How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis

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Objective **To quantify the effect of first-line antihypertensive treatment with beta-blockers on mortality, morbidity and withdrawal rates, compared with the other main classes of antihypertensive agents.**

Methods **We identified eligible trials by searching the Cochrane Controlled Trials Register, Medline, Embase, reference lists of previous reviews, and contacting researchers. We extracted data independently in duplicate and conducted meta-analysis by analysing trial participants in groups to which they were randomized, regardless of subsequent treatment actually received.**

Results **Thirteen trials with 91 561 participants, meeting inclusion criteria, compared beta-blockers to placebo (four trials; $n = 23\,613$), diuretics (five trials; $n = 18\,241$), calcium-channel blockers (CCBs) (four trials; $n = 44\,825$), and renin–angiotensin system (RAS) inhibitors, namely angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (three trials; $n = 10\,828$). Compared to placebo, beta-blockers reduced the risk of stroke (relative risk 0.80; 95% confidence interval 0.66–0.96) with a marginal fall in total cardiovascular events (0.88, 0.79–0.97), but did not affect all-cause mortality (0.99, 0.88–1.11), coronary heart disease (0.93, 0.81–1.07) or cardiovascular mortality (0.93, 0.80–1.09). The effect on stroke was less than that of CCBs (1.24, 1.11–1.40) and RAS inhibitors (1.30, 1.11–1.53), and that on total cardiovascular events less than that of CCBs (1.18, 1.08–1.29). In addition, patients on beta-blockers were more likely to discontinue treatment than those on diuretics (1.80; 1.33–2.42) or RAS inhibitors (1.41; 1.29–1.54).**

Conclusion **Beta-blockers are inferior to CCBs and to RAS inhibitors for reducing several important hard end points. Compared with diuretics, they had similar outcomes, but were less well tolerated. Hence beta-blockers are generally suboptimal first-line antihypertensive drugs. *J Hypertens* 24:2131–2141 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Hypertension is an important public health problem in both industrialized and low and middle income countries, due to its high prevalence [1] and associated morbidity and mortality [2]. Although half of treated patients fail to achieve the desired blood pressure [3,4], the rationale for treating hypertension has achieved great impetus with the finding that even small reductions in blood pressure could significantly reduce associated morbidity and mortality risks [5–7].

Beta-blockers have long been used as first-line therapy for hypertension because they were thought to have long-term favourable effects on all-cause and cardiovascular mortality [8–10], but the robustness of the evidence for initiating antihypertensive therapy with beta-blockers has been challenged [11–13]. In a recent meta-analysis [14], Lindholm and colleagues compared beta-blockers to all other antihypertensive drugs taken together, and found that stroke reduction was suboptimal. However, beta-blockers might have different comparative outcomes versus the various other classes of drugs. For instance, several studies have claimed that calcium-channel blockers (CCBs) are better than other antihypertensive agents in preventing stroke, but might be less good at preventing coronary heart disease [15–17]. Thus, it is important to know to what extent the comparisons made by Lindholm and colleagues [13,14] relate to beta-blockers versus specific classes of antihypertensive drugs such as diuretics, CCBs, or renin–angiotensin system (RAS) inhibitors [that is, the angiotensin-converting enzyme inhibitors (ACE-Is)

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and angiotensin receptor blockers (ARBs)]. In general, beta-blockers might be better or worse than one specific class of drugs for one specific end point, so that comparing beta-blockers with all other classes taken together [13,14] could be fallacious. In addition, the tolerability of a medication is as important to the clinician and the patient as is the effectiveness; but Lindholm and colleagues did not provide data on this aspect when comparing beta-blockers to other antihypertensive agents.

We thus undertook a systematic review and meta-analysis to reassess the place of beta-block as first-line therapy for hypertension relative to each of the other major class of antihypertensive drugs.

Methods

This systematic review was performed according to a published protocol [18] and reported following the QUORUM checklist [19].

Search strategy

We searched the Cochrane Controlled Trials Register, Medline, Embase, the Cochrane Databases of Systematic Reviews, and the York Database of Abstracts of Reviews of Effectiveness for randomized controlled trials and systematic reviews published by September 2005. We used the search terms 'adrenergic beta-antagonists' [MeSH], 'beta (blockers)' and 'hypertension' [MeSH] combined with the Cochrane Collaboration's optimally sensitive strategy for identifying randomized controlled trials [20]. We supplemented the search by screening bibliographies of identified articles and proceedings of international hypertension conferences, and contacting hypertension experts and pharmaceutical companies for unpublished studies.

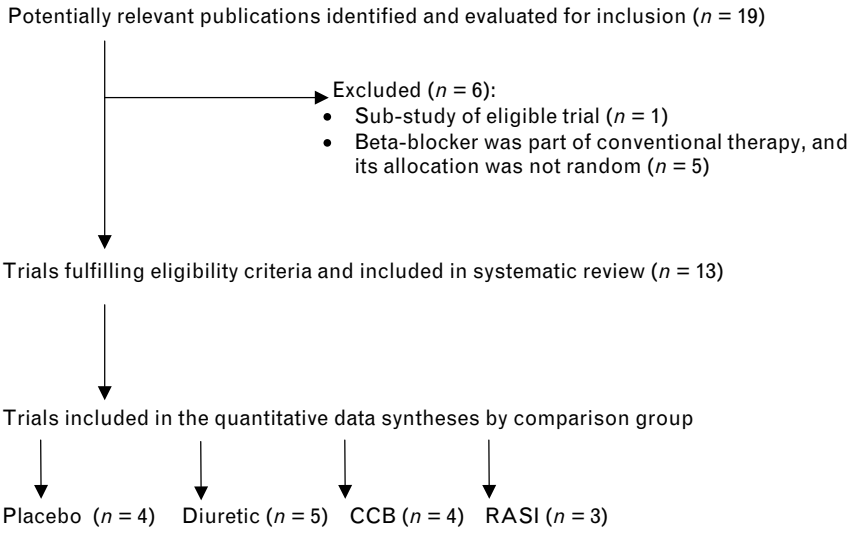
Study selection and validity assessment

At least two of three authors (H.A.B., C.S.W. and J.A.V.) independently assessed study eligibility and quality, and extracted data, with disagreements resolved by consensus. We included randomised, controlled trials which assessed the effectiveness of initiating in a trial (that is, monotherapy or first-line drug in a stepped care approach) antihypertensive treatment with beta-blockers on mortality and morbidity end points, in hypertensive men and non-pregnant women aged 18 years or older. Hypertension was defined by cut-off points operating at the time of the trial under consideration. We then assessed the methodological quality of each included trial by the adequacy of allocation concealment; blinding of study participants, investigators and outcome assessors; proportion of participants lost to follow-up; and proportion of participants on assigned treatment at the end of the study.

Data abstraction and synthesis

The primary outcome was all-cause mortality and secondary outcome measures included fatal and non-fatal coronary heart disease (CHD), fatal and non-fatal stroke, cardiovascular mortality, total cardiovascular events [that is, fatal and non-fatal CHD and stroke (and congestive heart failure and transient ischaemic attacks, when reported)], and discontinuation of allocated treatment due to adverse effects. We expressed study results as relative risks (RR) with 95% confidence intervals (CI) and conducted meta-analysis by analysing trial participants in groups to which they were randomized, regardless of which or how much treatment they actually received, using the Cochrane Collaboration's Review Manager 4.2 (website: http://www.cc-ims.net/RevMan). We used the Cochrane's Q test to assess statistical heterogeneity

Fig. 1



Flow chart of randomized controlled trials through the systematic review. CCB, calcium-channel blocker; RASI, renin–angiotensin system inhibitor. Three trials compared more than two classes of antihypertensive drugs.

between studies and, in the absence of significant heterogeneity ($P > 0.1$), pooled the data using a fixed effects method [21]. Otherwise, we used the random effects model [22] and investigated the cause of heterogeneity by stratified analysis, with reference to the characteristics of the studies included in the meta-analysis.

In addition, we used Higgins I^2 statistic to quantify inconsistency across the studies included in the meta-analysis [20,23,24]. The test statistic describes the percentage of the variability in effect estimates that is due to true heterogeneity rather than chance. The closer the I^2 value is to 100%, the more likely it is that true heterogeneity exists and therefore the less reliable the pooled estimate becomes.

Results

Study characteristics

The search results and selection of studies in the systematic review are summarized in Fig. 1. Of 19 potentially eligible randomized controlled trials, six were excluded (Table 1) either because every participant in the 'beta-blocker' arm did not receive a beta-blocker and the allocation to a beta-blocker was not random [25–29], or the trial was a substudy of an included trial [30]. Thirteen trials with 91 561 participants that met our inclusion criteria (Table 2) compared beta-blockers to

Table 1 Characteristics of excluded studies

Trial	Comparisons	Reason for exclusion
CAPP 1999 [27]	Conventional antihypertensives (atenolol, metoprolol or hydrochlorothiazide or bendrofluazide) versus captopril	Trial participants were not randomly assigned to a beta-blocker *per se*. In the arm with a beta-blocker, participants were randomized to either a beta-blocker or a diuretic; and the choice of the 'conventional drug' was not random.
CONVINCE 1998 [26]	Atenolol or hydrochlorothiazide versus verapamil	As above
NORDIL 2000 [29]	Conventional therapy (beta-blocker or diuretic) versus diltiazem	As above
STOP 1991 [25]	Anti-hypertensive treatment (atenolol, metoprolol, pindolol or hydrochlorothiazide plus amiloride) versus placebo	As above
STOP-2 1999 [28]	Conventional antihypertensives (atenolol, metoprolol, pindolol or hydrochlorothiazide plus amiloride) versus newer drugs (enalapril, lisinopril, felodipine or isradipine)	As above
MAPHY 1988 [30]	Metoprolol versus thiazide diuretic	Sub-set of the HAPPHY trial [37]

Table 2 Characteristics of included studies

Trial	Beta-blocker	Comparison drug(s)	Age (years)		Blood pressure (mmHg)	Baseline (SBP/DBP)	Total participants	Mean follow-up (years)
			Entry criteria	Mean	Entry criteria			
Coope 1986 [34]	Atenolol	Untreated	60–79	65	SBP ≥ 170 or DBP ≥ 105	196.7/99.7	884	4.4
IPPPSH 1985 [31]	Oxprenolol	Placebo	40–64	52.2	DBP 100–125	173.2/107.9	6357	4
MRC 1985 [32]	Propranolol	Placebo Diuretic	35–64	52	SBP < 200 and DBP < 115	162.0/98.5	17 354	4.9
MRCOA 1992 [33]	Atenolol	Placebo Diuretic	65–74	70.3	SBP 160–209 and DBP < 115	184.0/91.0	4396	5.8
Berglund 1981 [36]	Propranolol	Diuretic	47–54	50.8	SBP > 170 or DBP > 105	174.0/105.5	106	10
HAPPHY 1987 [37]	Atenolol, metoprolol, propranolol	Diuretic	40–64	52.2	DBP 100–130	166.0/107.9	6569	3.8
VA COOP 1982 [35,38]	Propranolol	Diuretic	21–65	49.2	DBP 95–114	146.3/101.5	683	1
AASK 2002 [39]	Metoprolol	CCB RASI (ACEI)	18–70	54.6	DBP ≥ 95	150.0/96.0	1094	4.1
UKPDS-39 1998 [43]	Atenolol	RASI (ACEI)	25–65	56.4	SBP ≥ 160 and/or DBP ≥ 90; or SBP ≥ 150 and/or DBP ≥ 85 in known hypertensives	159.0/93.0	758	8.4
LIFE 2002 [44]	Atenolol	RASI (ARB)	55–80	66.9	DBP 95–115 and/or SBP 160–200	174.5/97.7	9193	4.8
ASCOT 2005 [42]	Atenolol	CCB	40–79	62.9	Untreated HBP: SBP > 160 and/or DBP > 100 or treated HBP: SBP > 140 and/or DBP > 90, plus 3 cardiovascular risk factors	164.0/94.7	19 257	5.5
ELSA 2002 [41]	Atenolol	CCB	45–75	56	SBP 150–210 and DBP 95–115	163.1/101.3	2334	3.75
INVEST 2003 [40]	Atenolol	CCB	>50	66.1	SBP > 140 or DBP > 90	150.8/87.2	22 576	2.7

RASI, renin–angiotensin system inhibitor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; HBP, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

placebo or no treatment [31–34], diuretics [32,33,35–38], CCBs [39–42], ACE-Is [39,43], or ARBs [44].

Three trials compared a beta-blocker to more than one agent [32,33,39]. Seven trials included participants aged 65 or younger [31,32,35–39,43], and the rest included older patients. All included trials were conducted in industrialized countries, largely western Europe and North America. Nine studies included participants of both sexes [31–34,39,41,42,44] and eight provided information on race or ethnicity [31,35,37–39,41–44], with most participants being caucasian males; except for the Veterans Administration (56.8% African Americans) [35,38] and the African American Study of Kidney Disease and Hypertension (100% African Americans) trials [39]. Treatment allocation was adequately concealed in eight trials [31–34,41–44] and one trial did not blind outcome assessors [43]. Loss to follow-up was low (0–10%) in 10 trials [31,35–39,41–44], high (19–25%) in two [32,33] and not reported in one [34]. Beta-blockers reduced systolic and diastolic blood pressures relative to placebo by about 11 and 6 mmHg, respectively (Table 3). However, the respective reductions in systolic and diastolic blood pressures were less than 3 and 1 mmHg for diuretics, 1 and 1 mmHg for RAS inhibitors, and 1 and 1 mmHg for CCBs (Table 3).

Data synthesis

Beta-blockers versus placebo or no treatment

Compared to placebo or no treatment (Fig. 2), beta-blockers significantly reduced the risk of stroke (four trials, $n = 23\,613$ participants; RR 0.80, 95% CI 0.66–0.96) and total cardiovascular events (four trials, $n = 23\,613$; RR 0.88, 95% CI 0.79–0.97). The corresponding number-needed-to-treat with a beta-blocker over 5 years to prevent one event was 211 for stroke and 140 for any cardiovascular event. There was no evidence that beta-blockade lowered the risk of all-cause mortality, CHD or cardiovascular mortality. Trial participants on a beta-blocker were no more likely than those receiving a placebo to discontinue treatment (three trials, $n = 22\,729$; RR 2.34, 95% CI 0.84–6.52). However, for this outcome, there was significant heterogeneity between the trials ($P < 0.001$, $I^2 = 99.5\%$); with no difference in the likelihood of discontinuing treatment with oxprenolol (one trial, $n = 6357$; RR 0.95, 95% CI 0.87–1.04) and an increased likelihood with propranolol or atenolol (two trials, $n = 16\,372$; RR 3.67, 95% CI 1.99–6.79).

Beta-blockers versus diuretics

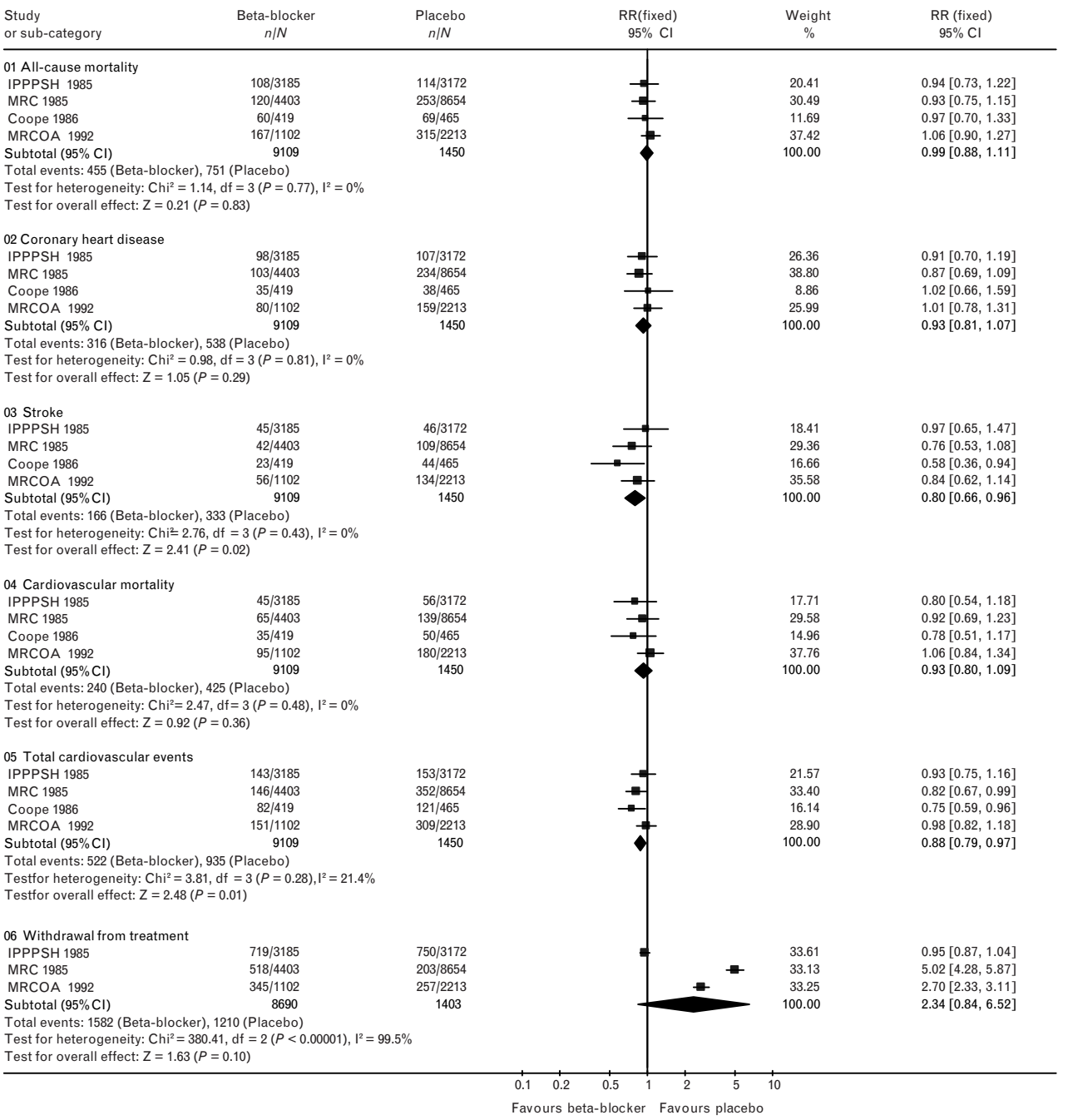
We detected no difference in the effects of beta-blockers and diuretics (five trials; $n = 18\,241$) on the risk of all-cause mortality, CHD, stroke, cardiovascular mortality and total cardiovascular events (Fig. 3). Some caution is warranted in the interpretation of these overall findings as significant heterogeneity of effect was found in relation to a number of outcomes. Furthermore, in the two largest trials [33,34], beta-blockade decreased the systolic BP by 3.5 and 1 mmHg (Table 3). There was an even greater difference in a third but much smaller study [35]. With regards to stroke, the lack of homogeneity among trials ($P = 0.01$, $I^2 = 72.9\%$) may be related to the type of beta-blockade. There was an increase in the risk of stroke with the use of non-selective beta-blockers (propranolol) (RR 2.28, 95% CI 1.31–3.95) but no difference with cardioselective beta-blockers (atenolol or metoprolol): RR 1.00, 95% CI 0.74–1.33 ($P = 0.12$, $I^2 = 59.6$). Compared to trial participants on a diuretic, those on a beta-blocker had a greater likelihood of discontinuing treatment due to side effects (RR 1.80, 95% CI 1.33–2.42).

Table 3 Comparison of blood pressure changes in the comparator groups

Trial	Beta-blocker	Comparison drug	Blood pressure differences (mmHg) beta-blocker and comparison drug[a]	
			Systolic	Diastolic
Coope 1986 [34]	Atenolol	Placebo	−18.0	−11.0
IPPPSH 1985 [31]	Oxprenolol		−4.1	−1.5
MRC 1985 [32]	Propranolol		−9.5	−5.0
MRCOA 1992 [33]	Atenolol		−13.0	−7.0
Berglund 1981 [36]	Propranolol	Diuretic	−4.0	+2.0
HAPPHY 1987 [37]	Atenolol, metoprolol or propranolol		0.0	−1.0
MRC 1985 [32]	Propranolol		+3.5	+1.0
MRCOA 1992 [33]	Atenolol		+1.0	−0.5
VA COOP 1982 [35,38]	Propranolol		+7.0	+1.6
AASK 2002 [39]	Metoprolol	RAS-I (ACEI)	0.0	−1.0
UKPDS-39 1998 [43]	Atenolol		−1.0	−1.0
LIFE 2002 [44]	Atenolol	RAS-I (ARB)	+1.1	−0.2
ASCOT 2005 [42]	Atenolol	CCB	−1.8	−2.1
AASK 2002 [39]	Metoprolol		+2.0	0.0
ELSA 2002 [41]	Atenolol		+0.2	−0.1
INVEST 2003 [40]	Atenolol		+0.3	+0.2

RASI, Renin–angiotensin system inhibitor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker. [a]'Minus sign' means beta-blocker arm had lower blood pressure, and 'plus sign' means beta-blocker arm had higher blood pressure than comparison drug.

Fig. 2



The effectiveness and safety of beta-blockers compared to placebo. *n*/*N*, number of events/number randomized; RR, relative risk; CI, confidence intervals. Meta-analysis was done using the fixed effect method for all end points except withdrawal from treatment, where the random effects method was used due to significant between-study heterogeneity of effect.

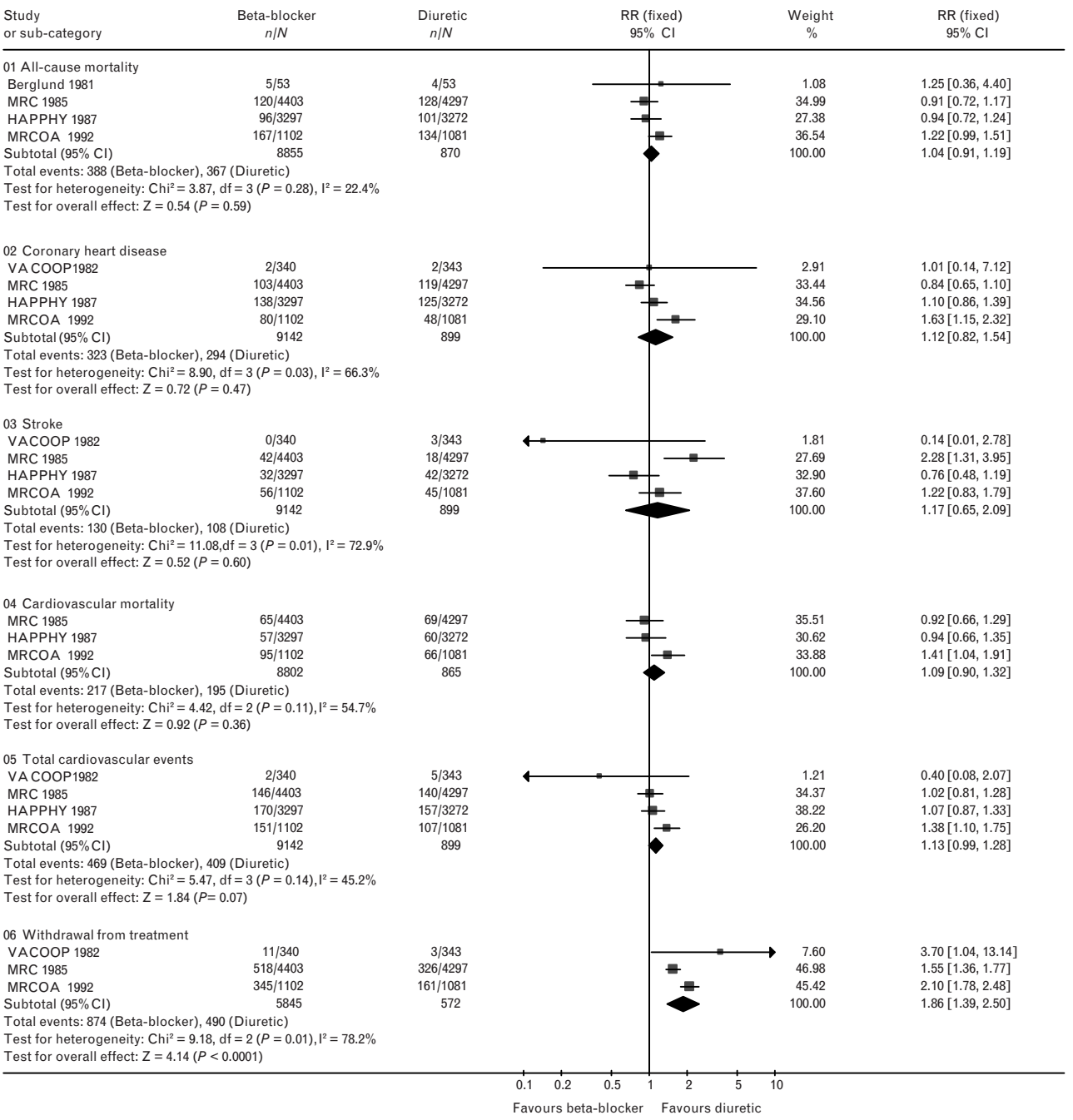
Beta-blockers versus calcium-channel blockers

Compared to CCBs (Fig. 4), beta-blockers were less effective in reducing the risk of all-cause mortality (RR 1.06, 95% CI 1.00–1.14), stroke (RR 1.24, 95% CI 1.11–1.40) and total cardiovascular events (RR 1.18, 95% CI 1.08–1.29). There was no difference in the effects on CHD, cardiovascular mortality and withdrawal from randomly allocated treatment.

Beta-blockers versus renin–angiotensin system inhibitors

Due to the small number of trials with ACE-Is (two trials, $n = 1635$) and ARBs (one trial, $n = 9193$), we combined

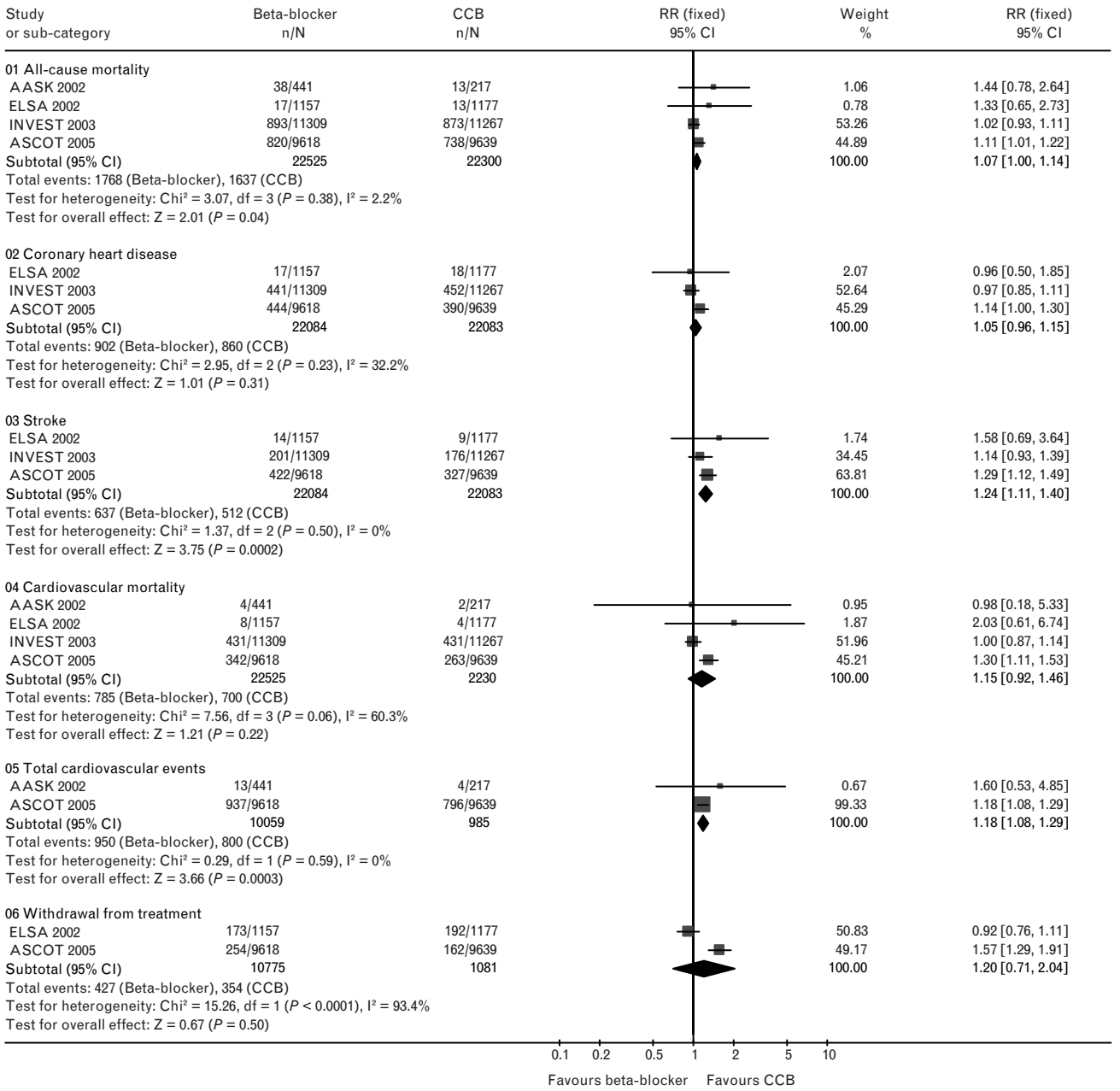
Fig. 3



The effectiveness and safety of beta-blockers compared to diuretics. *n*/*N*, number of events/number randomized; RR, relative risk; CI, confidence intervals. Meta-analysis was conducted using the random effects method for coronary heart disease, stroke and withdrawal from treatment due to significant heterogeneity of effect, and by the fixed effects method for the other end points.

data for the two classes of RAS inhibitors (Fig. 5). Beta-blockade failed to reduce the risk of stroke to the level attained with RAS inhibition (RR 1.30, 95% CI 1.11–1.53) and led to significant withdrawals from randomized treatment (RR 1.41, 95% CI 1.29–1.54) (two trials, $n = 9951$); but there were no significant differences in their effects on the risk of all-cause mortality (three trials; $n = 10\,828$), CHD (two trials, $n = 9951$), cardiovascular mortality (three trials; $n = 10\,828$), and total cardiovascular events (three trials; $n = 10\,828$). However, there was significant heterogeneity of effect on the risk of total cardiovascular events ($P = 0.02$, $I^2 = 73.8\%$), with the effect of beta-blockers being similar to that of ACE-Is (two trials, $n = 1635$; RR 0.82, 95% CI 0.64–1.05;

Fig. 4



The effectiveness and safety of beta-blockers compared to calcium-channel blockers. CCB, calcium-channel blocker; *n*/*N*, number of events/number randomized; RR, relative risk; CI, confidence intervals. Meta-analysis was conducted using the random effects method for cardiovascular mortality and withdrawal from treatment, due to significant heterogeneity of effect, and by the fixed effects method for the other end points.

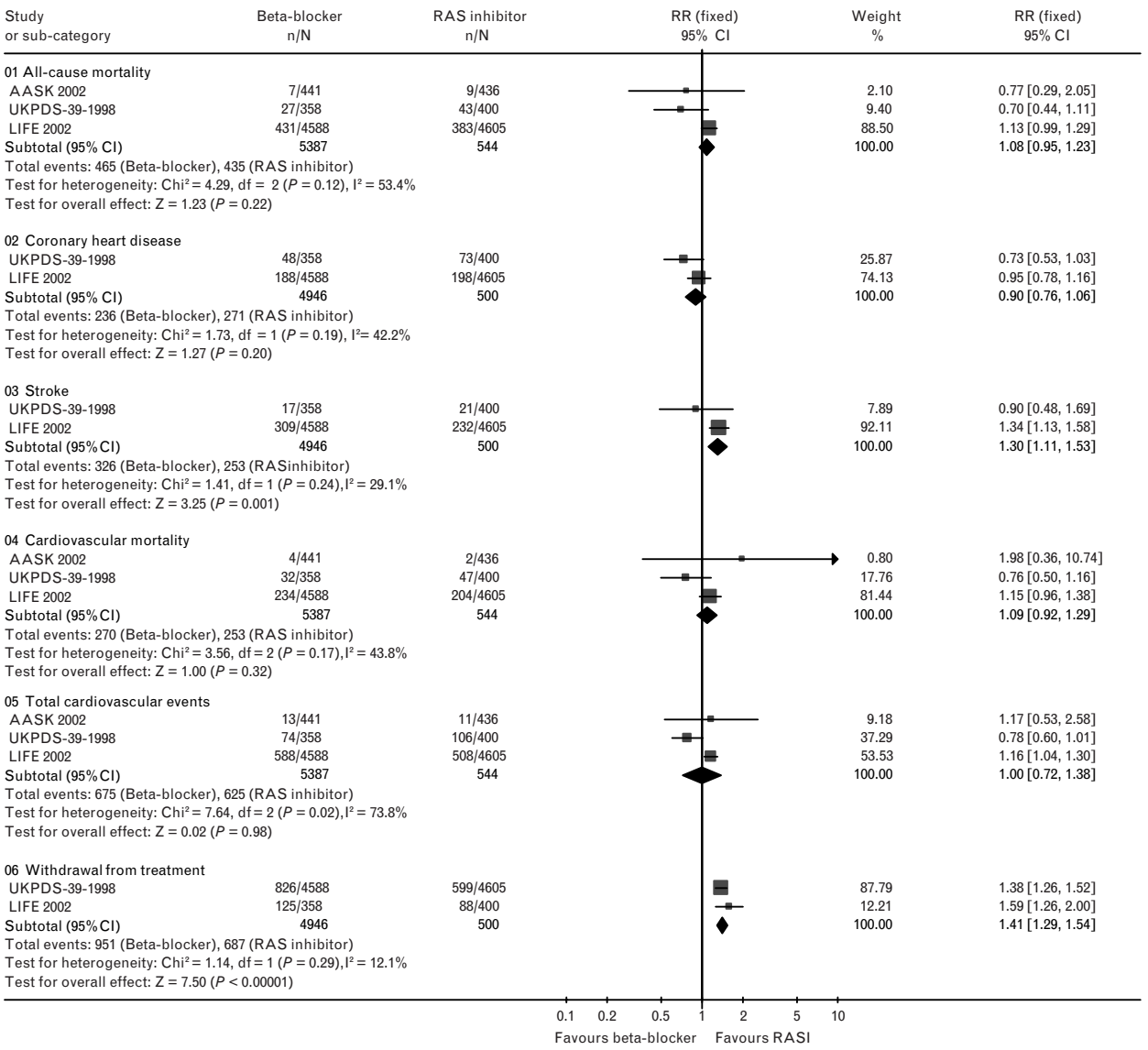
$I^2 = 0\%$) but less than that of the ARBs (one trial, $n = 9193$; RR 1.16, 95% CI 1.04–1.30).

Discussion

Summary of findings and comparison with other studies

We show that beta-blockers are inferior to CCBs for effects on all-cause mortality, stroke and cardiovascular mortality, and to RAS inhibition for all-cause mortality and stroke. By comparing beta-blockers with all other therapies taken together, Lindholm *et al.* [14] were only able to show an inferiority of beta-blockade on stroke reduction. Because of the smaller numbers of participants in our comparisons, greater statistical variation could be expected; hence we used the Higgins I^2 statistic to evaluate the consistency of the evidence [23,24]. The use of this statistic allows us to assess the percentage of variation across studies that is

Fig. 5



The effectiveness and safety of beta-blockers compared to renin-angiotensin system inhibitors. RAS, renin–angiotensin system; *n/N*, number of events/number randomized; RR, relative risk; CI, confidence intervals. Meta-analysis was conducted using the fixed effect method for all end points except total cardiovascular events, where we used the random effects method due to significant between-study heterogeneity of effect.

due to true heterogeneity rather than chance; with a low value (e.g. 0%) indicating little heterogeneity.

In our meta-analysis, heterogeneity was very low for the outcomes of beta-blockade versus placebo or no treatment (Fig. 2). We found a modest 20% reduction in stroke by beta-blockade versus placebo with four studies, which is almost exactly the same percentage value as found by Lindholm *et al.* [14] using seven studies. With their wider inclusion criteria, Lindholm *et al.* included three small studies not considered by us, which resulted in some inconsistency in their findings. By contrast, our four studies have excellent homogeneity as measured by a Higgins I^2 value of 0% (Table 4). Thus we are able to give additional validation to one of the crucial findings of Lindholm *et al.* [14], namely that stroke reduction by beta-blockade is suboptimal. We also demonstrate a high degree of consistency of evidence for the comparisons of beta-blockers versus CCBs (Fig. 4 and Table 4) for all-cause mortality ($I^2 = 2.2\%$), stroke ($I^2 = 0\%$) and total cardiovascular events ($I^2 = 0\%$), but with less homogeneity for coronary heart disease ($I^2 = 32.2\%$) and cardiovascular mortality ($I^2 = 60.3\%$). For the comparison of beta-blockers versus RAS inhibitors (Fig. 5), the Higgins I^2 values for stroke and withdrawal rates also demonstrate a high degree of consistency across the studies, making

Table 4 Degree of heterogeneity assessed by the Higgins I^2 statistic

	Beta-blocker versus placebo	Beta-blocker versus diuretics	Beta-blocker versus CCB	Beta-blocker versus RASI
All-cause mortality	0%	22.4%	2.2%	53.6%
Coronary heart disease	0%	66.3%	32.2%	42.2%
Stroke	0%	72.9%	0%	29.1%
Cardiovascular mortality	0%	54.7%	60.3%	43.8%
Total cardiovascular events	21.4%	45.2%	0%	73.8%
Withdrawals	99.5%	78.2%	93.4%	12.1%

CCB, calcium-channel blocker; RASI, renin–angiotensin system inhibitors.

our conclusions more secure [23,24]. For the comparison with diuretics, there were no major differences in the clinical outcomes (Fig. 3). However, the rate of withdrawal was higher with beta-blockers. Despite the high Higgins I^2 value for the three studies assessing this end point, inspection of the data shows a relative risk greater than 1 in each of the studies, with confidence intervals that do not overlap unity (Fig. 3). Thus despite considerable heterogeneity ($I^2 = 78.2\%$), we believe that the conclusion that the withdrawal rate was significantly higher with beta-blockers versus diuretics is valid.

Limitations of our study

The major weaknesses of our review relate to inherent defects in the original studies. The emphasis was often on the results with first drug used, whereas in most studies combination therapy had to be used to help achieve the blood pressure goals. Thus the results were often confounded by the use of other drugs. The dropout rates were high in two of the diuretic studies [32,33], potentially introducing bias. Furthermore, the arguments of Zanchetti [45] – that focusing on event-driven hypertension studies, which are generally limited to more elderly persons, does not include the full picture – need to be kept in mind. Thus it may be that only those with complicated hypertension or advanced disease are included in studies, thereby ignoring the possible differing benefits of different antihypertensives on different organs of the body and on different stages of disease development [45]. A further problem is that in the two arms of the studies we analysed, and especially in the case of the comparison with diuretics, there were discrepancies between the achieved blood pressure levels (Table 3), and even small blood pressure differences may be linked to significant differences in outcomes [6,7]. However, there were no consistent differences in the blood pressure reduction between beta-blockers and the other agents used (Table 3) to explain the outcome differences we found. Yet another limitation is that we combined ACE-Is and ARBs, potentially different, as we believed that the similarities between these agents as antihypertensives outweighed relatively small potential differences.

Are vasodilating beta-blockers different?

A limitation both of our study and that of Lindholm and coworkers is that the newer vasodilating beta-blockers could not be analysed, there being no outcome studies of these agents on hypertensives. The mechanisms that we considered to explain the failure of beta-blockers to reduce stroke as much as they should were twofold, namely a greater risk of new diabetes [46–48], and the failure to decrease central aortic pressure as much as brachial pressure, as shown in the CAFE study [49]. New diabetes may require years to develop cardiovascular complications [50] so that we favour the mechanism involving lesser reduction of central aortic pressure by beta-blockers. Theoretically, vasodilating beta-blockers such as carvedilol and nebivolol [51,52] should better be able to reduce central pressures than conventional beta-blockers, because vasodilation may favourably alter the pattern of the pressure wave reflecting back from the periphery, thereby lowering the central pressure [49]. Nonetheless, these two beta-blockers also cause the bradycardia that is thought to be the principal mechanism accounting for lesser ability of atenolol $\pm$ thiazide to lower the central pressure than amlodipine $\pm$ perindopril [49]. Thus event-driven outcome studies would be required to show that stroke is adequately reduced by these newer beta-blockers.

Hypertension with angina

Our report is also indirectly relevant to the issue of choice of antianginal agent for those with both hypertension and effort angina. Several guidelines propose that this combination is a 'compelling' indication for the use of beta-blockers. However, we show that compared with CCBs, beta-blockers do not affect the risk of developing coronary heart disease but are less effective in reducing the risk of stroke by 24% (Fig. 4) and total cardiovascular events by 18%, both with a very high degree of homogeneity ($I^2 = 0\%$). Other data also support the view that beta-blockers do not decrease new onset coronary heart disease in hypertensives [14,53]. Nonetheless beta-blockers remain with CCBs as the only antianginal antihypertensives.

In conclusion, our results support the view that, in general, beta-blockers are not the ideal choice for first-line therapy of hypertension. Specifically, they compare poorly for several outcome measures with therapy by calcium-channel blockers or renin–angiotensin system inhibitors. In the case of diuretics, although the outcome data are similar, there is a higher withdrawal rate with beta-blockers. Thus this meta-analysis extends the results of previous meta-analyses by showing that beta-blockers

are inferior choices when compared to the other major classes of antihypertensive agents that we studied.

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