European Heart Journal (2008) **29**, 2669–2680
doi:10.1093/eurheartj/ehn427

Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials

Fiona Turnbull*, Mark Woodward, Bruce Neal, Federica Barzi, Toshiharu Ninomiya, John Chalmers, Vlado Perkovic, Nicole Li, S MacMahon and the Blood Pressure Lowering Treatment Trialists' Collaboration†

Blood Pressure Lowering Treatment Trialists' Collaboration, The George Institute for International Health, University of Sydney, PO Box M201, Missenden Road, Sydney, NSW 2050, Australia

Received 13 March 2008; revised 31 July 2008; accepted 29 August 2008; online publish-ahead-of-print 13 October 2008

This paper was guest edited by Prof. Gregory Y.H. Lip, University Department of Medicine, City Hospital, Birmingham, UK.

See page 2585 for the editorial comment on this article (doi:10.1093/eurheartj/ehn451)

Aims Large-scale observational studies show that lower blood pressure is associated with lower cardiovascular risk in both men and women although some studies have suggested that different outcomes between the sexes may reflect different responses to blood pressure-lowering treatment. The aims of these overview analyses were to quantify the effects of blood pressure-lowering treatment in each sex and to determine if there are important differences in the proportional benefits of treatment between men and women.

Methods and results Thirty-one randomized trials that included 103 268 men and 87 349 women contributed to these analyses. For each outcome and each comparison summary estimates of effect and 95% confidence intervals were calculated for men and women using a random-effects model. The consistency of the effects of each treatment regimen across the sexes was examined using χ^2 tests of homogeneity. Achieved blood pressure reductions were comparable for men and women in every comparison made. For the primary outcome of total major cardiovascular events there was no evidence that men and women obtained different levels of protection from blood pressure lowering or that regimens based on angiotensin-converting-enzyme inhibitors, calcium antagonists, angiotensin receptor blockers, or diuretics/beta-blockers were more effective in one sex than the other (all *P*-homogeneity > 0.08).

Conclusion All of the blood pressure-lowering regimens studied here provided broadly similar protection against major cardiovascular events in men and women. Differences in cardiovascular risks between sexes are unlikely to reflect differences in response to blood pressure-lowering treatments.

Keywords Blood pressure • Prospective overviews • Randomised trials • Blood pressure-lowering treatment • Major cardiovascular events • Subgroup analyses • Gender

Introduction

Overviews of large observational studies suggest that the age-adjusted association between usual systolic blood pressure and the risk of stroke and ischaemic heart disease is similar for men and women.[1,2] However, data from clinical trials defining the separate effects of blood pressure-lowering treatments on major cardiovascular events in men and women are less clear. While some studies have suggested different effects for men and women, particularly those of a younger age,[3] others have

* Corresponding author. Tel: +61 2 9993 4563, Fax: +61 2 9993 4502, Email: fturnbull@george.org.au

† Members listed in Acknowledgements.

demonstrated similar proportional reductions in the risk of major cardiovascular events for men and women.[4,5] Definitive answers to whether differences in the efficacy of treatments exist between men and women have not been provided by these studies, in large part because of their low statistical power but also because they have not examined all commonly used blood pressure-lowering regimens in patients of diverse age. This gap in evidence is important especially in view of the fact that cardiovascular mortality rates among younger women have increased in recent years and that blood pressure is a major modifiable risk factor.

The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) was established in 1995 with the goal of performing a series of prospective overviews of randomized trials investigating the effects of a range of different blood pressure-lowering regimens on serious cardiovascular disease events.[6] The group, comprising the principal investigators of large-scale randomized trials of blood pressure-lowering regimens, defined the criteria for these overviews in advance. These included trial eligibility, primary and secondary outcomes, treatment comparisons, and subgroup analyses, including by sex. The objectives of the sex subgroup analyses, reported here, are to quantify the benefits associated with different treatment regimens in males and females, and to determine if there are important differences in the effects of different blood pressure-lowering regimens between the two sexes.

Methods

Trial eligibility criteria and search strategy

Trials are eligible for inclusion in the Collaboration's overviews if they meet one of the following criteria: (1) randomization of patients between a blood pressure-lowering agent and control (placebo or less intensive blood pressure-lowering regimen) or (2) randomization of patients between regimens based on different classes of blood-pressure-lowering drug. Trials are also required to have a minimum of 1000 patient-years planned follow-up in each randomized group and must not have presented or published their main results prior to finalization of the overview protocol in July 1995. Trials with factorial assignment of patients to other interventions, such as aspirin and cholesterol lowering, are eligible, but trials in which any such additional randomized interventions are assigned jointly with the blood pressure-lowering treatment are not eligible, since the effects of the blood pressure-lowering treatments would be confounded by the effects of the other treatments. Potentially eligible trials, both investigator and industry-initiated, are identified on an ongoing basis by a number of methods, including computer-aided literature searches, scrutiny of the reference lists of trial reports and review articles, scrutiny of abstracts and meeting proceedings, and enquiry among colleagues, collaborators, and industry. For the analyses reported here, all eligible trials for which data had been received and checked by the end of 2006 were included. Additional information about the identification of trials and inclusion criteria are contained in the published protocol.[6]

Treatment comparisons

Within the broad group of trials comparing an active agent and control, separate overviews were conducted for (i) angiotensin-converting-enzyme (ACE) inhibitor-based regimens with placebo; (ii) calcium antagonist-based regimens with placebo, and (iii) more intensive with less intensive blood pressure-lowering regimens. Within the broad group of trials comparing different active agents, separate overviews were conducted for (i) ACE inhibitor-based regimens with conventional therapy (diuretic- or beta-blocker-based regimens); (ii) calcium antagonist-based regimens with conventional therapy; and (iii) ACE inhibitor-based regimens with calcium antagonist-based regimens. Comparisons of an angiotensin receptor blocker (ARB)-based regimen with another regimen were treated as a separate series of overviews. Three ARB trials[7–9] were available for these analyses. The SCOPE study[7] was a placebo-controlled study in which active treatment was initiated in the placebo group early in the study (starting with diuretic-based regimens but with the addition of agents other than ACE inhibitors and ARBs, as required). The RENAAL trial[8] used a placebo while simultaneously attempting to achieve blood pressure reductions in both randomized groups (using blood pressure-lowering agents other than ACE-inhibitors and the specific trial intervention treatments). The MOSES trial was a head-to-head comparison of an ARB and calcium antagonist.[9] Since all these included control treatment with agents other than ARBs, we analysed them as one group.

Primary outcomes

The six primary outcomes were defined according to the ninth revision of the International Classification of Disease (ICD) and were prespecified in the BPLTTC protocol. These were (i) non-fatal stroke or death from cerebrovascular disease (ICD 430–438); (ii) non-fatal myocardial infarction or deaths from CHD, excluding sudden deaths (ICD 410–414); (iii) heart failure causing death or requiring hospitalization (ICD 428); (iv) total major cardiovascular events (stroke, CHD events, heart failure, other cardiovascular death); (v) total cardiovascular deaths (ICD 396–459); and (vi) total mortality. Maximum power for these subgroup analyses is achieved for the combined outcome of total major cardiovascular events and reporting is focused accordingly.

Data collection and statistical analyses

Individual patient data (IPD) or summary tabular data were sought directly from each trial investigator. The data requested included participant characteristics recorded at screening or randomization, selected measurements made during follow-up, and details of the occurrence of all primary outcomes during the scheduled follow-up period. The blood pressure reduction in each trial arm was calculated separately for men and women as the difference between the mean blood pressure during follow-up and the mean blood pressure at baseline for each patient group. Mean levels of baseline characteristics and the mean difference in blood pressure reductions between randomized groups were likewise calculated separately for men and women with estimates from each individual study weighted in proportion to the number of individuals in that study. Meta-analyses of the effects of randomized treatments used the 'metan' routine in STATA (Release 10.0. Stata Corporation, College Station, TX, USA). For each trial and each outcome, estimates of relative risk (RR) and its variance were calculated separately for men and women according to the principle of intention-to-treat.[6] Each participant could contribute only the first event in any category to the calculation for each outcome, but might contribute an event to analyses of several outcomes. Pooled estimates of effect and 95% confidence intervals (CI) were calculated using a random-effects model and inverse variance weighting (weighting by the precision of each trial). The constancy of the results for males and females was tested using χ^2 tests of homogeneity. A P-value for the test of homogeneity that was < 0.05 was taken to indicate that the difference between the effects in the two patient groups was unlikely to have occurred simply by chance. Subsidiary

analyses were conducted to determine whether there was an age–sex interaction. Recently reported age subgroup analyses[10] examining the effects of blood pressure-lowering regimens in pre-specified subgroups of patients aged < 65 and ≥ 65 years did not demonstrate any difference in the treatment effects of blood pressure-lowering regimens according to patient age. In these current analyses, we compared the male:female RR reductions in patients categorized according to the original pre-specified criteria (< 65 and ≥ 65 years) and where possible, using < 50 and ≥ 50 years as the age cut points. The latter cut points were chosen *post hoc* to explore whether treatment effects might vary between pre- and post-menopausal women. Sensitivity analyses were also conducted to determine whether exclusion of treatments other than those designed to reduce blood pressure (i.e. in factorial designs[4,11–15]) changed the conclusions. Data from eight trials[4,13,16–21] were used for subsidiary analyses examining the separate effects of regimens based on beta-blockers and on diuretics compared with other drug classes (ACE-inhibitor and calcium antagonist combined), according to patient's sex.

Results

Characteristics of trials and patients included

Of the 37 eligible trials, we included 31[4,8,9,11–15,17–42] (190 617 individuals) in these analyses. For the six remaining trials,[22,43–47] we could not extract data according to criteria specified in the original study protocol. Of the 190 617 individuals, 103 268 were men and 87 349 were women (*Table 1*). The average proportion of women in all trials was 46.8% (range 10.9–67.2%). The mean age for women was 63.0 years and for men 61.7 years.

Baseline blood pressure and blood pressure reductions

For all seven treatment comparisons the mean baseline blood pressures levels were slightly lower for men compared with women (*Table 2*). The differences in follow-up blood pressure levels between randomized groups were, however, highly comparable across the sexes for each of the treatment comparisons.

Primary outcomes

Overall, there were 6586 stroke events, 9400 CHD events, and 3522 heart failure events included in the analyses. Forty-one percent of CHD and heart failure events and 32% of stroke events occurred in women. The cardiovascular mortality rate was 4.4% for men and 3.4% for women, with approximately 40% of all deaths (cardiovascular and non-cardiovascular) occurring in women (*Table 3*).

Comparative effects of treatment in men and women

There was no evidence of a difference in the effects of blood pressure-lowering treatment regimens between men and women for the outcome of major cardiovascular events (all *P*-homogeneity ≥ 0.08) (*Figure 1A–C*) nor was there evidence of an interaction of sex with blood pressure-lowering treatment for the outcomes of coronary heart disease, heart failure, cardiovascular death, or total mortality (*Figure 2A–E*). For stroke, there was borderline significant evidence ($P = 0.05$) that women derived greater protection from regimens based on calcium antagonists than regimens based on ACE-inhibitors compared with their male counterparts but no difference for any of the other treatment comparisons made. Given that this significant interaction represents one of 42 different subgroup comparisons made, it is most likely attributable to chance (the probability of observing at least one significant interaction by chance with this number of comparisons is 0.88). Subsidiary analyses to examine the separate effects of regimens based on beta-blockers compared with other drug classes and those based on diuretics compared with other drug classes according to patient sex showed no evidence of a difference in the proportional risk reduction for major cardiovascular events between men and women (all $P > 0.90$). Similarly, the subsidiary analyses conducted to explore difference in treatment effects between men and women of different age showed no evidence of a difference between the subgroups when age was categorized as either < 65 and ≥ 65 years (all $P > 0.17$) or < 50 and ≥ 50 years (all $P > 0.11$). However, the latter comparison was limited by the small number of events in the younger age-group. Sensitivity analyses in which trials with randomized treatments other than blood pressure-lowering regimens were excluded made no material difference to the overall findings of the study.

Discussion

Initial overview analyses from the BPLTTC demonstrated broad comparability in the effects of the main classes of blood pressure-lowering regimens on a range of serious outcomes. More recent reports have shown that the pattern of benefits accrued from blood pressure lowering is similar in patients with and without diabetes[48] and in younger and older patients.[10] These analyses now show that the same is also true for men and women. These results lend strong support to current blood pressure guidelines[49–51] which make no specific recommendations for different blood pressure targets, or for management with particular classes of drug, on the basis of a patient's sex.

The results do not support the hypothesis that differential effects of blood pressure-lowering treatment in men compared with women might account for observed poorer outcomes among some groups of women. In the trials contributing to these overviews there were similar effects of the regimens on blood pressure in both sexes and there was no evidence of an interaction between sex and the effectiveness of treatment for any of the six outcomes studied. While beyond the scope of the analyses done here, it is likely that other factors account for the worse cardiovascular outcomes observed in some groups of women. For example, poor outcomes among women with a history of myocardial infarction[52] are more likely to be attributable to lower rates of referral for invasive management strategies (percutaneous coronary intervention or coronary artery bypass grafting)[53] or poorer compliance with medical therapies[52,54] than reduced effectiveness of blood pressure-lowering therapy. There is also some evidence that women may have worse risk factor profiles on admission to hospital compared with men[55,56] and in this situation the use of blood pressure-lowering would reduce the risks in both sexes but clearly would not remove underlying differences in risk between

Table 1 Characteristics of included trials

Trial and treatment comparison		*n*	Design	Age entry criteria	% Female	Follow-up
Trials comparing active treatment and placebo						
ACE inhibitor vs. *placebo*						
BENEDICT	Trandolapril vs. placebo	604	DB	≥18 years	48.8	3.6
DIAB-HYCAR	Ramipril vs. placebo	4912	DB	≥18 years	30.1	3.9
EUROPA	Perindopril vs. placebo	12 218	DB	≥18 years	14.6	4.2
HOPE	Ramipril vs. placebo	9297	DB	≥18 years	26.7	4.5
PART2	Ramipril vs. placebo	617	DB	≥18 years	18.5	4.7
PROGRESS	Perindopril (+/− indapamide) vs. placebo(s)	6105	DB	≥18 years	30.3	3.9
SCAT	Enalapril vs. placebo	460	DB	≥18 years	10.9	4.0
PREVEND-IT	Fosinopril vs. placebo	864	DB	≥18 years	35.1	3.8
Calcium antagonist vs.*placebo*						
BENEDICT	Verapamil vs. placebo	605	DB	≥18 years	47.9	2.6
NICOLE	Nisoldipine vs. placebo	826	DB	≥18 years	20.9	3.0
PREVENT	Amlodipine vs. placebo	825	DB	≥18 years	19.9	3.0
SYST-EUR	Nitrendipine vs. placebo	4695	DB	≥60 years	66.8	2.6
Trials comparing more intensive and less intensive regimens						
AASK	MAP ≤ 92 mmHg vs. 102–107 mmHg	1094	Open	≥18 years	38.8	4.1
ABCD (H)	DBP ≤ 75 mmHg vs. ≤90 mmHg	470	Open	≥18 years	32.6	5.3
ABCD (N)	DBP 10 mmHg below baseline vs. 80–89 mmHg	480	Open	≥18 years	45.4	5.3
HOT[a]	DBP ≤ 80 mmHg vs. ≤ 85 or ≤ 90 mmHg	18 790	Open[b]	≥18 years	47.3	3.8
UKPDS-HDS	DBP < 85 mmHg vs. < 105 mmHg	1148	Open	≥18 years	44.5	8.4
Trials comparing regimens based on angiotensin receptor blockers and control regimens						
MOSES	Eprosartan vs. nitrendipine	1352	DB	≥18 years	45.8	4.8
RENAAL	Losartan vs. placebo[c]	1513	DB	≥18 years	36.8	3.4
SCOPE	Candesartan vs. placebo[c]	4937	DB	70–89 years	64.5	4.5

Trials comparing regimens based on different drug classes						
AASK	Ramipril vs. metoprolol	877	DB	≥18 years	38.7	4.1
ALLHAT	Lisinopril vs. chlorthalidone	24 309	DB	≥18 years	46.7	4.9
ANBP2	Enalapril vs. hydrochlorothiazide	6083	Open[c]	≥18 years	51.1	4.1
CAPPP	Captopril vs. β-blocker or diuretic	10 985	Open[c]	≥18 years	46.5	6.1
STOP-2	Enalapril or lisinopril vs. atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	4418	Open[c]	70-84 years	67.2	5.0
UKPDS-HDS	Captopril vs. atenolol	758	DB	≥18 years	45.9	8.4
Calcium antagonist vs. *diuretic- or β-blocker*						
AASK	Ramipril vs. metoprolol	658	DB	≥18 years	38.9	4.1
ALLHAT	Amlodipine vs. chlorthalidone	24 303	DB	≥18 years	47.1	4.9
CONVINCE	COER-Verapamil vs. hydrochlorothiazide or atenolol	16 476	DB	≥18 years	56.0	3.0
ELSA	Lacidipine vs. atenolol	2334	DB	≥18 years	45.6	4.0
INSIGHT	Nifedipine GITS vs. hydrochlorothiazide + amiloride	6321	DB	≥18 years	53.7	4.0
INVEST	Verapamil vs. Atenolol	22 576	Open	≥50 years	52.1	2.7
NICS-EH	Nicardipine vs. trichlormethiazide	429	DB	≥60 years	67.1	5.0
NORDIL	Diltiazem vs. β-blocker or diuretic	10 871	Open[c]		51.4	5.0
STOP-2	Felodipine or isradipine vs. atenolol or metoprolol or pindolol or hydrochlorothiazide+amiloride	4409	Open[c]	70–84 years	67.0	5.0
VHAS[39]	Verapamil vs. chlorthalidone	1414	DB/Open	≥18 years	51.1	2.0
ACE inhibitor vs. *calcium antagonist*						
AASK	Ramipril vs. metoprolol	653	DB	≥18 years	39.1	4.1
ABCD (H)	Enalapril vs. nisoldipine	470	DB	≥18 years	32.6	5.3
ABCD (N)	Enalapril vs. nisoldipine	480	DB	≥18 years	45.4	5.3
ALLHAT	Lisinopril vs. amlodipine	18 102	DB	≥18 years	46.8	4.9
BENEDICT	Trandolapril vs. verapamil	605		≥18 years	46.8	
JMIC-B	ACE inhibitor vs. nifedipine	1647	Open[c]	≥18 years	31.1	3.0
STOP-2	Enalapril or lisinopril vs. felodipine or isradipine	4401	Open[c]	70–84 years	66.1	5.0

Afr, African American; CHD, coronary heart disease; COER, controlled onset-extended release; CVD, cardiovascular disease; DB, double-blind; DBP, diastolic blood pressure; DM, diabetes mellitus; GITS, gastrointestinal transport system; HBP high blood pressure; MAP, mean arterial pressure; *n*, number of all randomized participants (with and without diabetes); RF, other CVD risk factor.

[a]HOT trial data analysed as most intensively treated group vs. others.

[b]PROBE (Prospective, Randomized, Open with Blinded Endpoint evaluation) design trials.

[c]These placebo-controlled trials either had similar blood-pressure goals in each randomized group or introduced active treatment into the placebo arm for another reason for a large proportion of participants prior to the completion of follow-up.

Table 2 Mean baseline characteristics and follow-up blood pressure differences between randomized groups in subgroups of men and women

Trial	Men ($n=103\,268$)				Women ($n=87\,349$)			
	n	Age (years)	Baseline SBP/DBP (mmHg)	Difference in SBP/DBP (mmHg)	*n*	Age (years)	Baseline SBP/DBP (mmHg)	Difference in SBP/DBP (mmHg)
ACE-I vs. placebo	26 724	62.7	139/82	−4.4/−2.1	8353	64.4	144/82	−4.6/−2.0
CA vs. placebo	3186	63.6	153/83	−7.6/−3.1	3765	68.8	168/85	−9.0/−3.5
More vs. less	11 792	60.0	165/104	−4.3/−3.6	10 190	61.6	169/104	−3.7/−3.3
ARB vs. other	3442	69.4	158/88	−1.8/−1.2	4360	73.7	163/89	−1.5/−1.0
ACE-I vs. D/BB	24 196	63.8	154/90	+1.7/+0.1	23 234	65.6	160/90	+1.8/+0.6
CA vs. D/BB	43 086	60.4	143/84	+0.9/−0.3	46 705	61.2	145/83	+0.6/−0.2
ACE-I vs. CA	13 559	66.5	151/87	+0.9/+0.6	12 799	68.5	158/87	+1.0/+1.1

ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; CA, calcium antagonist; D/BB, diuretic or beta-blocker.

Table 3 Numbers and proportion of individuals suffering major cardiovascular events in subgroups of men and women

Gender	*n*	Stroke		CHD		Heart failure		Major CVD		CV death		Total mortality	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Male	103 268	3871	2.9	6350	6.1	2079	2.0	12 154	11.8	4572	4.4	8776	8.5
Female	87 349	2715	3.1	3050	3.5	1443	1.7	7181	8.2	2972	3.4	5879	6.7

CHD, coronary heart disease; CVD, cardiovascular disease.

them. These analyses also suggest that the trend for increasing cardiovascular mortality rates among younger women is not attributable to reduced efficacy of blood pressure-lowering regimens in this group compared with older, post-menopausal women. However, these analyses were *post hoc* and relatively low powered and thus should be interpreted with caution.

Previous overviews addressing the effects of blood pressure-lowering treatments in men and women have been much smaller (seven trials including 20 802 women and 19 975 men)[3] and have provided data that concern primarily the effects of older blood pressure-lowering regimens. The conclusions from these new analyses add substantially to those prior reports both because much large numbers of individuals were involved (31 trials including 87 349 women and 103 268 men) and because evidence about the effects of newer treatment regimens is included. In these overviews, precision in the estimates of treatment effects in the male and female subgroups was maximized by using the combined endpoint of total major cardiovascular events as the primary outcome for these analyses. Focusing on this endpoint for which the event count is largest also serves to maximize the power of the analyses to detect real differences in the effects of the treatment regimens between sexes. The one borderline significant result for heterogeneity between treatment effects in men and women for stroke is almost certainly a chance finding given the large number of comparisons made. In addition to controlling for random errors through the accumulation of large volumes of data the overview methodology employed here also controls for systematic errors. Pre-specification of the criteria for inclusion of trials, the comparisons to be studied, and the outcomes to be reported in addition to the format of the subgroup analyses themselves, all serve as reassurance about the likely reliability of the overview findings and the conclusions drawn. The analyses have two limitations which warrant discussion. First, data defined by the pre-specified criteria were not available for all eligible trials. However, limited subsidiary analyses including published data from excluded studies did not change the overall study conclusions. Secondly, while the findings are based on intention-to-treat analyses, patients for whom the outcome was unknown were included as 'event-free'. In order to explore the impact of censoring, we compared the results of tabulated data (with a missing event coded as 'no event') and survival analyses (i.e. odds ratios vs. hazard ratios) using trials for which IPD were available. In these supplementary analyses, there were no differences in the risk of major cardiovascular events between men and women (all $P > 0.07$) for any of the pre-specified treatment comparisons.

In summary, these overviews provide clear evidence that a broad range of different blood pressure-lowering regimens will provide comparable protection against serious vascular complications in both men and women. In the short-to-medium term, the greatest absolute benefits of blood pressure reduction will be achieved among individuals at highest risk. While the patient's sex should contribute to their risk assessment, it need not otherwise influence decisions about the need for blood pressure-lowering therapy, the intensity of blood pressure reduction to be achieved, or the choice of drug class.

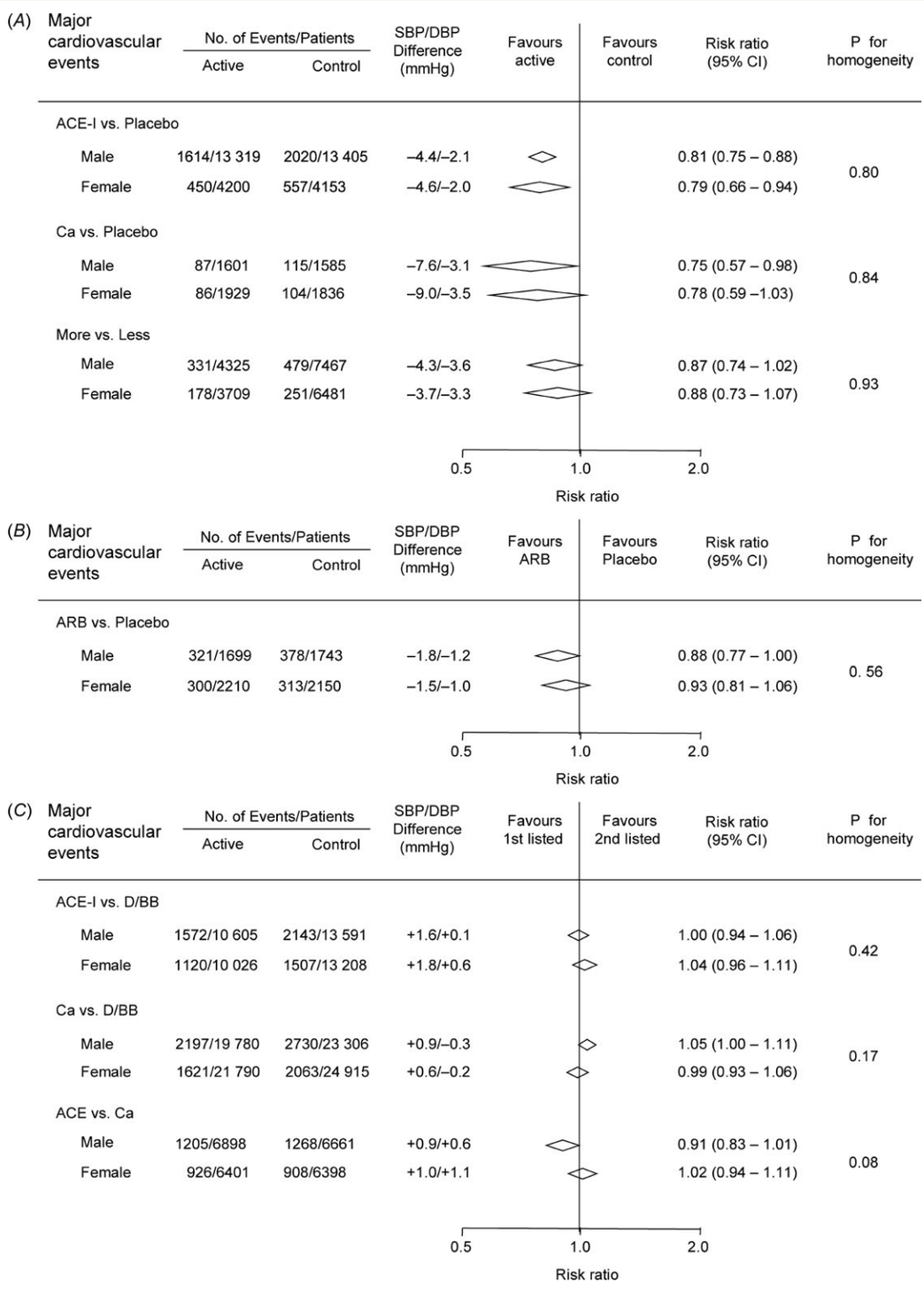


Figure 1 (*A*) Comparisons of blood pressure-lowering regimens against placebo or less intensive control. (*B*) Comparisons of angiotensin receptor blocker-based regimens with other regimens. (*C*) Blood pressure-lowering regimens based on different drug classes for the outcome of total major cardiovascular events, for men and women. SBP/DBP difference = overall mean blood pressure difference during follow-up between treatment groups (the actively treated group compared with the control group or the group assigned the first listed treatment compared with the group assigned the second-listed treatment), calculated by weighting the difference observed in each contributing trial by the number of individuals in the trial, separately for men and women. Negative blood pressure values indicate lower mean follow-up blood pressure levels in the first listed than in second listed groups. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; Ca, calcium antagonist; D/BB, diuretic or beta-blocker; More, more intensive blood pressure-lowering regimen; Less, less intensive blood pressure-lowering regimen.

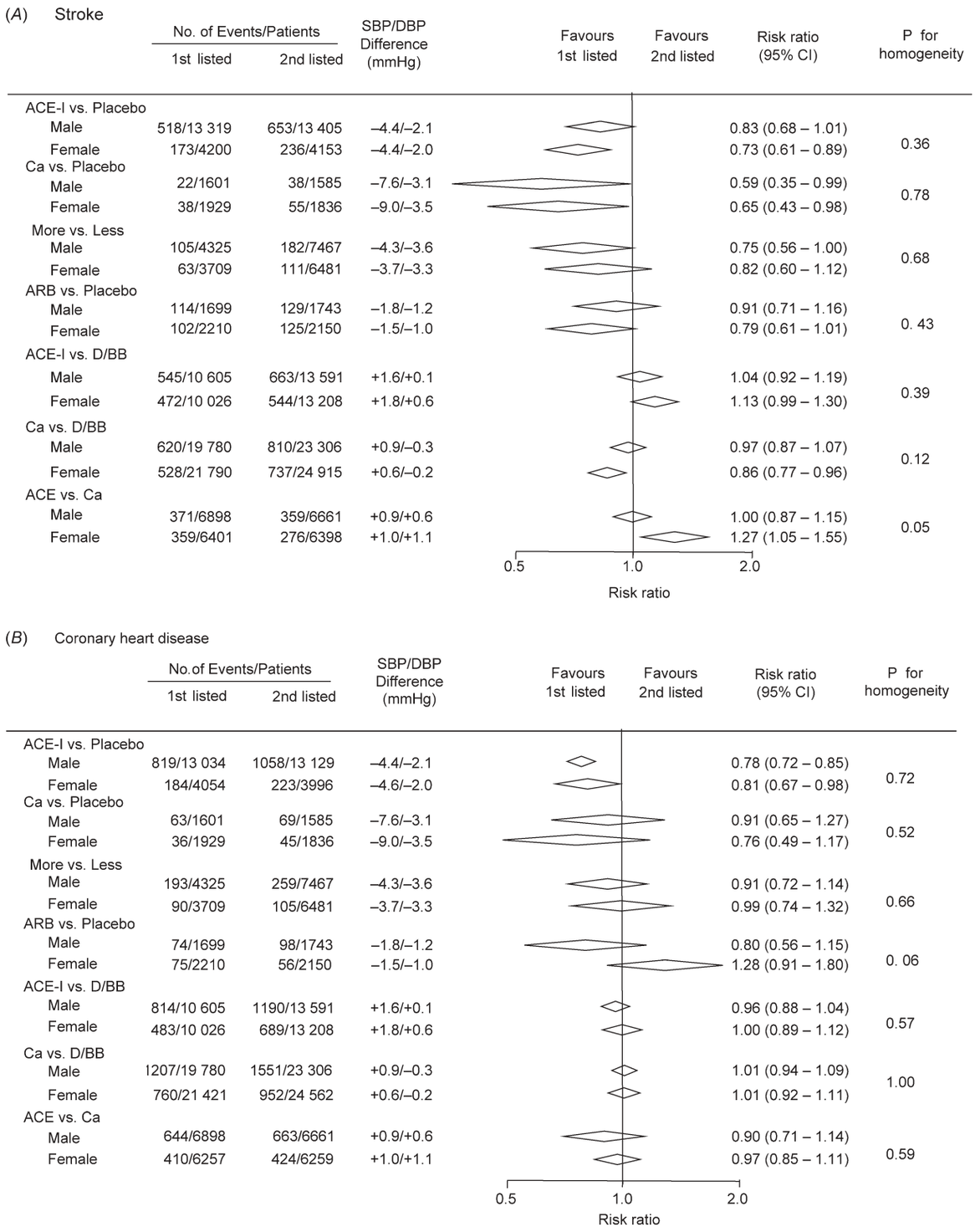
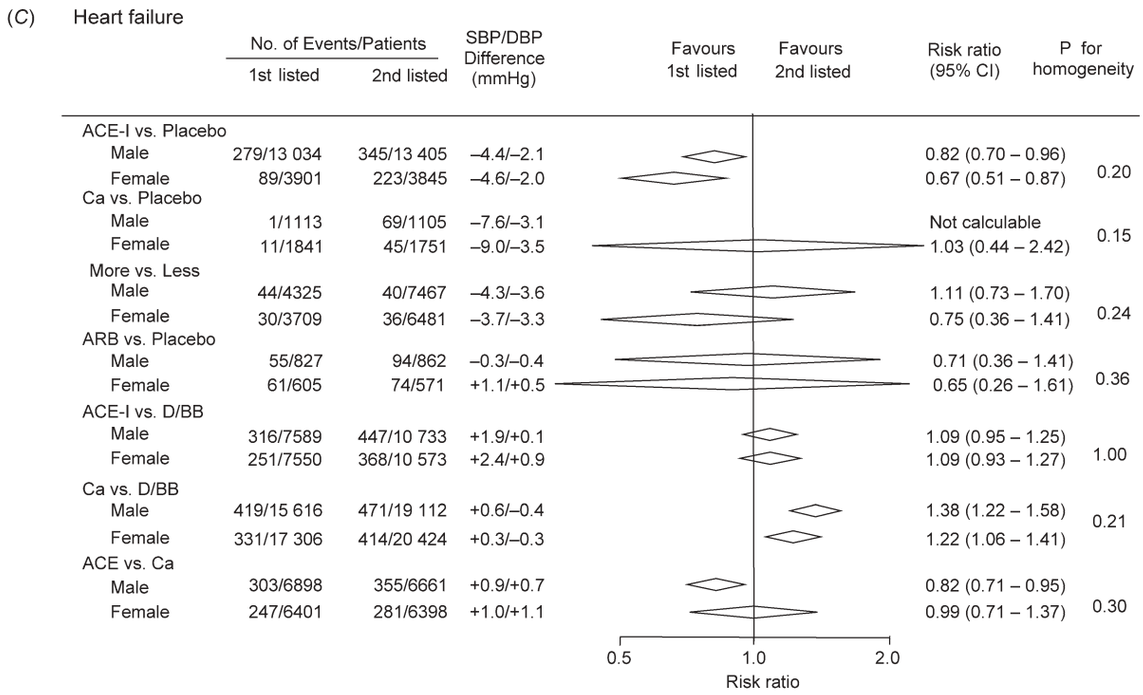


Figure 2 Comparisons of different blood pressure-lowering regimens, for men and women, on the outcomes of (*A*) Stroke. (*B*) Coronary heart disease. (*C*) Heart failure. (*D*) Cardiovascular death. (*E*) Total mortality. Abbreviations as listed in *Figure 1*.



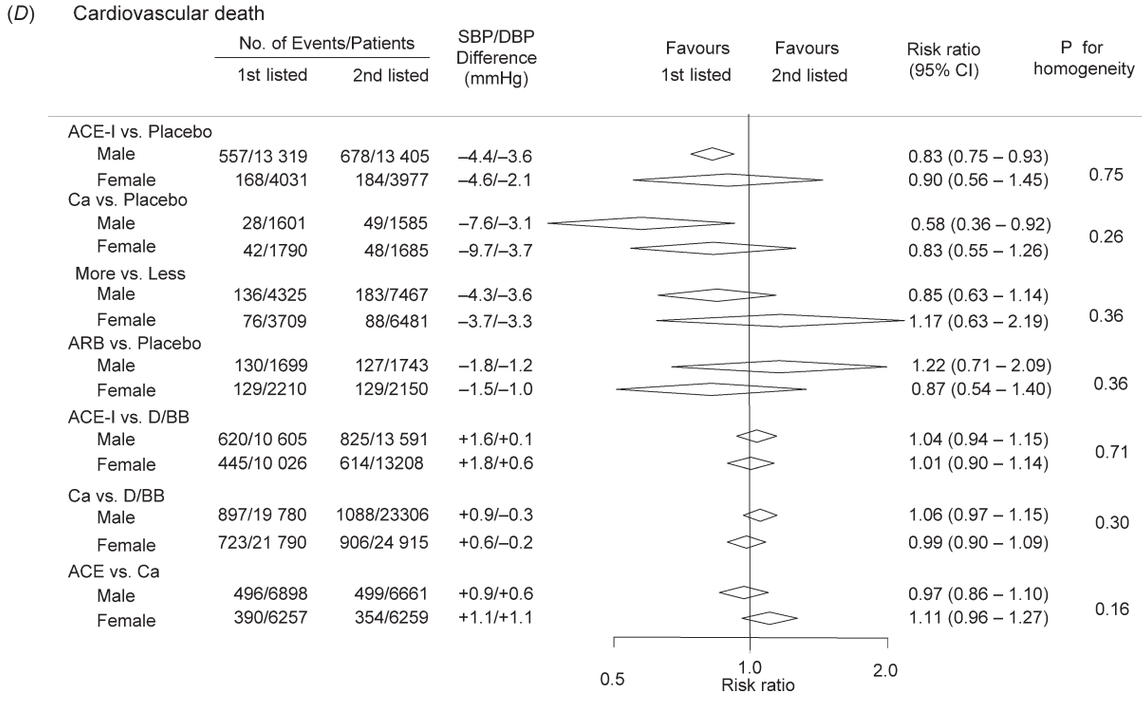


Figure 2 *Continued.*

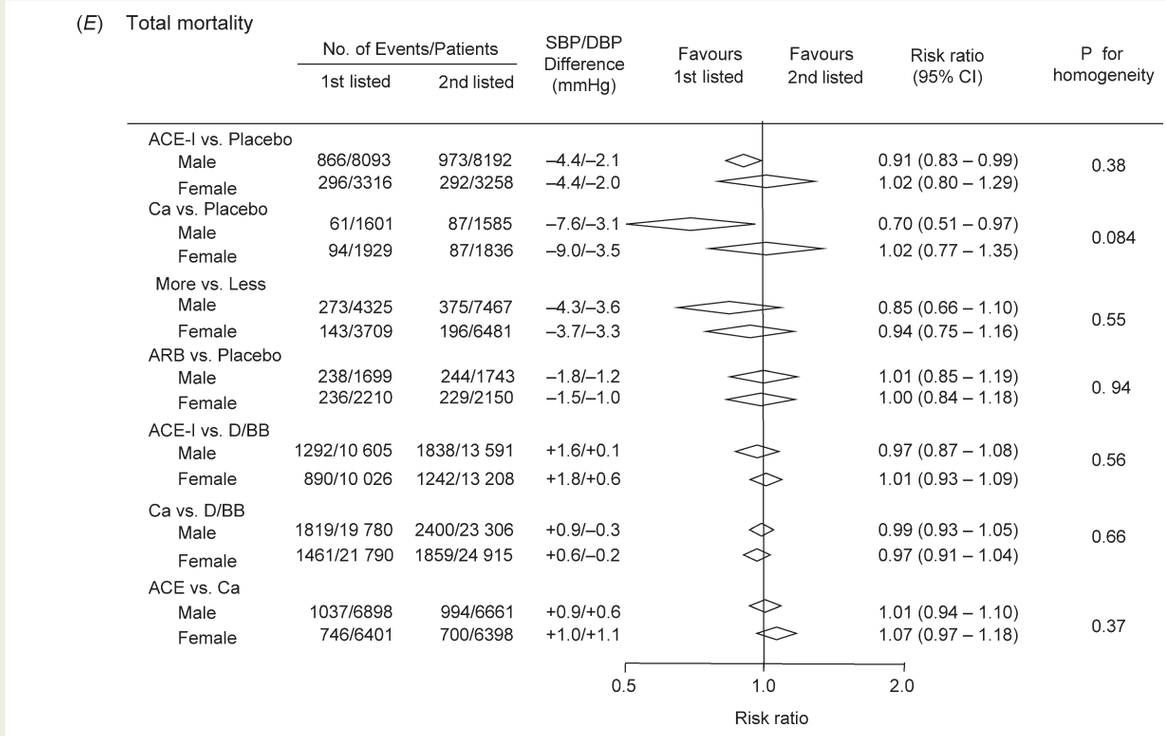


Figure 2 *Continued.*

Funding

B.N. was supported by a Fellowship awarded by the National Heart Foundation of Australia and the Collaboration Coordinating Centre by Program and Project Grants provided by the National Health and Medical Research Council of Australia. T.N. was supported by a Fellowship awarded by the Banyu Life Science Foundation and by an International Society of Hypertension Visiting Postdoctoral Fellowship awarded by the Foundation for High Blood Pressure Research Council of Australia.

Conflict of interest: none declared.

Appendix

Members of the Blood Pressure Lowering Treatment Trialists' Collaboration: L. Agodoa, C. Anderson, F. W. Asselbergs, C. Baigent, H. Black, B. Brenner, M. Brown, C. Bulpitt, R. Byington, J. Chalmers, R. Collins, J. Cutler, B. Dahlof, B. Davis, D. de Zeeuw, J. Dens, R. Estacio, R. Fagard, K. Fox, T. Fukui, L. Hansson (deceased), R. Holman, L. Hunsicker, Y. Imai, M. Ishii, Y. Kanno, J. Kostis, K. Kuramoto, E. Lewis, M. Lièvre, L. H. Lindholm, L. Liu, J. Lubsen, S. Lueders, S. MacMahon, E. Malacco, G. Mancia, M. Matsuzaki, B. Neal, S. Nissen, T. Ohkubo, T. Ogihara, C. Palmer, C. Pepine, M. Pfeffer, B. Pitt, P. Poole-Wilson, N. Poulter, M. Rahman, W. Remme, G. Remuzzi, A. Rodgers, P. Ruggenenti, T. Saruta, J. Schrader, R. Schrier, P. Sever, P. Sleight, J. Staessen, H. Suzuki, K. Teo, W.H. van Gilst, G. Viberti, J. Wang, P. Whelton, L. Wing, Y. Yui, S. Yusuf, A. Zanchetti. Collaboration Coordinating Centre: F. Barzi, J. Chalmers, N. Li, S. MacMahon, B. Neal, T. Ninomiya, V. Perkovic, F. Turnbull, M. Woodward. Writing Committee: F. Turnbull, M. Woodward, B. Neal, F. Barzi, T. Ninomiya, J. Chalmers, V. Perkovic, N. Li, S. MacMahon.

References

1. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular diseases in the Asia-Pacific region. *J Hypertens* 2003;**21**:707–716.
2. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
3. Quan A, Kerlikowske K, Gueffiyer F, Boissel J-P, the INDANA Investigators. Efficacy of treating hypertension in women. *J Gen Intern Med* 1999;**14**:718–729.
4. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA* 2002;**288**:2981–2997.
5. Gueffiyer F, Boutitie F, Boissel J-P, Pocock S, Coope J, Cutler J, Ekbom T, Fagard R, Friedman L, Perry M, Prineas R, Schron E. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomised controlled trials. *Ann Intern Med* 1997;**126**:761–767.
6. World Health Organisation-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure lowering treatments. *J Hypertens* 1998;**16**:127–137.
7. Lithell H, Hansson L, Skogg I, Elmfeldt D, Hofman A, Olofsson B, for the SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE). Principal results of a randomised double-blind intervention trial. *J Hypertens* 2003;**21**:875–886.
8. Brenner B, Cooper M, De Zeeuw D, Keane W, Mitch W, Parving H, Remuzzi G, Snapinn S, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–869.
9. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener H, for the MOSES Study Group. Morbidity and mortality

after stroke, eprosartan compared with nitrendipine for secondary prevention. *Stroke* 2005;**36**:1218–1226.
10. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward W, MacMahon S, on behalf of the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008;**336**: 1121–1123.
11. Teo K, Burton J, Buller C, Plante S, Catellier D, Tymchak W, Dzavik V, Taylor D, Yokoyama S, Montague T, for the SCAT Investigators. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis. The Simvastatin/enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000;**102**:1748–1754.
12. Estacio R, Jeffers B, Hiatt W, Biggerstaff S, Gifford N, Schrier R. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. *N Engl J Med* 1998;**338**: 645–652.
13. Wright J, Bakris G, Green T, Agodoa L, Appel L, Charleston J, Cheek D, Doublas-Baltimore J, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips R, Toto R, Middleton J, Rosstand S, for the African American Study of Kidney Disease Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;**288**:2421–2431.
14. Hansson L, Zanchetti A, Carruthers S, Dahlof B, Elmfeldt D, Julius S, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755–1762.
15. Asselbergs F, Diercks G, Hillege H, van Boven A, Janssen W, Voors A, de Zeeuw D, de Jong P, van Veldhuisen D, van Gilst W, Prevention of Renal Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004;**110**:2809–2816.
16. Pepine C, Handberg-Thurmond E, Marks R, Conlon M, Cooper-DeHoff R, Volkers P, Zellig P, for the International Verapamil SR/Trandolapril study (INVEST) investigators. Rationale and design of the International Verapamil SR/ Trandolapril study (INVEST): an Internet-based randomised trial in coronary heart disease patients with hypertension. *J Am Coll Cardiol* 1998;**32**:1228–1237.
17. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998;**317**:713–720.
18. Zanchetti A, Bond M, Hennig M, Neiss A, Mancia G, Dal Palu C, Hansson L, Magnani B, Rahn K-H, Reid J, Rodicio J, Safar M, Eckes L, Rizzini P, on behalf of the ELSA investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis. *Circulation* 2002;**106**:2422–2427.
19. Zanchetti A, Agabiti-Rosei E, Dal Palu C, Leonetti G, Magnani B, Pessina A. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomised treatment with either verapamil or chlorthalidone on intima-media thickness. *J Hypertens* 1998;**16**:1667–1676.
20. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. *Hypertension* 1999;**34**:1129–1133.
21. Wing L, Reid C, Ryan P, Beilin L, Brown M, Jennings G, Johnston C, McNeil J, Macdonald G, Marley J, Morgan T, West M, for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;**348**:583–592.
22. Dahlof B, Devereux R, Kjeldsen S, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm L, Nieminen M, Omvik P, Oparil S, Wedel H, for the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995–1003.
23. MacMahon S, Sharpe N, Gamble G, Clague A, Ni Mhurchu C, Clark T, Hart H, Scott J, White H, for the PART-2 Collaborative Research Group. Randomised, placebo-controlled trial of the angiotensin converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive vascular disease. *J Am Coll Cardiol* 2000;**36**:438–443.
24. Pitt B, Byington R, Furberg C, Hunninghake D, Mancinin G, Miller M, Riley WR. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000;**102**:1503–1510.
25. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033–1041.
26. Staessen J, Fagard R, Thijs L, Celis H, Arabidze G, Birkenhager W, Bulpitt C, de Leeuw P, Dollery C, Fletcher A, Forette F, Leonetti G, Nachev C, O'Brien E, Rosenfeld J, Rodicio J, Tuomilehto J, Zanchetti A, for the SYST-EUR Study Group. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension in Europe. *Lancet* 1997; **350**:757–764.
27. 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**:703–713.
28. HOPE (Heart Outcomes Prevention Evaluation) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
29. Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H, Bass T, Pepine C, Texter M, Haber H, Uprichard A, Cashin-Hemphill L, Lees R, for the QUIET Study Group. The QUinapril Ischemic Event Trial (QUIET): Evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001;**87**:1058–1063.
30. Dens J, Desmet W, Coussement P, De Scheerder I, Kostopoulos K, Kerdsinchai P, Supanantaroek C, Piessens J. Usefulness of nisoldipine for prevention of restenosis after percutaneous transluminal coronary angioplasty (Results of the NICOLE study). *Am J Cardiol* 2001;**87**:28–33.
31. Schrier R, Estacio R, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;**61**:1086–1097.
32. Hansson L, Lindholm L, Niskanen L, Lanke L, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg B, Wester P, Bjorck J-E, for the Captopril Prevention Project (CAPPP) Study Group. Effect of angiotensin converting enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;**353**:611–616.
33. Hansson L, Lindholm L, Ekbom T, Dahlof B, Lanke J, Schersten B, Wester P-O, Hedner T, de Faire U, for the STOP-Hypertension-2 study group. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;**354**:1751–1756.
34. Black H, Elliot W, Grandits G, Grambsch P, Lucente T, White W, for the CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial. *JAMA* 2003;**289**: 2073–2082.
35. Brown M, Palmer C, Castaigne A, de Leeuw P, Mancia G, Rosenthal T, Ruilope L. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;**356**:366–372.
36. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen S, Lindholm L, Syvertsen J, Lanke J, deFaire U, Dahlof B, Karlberg B, for the NORDIL study group. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;**356**:359–365.
37. Malacco E, Gnemmi A, Romagnoli A, Coppini A, on behalf of the SHELL Study Group. Systolic hypertension in the elderly: long-term lacidipine treatment. *J Cardiovasc Pharmacol* 1994;**23**(Suppl. 5):S62–S66.
38. Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C, for the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004;**27**:181–191.
39. Ruggenenti P, Fassi A, Ilieva A, Bruno S, Iliev I, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini A, Remuzzi G, Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004;**351**:1941–1951.
40. Marre M, Lievre M, Chatellier G, Mann J, Passa P, Menard J, on behalf of the DIABHYCAR study investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;**328**:495.
41. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
42. Pepine C, Handberg E, Cooper-DeHoff R, Marks R, Kowey P, Messerli F, Mancia G, Cangiano J, Garcia-Barreto D, Keltai M, Erdine S, Bristol H, Kolb H, Bakris G, Cohen J, Parmley W, INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with

coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;**290**:2805–2816.
43. The PEACE trial investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–2068.
44. Poole-Wilson P, Lubsen J, Kirwan B, van Dalen F, Wagener G, Danchin N, Just H, Fox K, Pocock S, Clayton T, Motro M, Parker J, Bourassa M, Dart A, Hildebrandt P, Hjalmarson A, Kragten J, Molhoek G, Otterstad J, Seabra-Gomes R, Soler-Soler J, Weber S, A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;**364**:849–857.
45. Lewis E, Hunsicker L, Clarke W, Berl T, Pohl M, Lewis J, Ritz E, Atkins R, Rohde R, Raz I, for the Study Collaborative Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–860.
46. Dahlof B, Sever P, Poulter N, Wedel H, Beevers D, Caulfield M, Collins R, Kjeldson S, Kristinsson A, McInnes G, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, for the ASCOT investigators. Prevention of cardiovascular events with an anti-hypertensive regimen of amlodipine adding perinopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandanavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895–906.
47. Julius S, Kjeldsen S, Weber M, Brunner H, Ekman S, Hansson L, Hua T, Laragh J, McInnes G, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, group. Vt. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
48. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus; results of propsectively designed overviews. *Arch Intern Med* 2005;**165**:1410–1419.
49. Chobanian AV, BG, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the National High Blood Pressure Education Program Coordination Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;**289**:2560–2572.
50. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. *J Hypertens* 2007;**25**:1105–1187.
51. Williams B, Poulter N, Brown M, Davis M, McInnes G, Potter J, Sever P, Thom S. British Hypertension Society Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. *J Hum Hypertens* 2004;**18**:139–185.
52. Vaccarino V, Parsons L, Every N, Barron H, Krumholz H, for the National Registry of Myocardial Infarction 2 Participants. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med* 1999;**341**:217–225.
53. Wong C, Froelicher E, Bacchetti P, Gee L, Selby J, Lundstrom R. In a managed care setting, are there sex differences in the use of coronary angiography after acute myocardial infarction? *Am Heart J* 1998;**135**:435–442.
54. Vaccarino V, Krumholz H, Yarzebski J, Gore J, Goldberg R. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001;**134**:173–181.
55. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day fatality of 3991 events in men and 1551 events in women. *Circulation* 1996;**93**:1981–1992.
56. Ong K, Tso A, Lam K, Cheung B. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. *Hypertension* 2008;**51**:1142–1148.