Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: **β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.**

Methods: **The Cochrane Library and PubMed were searched for β blocker treatment in patients with primary hypertension. Data were then entered into the Cochrane Collaboration Review Manager package and were summarised in meta-analyses. 13 randomised controlled trials (n=105 951) were included in a meta-analysis comparing treatment with β blockers with other antihypertensive drugs. Seven studies (n=27 433) were included in a comparison of β blockers and placebo or no treatment.**

Findings: **The relative risk of stroke was 16% higher for β blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.**

Interpretation: **In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.**

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Introduction

For three decades, β blockers have been widely used in the treatment of hypertension and are still recommended as first-line drugs in hypertension guidelines.[1,2] Moreover, after myocardial infarction and in patients with heart failure, treatment with β blockers prevents re-infarction, hospitalisation for heart failure, and premature death.[3–6] The effect of β blockers as a treatment for primary hypertension has been challenged.[7,8] A preliminary analysis has shown that atenolol is not very effective in hypertension.[9] To avoid unnecessary harm to patients, the role of other β blockers needs to be investigated. Here, we substantially enlarge the data on atenolol and analyse the effect of different β blockers on stroke, myocardial infarction, and mortality of all causes (n=127 879).

Methods

The eligibility criteria for inclusion in the present meta-analyses were: randomised controlled trial; treatment of primary hypertension; β blocker as first-line antihypertensive drug in at least 50% of all patients in one treatment group; and outcome data for all-cause mortality, cardiovascular morbidity, or both. Data were then entered into the Cochrane Collaboration review manager programme (RevMan version 4.2). Heterogeneity between the studies was assessed with χ^2 test and the chosen summary statistic variable was the reduction in relative risk (RR). When the p value for heterogeneity in any analysis was less than 0·10, the random model was used for calculations.

The studies were analysed in two main groups: studies comparing β blockers with other drugs in primary hypertension, and those comparing β blockers with placebo or no treatment. Data were analysed for all β blockers and for three subgroups: non-atenolol β blockers; mixed β blockers and diuretics when more than 50% of patients started on a β blocker; and atenolol. Data in all groups are provided for stroke, myocardial infarction, and death from all causes. Heart failure was not included since many trials did not have adequate data.

Search strategy and selection criteria

Initially, the Cochrane Library and PubMed were searched for systematic reviews of β blocker treatment in hypertensive patients (("adrenergic β antagonists" [MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR β blocker [Text Word]) AND ("hypertension" [MeSH Terms] OR hypertension [Text Word]) AND ("classification" [MeSH Terms] OR systematic [Text Word])) or (("adrenergic β antagonists" [MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR beta blocker [Text Word]) AND ("hypertension" [MeSH Terms] OR hypertension [Text Word]; limited to meta-analysis).

Thereafter, PubMed was searched for randomised controlled clinical trials (RCTs); ("hypertension" [MeSH Terms] OR hypertension [Text Word]) AND ("adrenergic β antagonists"[MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR beta blocker [Text Word]) AND (("cerebrovascular disorders" [MeSH Terms] OR Cerebrovascular disorders [Text Word]) OR ("myocardial infarction" [MeSH Terms] OR myocardial infarction [Text Word])). Finally, we included the recently published ASCOT-BPLA trial[10] in the analyses.

	Patients*	Mean age (years)	Follow-up (years)	β blocker	Comparison drug	Baseline blood pressure	Blood pressure change β blocker– comparison drug
β blocker trials (year)							
MRC I (1985)[16]	8700	52	5·5	Propranolol	BFZ	161/98 mm Hg	+4/+1 mm Hg†
	13 057			Propranolol	Placebo	161/98 mm Hg	−9/−5 mm Hg†
IPPPSH (1985)[27]	6357	52	4·0	Oxprenolol	Placebo	173/108 mm Hg	−3·8/−1·2 mm Hg
HEP (1986)[28]	884	68·8	4·4	Atenolol	Open control	196/99 mm Hg	−18/−11 mm Hg
Berglund (1986)[17]	106	50	10	Propranolol	BFZ	170/105 mm Hg	na/+1 mm Hg‡
HAPPHY (1988)[14]	6569	52·2	3·8	Atenolol	HCTZ	166/107 mm Hg	0/−1 mm Hg
				Metoprolol	BFZ		
				Propranolol			
MRC Old (1992)[18]	2183	70·3`	5·8	Atenolol	HCTZ/Ami	185/91 mm Hg	+1·0/−0·5 mm Hg§
	3748			Atenolol	Placebo	185/91 mm Hg	−13·5/−7·0 mm Hg§
Yurenev (1992)[19]	304	45·5	4·0	Propranolol	Non-β blocker	168/106 mm Hg	+3·4/+1·4 mm Hg
Dutch TIA (1993)[29]	1473	52% >65 years	2·6	Atenolol	Placebo	158/91 mm Hg	−5·8/−2·9 mm Hg¶
TEST (1995)[30]	720	70·4	2·6	Atenolol	Placebo	161/89 mm Hg	−4/−3 mm Hg‖
UKPDS (1998)[20]	758	56·2	9	Atenolol	Captopril	159/94 mm Hg	−1/−1 mm Hg
LIFE (2002)[21]	9193	66·9	4·8	Atenolol	Losartan	174/98 mm Hg	+1·1/−0·2 mm Hg
ELSA (2002)[22]	2334	56·0	3·75	Atenolol	Lacidipine	163/101 mm Hg	+0·2/−0·1 mm Hg
INVEST (2003)[23]	22 576	66·1	2·7	Atenolol	Verapamil	151/87 mm Hg	Probable <1 mm Hg
ASCOT-BPLA (2005)[10]	19 257	63·0	5·7	Atenolol	Amlodipine	164/95 mm Hg	+2·7/+1·9 mm Hg**
Mixed β-blocker trials							
STOP (1991)[31]	1627	75·7	2·1	Atenolol	Placebo	195/102 mm Hg	−19·5/−8·1
				Metoprolol			
				Pindolol			
				HCTZ/Ami			
STOP-2 (1999)[24]	6614	76·0	5·0	Atenolol	Enalapril	194/98 mm Hg	−0·3/+0·2 mm Hg††
				Metoprolol	Lisinopril		
				Pindolol	Felodipine		
				HCTZ/Ami	Isradipine		
NORDIL (2000)[25]	10 881	60·4	4·5	Any diuretic	Diltiazem	173/106 mm Hg	−3·0/0·0 mm Hg‡‡
				Any β blocker			
CONVINCE (2003)[26]	16 476	65·6	3·0	Atenolol	Verapamil	150/87 mm Hg	+0·1/+0·7 mm Hg**
				HCTZ			

*Two trials[16,18] had 3 treatment groups, so patients on β blockers in these two trials counted twice. Therefore only 127 879 patients included in all 18 trials. †After 4 years. ‡Blood pressure data estimated from figure. §Data estimated from figure in main publication. ¶Data 4 months after randomisation. ‖Data 1 month after randomisation. **Mean during the whole study. ††Mean from baseline to the last follow-up among patients alive at 24 months. ‡‡Mean from baseline to the last follow-up in patients remaining in the study for at least 24 months. HCTZ/Ami=Hydrochlorothiazide/amiloride. HCTZ=Hydrochlorothiazide. BFZ=Bendroflumethiazide. na=not available.

***Table*: Trials included in the meta-analyses**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 16 studies comparing β blockers with other antihypertensive treatment. Three of these studies were excluded: the large Captopril Prevention Project (CAPPP) study,[11] comparing conventional treatment (diuretics and β blockers) with captopril, because the number of patients treated with β blockers was not registered (Lanke J, personal communication); the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial (comparing metoprolol with a thiazide diuretic) because that study was a post-hoc follow-up of a subgroup of patients who were already included in the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial;[12–14] and a small trial (n=394) comparing propranolol with a thiazide diuretic because there was a suboptimum registration of the seven clinical events and a major blood pressure difference between the two active treatment groups.[15] Hence, 13 studies were included in the present meta-analysis, (table, figure 1, A–D).[10,14,16–26] Two Medical Research Council studies (MRC and MRC-Old)[16,18] had three treatment groups, comparing a β blocker with a thiazide diuretic and with placebo, and are therefore also included here. Studies with several first-line treatment options, but which had a β blocker in at least 50% the patients in one treatment group, were analysed separately (table, figure 1, C) and are referred to as mixed trials.[24–26]

In all trials comparing β blockers with other drugs (n=105 951, figure 1, A), the relative risk of stroke was 16% higher with β blockers (95% CI 4–30%; p=0·009) than with other drugs. All-cause mortality showed a tendency in the same direction, the relative risk being increased by 3% for β blockers (–1 to 8%); p=0·14. There was, however, no difference for myocardial infarction. When the three subgroups of β blocker studies were looked at separately, the most prominent difference for the risk of stroke was shown for atenolol (26% [15–38%]; p<0·0001; n=56 301, figure 1, D)and for the β blockers in the mixed trials (9%, –2 to 21%; p=0·13; n=33 971, figure 1, C). In the non-atenolol trials (n=9004,

figure 1, B), there were few clinical events (eg, only 77 strokes), so the results were inconclusive.

Seven studies comparing β blockers with placebo or with no antihypertensive treatment were included in the meta-analysis (27 433, table, figure 2, A–C).[16,18,27–31] The relative risk of stroke was reduced by 19% with β blockers (7–29%). STOP Hypertension was the only mixed trial. In this trial, the risk of stroke was reduced by 45% (15–65%) and the risk of death from all causes by 43% (15–61%).[31] The two studies in which the mean blood pressure reduction in the active treatment group was substantial (HEP [Hypertension in Elderly Patients][28] and STOP Hypertension[31]) showed the best effect of active treatment, indicating that most patients were treated with additional drugs, mainly thiazide diuretics. The effect seemed similar in the three subgroups of β blocker trials.

The number of patients who were treated with a β blocker in the mixed trials varied. In STOP hypertension

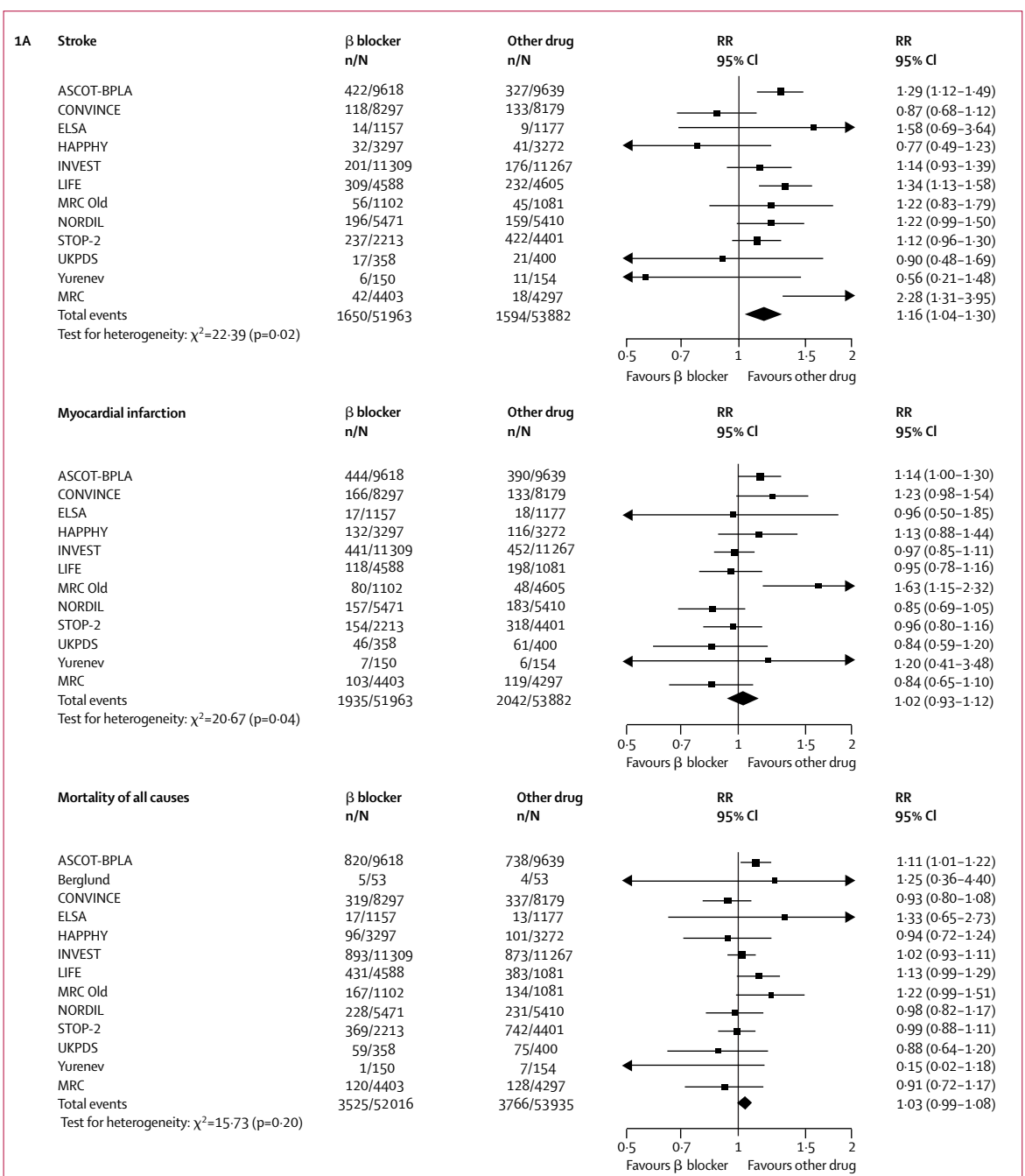
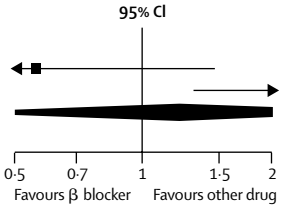


Figure 1, A: **Outcome data for all β blockers versus other antihypertensive treatment**

Figure 1, B: Outcome data for non-atenolol β blockers versus other antihypertensive treatment

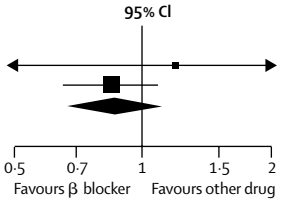
1B Stroke

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
Yurenev	6/150	11/154		0·56 (0·21–1·48)
MRC	42/4403	18/4297		2·28 (1·31–3·95)
Total events	48/4553	29/4451		1·20 (0·30–4·71)
Test for heterogeneity: χ^2=6·09 (p=0·01)				



Myocardial infarction

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
Yurenev	7/150	6/154		1·20 (0·41–3·48)
MRC	103/4403	119/4297		0·84 (0·65–1·10)
Total events	110/4553	125/4451		0·86 (0·67–1·11)
Test for heterogeneity: χ^2=0·39 (p=0·53)				



Mortality of all causes

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
Berglund	5/53	4/53		1·25 (0·36–4·40)
Yurenev	1/150	7/154		0·15 (0·02–1·18)
MRC	120/4403	128/4297		0·91 (0·72–1·17)
Total events	126/4606	139/4504		0·89 (0·70–1·12)
Test for heterogeneity: χ^2=3·21 (p=0·20)				

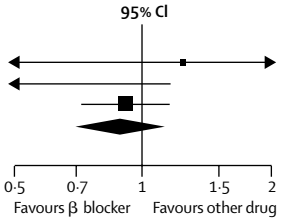
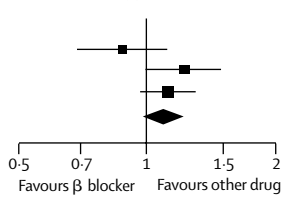


Figure 1, C: Outcome data for mixed β blocker/diuretics versus other antihypertensive treatment

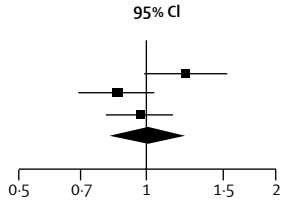
1C Stroke

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
CONVINCE	118/8297	133/8179		0·87 (0·68–1·12)
NORDIL	196/5471	159/5410		1·22 (0·99–1·50)
STOP-2	237/2213	422/4401		1·12 (0·96–1·30)
Total events	551/15981	714/17990		1·09 (0·98–1·21)
Test for heterogeneity: χ^2=4·31 (p=0·12)				



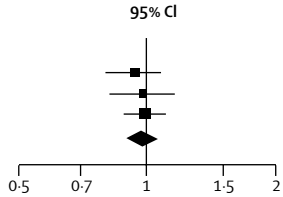
Myocardial infarction

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
CONVINCE	166/8297	133/8179		1·23 (0·98–1·54)
NORDIL	157/5471	183/5410		0·85 (0·69–1·05)
STOP-2	154/2213	318/4401		0·96 (0·80–1·16)
Total events	477/15981	634/17990		1·00 (0·81–1·22)
Test for heterogeneity: χ^2=5·72 (p=0·06)				



Mortality of all causes

	β blocker n/N	Other drug n/N	RR 95% CI	RR 95% CI
CONVINCE	319/8297	337/8179		0·93 (0·80–1·08)
NORDIL	228/5471	231/5410		0·98 (0·82–1·17)
STOP-2	369/2213	742/4401		0·99 (0·88–1·11)
Total events	916/15981	1310/17990		0·97 (0·89–1·05)
Test for heterogeneity: χ^2=0·37 (p=0·83)				



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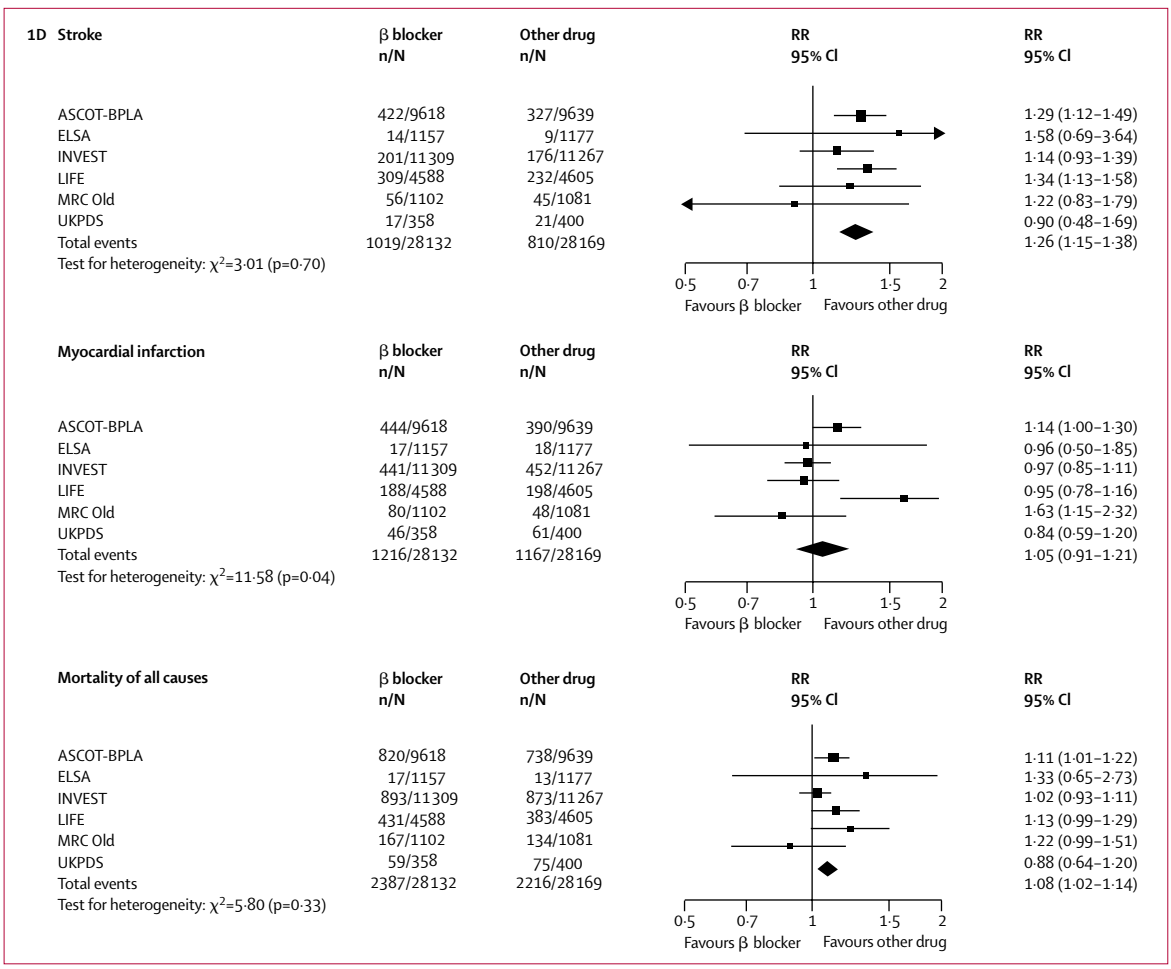

Figure 1, D: **Outcome data for atenolol versus other antihypertensive treatment**

(Swedish Trial in Old Patients with hypertension),[31,32] 68% received a β blocker (metoprolol, pindolol, or atenolol) at randomisation; we have no data at final visit. In CONVINCE (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints),[26] 54% received atenolol at randomisation and 43% at the final visit. In STOP hypertension-2 (metoprolol, pindolol, or atenolol),[24] the figures were 74% and 62%, respectively, and in NORDIL (NORdic DILtiazem study,[25] any β blocker) 75% and 70%, respectively (Lanke J, personal communication).

Discussion

β blocker treatment of patients with primary hypertension was associated with a substantially higher risk of stroke than treatment with other antihypertensive agents. This was the case when all β blockers were analysed together and when the studies with atenolol were analysed separately. There was also a strong tendency in the same direction when the mixed trials were analysed. In the non-atenolol subgroup, documentation was poor, with surprisingly few studies and few clinical events. The HAPPHY trial[14] was not included because about half the patients treated with β blockers were given atenolol, and the MAPHY trial[12–13] was excluded for reasons stated in Results. In three of the mixed trials from Scandinavia (STOP Hypertension, STOP Hypertension 2, and NORDIL), about two-thirds of patients were treated with β blockers from the beginning of the trial, or by the time of the final visit. In the CONVINCE trial[26] the frequency was about 50%. Hence, our data strengthen the finding of the network meta-analysis of different antihypertensive drugs published by Psaty and colleagues,[33] in which low-dose diuretics did better than β blockers. Altogether, one must conclude that β blockers in primary hypertension are not as effective as other antihypertensive medication and we see no reason to limit this conclusion to atenolol.

β blockers reduced the risk of stroke by about half (19%) of that expected from previous hypertension trials—eg, 38% in the meta-analysis by Collins and colleagues,[34] which is most frequently referred to in hypertension guidelines. In our analysis, treatment with β blockers did not reduce the risk of myocardial infarction or mortality. Hence, to say that β blockers do not have an effect in

patients with primary hypertension would be incorrect, but clearly their effect is suboptimum.

Why has this suboptimum effect of β blockers not influenced the people who draw up hypertension guidelines? One reason could be that β blockers have been analysed together with diuretics, assuming that so-called old drugs or conventional treatment—ie, drugs synthesised around the same time—would have the same treatment effects.[35,36] Another reason could be that the largest studies, consisting of more than 69 000 of about 127 000 patients, have been published fairly recently (since 2002).[10,21–23,26] Our present results might affect the interpretation of two of the latest large hypertension trials—the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study[21] and the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) trial[10]—both of which claim the superiority of newer antihypertensive drugs. Our analyses suggest an alternative interpretation is that the β blocker in these two mega-trials had a less than optimum cardiovascular effect.

Messerli and colleagues[7] have previously questioned hypertension treatment with β blockers in elderly patients in a meta-analysis, although this analysis included only two studies reporting clinical events. Beevers and co-workers[8] have also questioned the use of β blockers, reviewing the results of earlier studies without further analysing their outcome, ie, no meta-analyses were reported.

Because β blockers lower blood pressure to the same extent as other antihypertensive agents, the question arises about possible mechanisms to explain why their

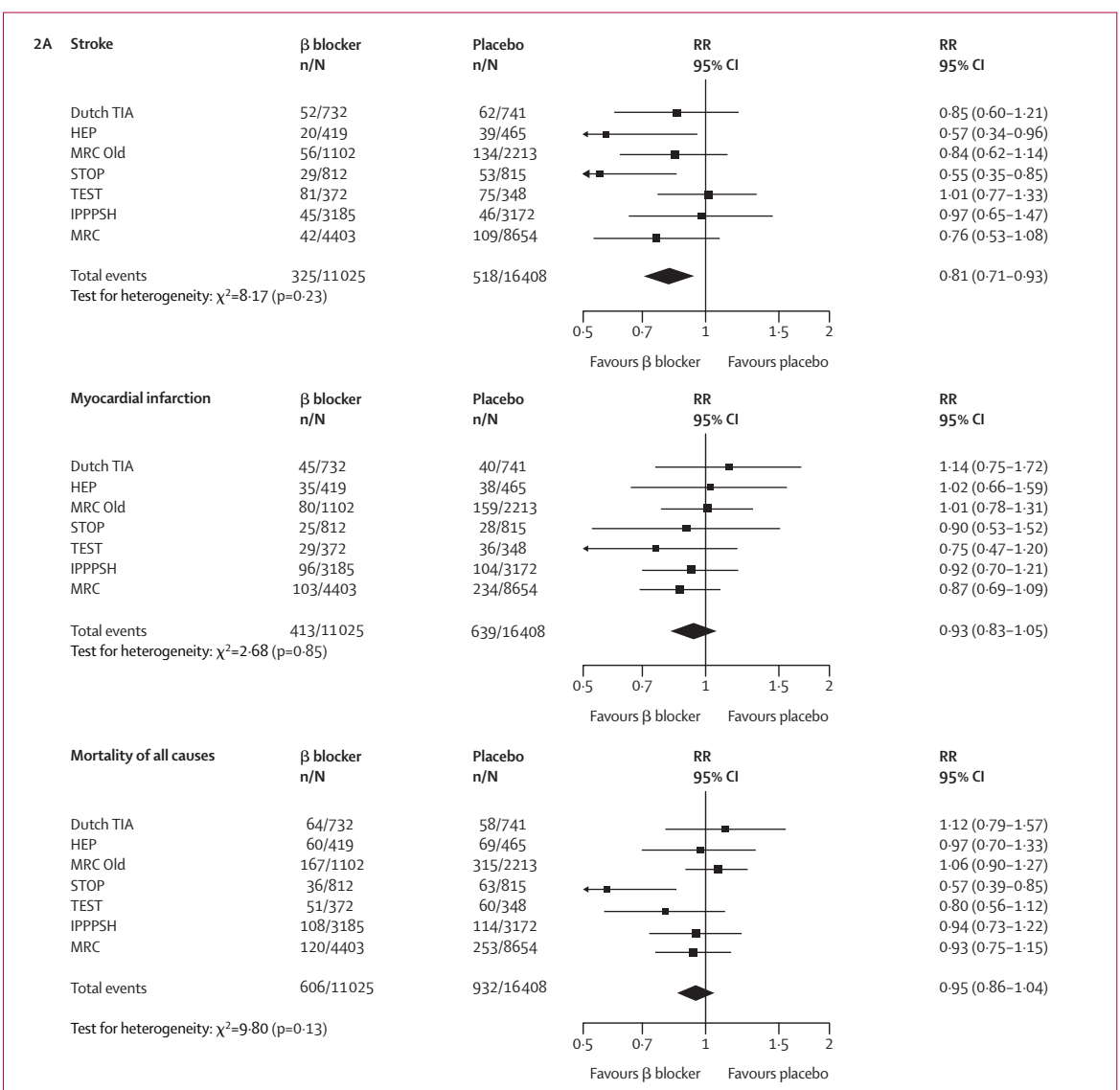

Figure 2, A: **Outcome data for all β blockers versus placebo or no treatment**

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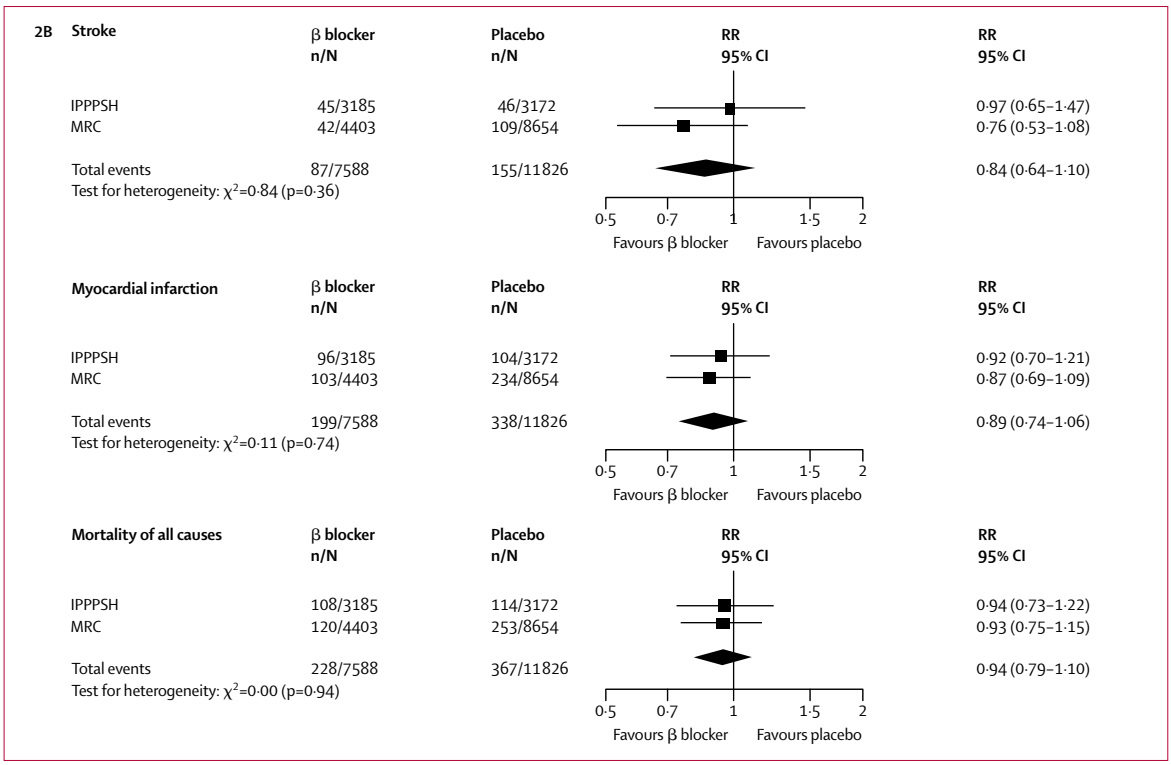

Figure 2, B: Outcome data for non-atenolol β blockers versus placebo

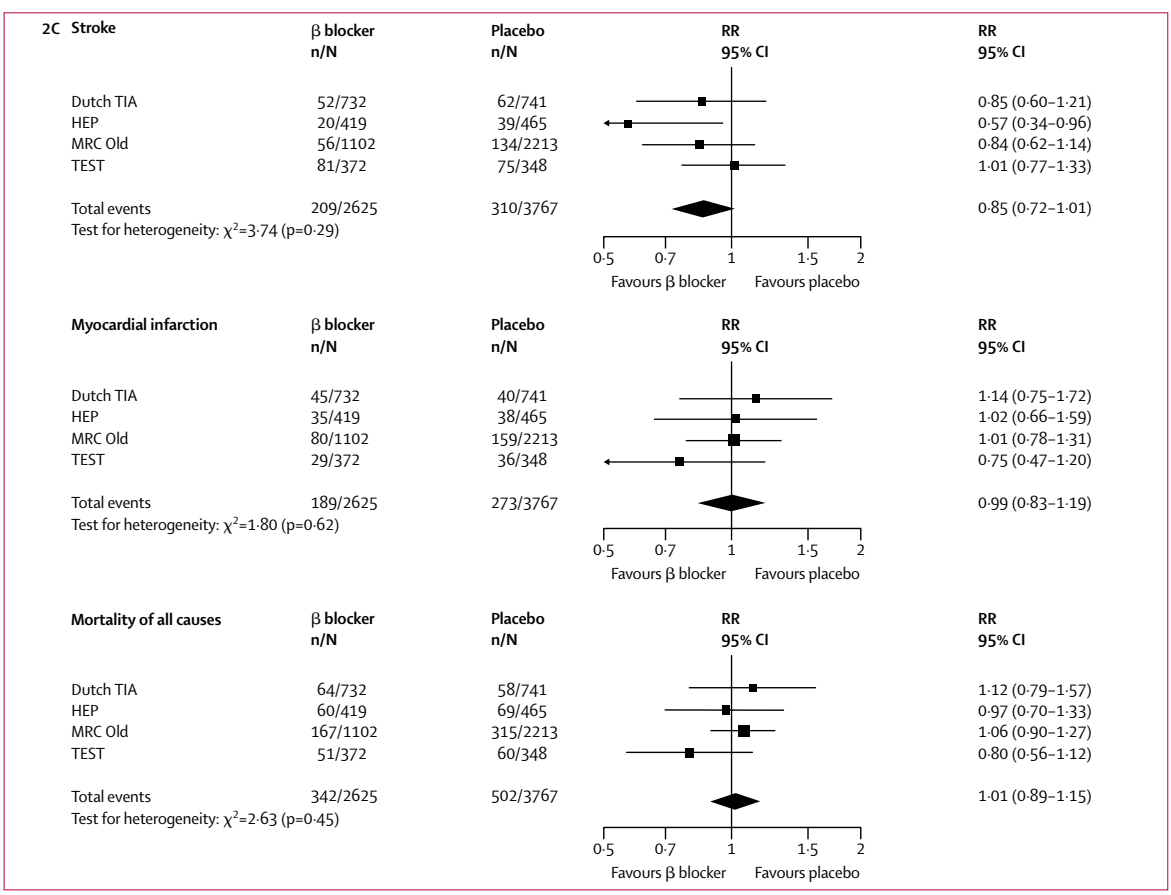

Figure 2, C: Outcome data for atenolol versus placebo or no treatment

preventive effect is not as good as other antihypertensive drugs. β blockers have effects on both glucose and lipid metabolism that theoretically could increase the risk of cardiovascular disease. However, these effects are no more pronounced than those seen with thiazide diuretics, and to single out this negative effect of the β blockers as the only explanation for their less favourable outcome on stroke morbidity would be difficult. The negative metabolic effects are more pronounced when β blockers are given in combination with thiazide diuretics.[37] This combination therapy of so-called conventional drugs was used in one of the treatment groups in both the ASCOT-BPLA[10] and INVEST (International Verapamil-Trandolapril)[23] trials.

Several studies have shown differences in haemodynamic effects of β blockers in comparison with other antihypertensive drugs. Systolic blood pressure is not the same throughout the arterial tree; it is lower centrally in the aorta and higher peripherally.[38] This difference is mainly because of the pulse wave reflections from the arterial wall in the periphery adding to the propagating pulse wave.[38] Treatment with β blockers results in reduced brachial blood pressure but does not lower central systolic blood pressure as much as treatment with angiotensin-converting enzyme (ACE) inhibitors, diuretics, and calcium antagonists.[38-40] Regression of left ventricular hypertrophy is also more closely correlated with central blood pressure than brachial blood pressure,[41] which could explain the less beneficial effect on left ventricular hypertrophy of β blockers as compared with other antihypertensive drugs.[42]

More than a quarter of the world's adult population, totalling nearly one billion people, have hypertension,[43] and far too many—eg, more than 2 million in the UK[44]—are still treated with β blockers (mainly for hypertension) even though better and affordable drugs are available. When monotherapy is prescribed, the various drug classes—thiazide diuretics, ACE inhibitors, calcium antagonists, angiotensin-receptor blockers, and β blockers ordinarily used to treat hypertension today—seem to be equally effective at lowering brachial blood pressure.[45] Thus, use of the least expensive equivalent medication whenever possible would reduce drug costs and improve cost effectiveness compared with the current prescription patterns.[46] In Sweden in 2004, the approximate daily costs of most drugs that lower blood pressure was €0·10 for thiazide diuretics, ACE inhibitors, calcium antagonists, and β blockers.[46] The cost of angiotensin-receptor blockers was, however, substantially higher, at about €1 per day.[46] Hence, switching hypertension treatment from β blockers to other low-cost antihypertensive drugs in patients without heart disease should have a major health effect without increasing the cost. Such a change, however, should be carried out slowly and under a doctor's supervision.

In a worldwide perspective, an analysis of the outcome of the LIFE trial showed that about 125 000 strokes could be prevented in 5·5 years in the old 15-member EU if β blocker-based treatment was replaced by treatment based on an angiotensin receptor blocker.[47] The outcome of the ASCOT-BPLA trial[10] showed a stroke reduction close to that seen in LIFE (23 *vs* 25%),[21] where treatment based on a calcium antagonist was given instead of a treatment based on a β blocker. Hence the worldwide stroke reduction should also be substantial with this change of therapy.[10]

There are some limitations of our meta-analyses. First, we have not been able to relate the outcome of the trials to the dose and dosing of the drugs given. Second, since the trials were published during two decades, patient characteristics and hypertension care might have changed, aspects that are difficult to account for. Finally, data for attained blood pressure throughout the trials have not been available and therefore outcome cannot be adjusted for blood pressure control.

β-blocker treatment in primary hypertension has about half the effect on the stroke risk of that expected from previous hypertension trials. Moreover, in comparison with other antihypertensive drugs, the effect of β blockers is clearly suboptimum with a higher risk of stroke. We therefore believe that β blockers should not remain as first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

Contributors

All authors contributed to the planning, analysis, and interpretation of the results as well as to the writing of the paper.

Conflict of interest statement

L H Lindholm is the president elect of the International Society of Hypertension (ISH) and has served on the steering committees of many of the large hypertension trials. B Carlberg was one of the regional co-ordinators in Sweden of the ASCOT trial. All authors participated in the working group (with L H Lindholm as chair) on Moderately Elevated Blood Pressure 2001–04 of the Swedish Council on Technology Assessment in Health Care; L H Lindholm (chair) and O Samuelsson also participated in 1991–94. No grants from the pharmaceutical industry or other external sponsors have been received for this work.

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