Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003

Jan A. Staessen, Ji-Guang Wang and Lutgarde Thijs

Background **In a meta-analysis published in October 2001, we reported that new and old classes of antihypertensive drugs had similar long-term efficacy and safety. Furthermore, we observed that in clinical trials in hypertensive or high-risk patients gradients in systolic pressure accounted for most differences in outcome.**

Objective **To test whether our previous conclusions would hold, we updated our quantitative overview with new information from 14 clinical trials presented before 1 March 2003.**

Methods **To compare new and old antihypertensive drugs, we computed pooled odds ratios from stratified 2 × 2 contingency tables. If Zelen's test of heterogeneity was significant, we used a random effects model. In a meta-regression analysis, we correlated odds ratios with corresponding between-group differences in systolic pressure. We then contrasted observed odds ratios with those predicted from gradients in systolic pressure.**

Main outcomes **Differences in achieved systolic blood pressure and incidence of total and cardiovascular mortality, cardiovascular events, stroke, myocardial infarction and heart failure.**

New versus old drugs **In 15 trials, 120 574 hypertensive patients were randomized to old drugs (diuretics or β-blockers) or new agents [calcium-channel blockers, α-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin type-1 receptor (AR1) blockers]. Old and new drugs provided similar protection against total and cardiovascular mortality and fatal plus non-fatal myocardial infarction. Calcium-channel blockers, including (−8%, $P = 0.07$) or excluding verapamil (−10%, $P = 0.02$), as well as AR1 blockers (−24%, $P = 0.0002$) resulted in better stroke prevention than did the old drugs, whereas the opposite trend was observed for ACE inhibitors (+10%, $P = 0.03$). The risk of heart failure was higher ($P < 0.0001$) on calcium-channel blockers (+33%) and α-blockers (+102%) than on conventional therapy involving diuretics.**

Meta-regression **Between-group differences in achieved systolic pressure ranged from 0.1 to 3.2 mmHg in seven actively controlled trials (73 237 patients), and from 2.1 to 22.1 mmHg in seven studies comparing varying intensities of blood pressure lowering (11 128 patients). For these 14 new trials, we predicted outcome from achieved systolic blood pressure using our previously published meta-regression models based on 30 trials with 149 407 patients. In general, predicted and observed odds ratios were similar. Larger reductions in systolic pressure (weighted mean 1.8 mmHg) in two trials accounted for the advantage of AR1 blockers over conventional therapy in the prevention of stroke. Only for cardiovascular mortality in very old patients ($P = 0.02$) and for cardiovascular events and myocardial infarction in old Australians ($P < 0.05$), the observed odds ratios deviated from our predictions based on the gradients in systolic blood pressure.**

Interpretation **The hypothesis that new antihypertensive drugs, such as calcium-channel blockers, α-blockers, ACE inhibitors or AR1 blockers might influence cardiovascular prognosis over and beyond their antihypertensive effects remains unproven. The finding that blood pressure differences largely accounted for cardiovascular outcome emphasizes the desirability of tight blood pressure control. However, the level to which blood pressure must be lowered to achieve maximal benefit remains currently unknown.** *J Hypertens* **21:1055–1076 © 2003 Lippincott Williams & Wilkins.**

Journal of Hypertension 2003, **21**:1055–1076

Keywords: blood pressure, clinical trial, heart failure, morbidity, mortality, myocardial infarction, prevention, stroke

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Sponsorship: J.-G.W. was supported by the bilateral scientific collaboration between the People's Republic of China and Flanders, Belgium (BIL 02/10).

Conflict of interest: J.A.S. did *ad hoc* consultancies for pharmaceutical companies with commercial interests in the cardiovascular field and received funding for studies, seminars, and travel from such companies.

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Received 23 March 2003 **Revised** 6 April 2003
Accepted 9 April 2003

Introduction

For recently published overviews [1,2], we extracted summary statistics from nine actively controlled trials testing new antihypertensive drugs versus conventional therapy in 62 605 patients [3–11]. Compared with old drugs (diuretics and β-blockers), calcium-channel blockers and angiotensin converting enzyme (ACE) inhibitors offered similar overall protection. Calcium-

0263-6352 © 2003 Lippincott Williams & Wilkins

DOI: 10.1097/01.hjh.0000059044.65882.db

channel blockers provided 13.5% more reduction in the risk of stroke (95% confidence interval 1.3–24.2%, $P = 0.03$) and 19.2% less reduction in the risk of myocardial infarction (95% confidence interval 3.5–37.3%, $P = 0.01$). Furthermore, a meta-regression analysis across 30 trials [3,4,6–9,11–39] including 149 407 patients demonstrated that most odds ratios in recent trials could be explained by achieved differences in systolic pressure [1,2,40].

Since the publication of our overviews [1,2], several large trials have either been published or had their main outcome results announced at major international conferences or at various websites on the internet [41–65]. The purpose of this article was to update our quantitative overview [1,2] with the new information from clinical trials that became available before 1 March 2003 and to test whether our previously published conclusions [1,2] would hold.

Methods

Acquisition and selection of trials

We described our search strategy in detail in our previous report [1]. In short, we focused on outcome trials, which tested drugs with blood pressure-lowering activity in normotensive or hypertensive subjects without heart failure. The other criteria for the studies to be included were: a randomized controlled design, publication in a peer-reviewed journal, inclusion of patients with hypertension, assessment of blood pressure and cardiovascular events, follow-up for 2 years or longer, and sample size of 100 or more. For the present analysis, we also accepted large-scale trials of which the main results had been presented at international meetings with confirmatory information made available by the authors [61] or published on the internet [64] and studies with shorter follow-up but high incidence of events [59].

We first compared outcomes among patients randomized to initial treatment with diuretics or β-blockers and those started on newer agents such as calcium-channel blockers, ACE inhibitors, α-blockers, or angiotensin type-1 receptor (AR1) blockers. For this part of our analysis [1], we previously identified 11 studies [3–11,66,67], including the doxazosin arm of the ALLHAT trial [9]. However, we excluded one trial [66] because randomization was not between old and new drugs, but between special intervention and usual care. We dismissed a second study [67] because cardiovascular outcomes were only published in aggregate form. For the present update, we considered the amlodipine and lisinopril arms of the ALLHAT trial [50] plus 11 other comparative trials, including the short-term [45,68] and long-term [52,68] follow-up of the AASK patients, ANBP2 [41,55], ASCOT [69], CONVINCE [57,60], ELSA [47,53,70], the HYVET pilot trial [56,59] [Dr C.J. Bulpitt presented the outcome results of the HYVET pilot trial on 24 June 2002 at the joint 19th/12th Scientific Meeting of the International/European Society of Hypertension (Prague)], INVEST [71], LIFE [48,49,72,73], PHYLLIS [74,75], SCOPE [58,65], and SHELL [76]. For the comparison between new versus old drugs, we could not extract the endpoints of interest from the AASK publications [45,52,68]. As of 1 March 2003, at the time of writing of this article, the blood pressure lowering arm of ASCOT [69] was still ongoing and, to the best of our knowledge, the results of INVEST [71] and SHELL [76] were not yet available. PHYLLIS patients [75] experienced few cardiovascular endpoints. Thus, our overall analysis of comparative studies included 15 trials [3–11,47,49,50,55,59,60,65]. We combined three smaller trials [3,5,10], which tested a calcium-channel blocker against a thiazide. In these trials [3,5,10], the rate of cardiovascular complications was less than 40 events in 414 Japanese patients followed up for 5 years [5] or below one event per 1000 patient-years [3,10].

We did not engage in comparisons of old versus old drugs (β-blockers versus diuretics [77–79]) or new versus new agents (ACE inhibitors or AR1 blockers versus calcium-channel blockers [43,46,80–84]). Fewer of such studies were available than for the comparison of old with new drugs. Large-scale studies that included results falling within this category were primarily designed to compare either active therapy with no treatment [16,17,46] or new drug classes with diuretics [6,50]. Moreover, for comparisons within the same generation of antihypertensive drugs, the choice of the reference treatment would have been an arbitrary one [6,16,17,50,77–81].

In a meta-regression analysis [1,2], we calculated the relationship between the odds ratios of experimental versus reference treatment and the corresponding baseline-corrected differences in systolic blood pressure between randomized groups. We excluded from analysis two comparative trials for the reasons outlined above [66,67], seven smaller trials in hypertension [85–90] which, in keeping with our prespecified exclusion criteria, accumulated fewer than 100 randomized patients [89–91] or less than 2 years of follow-up [86–88], or did not provide information on systolic pressure [87] or cardiovascular events [85]. Because achieved systolic pressure [92] was not reported, we also excluded the HDFP trial [92] as well as one placebo-controlled trial on the progression of atherosclerotic disease under treatment with quinapril [93]. Thus, our meta-regression analysis [2] involved 30 trials with 149 407 enrolled patients: nine actively controlled trials [3–11]; the HOT trial [31], which investigated three levels of diastolic blood pressure control; three placebo-controlled trials in isolated systolic hypertension (SHEP

[18], Syst-China [30,94] and Syst-Eur [21]); six placebo-controlled trials in normotensive or hypertensive patients at high cardiovascular risk (HOPE [33], PART2 [36], PATS [23], PROGRESS [38], SCAT [37] and RENAAL [39]); and 11 older trials testing the efficacy of antihypertensive drugs against no treatment (HEP [14] and OSLO [26]) or placebo (ATMH [22], EWPHE [12], HSCS [27], MRC1 [17], MRC2 [16], STOP1 [15], STONE [19], USPHS [28], and VACS [29]). Because of the similarity in design and the low number of events, we combined in the meta-regression analysis four smaller trials published in 1980 or earlier [26–29] as well as two placebo-controlled trials on the progression of atherosclerosis involving ACE inhibitors [36,37].

We tested the statistical difference between the odds ratios predicted by our meta-regression model and those available from the recent literature. For this part of our overview, we considered six trials of blood pressure-lowering therapies (DIABHYCAR [62–64], HYVET [56,59], IDNT2 [46,54], IRMA2 [95], NICOLE [61], PREVENT [42,44]), seven trials of new versus old drugs (ALLHAT [50], ANBP2 [41,55], CONVINCE [57,60], ELSA [47,53,70], LIFE [48,49, 72,73], SCOPE [58,65], and SHELL [76]), and two studies testing tight versus usual blood pressure control (AASK [52] and ABCD/NT [43,51]). IRMA2 [95] did not report the number of cardiovascular events. SHELL [76] is not yet published. We therefore excluded these two trials [76,95].

Outcomes

We based our analysis on the summary statistics reported in the literature [3–39,44,46,47,49–52,55,65], at meetings [59] or via the internet [64], and on information provided by the investigators [61]. For LIFE [49] and IDNT2 [46], we also consulted minutes of public hearings at the Food and Drug Administration (FDA), Rockville, Maryland, USA.

With the exception of fatal combined with non-fatal events in the EWPHE trial [12,13], all outcome results were reported on the basis of an intention-to-treat principle. The EWPHE trial [12,13] was among the early intervention studies on the treatment of hypertension. It was planned in 1971. Patients who were randomized and left the double-blind part of the study were followed up until 1 July 1984, but only the date and cause of death were recorded.

For the comparison between new and old drug classes, we extracted from the reports on 15 trials [3–11, 47,49,50,55,59,60,65] total and cardiovascular mortality, the number of cardiovascular events, fatal and non-fatal strokes excluding transient ischaemic attacks, fatal and non-fatal myocardial infarctions, and fatal and non-fatal cases of heart failure. For two trials [46,50], the definition of myocardial infarction also included coronary [50] or sudden death [46]. Starting from published reports [3–39,44,46,47,49–52,55,60,61,64,65], we had no other option than to accept the definitions of events as given by the investigators. For 19 trials [4,6–8,15, 31,33,37–39,46,47,49,50,52,55,60,64,65], the term 'all cardiovascular events' refers to the primary composite endpoint [4,6–8,15,31,33,37,49,60,64,65] or to another composite cardiovascular endpoint [38,39,46,47,50,52, 55] presented in the published reports. For the Syst-Eur [21,96,97] and Syst-China trials [30,94], we used individual patient records and the published definitions of all cardiovascular events. For the other studies, we summed up the major cardiovascular events. Since more than one event may have occurred in an individual, this approach is likely to have slightly overestimated the overall number of patients with cardiovascular complications.

Statistical methods

We determined the relative benefit of new versus old drug classes from the odds ratios in stratified 2×2 contingency tables [98]. We employed StatXact for Windows (CYTEL Software Corporation, Cambridge, Massachusetts, USA), version 4.0, to check the homogeneity of the odds ratios by Zelen's test and to compute exact 95% confidence intervals [99]. In the presence of significant heterogeneity, we applied a random effects model to compute pooled estimates [100]. To permit comparisons with other overviews [98,101–105], we also derived the standard deviations (SD) of the pooled odds ratios by analogy with the asymptotic approach by dividing the logarithmically transformed 95% confidence interval by (2×1.96). All reported P values are for two-sided hypotheses.

We used the SAS statistical package (SAS Institute, Cary, North Carolina, USA), version 8.1, to correlate odds ratios of experimental versus reference treatment with the corresponding baseline-adjusted differences in systolic blood pressure between randomized groups. Within each trial, the reference group consisted of patients left untreated [14,26] or allocated placebo [12,15–19,21–23,26–30,33,36,38,39], or the patients randomized to older drug classes [3–11] or to a treatment strategy leading to less blood pressure control [31,32]. For these calculations, odds ratios were logarithmically transformed. The regression lines were weighted by the inverse of the variance of the individual odds ratios [106]. Net treatment effects on blood pressure were determined by subtracting the mean change in the experimental group from the corresponding mean change in the reference group. To standardize estimates of relative risk across trials, whenever possible, we computed observed odds ratios with exact 95% confidence intervals from 2×2 contingency tables. However, if the number of events was unavailable

from the reports, we used published estimates of adjusted relative risk. We derived the predicted odds ratios from our previously published meta-regression models [2]. We compared predicted odds ratios with those available from the literature [44,46,47,49–52, 55,59–61,64,65] by means of a z-test statistic.

Results

New versus old antihypertensive drugs

Our previous overviews [1,2] of actively controlled studies included nine trials [3–11] and 62 605 patients, of whom 29 280 had been randomized to new agents and 33 325 to old drugs. We added seven trials [47,49,50,55,59,60,65] with 73 237 patients, of whom 38 015 were allocated first-line treatment with calcium-channel blockers [47,50,60], ACE inhibitors [50,55,59], or AR1 blockers [49,65] and 35 222 were started on diuretics or β-blockers. Thus, with regard to the comparison between new and old antihypertensive drugs, the present overview includes 15 trials [3–11,47,49, 50,55,59,60,65] and 120 574 patients.

The nine trials previously reviewed [1,2] were ALLHAT/Dox [9], CAPPP [4,24], INSIGHT [7,107], MIDAS [3], NICS [5], NORDIL [8], STOP2 [6], UKPDS [11,32] and VHAS [35]. Their main characteristics are summarized in reference [1]. A description of the more recent trials [47,49,50,55,59,60,65] appears in Table 1.

Calcium-channel blockers versus conventional therapy

Nine trials [3,5–7,10,26,47,50,60] with 67 435 randomized patients compared calcium-channel blockers with old drugs. We combined three smaller trials for analysis [3,5,10]. For none of the outcomes considered in our analysis, including all-cause mortality (Fig. 1), cardiovascular death (Fig. 2), all cardiovascular events (Fig. 3), stroke (Fig. 4), myocardial infarction (Fig. 5) and heart failure (Fig. 6), the *P*-values for heterogeneity reached statistical significance ($0.12 \leqslant P \leqslant 0.95$).

The pooled odds ratios expressing possible benefit of calcium-channel blockers over old drugs were close to unity and non-significant for total mortality (0.98, 95% confidence interval 0.92–1.03, $P = 0.42$), cardiovascular death (1.03, 95% confidence interval 0.95–1.11, $P = 0.51$), all cardiovascular events (1.03, 95% confidence interval 0.99–1.08, $P = 0.15$) and myocardial infarction (1.02, 95% confidence interval 0.95–1.10, $P = 0.61$). Calcium-channel blockers provided slightly better protection against fatal and non-fatal stroke than old drugs. For the nine trials combined [3,5–7,10,26, 47,50,60], the odds ratio for stroke was 0.92 (95% confidence interval 0.84–1.01, $P = 0.07$). After exclusion of CONVINCE [60], the only large trial based on verapamil, the odds ratio for stroke was 0.90 and reached significance (95% confidence interval 0.82–0.98, $P = 0.02$). For heart failure, calcium-channel blockers provided less protection than conventional therapy, regardless of whether (1.33, 95% confidence interval 1.22–1.44, $P < 0.0001$) or not (1.33, 95% confidence interval 1.22–1.46, $P < 0.0001$) we incorporated the CONVINCE trial [60] in the pooled estimates.

ACE inhibitors versus conventional therapy

Six trials [4,6,11,50,53,59] with 47 410 randomized patients compared ACE inhibitors with old drugs. For all-cause mortality (Fig. 1), cardiovascular death (Fig. 2), stroke (Fig. 4) and myocardial infarction (Fig. 5), *P*-values indicating heterogeneity among the trials of ACE inhibitors were non-significant ($0.16 \leqslant P \leqslant 0.90$). In contrast, for all cardiovascular events (Fig. 3, $P = 0.006$) and heart failure (Fig. 6, $P = 0.04$) heterogeneity was significant due to the ALLHAT findings [50]. Compared with chlorthalidone [50], ALLHAT patients allocated lisinopril had greater risks of stroke (1.15, 95% confidence interval 1.02–1.30, $P = 0.02$), heart failure (1.19, 95% confidence interval 1.07–1.31, $P < 0.001$), and hence combined cardiovascular disease (1.10, 95% confidence interval 1.05–1.16, $P < 0.001$).

The pooled odds ratios expressing possible benefit of ACE inhibitors over conventional therapy were close to unity and non-significant for total mortality (1.00, 95% confidence interval 0.94–1.06, $P = 0.89$), cardiovascular death (1.02, 95% confidence interval 0.94–1.11, $P = 0.61$), all cardiovascular events (1.03, 95% confidence interval 0.94–1.12, $P = 0.59$), myocardial infarction (0.97, 95% confidence interval 0.90–1.04, $P = 0.39$), and heart failure (1.04, 95% confidence interval 0.89–1.22, $P = 0.64$). Compared with old drugs, ACE inhibitors gave slightly less protection against stroke, with a pooled odds ratio of 1.10 (95% confidence interval 1.01–1.20, $P = 0.03$).

AR1 blockers versus conventional therapy

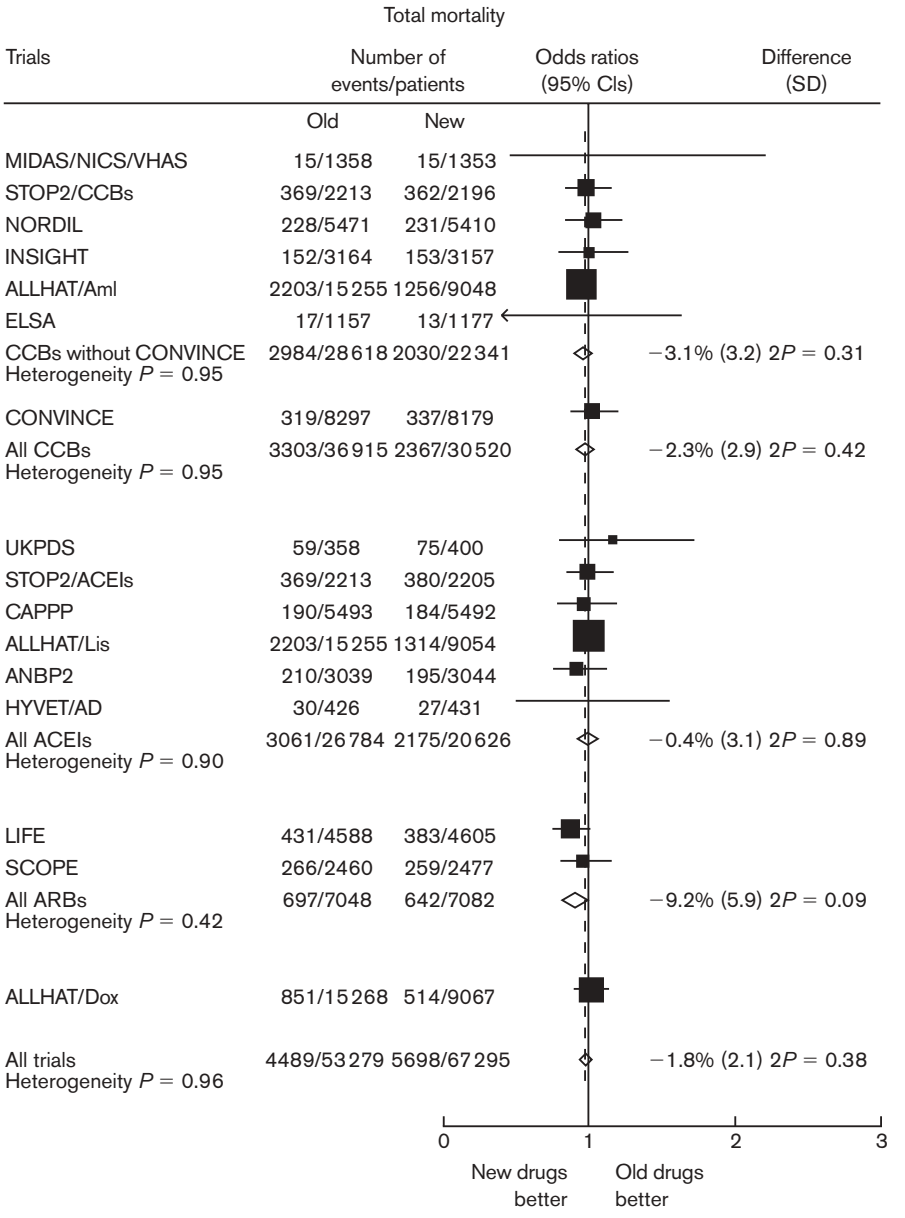
The LIFE trial tested losartan *versus* atenolol as first-line treatment in hypertensive patients with left ventricular hypertrophy [48,49,72,73]. SCOPE [58,65] was set up as a double-blind placebo-controlled trial. However, open-label antihypertensive drugs, which mainly consisted of diuretics, β-blockers, or both classes of old drugs, were added to the double-blind study medication in a considerably greater proportion of the patients randomized to placebo than in those allocated candesartan (Table 1). There was no statistical heterogeneity ($0.42 \leqslant P \leqslant 0.99$) between the results of these two trials [49,65]. Compared with control, treatment initiated with an AR1 blocker provided similar protection against total mortality (Fig. 1), cardiovascular death (Fig. 2), and myocardial infarction (Fig. 5). The pooled odds ratios were 0.91 (95% confidence interval 1.81–1.02, $P = 0.09$), 0.89 (95% confidence interval 0.77–1.04, $P = 0.15$), and 1.08 (95% confidence interval

Table 1 Recent trials of new *versus* old drug classes

	ALLHAT/Aml	ALLHAT/Lis	ANBP2	CONVINCE	ELSA	HYVET/AD	LIFE	SCOPE
Reference(s)	[50]	[50]	[41,55]	[57,60]	[47,53]	[56,59]	[48,49]	[58,65]
Degree of blinding	Double	Double	PROBE	Double	Double	PROBE	Double	Double
Number of patients	24 303	24 309	6083	16 476	2334	857	9193	4937
Reference (old drugs)	15 255	15 255	3039	8297	1157	426	4588	2460
Experimental (new drugs)	9048	9054	3044	8179	1177	431	4605	2477
Treatment								
Old drug(s)	Chlorthalidone	Chlorthalidone	Diuretics	Atenolol or HCTZ	Atenolol	BFMT or other thiazide	Atenolol plus HCTZ	Placebo plus open-label AH drugs[e]
New drug(s)	Amlodipine	Lisinopril	ACEIs	COER-verapamil	Lacidipine	ACEIs	Losartan plus HCTZ	Candesartan
Primary endpoint	CM+MI	CM+MI	ACM+CV	CVM+S+MI	Rate of CIMT	ACM+S	CVM+S+MI	CVM+S+MI
Mean age (years)	66.9	66.9	72.0	65.6	56.0	83.8	66.9	76.4
Mean systolic/diastolic BP (mmHg)								
At randomization	146/84[a]	146/84[a]	167/91	150/87[a]	164/101	181/100	174/98	166/90[a]
Difference during follow-up[b]	−1.1[c]/+0.6[e]	−2.3[c]/+0.2	−1.4[c]/∼0	+0.1/+0.7	+0.6/+0.2	+1.4/∼0	+1.1[c]/+0.2 (+3.0[c]/∼0)[f]	+3.2[c]/+1.6[c]
Mean serum creatinine (mmol/l)	78	78	–	–	84	102	86	88
Proportion of patients (%)								
Women	47.1	46.7	49.0	55.4	45.2	63.5	54.0	64.5
AH drug treatment before entry	90.2	90.2	62.0	83.5	63.3	47.5	72.2	52.7
History of CV complications[d]	36.1	36.4	15.0	12.3	2.4	6.9	23.9	8.4
Left ventricular hypertrophy	21.0	20.7	. . .	12.3	–	–	100	–
Diabetes mellitus	36.4	36.0	7.0	19.8	7.4[g]	–	13.0	12.1
Mean or median follow-up (years)	4.9	4.9	4.1	3.0	3.7	1.1	4.8	3.7

ACEI, angiotensin-converting enzyme inhibitor; ACM, all-cause mortality; AH, antihypertensive; BFMT, bendroflumethiazide; COER, controlled onset-extended release; CM, coronary mortality; CV, cardiovascular; CIMT, carotid intima–media thickening; CVM, cardiovascular mortality; HCTZ, hydrochlorothiazide; MI, non-fatal myocardial infarction; PROBE, prospective randomized open blinded end-point study; S, non-fatal stroke. Acronyms of trials are explained in the Appendix of this article. [a]Blood pressure at entry was measured on antihypertensive medication in previously treated patients. [b]Negative values indicate tighter blood pressure control on old drug classes. [c]Significant difference in achieved blood pressure between randomized groups. [d]History of myocardial infarction, stroke excluding transient ischaemic attack, or surgical or percutaneous revascularization. [e]88% of the SCOPE patients allocated placebo were on open-label antihypertensive treatment, mainly diuretics (62%) or β-blockers (26%). [f]Measured at the last visit before an event or before completion of the trial. The corresponding blood pressure changes in 1195 diabetic patients are given between parentheses. [g]Fasting blood glucose concentration $>$ 126 mg/dl [53].

Fig. 1



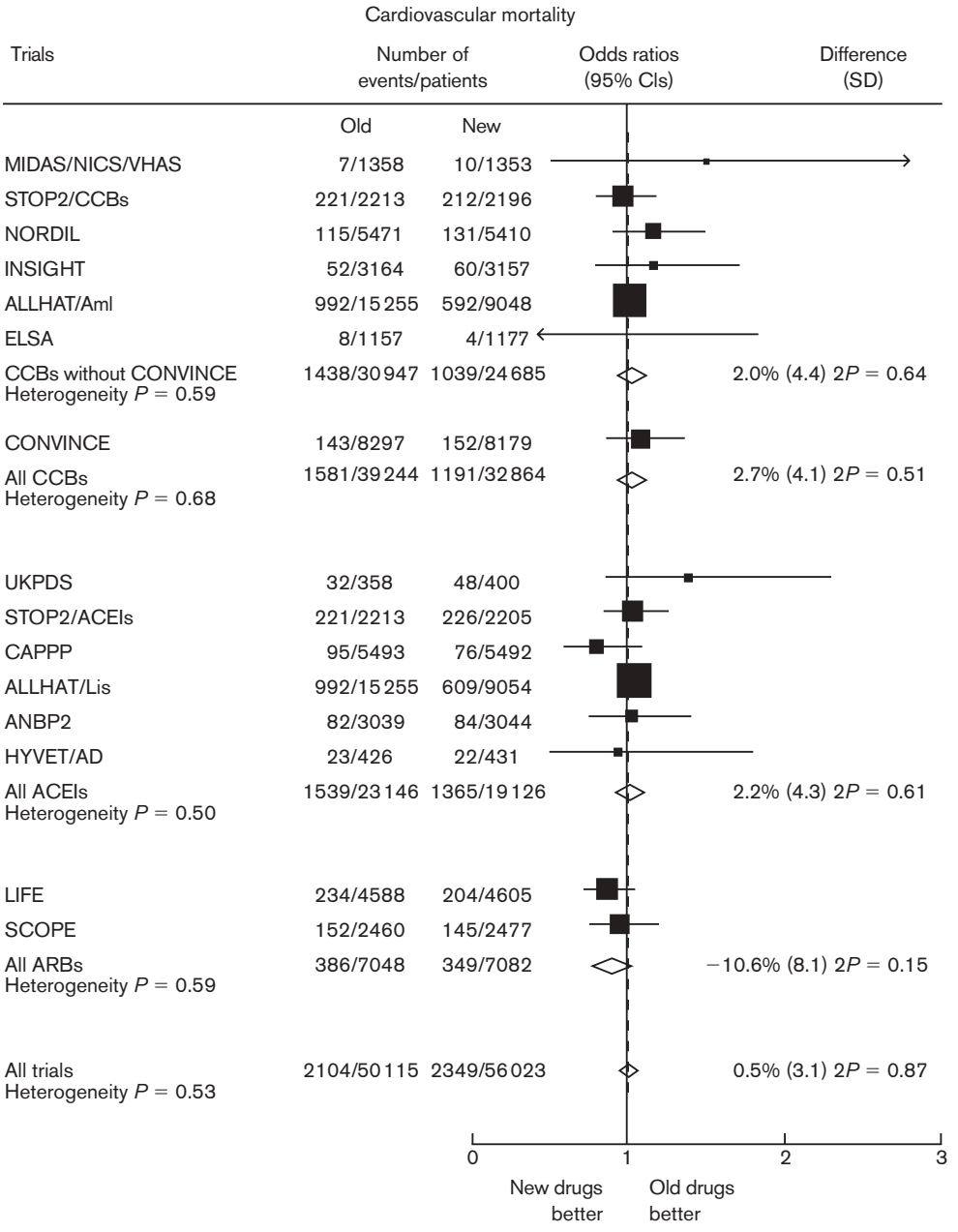
Effects of antihypertensive treatment on total mortality in trials comparing new with old antihypertensive drugs. Solid squares represent the odds ratios in trials and have a size proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines, and those for the pooled odds ratios by diamonds. Acronyms of trials are explained in the Appendix of this article.

0.90–1.29, $P = 0.42$), respectively. The corresponding estimates for stroke (Fig. 4) and all cardiovascular events (Fig. 3) were 0.76 (95% confidence interval 0.65–0.88, $P = 0.0002$) and 0.86 (95% confidence interval 0.77–0.95, $P = 0.004$), respectively.

New compared with old drugs

Across 15 trials [3–11,47,49,50,55,59,60,65], outcomes for total mortality (Fig. 1), cardiovascular death (Fig. 2) and myocardial infarction (Fig. 5) were consistent ($0.32 \leqslant P \leqslant 0.96$). The pooled odds ratios did not deviate from unity, averaging 0.98 (95% confidence interval 0.94–1.02, $P = 0.38$), 1.00 (95% confidence interval 0.95–1.07, $P = 0.87$) and 1.00 (95% confidence interval 0.95–1.06, $P = 0.88$), respectively. In contrast, for all cardiovascular events (Fig. 3), stroke (Fig. 4) and heart failure (Fig. 6), there was significant heterogeneity ($P \leqslant 0.001$) across the 15 trials [3–11,47,49,50,55,

Fig. 2



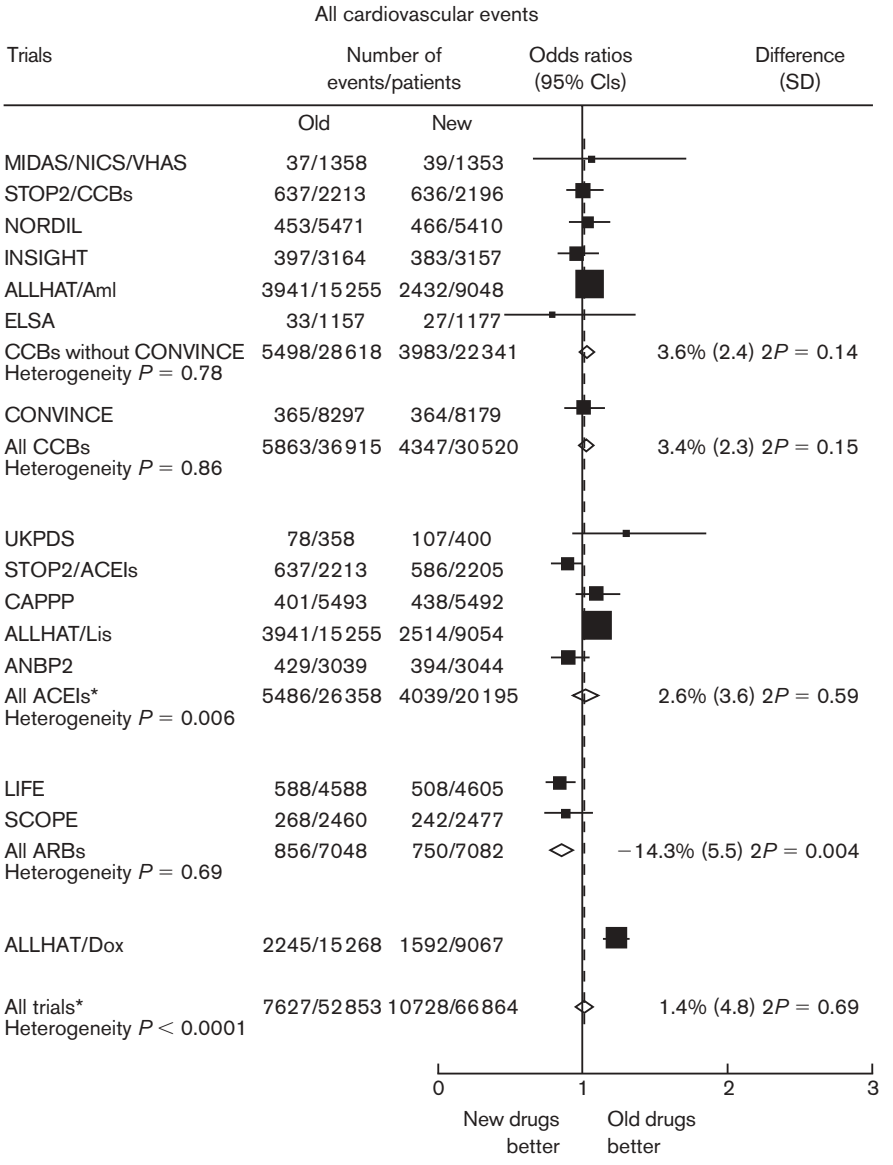
Effects of antihypertensive treatment on cardiovascular mortality in trials comparing new with old antihypertensive drugs. For further explanation, see Fig. 1.

59,60,65], which was largely due to the ALLHAT results [9,50]. For all cardiovascular events and stroke, the overall odds ratios were 1.01 (95% confidence interval 0.95–1.09, $P = 0.69$) and 0.98 (95% confidence interval 0.88–1.08, $P = 0.64$), respectively. Compared with conventional therapy, new drugs offered less protection against heart failure, with a pooled odds ratio of 1.23 (95% confidence interval 1.03–1.47, $P = 0.02$).

Meta-regression analysis

We derived predicted odds ratios from meta-regression models involving 30 trials and 149407 patients [3–12, 14–19,21–23,26–31,33,36–39,94]. As previously reported [1,2], the meta-regression line relating the odds ratios for cardiovascular mortality to the corresponding within-trial differences in systolic pressure was linear. For all cardiovascular events (Fig. 7), stroke and myo-

Fig. 3



Effects of antihypertensive treatment on all cardiovascular events in trials comparing new with old antihypertensive drugs. Asterisks indicate significant heterogeneity and pooled estimates calculated from a random effects model. For further explanation, see Fig. 1.

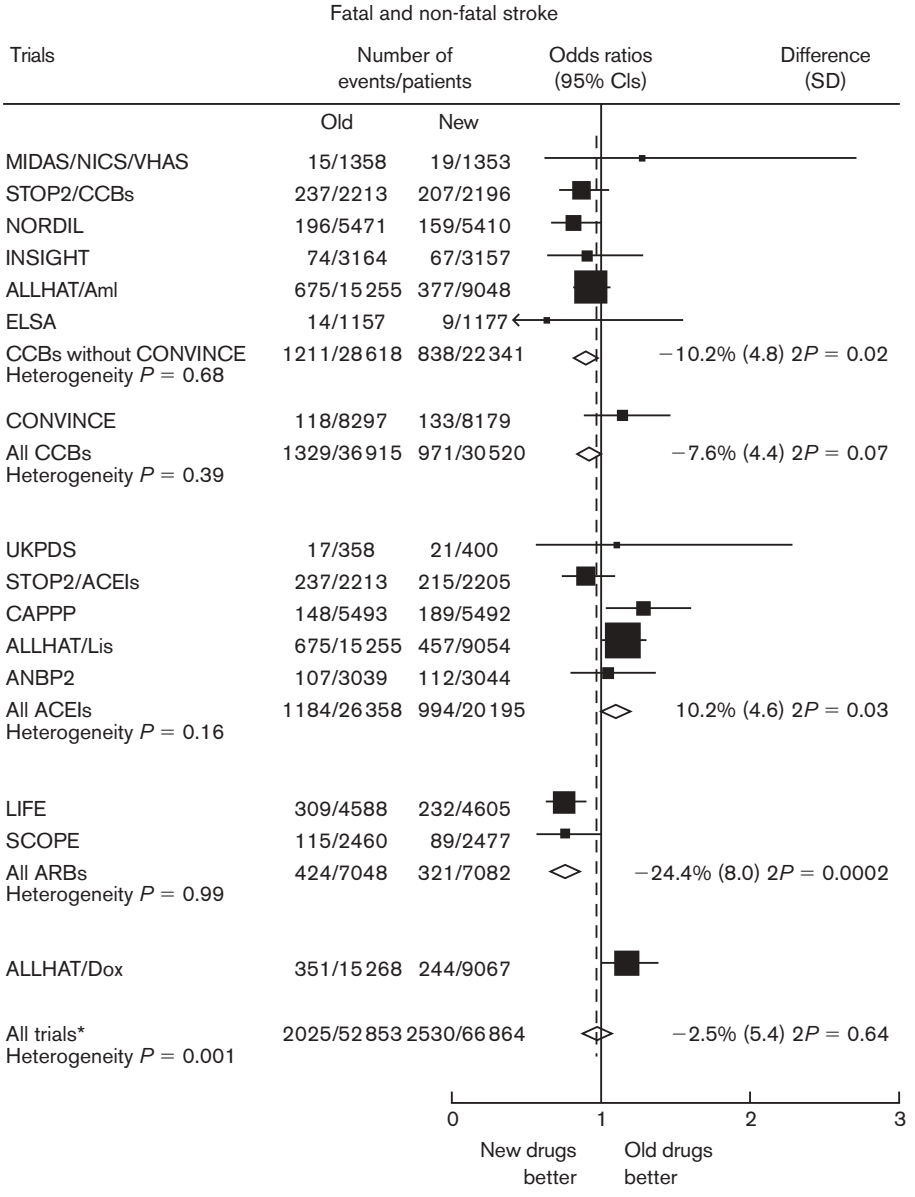
cardial infarction, these relationships were curvilinear. For these fatal and non-fatal outcomes combined, there was no further benefit if the within-trial differences in systolic blood pressure exceeded ~15 mmHg. Because in our meta-regression analysis the odds ratios respected the randomization, and because within each trial the patients had similar characteristics at entry, adjustment for the baseline systolic pressure did not materially alter the position of the regression lines.

Predicted *versus* observed odds ratios

In addition to the seven trials comparing new with old drug classes (Table 1 [47,49,50,55,59,60,65]), our literature search revealed seven intervention studies of blood pressure-lowering therapies (Table 2), which qualified for the comparison between observed and predicted [1,2] odds ratios. Two recently reported studies tested tight versus usual blood pressure control [51,52] and five trials compared blood pressure-lowering therapy with placebo [44,46,61,64] or no treatment [59]. The characteristics of these additional studies [44,46,51, 52,59,61,64] are summarized in Table 2.

In the studies testing new antihypertensive drugs versus conventional therapy (Table 1), significant differences in systolic blood pressure between randomized

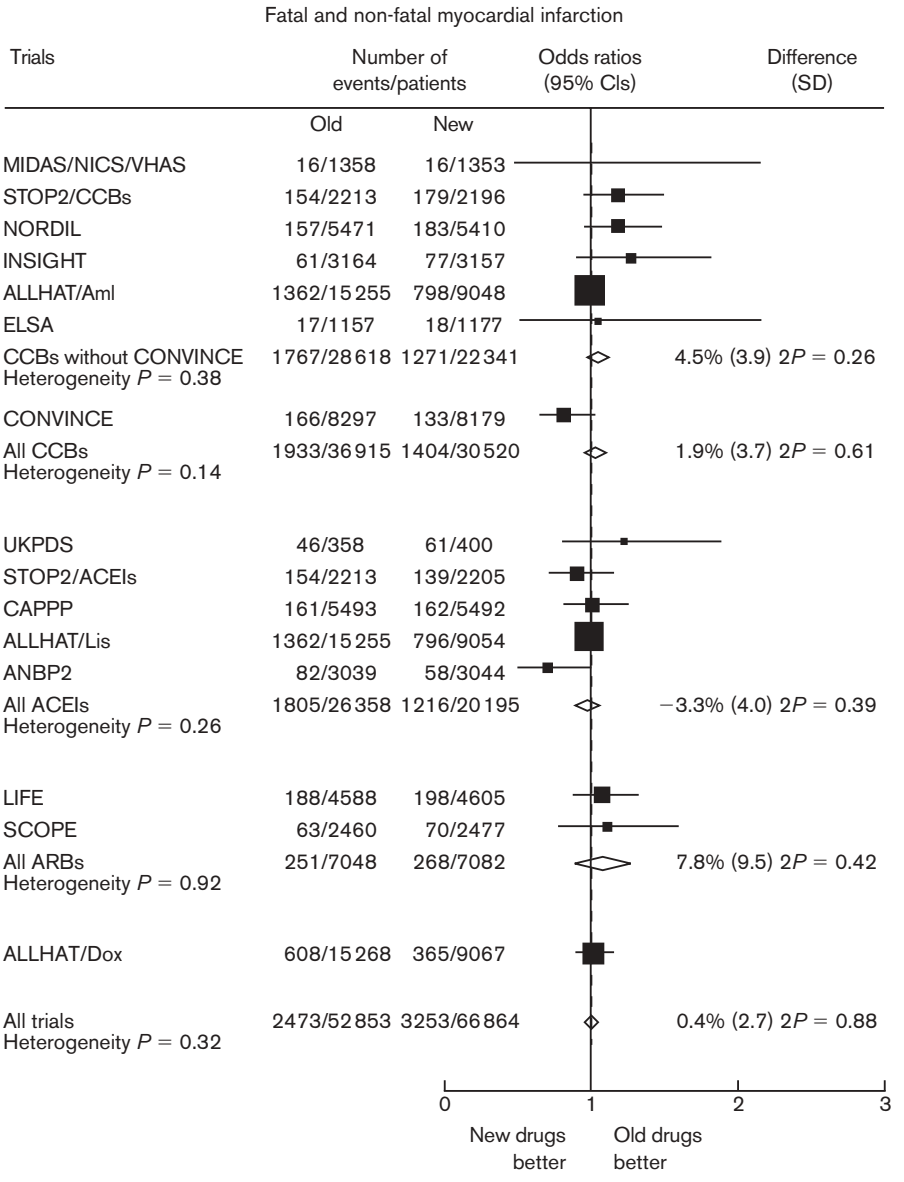
Fig. 4



Effects of antihypertensive treatment on fatal and non-fatal stroke in trials comparing new with old antihypertensive drugs. The asterisk indicates significant heterogeneity and pooled estimates calculated from a random effects model. For further explanation, see Fig. 1.

groups were observed in ALLHAT/Aml [25,50], ALLHAT/Lis [25,50], ANBP2 [41,55], SCOPE [58,65], and LIFE [48,49,72,73], but not in CONVINCE [57,60], ELSA [47,53] and HYVET/AD [56,59]. Taking conventional therapy with diuretics and β-blockers as the reference, the on-treatment systolic pressure was higher on amlodipine in ALLHAT/Aml (1.1 mmHg), on lisinopril in ALLHAT/Lis (2.3 mmHg), and on ACE inhibitors in ANBP2 (1.4 mmHg). In contrast, in LIFE/All (1.1 mm Hg) and LIFE/DM (3.0 mmHg), as well as in SCOPE (3.2 mmHg), systolic blood pressure was significantly higher in the reference group on conventional therapy than in the patients allocated losartan or candesartan, respectively. In general, for none of the reviewed outcomes in any of these trials (Table 3) we detected significant differences between the observed and predicted odds ratios. Myocardial infarction, and consequently all cardiovascular events in the ANBP2 trial [55], constituted the only significant exceptions ($P < 0.05$, Table 3). In the ANBP2 patients randomized to ACE inhibition, systolic blood pressure was on average 1.4 mmHg higher than in those allocated

Fig. 5

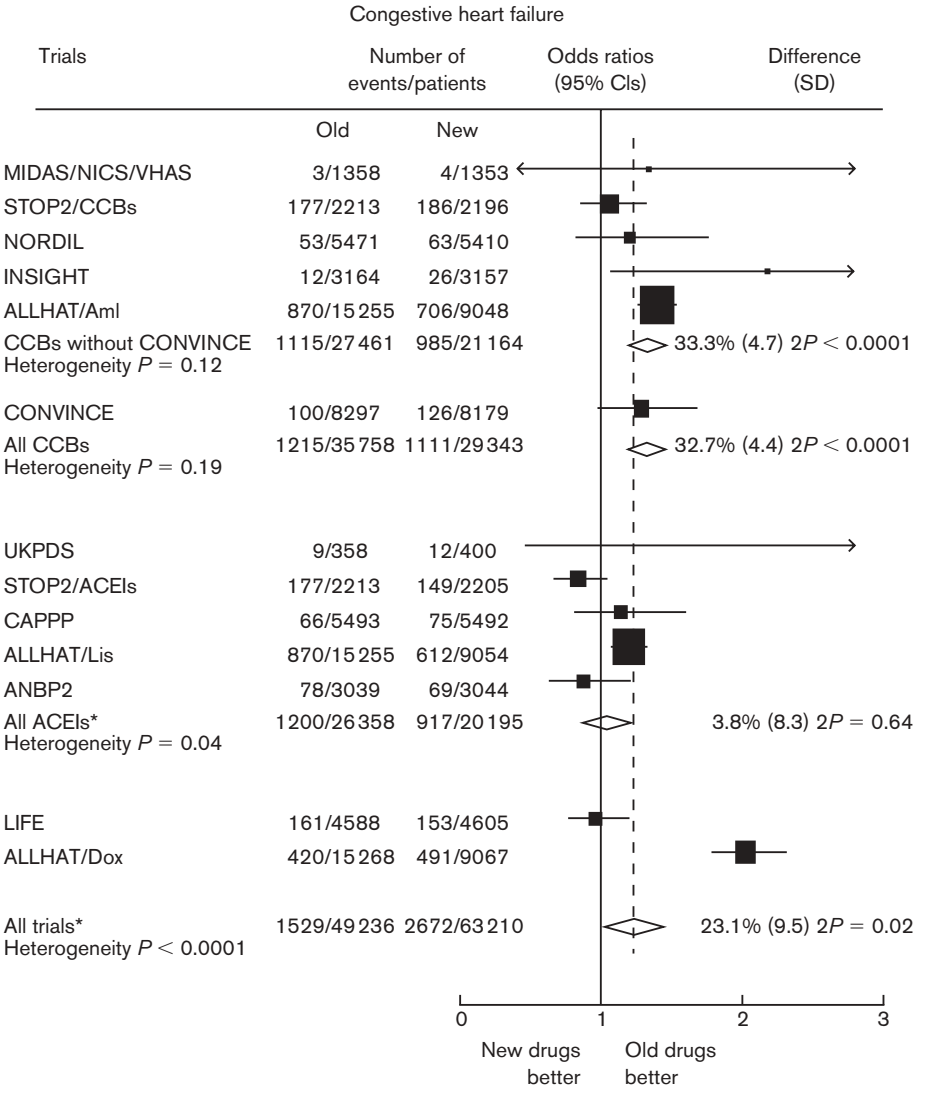


Effects of antihypertensive treatment on fatal and non-fatal myocardial infarction in trials comparing new with old antihypertensive drugs. For further explanation, see Fig. 1.

diuretic treatment [55]. The predicted odds ratios therefore tended to be higher than unity, whereas for all cardiovascular events (1.10 versus 0.90, $P = 0.046$) and myocardial infarction (1.08 versus 0.70, $P = 0.084$) the opposite was observed. For myocardial infarction (Table 3), borderline differences between observed and predicted odds ratios in favour of ACE inhibition were also observed in ALLHAT/Lis, both in all patients (1.14 versus 0.98, $P = 0.08$) and in those aged 65 years or more (1.20 versus 1.01, $P = 0.08$).

For the seven other trials [44,46,51,52,59,61,64], observed and predicted odds ratios were similar, with the exception of cardiovascular mortality in HYVET/BP (Table 4). In spite of a 22.5 mmHg lower systolic blood pressure in the patients randomized to active treatment than in those left untreated, cardiovascular mortality did not decrease (observed odds ratio 1.19, predicted 0.55, $P = 0.02$). For all cardiovascular events in AASK [52] and for stroke in DIABHYCAR [64], the observed odds ratios tended to be higher than those predicted for

Fig. 6



Effects of antihypertensive treatment on fatal and non-fatal heart failure in trials comparing new with old antihypertensive drugs. Asterisks indicate significant heterogeneity and pooled estimates calculated from a random effects model. For further explanation, see Fig. 1.

tight versus usual blood pressure control (observed 0.88, predicted 0.60, $P = 0.07$ [52]) or for ramipril versus placebo (observed 1.07, predicted 0.82, $P = 0.09$ [64]), respectively.

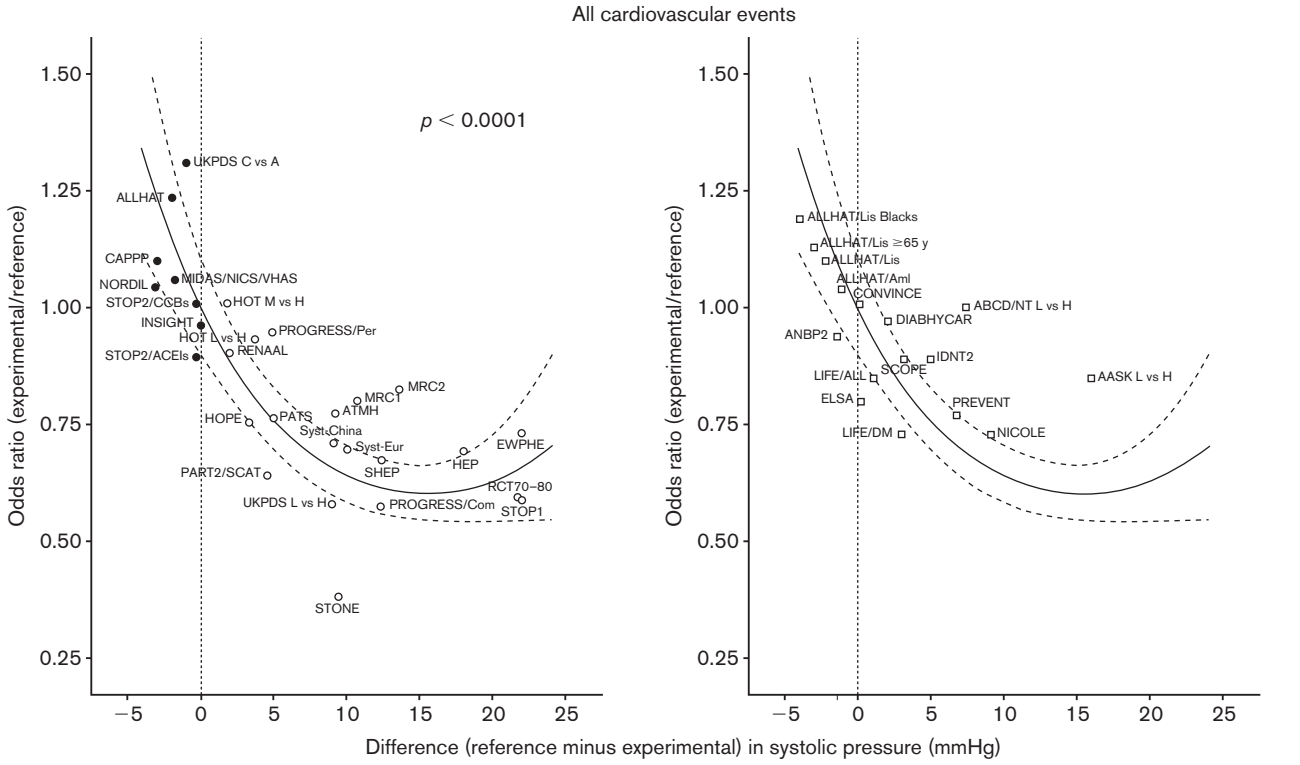
Discussion

The main finding of our overview was that, in general, new and old classes of antihypertensive drugs provided similar cardiovascular protection. For prevention of stroke and congestive heart failure, the published outcome results suggested that certain drug classes might offer a selective benefit. However, further analyses demonstrated that in 13 recent clinical trials [44,46,47, 49–52,55,59–61,64,65] most differences in specific cardiovascular endpoints were due to gradients in achieved systolic blood pressure or could be explained by design features of the trials.

Prevention of stroke

In 2001, we noticed that compared with diuretics and β-blockers, calcium-channel blockers gave 13.5% more reduction in the risk of stroke [1]. These findings [1] were in keeping with an overview published by the Blood Pressure Lowering Treatment Trialists' Collaboration [104,108]. In 2000, starting from both individual patient records and summary tabular data [108], this consortium reviewed five trials [5–8,35] including 23 454 patients [104]. Among patients assigned calcium-channel blockers, the risk of stroke was 13.0% lower than in the controls allocated diuretics or β-blockers. In

Fig. 7



Relationship between odds ratios for cardiovascular events and corresponding differences in systolic blood pressure (left panel). Odds ratios were calculated for experimental versus reference treatment. Blood pressure differences were obtained by subtracting achieved levels in experimental groups from those in reference groups. Negative values indicate tighter blood pressure on control than on reference treatment. The regression lines were plotted with 95% confidence interval and were weighted for the inverse of the variance of the individual odds ratios. Results of recent trials were plotted superimposed on the meta-regression line (right panel). Acronyms of trials are explained in the Appendix of this article.

our current analysis, the number of trials increased from six [1] to nine [3,5–8,35,47,50,60] and the number of randomized patients from 24 322 [1] to 67 435. Our updated calculations confirmed that calcium-channel blockers of the dihydropyridine and benzothiazepine (diltiazem) subtypes conferred 10.2% greater protection against stroke than diuretics and β-blockers. All calcium-channel blockers bind to a specific receptor domain situated on the α1-subunit of the L-type calcium channel [109]. Amlodipine also binds to diltiazem receptors [109]. These pharmacological characteristics, but, more importantly, the low probability of heterogeneity among the trials involving dihydropyridines and diltiazem, provided the rationale for combining these two subclasses of calcium-channel blockers.

Verapamil is a calcium-channel blocker of the phenylalkylamine subclass. Two large-scale trials, INVEST [71] and CONVINCE [57,60], compared long-acting verapamil with an atenolol-based regimen [71] or with diuretics and β-blockers [57,60]. The INVEST [71] results are due to be published in 2003. Against the recommendation of the Data Safety and Monitoring Board, CONVINCE [57,60] stopped prematurely, so that its results remained inconclusive with respect to the prespecified equivalence boundaries. Stroke was a component of the primary endpoint [57]. When we added the CONVINCE results to our pooled estimate for the benefit of calcium-channel blockers over conventional therapy in stroke prevention, this parameter decreased from 10.2 to 7.6%. Verapamil has less selectivity for vascular tissue than dihydropyridines and diltiazem [109]. Nevertheless, the *P*-values for heterogeneity did not suggest that the effects of verapamil were statistically distinct from those of the other subtypes of calcium-channel blockers.

In the previous round of our meta-analysis [1], we reviewed three trials [4,6,11], including 16 551 patients randomized to ACE inhibitors or conventional therapy. Both treatment modalities gave similar protection against cerebrovascular accidents [1]. In the present analysis, the number of relevant trials increased to five [4,6,11,50,55] and the number of randomized patients

Table 2 Characteristics of other recent trials

	AASK	ABCD/NT	DIABHYCAR	HYVET/BP	IDNT2	NICOLE	PREVENT
Reference(s)	[45,52]	[43,51]	[62,64]	[56,59]	[46,54]	[61]	[42,44]
Degree of blinding	Open	Open	Double	PROBE	Double	Double	Double
Number of patients	1094	480	4912	1283	1715	819	825
Reference	554	243	–	426	569	411	408
Experimental	540	237	–	857	1146	408	417
Treatment							
Reference	MAP 102–107	DBP 80–89	Placebo	No treatment	Placebo	Placebo	Placebo
Experimental	MAP $<$ 92	DBP 70–79	Ramipril	Thiazides or ACEIs	Amlodipine or irbesartan	Nisoldipine	Amlodipine
Primary endpoint	GFR slope	GFR slope	ACM+S+MI+ER	ACM+S	ACM+ER+DSC	Rate of CA	Rate of CA
Mean age (years)	54.6	59.1	65.0	83.8	58.9	60.0	56.9
Mean systolic/diastolic BP (mmHg)							
At randomization	150/95[a]	136/84	146/83[a]	181/100	159/87	129/78	129/79[a]
Difference during follow-up[b]	+16[c]/+8[c]	+7.4[c]/+6.0[c]	+2.1[c]/1.0[c]	+22.5[c]/+11.0[c]	+5.0[c]/+3.0[c]	+9.1[c]/+3.3[c]	+6.8[c]/+3.7[c]
Mean serum creatinine (mmol/l)	179	101	88	106	148	–	–
Proportion of patients (%)							
Women	38.8	45.4	30.3	65.8	33.5	20.0	19.9
AH drug treatment before entry	97.3	0	53.0	47.9	28.1	40.5	33.8
History of CV complications[d]	–	11.5	10.6	7.5	5.0	42.5	47.9
Diabetes mellitus	0[e]	100	100	–	100	10.4	0[f]
Mean or median follow-up (years)	~5.4	5.3	4.5	1.1	2.6	3.0	3.0

ACM, all-cause mortality; AH, antihypertensive; CA, coronary atherosclerosis; CV, cardiovascular; DBP, diastolic target blood pressure expressed in mmHg; DSC, doubling of baseline serum creatinine concentration; ER, end-stage renal disease; GFR, glomerular filtration rate; MAP, mean arterial target pressure expressed in mmHg; MI, non-fatal myocardial infarction; S, non-fatal stroke. Acronyms of trials are explained in the Appendix of this article. [a]Blood pressure at entry was measured on antihypertensive medication in previously treated patients. [b]Positive values indicate tighter blood pressure control on experimental treatment. [c]Significant difference in achieved blood pressure between randomized groups. [d]History of myocardial infarction, stroke excluding transient ischaemic attack, or surgical or percutaneous revascularization. For the NICOLE trial [61], the proportion of patients with previous anterior myocardial infarction is given. [e]Fasting or random blood glucose concentration $\geqslant$ 140 mg/dl or $\geqslant$ 200 mg/dl, respectively [52]. [f]Fasting blood glucose concentration $\geqslant$ 200 mg/dl [44].

Table 3 Observed odds ratios and odds ratios predicted by between-group differences in systolic pressure in recent trials of new *versus* old drugs

Trial – type of event	ΔSBP[a]	Observed odds ratios[b]	Predicted odds ratios[c]	P[d]
ALLHAT/Aml [50]				
Cardiovascular mortality	−1.1	1.01 (0.90–1.12)	0.95 (0.80–1.13)	0.55
Cardiovascular events	−1.1	1.06 (0.99–1.12)	1.07 (0.95–1.21)	0.83
Stroke	−1.1	0.94 (0.82–1.07)	1.00 (0.89–1.12)	0.43
Myocardial infarction[f]	−1.1	0.99 (0.90–1.08)	1.06 (0.93–1.20)	0.37
ALLHAT/Lis [50]				
Cardiovascular mortality	−2.3	1.04 (0.93–1.15)	0.98 (0.82–1.18)	0.56
Cardiovascular events	−2.3	1.10 (1.04–1.17)	1.17 (1.02–1.35)	0.40
Stroke	−2.3	1.15 (1.01–1.30)	1.08 (0.94–1.24)	0.51
Myocardial infarction[f]	−2.3	0.98 (0.90–1.08)	1.14 (0.98–1.34)	0.08
ALLHAT/Lis – patients ⩾ 65 years [50]				
Cardiovascular events	−3.0	1.13 (1.06–1.20)[e]	1.24 (1.06–1.45)	0.27
Stroke	−3.0	1.13 (0.98–1.30)[e]	1.14 (0.98–1.32)	0.93
Myocardial infarction[f]	−3.0	1.01 (0.91–1.12)[e]	1.20 (1.01–1.43)	0.08
ALLHAT/Lis – black patients [50]				
Cardiovascular events	−4.0	1.19 (1.09–1.30)[e]	1.34 (1.12–1.61)	0.23
Stroke	−4.0	1.40 (1.17–1.68)[e]	1.23 (1.03–1.47)	0.31
Myocardial infarction[f]	−4.0	1.10 (0.94–1.28)[e]	1.29 (1.05–1.59)	0.20
ANBP2 [41,55]				
Cardiovascular mortality	−1.4	1.02 (0.74–1.41)	0.96 (0.81–1.14)	0.74
Cardiovascular events	−1.4	0.90 (0.78–1.05)	1.10 (0.97–1.24)	<0.05
Stroke	−1.4	1.05 (0.79–1.38)	1.02 (0.90–1.15)	0.83
Myocardial infarction	−1.4	0.70 (0.49–1.00)	1.08 (0.95–1.23)	0.02
CONVINCE [57,60]				
Cardiovascular mortality	+0.1	1.08 (0.85–1.37)	0.93 (0.79–1.08)	0.28
Cardiovascular events	+0.1	1.01 (0.87–1.18)	0.99 (0.89–1.10)	0.84
Stroke	+0.1	1.15 (0.89–1.48)	0.92 (0.83–1.02)	0.11
Myocardial infarction	+0.1	0.81 (0.64–1.03)	0.99 (0.89–1.09)	0.14
ELSA [47,53]				
Cardiovascular mortality	+0.6	0.49 (0.11–1.84)	0.92 (0.78–1.07)	0.36
Cardiovascular events	+0.6	0.80 (0.46–1.38)	0.96 (0.87–1.06)	0.52
Stroke	+0.6	0.63 (0.24–1.57)	0.89 (0.81–0.98)	0.46
Myocardial infarction	+0.6	1.04 (0.50–2.16)	0.96 (0.87–1.05)	0.83
HYVET/AD [59]				
Cardiovascular mortality	+1.4	0.94 (0.49–1.80)	0.90 (0.78–1.04)	0.91
LIFE – all patients [49]				
Cardiovascular mortality	+1.0	0.86 (0.71–1.05)	0.90 (0.78–1.05)	0.67
Cardiovascular events	+1.0	0.84 (0.74–0.96)	0.93 (0.85–1.02)	0.19
Stroke	+1.0	0.75 (0.63–0.90)	0.87 (0.79–0.95)	0.15
Myocardial infarction[b]	+1.0	1.07 (0.87–1.31)	0.93 (0.85–1.02)	0.24
LIFE – diabetic patients [48]				
Cardiovascular mortality	+3.0	0.62 (0.40–0.97)	0.86 (0.76–0.99)	0.16
Cardiovascular events	+3.0	0.74 (0.54–0.97)	0.84 (0.77–0.91)	0.34
Stroke	+3.0	0.80 (0.53–1.19)	0.78 (0.71–0.85)	0.90
Myocardial infarction[b]	+3.0	0.88 (0.53–1.32)	0.85 (0.78–0.93)	0.96
SCOPE [58,65]				
Cardiovascular mortality	+3.2	0.94 (0.74–1.20)	0.86 (0.76–0.98)	0.53
Cardiovascular events	+3.2	0.89 (0.73–1.07)	0.83 (0.76–0.90)	0.47
Stroke	+3.2	0.76 (0.57–1.02)	0.77 (0.71–0.84)	0.92
Myocardial infarction	+3.2	1.11 (0.77–1.59)	0.84 (0.77–0.92)	0.96

[a]ΔSBP is the difference in systolic pressure between randomized groups in mmHg, negative values indicating tighter blood pressure control on old drugs. [b]Observed odds ratios with exact 95% confidence intervals were calculated from the number of events (see Fig. 2 to Fig. 5) and the number of patients (Table 1) per group randomized in each trial by use of 2×2 contingency tables. [c]Odds ratios with 95% confidence interval predicted by meta-regression [1,2]. [d]Significance of the difference between observed and predicted odds ratios. [e]Relative risks for lisinopril *versus* chlorthalidone as reported in the subgroup analyses in reference [50]. [f]Fatal and non-fatal myocardial infarction in ALLHAT [50] also included other coronary deaths.

rose to 46 553. In contrast to our former conclusions [1], ACE inhibitors gave 10.2% less reduction in the risk of stroke than the old antihypertensive drugs. These results are in line with the secondary prevention trials in patients with a history of cerebrovascular disease, which tested inhibitors of the renin system [38,110] or indapamide [23] against placebo [38,110]. Neither atenolol in TEST [110] nor perindopril in the monotherapy arm of the PROGRESS study [38] reduced the incidence of stroke recurrence, whereas in the Chinese PATS trial [23] indapamide decreased recurrent stroke by 29%.

In two trials [55,65], AR1 blockers resulted in 24.4% better stroke prevention than did the old drugs, whereas the opposite was observed for doxazosin in

Table 4 Observed odds ratios and odds ratios predicted by between-group differences in systolic pressure in recent trials of blood pressure-lowering therapies

Trial – type of event	ΔSBP[a]	Events (*n*) control/experimental	Observed odds ratio[b]	Predicted odds ratio[c]	*P*[d]
AASK [45,52]					
Cardiovascular mortality	+16.0	16 /14	0.89 (0.40–1.98)	0.64 (0.55–0.74)	0.42
Cardiovascular events	+16.0	61 /53	0.88 (0.58–1.32)	0.60 (0.55–0.67)	0.07
ABCD/NT [43,51]					
Cardiovascular mortality	+7.4	9 /13	1.51 (0.58–4.08)	0.78 (0.70–0.87)	0.19
Cardiovascular events	+7.4	37 /36	1.00 (0.59–1.69)	0.69 (0.63–0.76)	0.17
Stroke	+7.4	13 /4	0.30 (0.07–1.00)	0.64 (0.59–0.71)	0.22
Myocardial infarction	+7.4	15 /19	1.33 (0.62–2.88)	0.73 (0.66–0.81)	0.13
DIABHYCAR [62,64]					
Cardiovascular mortality	+2.1	–	1.07 (0.85–1.35)[e]	0.88 (0.77–1.02)	0.16
Cardiovascular events	+2.1	739 (total)	0.97 (0.85–1.11)[e]	0.88 (0.80–0.96)	0.22
Stroke	+2.1	–	1.07 (0.80–1.44)[e]	0.82 (0.75–0.89)	0.09
Myocardial infarction	+2.1	–	0.89 (0.61–1.29)[e]	0.89 (0.81–0.97)	0.98
HYVET/BP [59]					
Cardiovascular mortality	+22.5	19 /45	1.19 (0.67–2.18)	0.55 (0.44–0.68)	0.02
IDNT2 [46,54]					
Cardiovascular mortality	+5.0	46 /89	0.96 (0.65–1.42)	0.82 (0.73–0.93)	0.46
Cardiovascular events	+5.0	146 /270	0.89 (0.70–1.14)	0.76 (0.70–0.83)	0.23
Stroke	+5.0	21 /32	0.75 (0.41–1.38)	0.71 (0.65–0.77)	0.85
Myocardial infarction[f]	+5.0	57 /84	0.71 (0.49–1.03)	0.79 (0.72–0.86)	0.60
NICOLE [42,44]					
Cardiovascular events	+9.1	216 /182	0.73 (0.55–0.97)	0.66 (0.60–0.72)	0.48
Stroke	+9.1	7 /4	0.57 (0.12–2.27)	0.61 (0.55–0.67)	0.93
Myocardial infarction	+9.1	13 /16	1.25 (0.56–2.86)	0.71 (0.64–0.79)	0.18
PREVENT [42,44]					
Cardiovascular mortality	+6.8	2 /7	0.28 (0.03–1.46)	0.79 (0.71–0.88)	0.22
Cardiovascular events	+6.8	30 /24	0.77 (0.42–1.39)	0.71 (0.64–0.77)	0.77
Stroke	+6.8	5 /5	0.98 (0.22–4.29)	0.66 (0.60–0.72)	0.60
Myocardial infarction	+6.8	20 /19	0.76 (0.39–1.48)	0.74 (0.67–0.82)	0.95

[a]ΔSBP is the difference in systolic pressure between randomized groups in mmHg, positive values indicating tighter blood pressure control on experimental treatment. [b]Observed odds ratios with exact 95% confidence intervals were calculated from the number of events (control/experimental) and the number of patients (Table 2) per group randomized in each trial by use of 2×2 contingency tables. [c]Odds ratio (95% confidence interval) predicted by meta-regression [1,2]. [d]Significance of the difference between observed and predicted odds ratios. [e]Relative risks for ramipril *versus* placebo as reported in reference [64]. [f]Fatal and non-fatal myocardial infarction in IDNT2 [46] included sudden death.

the ALLHAT trial (+17.5%, $P = 0.04$). A comprehensive overview of observational cohort studies recently highlighted that throughout middle and old age blood pressure is strongly and directly related to stroke mortality [111]. Hypertension is the most consistent and powerful predictor of stroke [111,112] and is involved in nearly 70% of all strokes [112]. It is therefore impossible to interpret the stroke results of our overview without taking into account the within-trial differences in achieved systolic blood pressure (see below).

Prevention of myocardial infarction

In 2001, we found that compared with diuretics and β-blockers, calcium-channel blockers gave 19.2% less reduction of the risk of myocardial infarction [1]. The corresponding pooled estimate reported by the Blood Pressure Lowering Treatment Trialists' Collaboration was 12.0% [108]. In the present update, the shortfall of calcium-channel blockers relative to conventional therapy disappeared as a result of the positive trend in favour of verapamil in CONVINCE (odds ratio 0.81, $P = 0.08$ [60]) and the similar coronary outcomes on amlodipine and chlorthalidone in ALLHAT (odds ratio 0.99, $P = 0.79$ [50]). Furthermore, both in our previous [1,2] and current analysis, ACE inhibitors and old drugs performed equally well in the prevention of myocardial infarction. ANBP2 [41,55] was the only actively controlled trial of ACE inhibitors, which showed a borderline significant benefit of ACE inhibition over conventional therapy in the prevention of fatal and non-fatal myocardial infarction (odds ratio 0.70, 95% confidence interval 0.45–1.00, $P = 0.048$). Thus, on balance, all new drugs and conventional therapy prevent coronary complications to the same extent. This conclusion is supported by the observation that none of the *P*-values for heterogeneity reached statistical significance.

Prevention of heart failure

The risk of heart failure was higher on calcium-channel blockers than on conventional therapy without heterogeneity among the trials. In individual studies, the risk of heart failure was significantly increased on nifedipine

in INSIGHT (odds ratio 2.18, $P = 0.03$ [7]) and on amlodipine in ALLHAT (odds ratio 1.40, $P < 0.001$ [50]) with a similar trend in CONVINCE on verapamil (odds ratio 1.28, $P = 0.07$ [60]). Calcium-channel blockers reduce left ventricular afterload. However, neuroendocrine activation in response to arterial vasodilatation and the direct negative inotropic action on the myocardium may elicit heart failure in predisposed patients [113]. Nevertheless, on top of diuretics and/or ACE inhibitors, long-acting dihydropyridines [114,115], diltiazem [116] and verapamil [117] can be used in patients with left ventricular dysfunction to lower blood pressure or to treat angina pectoris.

Overall, the newer agents performed 23.1% worse in the prevention of heart failure than did conventional therapy initiated with diuretics or β-blockers. This is not surprising, because both diuretics and β-blockers belong to the standard of care for this condition [118]. The same is true for ACE inhibitors given on top of digitalis and diuretics. AR1 blockers are only indicated as an alternative to ACE inhibitors when class-specific side-effects, such as cough, occur [118]. In this respect, the higher risk of heart failure on lisinopril in ALLHAT (odds ratio 1.20, $P = 0.001$ [50]) is contra-intuitive, whereas the results of the ALLHAT doxazosin arm (odds ratio 2.18, $P < 0.001$ [9]) were in line with previous studies [119]. In trials of ACE inhibitors in patients with heart failure [118] or high cardiovascular risk [33,38], these agents were always combined with diuretics. In contrast to current practice, in therapy-resistant ALLHAT patients, lisinopril had to be associated with sympatholytic agents and/or hydralazine before diuretics could be added [50]. At 5 years, the crossover rate from lisinopril to chlorthalidone was only 24.2% [50]. This and other factors (see below) probably contributed to the higher risk of heart failure associated with lisinopril in ALLHAT [50].

The comparison of the newer agents with conventional therapy for heart failure outcomes revealed strong heterogeneity among the trials, which was largely due to ALLHAT [9,50]. The diagnosis of heart failure depends on clinical judgement and is difficult to make or to standardize, even among specialists. In ALLHAT, a trial largely conducted in primary care, the diagnosis only required the presence of one symptom and one sign [120]. When a large excess of heart failure became evident in the doxazosin arm [9], the blinded Endpoints Subcommittee reviewed a one-time sample of 50 fatal or hospitalized cases [120], representing 1.9% of all heart failure diagnoses ($n = 2679$ [9,50]). For the overwhelming majority of the cases, the diagnosis was accepted as reported by the investigators. Heart failure in ALLHAT was therefore only a weak component of a secondary endpoint, which did not lead to an increase in cardiovascular [50] or total [9,50] mortality. Furthermore, at randomization, 90.2% of the ALLHAT patients were already on antihypertensive treatment, presumably involving diuretics in most cases. Thus, patients allocated amlodipine, lisinopril or doxazosin were at risk of rapidly losing the protection of their previous diuretic treatment, whereas in those of the chlorthalidone group the volume-dependent signs and symptoms of heart failure remained suppressed. These design features of ALLHAT likely explain why, for heart failure, the Kaplan–Meier estimates separated immediately after randomization [9,50]. Because of the weight of ALLHAT in our overview, the pooled estimates for heart failure must be interpreted cautiously.

Role of blood pressure reduction

Until recently, the consensus interpretation of the evidence produced by the outcome trials in hypertensive patients [3–9,11,12,14–23,26–32,35–38,57,60,72,94,96,97,121] was that blood pressure is a risk factor amenable to intervention, lower levels leading to fewer complications. However, the HOPE trial [33,34] gave rise to the hypothesis that ACE inhibitors might reduce cardiovascular complications beyond blood pressure control. Subsequently, published trials of AR1 blockers in hypertensive patients with renal failure [39,46,95] or left ventricular hypertrophy [48,49] reinforced this hypothesis.

In middle-aged and older patients, systolic pressure is the prevailing blood pressure component with regard to cardiovascular prognosis [122,123]. In a quantitative overview involving 1 million subjects, the Prospective Studies Collaboration demonstrated that small gradients in blood pressure similar to those observed in recent trials might account for substantial differences in cardiovascular outcomes [111]. In keeping with the prospective cohort studies [111], our previous overview [1,2] showed that in most trials in patients with hypertension or high cardiovascular risk published in 2001 or before, most outcomes could be attributed to the within-trial differences in systolic blood pressure. Stroke in the NORDIL [8] and PROGRESS [38] trials constituted the only exceptions [1,2]. Indeed, in NORDIL [8], the risk of stroke was lower on diltiazem (odds ratio 0.81, 95% confidence interval 0.65–1.01) than on conventional drugs, despite a 3.1 mmHg higher systolic pressure on the calcium-channel blocker. In the perindopril-only subgroup of the PROGRESS trial [38], systolic pressure was reduced by 5 mmHg, but monotherapy with the ACE inhibitor did not affect either the risk of all cardiovascular events (odds ratio 0.96, 95% confidence interval 0.80–1.15) or that of stroke recurrence (odds ratio 0.95; 95% confidence interval 0.77–1.19). We did not compute a meta-regression line for heart failure, because of 30 trials only 13 reported on this endpoint [1,2].

In the present overview, we compared observed and predicted odds ratios in 13 trials [44,46,47,49–52,55,59–61,64,65] which were all published after we had constructed our meta-regression models [1]. To standardize our analysis, we did not use adjusted relative risks as published in the reviewed articles. Instead, we recalculated the observed odds ratios from the number of events and the number of patients per group randomized in each trial by use of 2×2 contingency tables.

Among seven recent trials of new agents versus conventional therapy [47,49,50,55,59,60,65], observed and predicted odds ratios were similar. Only for myocardial infarction (0.70 versus 1.08) and hence all cardiovascular events (0.90 versus 1.10) in the ANBP2 trial [55], the odds ratios for ACE inhibitor-based treatment versus conventional therapy were significantly lower than those predicted by the achieved systolic blood pressure, which was 1.4 mmHg lower in the patients allocated conventional therapy. Similar trends were observed for myocardial infarction in the lisinopril arm of the ALLHAT trial [50], both in all patients (0.98 versus 1.14) and in those aged 65 years or more (1.01 versus 1.20), whose systolic blood pressure was respectively 2.3 and 3.0 mmHg higher than in the corresponding controls of the chlorthalidone group. Thus, if one accounts for achieved systolic pressure, ACE inhibitors in Caucasian hypertensive patients seem to offer slightly greater protection against coronary complications than conventional therapy. These findings are in line with the secondary prevention trials in patients with acute myocardial infarction [124,125]. Moreover, taking into account the achieved blood pressure solves the apparent contradictions between ALLHAT [50] and ANBP2 [55] with regard to the coronary protection due to ACE inhibition in hypertensive patients of Caucasian extraction.

For stroke, there were no differences between predicted odds ratios and those observed in seven recent trials of new versus old drugs [47,49,50,55,59,60,65]. The achieved systolic blood pressure levels and associated stroke rates in the lisinopril arm of the ALLHAT trial [50] corroborate the concept that older and black patients usually have a low-renin volume-expanded type of hypertension, which responds better to initial treatment with diuretics or calcium-channel blockers [126–129]. In two trials comparing AR1 blockers [49,65] with conventional therapy, lower achieved systolic blood pressure explained the better outcomes on losartan [48,49] or candesartan [130]. Both trials had a double-blind design and conventional therapy was associated with the study medication in an open-label fashion. The systolic gradient was larger in SCOPE [130] than in LIFE [48,49], but the *P*-value for heterogeneity in the stroke outcomes was non-significant. As discussed elsewhere [131], our present findings are at variance with the LIFE investigators' interpretation that claimed benefit beyond blood pressure control for losartan versus atenolol [48,49]. To what extent unopposed stimulation of the type-2 angiotensin II receptor in the brain contributes to the divergent stroke outcomes on ACE inhibitors and AR1 receptor blockers relative to conventional therapy remains to be elucidated [132].

We also evaluated observed and predicted odds ratios in five recently published trials of blood pressure lowering therapies [44,46,51,52,59,61,64]. Again, observed and predicted odds ratios were similar, with three notable exceptions, which underscore the need for further research. First, in the pilot run of the HYVET trial [56,59], active treatment compared with no intervention lowered systolic blood pressure by 22.5 mmHg, but did not reduce cardiovascular mortality. The observed and predicted odds ratios were 1.19 and 0.55, respectively. Secondly, in the AASK trial [45,52], intensive blood pressure lowering compared with usual care (Table 2) led to a 16.0 mmHg differential in systolic blood pressure with less reduction in the cardiovascular event rate than expected (odds ratios 0.88 versus 0.60, $P = 0.07$). Finally, in DIABHYCAR [62–64], low-dose ramipril treatment compared with placebo reduced systolic blood pressure by 2.1 mmHg, but nevertheless did not lead to better stroke prevention (odds ratios 1.07 versus 0.82, $P = 0.09$).

Clinical implications

Our overview has to be interpreted within the context of its limitations. Our analysis started from published summary statistics. The definitions of cardiovascular events and their validation differed across the trials. We probably achieved less standardization than is attainable in quantitative overviews based on individual patient data. Nevertheless, throughout our analyses, we always respected the randomization within trials. Although we did not determine to what extent blood pressure should be lowered, our findings strongly emphasize that blood pressure control is of paramount importance in the prevention of cardiovascular complications.

Thiazide diuretics are relatively inexpensive, at least as far as the cost of acquisition is concerned, but so are increasingly other classes of antihypertensive drugs [133]. No data prove the ALLHAT conclusion [50] that for a disorder requiring lifelong therapy thiazides are most cost-effective to initiate antihypertensive therapy [133]. What ALLHAT [50] and other trials [126–129] clarified is that blood pressure responses to various classes of antihypertensive drugs differ according to age and race. If blood pressure control is the major determinant of the prognosis of hypertensive patients, the inescapable consequence is that antihypertensive ther-

apy should be individualized and initiated with the drug class that is most likely to work in each individual patient, taking into account other risk factors and co-morbid conditions [134]. In over 60% of patients, optimization of treatment at acceptable levels of tolerance requires rotation through and combination of several drug classes. The blood pressure lowering activities of ACE inhibitors and β-blockers are additive to those of thiazides and calcium-channel blockers and vice-versa [128,129]. Patients younger than 50 years may be started on ACE inhibitors or β-blockers and switched to thiazides or calcium-channel blockers if blood pressure remains uncontrolled, whereas older patients may proceed in the reverse order [128,129].

Conclusions

The hypothesis that new antihypertensive drugs, such as calcium-channel blockers, α-blockers, ACE inhibitors or AR1 blockers might influence cardiovascular prognosis over and beyond their antihypertensive effect remains unproven. The finding that blood pressure differences largely accounted for cardiovascular outcome emphasizes the need of tight blood pressure control. However, the level to which blood pressure must be lowered to achieve maximal benefit remains currently unknown.

Acknowledgements

The authors gratefully acknowledge the help of many colleagues in the retrieval of supporting evidence. We are especially indebted to Joseph Dens, Afdeling Cardiologie, Universitair Ziekenhuis Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium for additional information on the NICOLE trial.

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Appendix

Acronyms of trials

AASK (the African American Study of Kidney disease and hypertension [45,52,68]); ABCD (Appropriate Blood Pressure Control in Diabetes trial [43,51,80, 82,83]); ABCD/HT (Appropriate Blood Pressure Control in Diabetes trial – nisoldipine versus enalapril in hypertensive patients [80,82,83]); ABCD/NT (Appropriate Blood Pressure Control in Diabetes trial – tight versus usual blood pressure control in normotensive patients [51]); ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [9,25,50]); ALLHAT/Aml (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – amlodipine versus chlorthalidone [50]); ALLHAT/Dox (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – doxazosin versus chlorthalidone [9]); ALLHAT/Lis (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – lisinopril versus chlorthalidone [50]); ANBP2 (Australian comparative outcome trial of angiotensin-converting enzyme inhibitor- and diuretic-based treatment of hypertension in the elderly [41,55]); ASCOT (the Anglo-Scandinavian Cardiac Outcomes Trial [69]); ATMH (Australian Trial in Mild Hypertension [22]); CAPPP (CAptopril Prevention Project [4,24]); CONVINCE (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints Trial [57,60]); DIABHYCAR (the non-insulin-dependent DIAbetes, HYpertension, microalbuminuria or proteinuria, Cardiovascular events, and ramipril study [62–64]); ELSA (European Lacidipine Study on Atherosclerosis [47,53,70]); EWPHE (trial conducted by the European Working Party on High blood pressure in the Elderly [12,13]); HDFP (Hypertension Detection and Follow-up Program [92]); HEP (trial of Hypertension in Elderly Patients in primary care [14]); HOPE (Heart Outcomes Prevention Evaluation study [33,34]); HOT (Hypertension Optimal Treatment trial [31]); HOT/LH (Hypertension Optimal Treatment trial [31] – 80 versus 90 mmHg as target diastolic pressure [31]); HOT/MH (Hypertension Optimal Treatment trial [31] – 85 versus 90 mmHg as target diastolic pressure [31]); HSCS (Hypertension-Stroke Cooperative Study [27]); HYVET (HYpertension in the Very Elderly pilot Trial [56,59]); HYVET/AD (HYpertension in the Very Elderly pilot trial – ACE inhibition versus diuretic treatment [56,59]); HYVET/BP (HYpertension in the Very Elderly pilot Trial – blood pressure lowering drugs versus no treatment [56,59]); IDNT2 (Irbesartan Diabetic Nephropathy Trial in patients with type-2 diabetes mellitus [46,54]); INSIGHT (International Nifedipine GITS Study – Intervention as a Goal for Hypertension Treatment [7,107]); INVEST (INternational VErapamil SR/trandolapril STudy [71]); IRMA2 (IRbesartan in patients with type-2 diabetes and Microalbuminuria study [95]); J-MIC (Japan Multicenter Investigation for

Cardiovascular drugs/therapies [84]); LIFE (Losartan Intervention For Endpoint reduction in hypertension study [48,49,72,73]); LIFE/All (Losartan Intervention For Endpoint reduction in hypertension study – all patients [49]); LIFE/DM (Losartan Intervention For Endpoint reduction in hypertension study – diabetic subgroup [48]); MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study [3]); MIDAS/NICS/VHAS (combined results of MIDAS, [3] NICS [5] and VHAS [35]); MRC1 (Medical Research Council trial of treatment of mild hypertension [17]); MRC2 (Medical Research Council trial of treatment of hypertension in older adults [16]); NICOLE (NIsoldipine in COronary artery disease in LEuven [61]); NICS (National Intervention Cooperative Study in elderly hypertensives [5]); NORDIL (NOrdic DILtiazem study [8]); OSLO (Oslo study on the treatment of mild hypertension [26]); PART2 (Prevention of Atherosclerosis with Ramipril Trial [36]); PART2/SCAT (combined results of PART2 [36] and SCAT [37]); PATS (Post-stroke Antihypertensive Treatment Study [23]); PHYLLIS (Plaque HYpertension Lipid Lowering Italian Study [74,75]); PREVENT (Prospective Randomized Evaluation of the Vascular Effects Norvasc Trial [42,44]); PROGRESS (perindopril PROtection aGainst REcurrent Stroke Study [38,121]); PROGRESS/Com (perindopril PROtection aGainst REcurrent Stroke Study [38,121] – group on combined therapy); PROGRESS/Per (perindopril PROtection aGainst REcurrent Stroke Study [38,121] – group on single-drug treatment); RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [39]); RCT70–80 (combined results of four smaller trials published from 1970 through 1980, including HSCS, [27] OSLO, [26] USPHS, [28] and VACS [29]); SCAT (Simvastatin/enalapril Coronary Atherosclerosis Trial [37]); SCOPE (Study on COgnition and Prognosis in the Elderly [58,65]); SHELL (Systolic Hypertension in the Elderly Long-term Lacidipine trial [76]); SHEP (Systolic Hypertension in the Elderly Program [18,20]); STONE (Shanghai Trial of Nifedipine in the Elderly [19]); STOP1 (Swedish Trial in Old Patients with hypertension [15]); STOP2 (Swedish Trial in Old Patients with hypertension–2 [6]); STOP2/ACEIs (angiotensin-converting-enzyme inhibitor arm of STOP2 [6]); STOP2/CCBs (calcium-channel blocker arm of STOP2 [6]); Syst-China (Systolic hypertension in China trial [30,94]); Syst-Eur (Systolic hypertension in Europe trial [21,96,97]); TEST (TEnormin after Stroke and TIA [110]); UKPDS (UKPDS hypertension in diabetes study [11,32]); UKPDS/CA (UKPDS hypertension in Diabetes Study – captopril versus atenolol [11]); UKPDS/LH (UKPDS hypertension in diabetes study – low versus high on-treatment blood pressure [32]); USPHS (United States Public Health Service hospitals cooperative study [28]); VACS (Veterans Administration Cooperative Study in patients with diastolic blood pressure averaging 90–114 mmHg [29]); VHAS (Verapamil in Hypertension and Atherosclerosis Study [35])