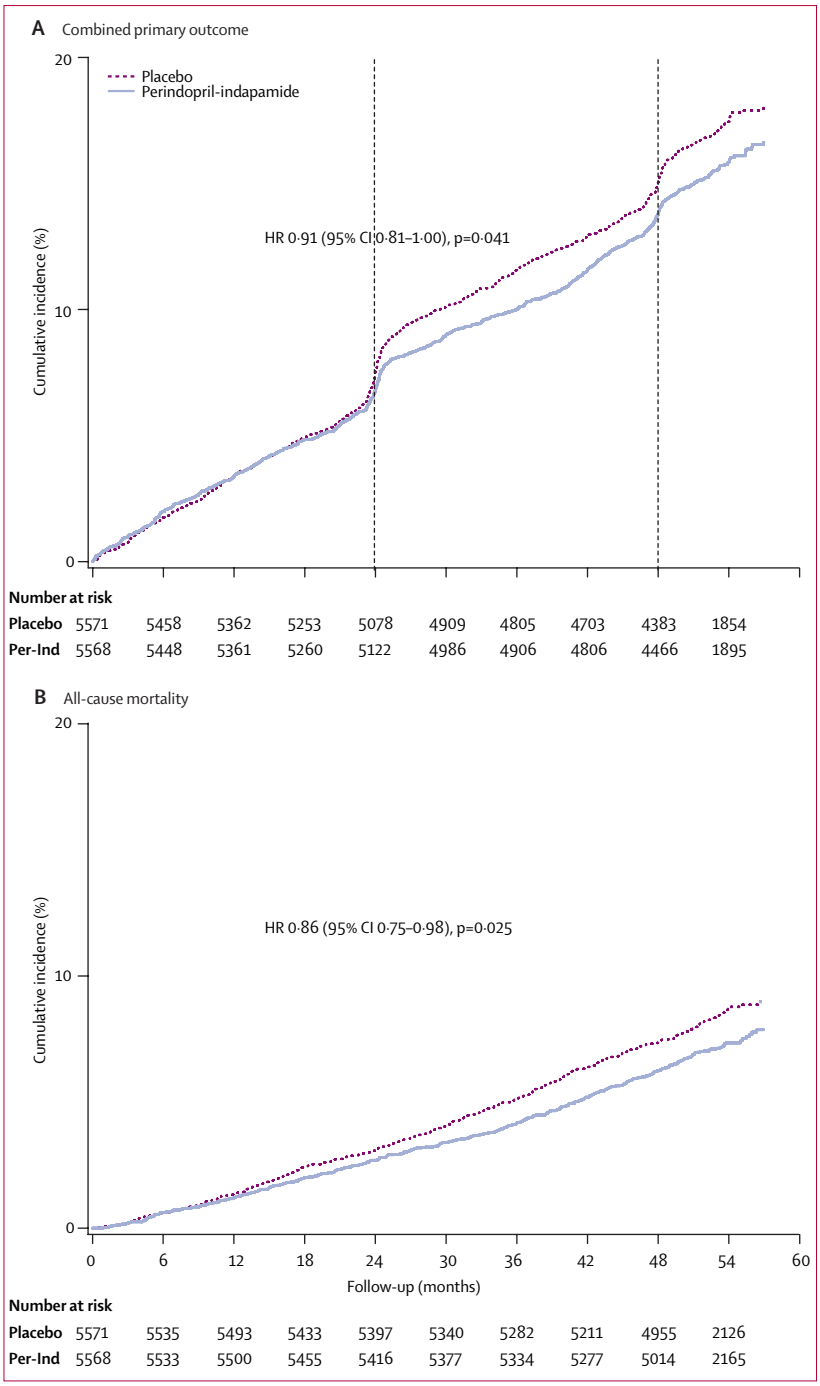

Figure 3: **For patients assigned active treatment or placebo, cumulative incidence of (A) combined major macrovascular or microvascular outcomes and (B) all-cause mortality**

Vertical broken lines indicate 24-month and 48-month study visits, at which additional information on microvascular events (measurement of urinary albumin-creatinine ratio and retinal examination) was obtained. For outcomes relating to these measurements, event times were recorded as the visit date. The curves were truncated at Month 57, by which time 99% of events had occurred. The effects of treatment (hazard ratios and p-values) were estimated from unadjusted Cox proportional hazard models that used all available data.

visits, information on adherence to, and tolerability of, study treatments, blood pressure, blood glucose, HbA_{1c}, lipid levels, and occurrence of study outcomes was obtained. Blood pressure was recorded as the mean of two measurements made after the patient was rested for at least 5 min in the seated position, using a standardised automated sphygmomanometer (Omron HEM-705CP, Tokyo, Japan). Additional information was obtained at the 2-year and 4-year follow-up visits, and included the urinary albumin-creatinine ratio, a formal retinal examination, a mini mental state examination, and a quality of life assessment.

The primary study outcomes were composites of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy [development of macroalbuminuria, doubling of serum creatinine to a level of at least 200 µmol/L, need for renal replacement therapy, or death due to renal disease] or retinopathy [development of proliferative retinopathy, macular oedema, or diabetes-related blindness, or retinal photocoagulation therapy]).

The secondary outcomes included all-cause mortality, cardiovascular death, major coronary events (death due to coronary heart disease [including sudden death] and non-fatal myocardial infarction), total coronary events (major coronary events, silent myocardial infarction, coronary revascularisation, or hospital admission for unstable angina), major cerebrovascular events (death due to cerebrovascular disease or non-fatal stroke), and total cerebrovascular events (major cerebrovascular events, transient ischaemic attack, or subarachnoid haemorrhage). Other secondary outcomes were heart failure (death due to heart failure, hospitalisation due to heart failure, or worsening New York Heart Association class), peripheral vascular disease, new or worsening nephropathy, new or worsening retinopathy, development of microalbuminuria, visual deterioration, new or worsening neuropathy, cognitive function, dementia, and hospitalisations. Results for all pre-specified outcomes are reported.

An Endpoint Adjudication Committee, masked to treatment allocation, reviewed source documentation for all individuals who had a suspected primary endpoint or who died during follow-up. Outcomes were coded according to the 10th revision of the International Classification of Diseases. An independent Data and Safety Monitoring Committee reviewed unblinded data at yearly intervals throughout follow-up. This committee was charged with informing the study investigators if, at any time, there emerged evidence, beyond reasonable doubt, of a difference between randomised groups in survival or evidence that was likely to materially alter the management of patients with diabetes.

Statistical analysis

ADVANCE was originally designed to provide at least 90% power to detect a 16% or greater reduction in the relative risks of both major macrovascular events and major microvascular events using a 5% two-tailed test

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 effects, two amendments dated Nov 30, 2005, were made to the study protocol: first, 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-specified 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 effects 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 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 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 figures as percentage reductions ([1–hazard ratio]×100). Differences 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 differences with their normally-approximated 95% CIs.[14] All p values were calculated from two-tailed tests of statistical significance 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 effects were obtained among subgroups of participants defined by age, sex, history of vascular disease, ancillary treatments, blood pressure, and HbA_{1c} at study entry. No subgroup analyses were pre-specified. Homogeneity of treatment effects 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.

Role of the funding source

ADVANCE was funded by grants from Servier and the National Health and Medical Research Council of Australia. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study. The Management Committee had final responsibility for the decision to submit for publication.

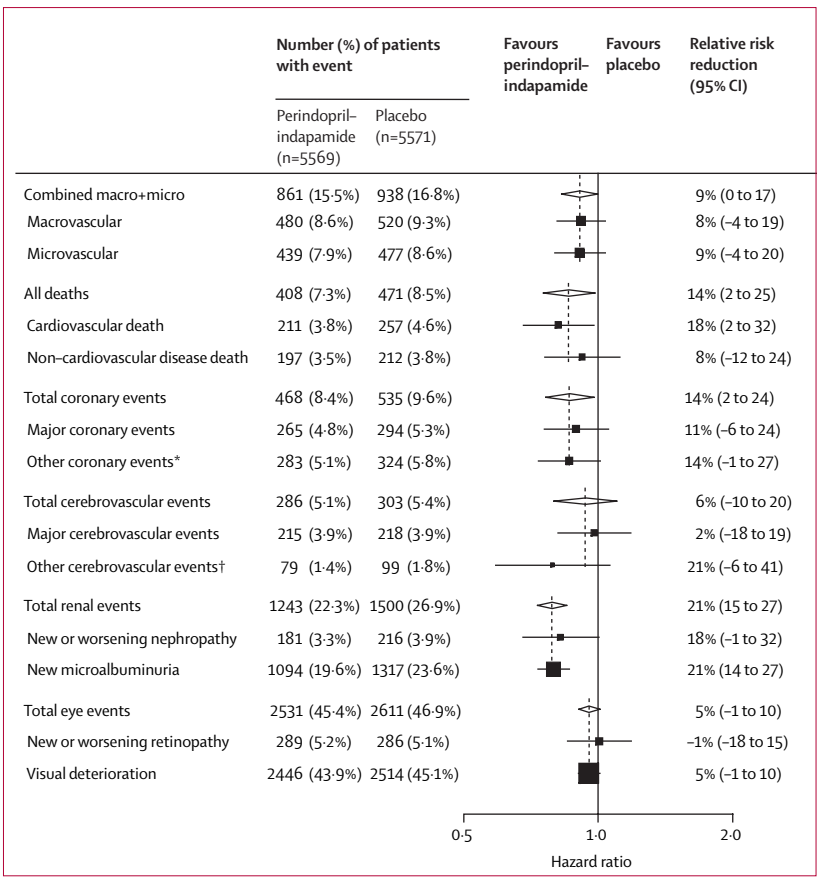

Figure 4: **Effects of study treatment on deaths, coronary events, cerebrovascular events, renal events, and eye events**

*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 effects. Vertical broken lines=point estimates for overall effect, 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 (figure 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

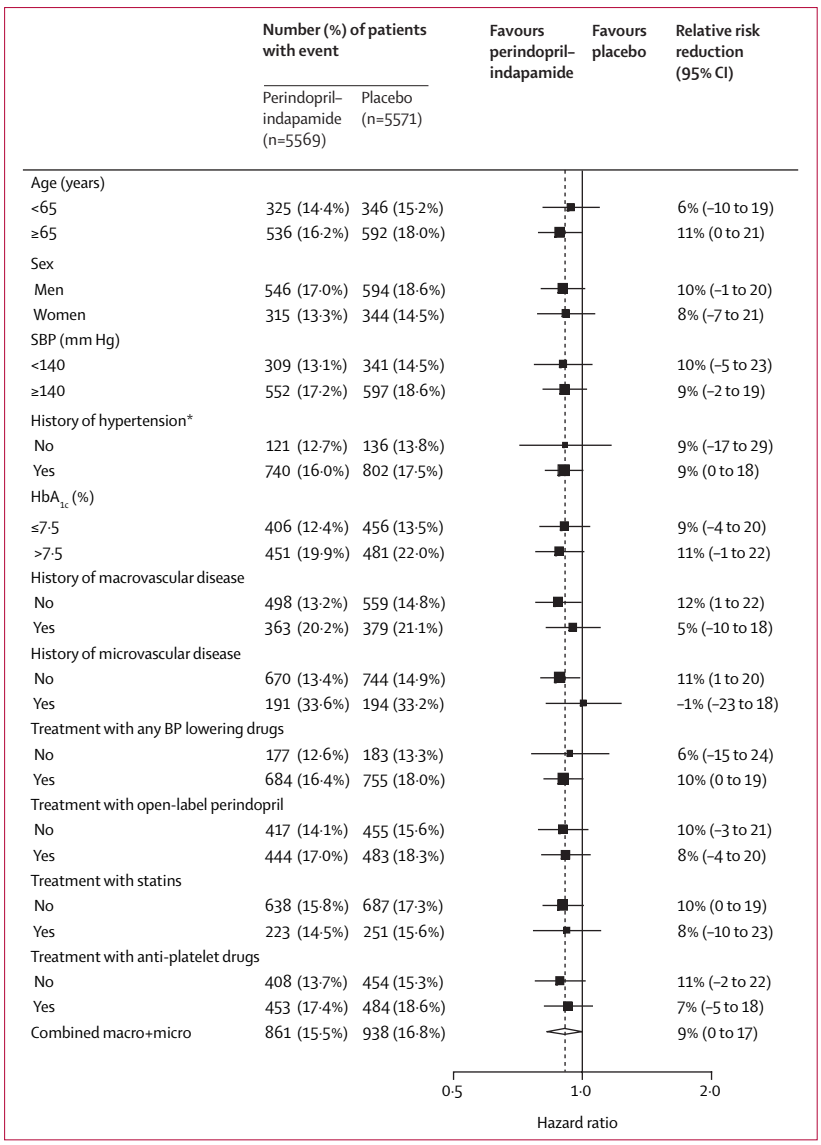

Figure 5: **Effects of study treatment on combined major macrovascular or microvascular events in subgroups of participants defined by characteristics at baseline**

*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 effect.

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 different 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 effects 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 difference 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 significant difference 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 significant 21% reduction in all renal events (95% CI 15–27%, p<0·0001), with a borderline significant reduction in new or worsening nephropathy (3·3% *vs* 3·9%; relative risk reduction 18% [–1 to 32%], p=0·055) and a significant 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 significant difference 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 significant effect 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 effects of study treatment on the combined major macrovascular and microvascular outcome were broadly consistent across a range of participant subgroups defined by baseline characteristics (p for heterogeneity all >0·1; figure 5). Additionally, there was no evidence of an interaction between the effect of treatment and baseline systolic blood pressure considered as a continuous variable (p>0·5). Similarly, there was no evidence of heterogeneity of treatment effects 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 fixed 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 significant. There were significant reductions in total coronary and renal events, but not in total cerebrovascular or diabetic eye events. The benefits 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 effects 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 effects of study drugs were dependent 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 effects 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 confirmed 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 effects of treatment are probably smaller than initially anticipated, the upper confidence limits remain consistent with true effects 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 effect were mostly in the same direction for other events not included in the primary outcomes (figure 4) and for the combined primary outcome, were similar in multiple subgroups defined by characteristics at baseline (figure 5).

Additionally, treatment effects on coronary events, cardiovascular death, and total mortality in ADVANCE were broadly consistent with effects 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 significant effect of study treatment on cerebrovascular events, the CIs for the treatment effect 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 effects of blood pressure lowering on stroke,[2,6] 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,[17] 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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References

1 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes; estimates for year 2000 and projections for 2030. *Diabetes Care* 2004; **21:** 1047–53.

2 Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. *Arch Intern Med* 2005; **165:** 1410–19.

3 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362:** 1527–35.

4 Strippoli GFM, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. *J Am Soc Nephrol* 2006; **17:** S153–55.

5 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317:** 703–13.

6 Asia Pacific Cohort Studies Collaboration. Systolic blood pressure, diabetes and the risk of cardiovascular diseases in the Asia-Pacific region. *J Hypertens* 2007; **25:** 1205–13.

7 Gu D, Reynolds K, Wu X, et al. Prevalence, awareness, treatment, and control of hypertension in China. *Hypertension* 2002; **40:** 920–27.

8 Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension* 2007; **49:** 69–75.

9 Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004; **43:** 10–17.

10 Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002; **20:** 1461–64.

11 Baker S, Priest P, Jackson R. Using thresholds based on risk of cardiovascular disease to target treatment for hypertension: modelling events averted and number treated. *BMJ* 2000; **320:** 680–85.

12 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326:** 1427–34.

13 ADVANCE Management Committee. Rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high-risk individuals with type 2 diabetes mellitus. Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation. *J Hypertens Suppl* 2001; **19:** S21–28.

14 Woodward M. Epidemiology: Study Design and Data Analysis. Second edition edn. Boca Raton: Chapman and Hall/CRC Press, 2005.

15 Shulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005; **365:** 1591–95.

16 Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.

17 Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355:** 253–58.

18 Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; **335:** 827–38.

19 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53.

20 Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction of heart failure: a combined analysis of three trials. *Lancet* 2006; **368:** 581–88.

21 Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction. *Arch Intern Med* 2006; **166:** 787–96.

22 Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351:** 1285–95.

23 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–305.

24 Stolk RP, Vingerling JR, Cruickshank JK, et al. Rationale and design of the AdRem study: Evaluating the effects of blood pressure lowering and intensive glucose control on vascular retinal disorders in patients with type 2 diabetes mellitus. *Contemp Clin Trials* 2007; **28:** 6–17.

25 Asia Pacific Cohort Studies Collaboration. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 2003; **26:** 360–66.

26 Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham Study. *JAMA* 1979; **241:** 2035–38.

27 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins. *Lancet* 2005; **366:** 1267–78.

28 Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006; **332:** 1115–24.

29 Ambrosi P, Villani P, Bouvenot G. Antiplatelet therapy for primary prevention in diabetes. *Diabetes Metab* 2006; **32:** 2S52–56.

30 Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 2006; **152:** 27–38.