Atenolol in hypertension: is it a wise choice?

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Summary

Background **Atenolol is one of the most widely used β blockers clinically, and has often been used as a reference drug in randomised controlled trials of hypertension. However, questions have been raised about atenolol as the best reference drug for comparisons with other antihypertensives. Thus, our aim was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients.**

Methods **Reports were identified through searches of *The Cochrane Library*, MEDLINE, relevant textbooks, and by personal communication with established researchers in hypertension. Randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension were included.**

Findings **We identified four studies that compared atenolol with placebo or no treatment, and five that compared atenolol with other antihypertensive drugs. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the four studies, comprising 6825 patients, who were followed up for a mean of 4·6 years on all-cause mortality (relative risk 1·01 [95% CI 0·89–1·15]), cardiovascular mortality (0·99 [0·83–1·18]), or myocardial infarction (0·99 [0·83–1·19]). The risk of stroke, however, tended to be lower in the atenolol than in the placebo group (0·85 [0·72–1·01]). When atenolol was compared with other antihypertensives, there were no major differences in blood pressure lowering between the treatment arms. Our meta-analysis showed a significantly higher mortality (1·13 [1·02–1·25]) with atenolol treatment than with other active treatment, in the five studies comprising 17 671 patients who were followed up for a mean of 4·6 years. Moreover, cardiovascular mortality also tended to be higher with atenolol treatment than with other antihypertensive treatment. Stroke was also more frequent with atenolol treatment.**

Interpretation **Our results cast doubts on atenolol as a suitable drug for hypertensive patients. Moreover, they challenge the use of atenolol as a reference drug in outcome trials in hypertension.**

Introduction

β blockers have long been considered to be well documented first-line drugs in the treatment of hypertension.[1] Moreover, atenolol is one of the most widely used β blockers clinically, and it has often been used as a reference drug in randomised controlled trials of hypertension.[2–5] Questions have been raised about β blockers as first-line treatment options in hypertension.[6] In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, losartan was shown to be more effective than atenolol in hypertensive patients with left ventricular hypertrophy.[4] Whether the result of the LIFE study was caused by a beneficial effect of losartan or a weak effect of atenolol on cardiovascular disease, or both, has been debated.[7] The effect of atenolol after myocardial infarction has also been questioned.[8] Hence, the aim of our investigation was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive individuals.

Methods

We reviewed randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension. Studies were identified though searching of *The Cochrane Library*, MEDLINE, textbooks, and by personal communication with established researchers in hypertension. The following keywords were used in the database search: atenolol (MESH) OR atenolol "text" AND cerebrovascular disorders (MESH) OR myocardial infarction (MESH); atenolol AND systematic; beta-blocker AND hypertension AND systematic.

The eligibility criteria for inclusion in the meta-analyses were: (1) primary hypertension, (2) randomised, controlled trial, (3) predefined criteria of myocardial infarction, stroke, and cardiovascular death, and (4) atenolol alone as the first-line drug in one of the treatment arms. Data from the studies that fulfilled the criteria were entered into the Cochrane Collaboration Review manager package (RevMan 4.2). Heterogeneity between the studies was assessed with χ^2 test and the chosen summary statistic variable was the reduction in relative risk.

Results

17 randomised controlled trials were identified in which atenolol was used in one of the treatment arms of hypertension (panel). Five studies were excluded since atenolol was one of two or more drug alternatives in the same treatment arm.[9–13] One was excluded since it compared multidrug strategies rather than individual agents.[14] Three studies were excluded since atenolol was an add-on drug.[15–17]

Panel: **Trials identified by search criteria**

Included trials comparing atenolol with placebo or no treatment

HEP (Treatment of Hypertension in Elderly Patients in Primary Care)[20]
Elderly hypertensive patients (aged 60–79 years) randomised to atenolol or control. Open study with untreated control group. Thiazide diuretics were added in 60% of the patients in the atenolol group.

Dutch TIA Trial (The Dutch Transitory Ischemic Attack trial)[18]
Patients with TIA or minor stroke randomised to atenolol or placebo. Not all patients were hypertensive but baseline mean blood pressure was 157/91 mm Hg.

TEST (Tenormin after Stroke and TIA)[19]
Patients with previous TIA or minor stroke and blood pressure over 140/85 mm Hg were randomised to atenolol or placebo.

MRC Old (Medical Research Council trial of treatment of hypertension in older adults)[2]
Patients aged 65–74 years randomised to treatment with atenolol, hydrochlorothiazide, or placebo. Thiazide diuretics were added in 16% of the patients in the atenolol group.

Included trials comparing atenolol with other antihypertensive drugs

MRC Old (Medical Research Council trial of treatment of hypertension in older adults)[2]
Patients aged 65–74 years randomised to treatment with atenolol, hydrochlorothiazide or placebo. Thiazide diuretics were added in 16% of the patients in the atenolol group.

UKPDS (UK Prospective Diabetes Study)[3]
Hypertensive patients with type 2 diabetes randomised to treatment with atenolol or captopril.

ELSA (European Lacidipine Study on Atherosclerosis)[22]
The primary aim of the study was to compare the effects of the calcium antagonist lacidipine with atenolol on carotid intima-media thickness in hypertensive individuals. During the study, 142 cardiovascular endpoints were recorded.

HAPPHY (The Heart Attack Primary Prevention in Hypertension trial)[21]
Hypertensive patients randomised to treatment with a β blocker or a diuretic. Individual centres used either only atenolol or only metoprolol in the β-blocker arm (and either only bendroflumethiazide or only hydrochlorothiazide in the diuretic arm). The results from all centres were published together. The only exception is all-cause mortality for which data have been published for atenolol versus diuretic.[23]

LIFE (The Losartan Intervention For Endpoint reduction study)[4]
Patients with hypertension and left ventricular hypertrophy randomised to losartan or atenolol.

Excluded trials where atenolol was one of many first-line drugs in the same treatment arm

STOP (The Swedish Trial in Old Patients with Hypertension)[9]
Elderly patients randomised to antihypertensive therapy or placebo in a double-blind design. Different centres used either atenolol, metoprolol, pindolol, or hydrochlothiazide/amiloride as the first drug.

STOP-2 (The Swedish Trial in Old Patients with Hypertension-2)[10]
Elderly patients were randomised to treatment with an ACE inhibitor, a calcium antagonist, or conventional therapy. Conventional therapy included one of atenolol, metoprolol, pindolol, or hydrochlorothiazide/amiloride according to the investigators' preferences.

CAPPP (The Captopril Prevention Project)[11]
Hypertensive subjects were randomised to either treatment with captopril or other therapy with any diuretic or β blocker, mainly bendroflumethiazide, hydrochlorothiazide, atenolol, or metoprolol.

NORDIL (The Nordic Diltiazem study)[12]
Hypertensive subjects were randomised to treatment with diltiazem or other therapy with any diuretic or β blocker.

CONVINCE (The Controlled Onset Verapamil Investigation of Cardiovascular End Points trial)[13]
Patients were randomised to treatment with verapamil or either atenolol or hydrochlorothiazide according to the investigators' preference for each individual.

INVEST (The International Verapamil-Trandolapril Study)[14]
Patients with hypertension and coronary heart disease were randomised to verapamil with the addition of trandolapril or to atenolol with the addition of hydrochlorothiazide. INVEST was, however, intended to compare multidrug strategies rather than individual agents.

Excluded trials where atenolol was a second-line drug

SHEP (The Systolic Hypertension in the Elderly Program)[15]
Elderly patients randomised to chlortalidone or placebo. Atenolol was the second-line drug after chlortalidone.

INSIGHT (The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment)[16]
Hypertensive patients were randomised to treatment with nifedipine or hydrochlorothiazide/amiloride. Atenolol was the second-line drug in both treatment groups.

ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[17]
Hypertensive patients were randomised to treatment with chlortalidone, amlodipine, lisinopril, or doxazosin.[24,25] If the blood pressure goal was not reached with the first line drug, atenolol was one of the three second-line drugs used in all four treatment arms.

TIA=transient ischaemic attack. ACE=angiotensin-converting enzyme.

In two studies that were included,[18,19] the population of interest was patients with stroke and in both these studies most patients were hypertensive. Of the eight studies included in the meta-analyses, one had three treatment arms and compared atenolol both with placebo and with a thiazide diuretic.[2] Three studies compared atenolol with placebo,[18,19] or with untreated controls,[20] and in the other four studies,[3,4,21,22] atenolol was compared with another antihypertensive drug.

Studies comparing atenolol with placebo or no treatment are described in the table and the outcome of the meta-analyses is shown in figure 1. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the four studies comprising 6825 patients who were followed up for a mean of 4·6 years, in the effect on all-cause mortality (relative risk 1·01 [95% CI 0·89–1·15]), cardiovascular mortality (0·99 [0·83–1·18]), or myocardial infarction (0·99 [0·83–1·19]). The stroke risk tended to be lower in the atenolol group than in controls (relative risk 0·85 [0·72–1·01]). The study with the most prominent impact on stroke outcome was the Hypertension in Elderly Patients trial (HEP), where active treatment reduced the risk of stroke by 43% by comparison with no treatment. Most patients (60%) randomised to active treatment with atenolol in that study were, however, also treated with other hypertensive drugs in addition to atenolol. The blood pressure difference between active and no treatment was also considerable in the HEP study (18/11 mm Hg), which was more than in the other studies listed (table).

Studies comparing atenolol with other antihypertensive drugs are described in the table and the outcome of the meta-analyses is shown in figure 2. There were no major differences in blood pressure lowering between the treatment arms. The meta-analysis showed a significantly higher mortality (relative risk 1·13 [95% CI 1·02–1·25]) with atenolol treatment than with other active treatment, in the five studies comprising 17 671 patients who were followed up for a mean of 4·6 years. Moreover, cardiovascular mortality tended to be higher with atenolol treatment (1·16 [1·00–1·34]) and the risk of stroke was more common with atenolol treatment (1·30 [1·12–1·50]).

Since the Losartan Intervention for Endpoint Reduction in Hypertension trial (LIFE) included about the same number of patients as the other listed studies together and hence had a great statistical impact on the overall analyses, a separate meta-analysis was done excluding the LIFE patients. As seen from figure 2, the differences between atenolol and the other antihypertensive treatments were similar with or without the LIFE patients.

Discussion

The present analysis casts doubts on atenolol as a suitable first-line drug for hypertensive patients. Moreover, it challenges the use of atenolol as a reference drug in outcome trials in hypertension. It is noteworthy that the superiority of atenolol over placebo or no treatment in reducing blood pressure did not result in a beneficial effect on mortality or myocardial infarction. The only study showing an advantage for atenolol was the open HEP study, in which one of the outcome variables—ie, stroke—was reduced by 43% in comparison with no treatment. However, in that study less than 20% of the patients in the atenolol group were treated with atenolol as monotherapy, and the blood pressure difference between the two study groups was considerable. When atenolol was compared with several other antihypertensive drugs, it was worse than the other drugs except in prevention of myocardial infarction, when the outcome was similar.

The blood pressure lowering effect of atenolol is not less than that of other antihypertensive drugs.[26,27] There are, however, other characteristics of atenolol that might explain the findings of the present meta-analyses. First,

Study acronym	Publication year	Number of patients	Mean age (years)	Follow-up (years)	Atenolol dose (mg)	Comparison drug	Baseline blood pressure (mm Hg)	Mean blood pressure change with atenolol (systolic/diastolic [mm Hg])
Atenolol *vs* placebo or no treatment								
HEP[20]	1986	884	68·8	4·4	100	Open control	197/99	−18·0/−11·0
MRC Old[2]	1992	3748	70·3	5·8	50–100	Placebo	183/91	−13·5/−7·0*
Dutch TIA[18]	1993	1473	52% >65 years	2·6	50	Placebo	158/91	−5·8/−2·9†
TEST[19]	1994	720	70·4	2·6	50	Placebo	161/89	−4·0/−3·0‡
Total		6825	70·0¶	4·6				
Atenolol *vs* other antihypertensive treatment								
HAPPHY[21]	1988	3203	52·2‡	3·0	100	hctz 50 mg or bftz 5 mg	166/107	0/−1·0§
MRC Old[2]	1992	2183	70·3	5·8	50–100	hctz 25 mg	183/91	−1·0/0·5*
UKPDS[3]	1998	758	56·2	9	50–100	Captopril 50–100 mg	159/94	−1·0/−1·0
LIFE[4]	2002	9193	66·9	4·8	50–100	Losartan 50–100 mg	174/99	1·1/0·2
ELSA[22]	2002	2334	56·0	3·75	50–100	Lacidipine 4–6 mg	163/101	−0·2/0·1
Total		17 671	62·8	4·6				

hctz=hydrochlorothiazide. bftz=Bendroflumethiazide. *Data estimated from figure in reference 2, 60 months after randomisation. †Data from reference 18, 4 months after randomisation. ‡Data from reference 19, 1 month after randomisation. §Data for atenolol, metoprolol, and propranolol together. ¶Excluding the Dutch TIA trial.

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

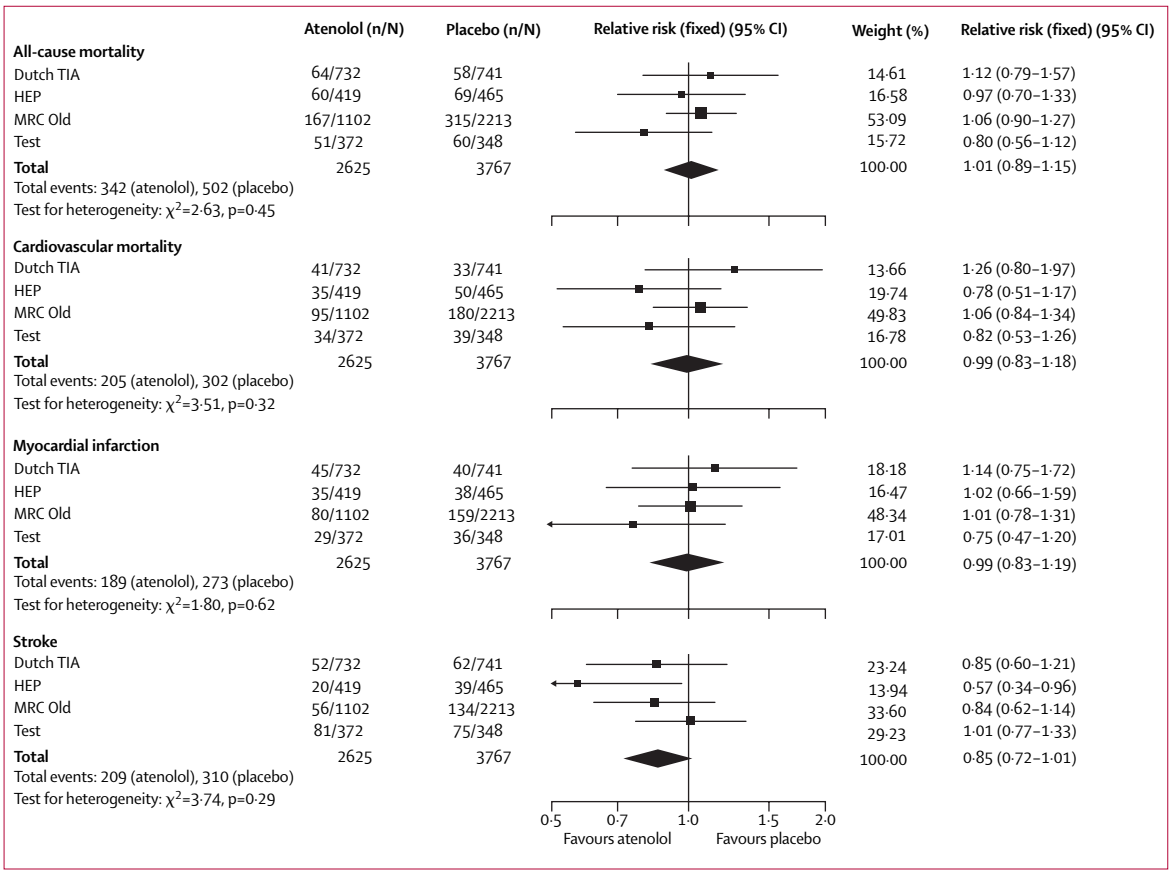

Figure 1: **Outcome data for atenolol versus placebo or no treatment**
n=number of patients with events. N=total number of patients. In the TEST study,[19] myocardial infarction was calculated as non-fatal myocardial infarction plus cardiac death.

atenolol differs from other β blockers in its low lipophilic profile. Data from studies in animals suggest that the ability to prevent ventricular fibrillation depends on the amount of β blocker in the central nervous system.[28,29] The hydrophilic atenolol has very low permeability into the nervous system. The positive outcome on coronary heart disease in the "extension" of one half of the HAPPHY trial, the MAPHY trial, in which metoprolol-based treatment was compared with thiazide-based treatment,[30] has been discussed on the basis of such pharmacological differences between β blockers.[31] A previous meta-analysis of studies on β blockers after myocardial infarction showed that metoprolol, timolol, and propranolol significantly prevented death in the long term.[8] Atenolol showed no such preventive effect and it was concluded that atenolol was inadequately evaluated for long-term use after myocardial infarction.[8] On the other hand, such a mechanism could hardly explain a lack of preventive effect on other cardiovascular complications.

Second, to our knowledge, the effect of atenolol on left ventricular hypertrophy has not been systematically assessed in long-term studies. The largest meta-analysis of the effect of different antihypertensive classes on left ventricular mass recently showed, however, that β blockers seemed to have less beneficial effect on regression of left ventricular hypertrophy than other drugs.[32] Third, many antihypertensive drugs correct the remodelling and endothelial dysfunction of small arteries seen in hypertension, but this finding has not been seen for atenolol.[33–35] In a recent investigation, researchers reported that when patients who were controlled for a long period on atenolol were switched to an angiotensin-1-receptor blocker, the arterial media/lumen diameter of resistance arteries decreased and endothelium-dependent relaxation increased.[36]

We did not analyse other β blockers. The effect of other β blockers in cardiac failure,[37,38] and after myocardial infarction, is well-documented.[8] However, in large hypertension trials, few researchers have specifically studied the outcome of different β blockers. Instead, β blockers were most often considered as a group,[6] which is also the case in hypertension guidelines.[1] In the Scandinavian studies, STOP,[9] CAPPP,[11] NORDIL,[12] and STOP-2,[10] it was not possible to split the β blockers into different types.

Hence, based on the results of our meta-analyses and on the effects of atenolol in other cardiovascular

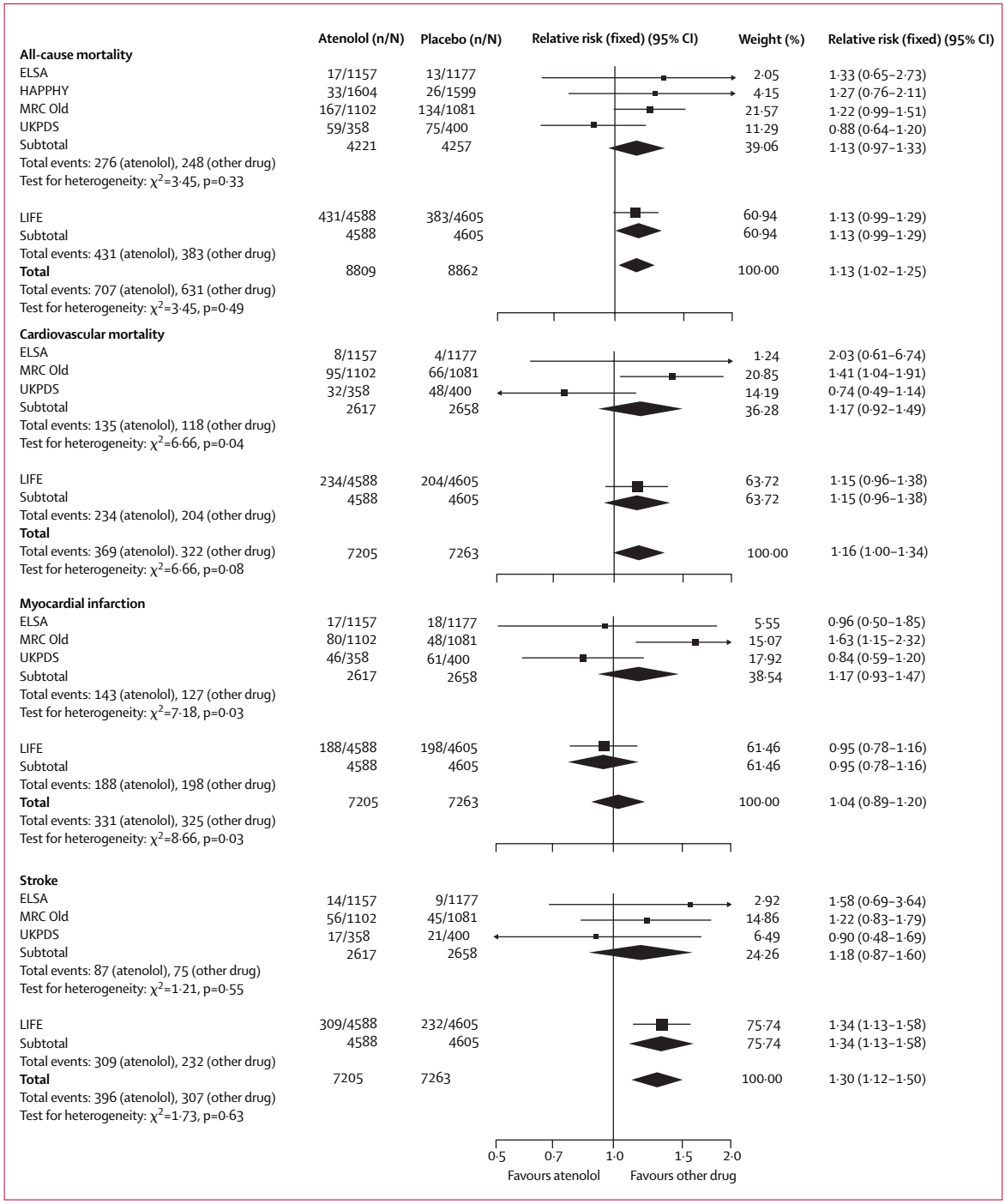

Figure 2: **Outcome data for atenolol versus other antihypertensive treatment**
n=number of patients with events. N=total number of patients.

disorders, we have doubts about the suitability of atenolol as a first-line antihypertensive drug and as a reference drug in outcome trials of hypertension.

Contributors

All authors contributed to data analysis and interpretation and wrote the report.

Conflict of interest statement

BC was a member of the ALPINE steering committee and the SCOPE clinical event committee, and has a local coordinating role in ASCOT. LHL received a research grant from AstraZeneca for ALPINE and was on the steering committee of LIFE. OS has received grants from the pharmaceutical industry (Parke-Davis and AstraZeneca), and is a member of AstraZeneca's CRESTOR Global Communications

Advisory Board. All authors are on the Working Group on High Blood Pressure of the Swedish Council on Technology Assessment (LHL chairs the hypertension group).

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