European Heart Journal (1999) **20,** 11–25
Article No. euhj.1998.1121, available online at http://www.idealibrary.com on IDEAL

Controversy

Treatment with beta-blockers for the primary prevention of the cardiovascular complications of hypertension

See page 5 for the Editorial comment on this article

Introduction

According to the 1997 guidelines from United States[1], diuretics and beta-blockers are classes of antihypertensive drugs that have been tested in long-term controlled clinical trials in hypertension and shown to reduce morbidity and mortality. Together with diuretics, beta-blockers are therefore recommended as first-line antihypertensive drugs, unless they are contra-indicated or unacceptable, or unless there are special indications for other agents.

In spite of these recommendations[1], the use of beta-blockers as first-line antihypertensive medication is declining worldwide[2,3], especially in older patients[3]. In 1995, beta-blockers accounted for only 11% of the antihypertensive drug prescriptions in the United States, compared with 18% in 1992. Over the same time span, the use of diuretics changed from 16% to 8%, that of angiotensin-converting enzyme inhibitors from 25% to 33%, and that of calcium channel blockers from 33% to 38%. Similarly, in elderly survivors of myocardial infarction, only 21% of eligible patients received a beta-blocker[4]. These observations show that, although expert committees recommended beta-blockers and diuretics for first-line treatment of hypertension, both drug classes are under-used. This article explores whether the published literature provides arguments in support of the resistance of physicians[5,6] to utilizing beta-blocker therapy.

Retrospective studies

In comparison with thiazides and the newer classes of antihypertensive drugs, beta-blockers effectively reduce blood pressure in hypertensive patients[7]. Several retrospective studies in hypertensive patients[8–16] have presented evidence suggesting that the incidence of fatal and non-fatal coronary heart disease is significantly lower in patients treated with beta-blockers than in untreated subjects or in patients taking other antihypertensive drugs.

In the Puget Sound case-control study[9], the crude estimate of the relative risk of hospitalization or death due to coronary heart disease in hypertensive patients treated with beta-blockers, compared with controls not receiving beta-blockers, was 0·71 (95% confidence interval: 0·52 to 0·97). After adjustment for the number of pharmacy visits, the relative risk of all coronary complications amounted to 0·87 (95% confidence interval: 0·62 to 1·21) and that of non-fatal myocardial infarction to 0·62 (95% confidence interval: 0·39 to 0·99)[9]. The demonstration of a dose–response relationship provided additional evidence that beta-blockers prevented non-fatal myocardial infarction in hypertensive patients[9].

In the British DHSS Hypertension Care Computing Project[15], men on beta-blockers had lower rates of total mortality and mortality from coronary heart disease. Their total mortality risk relative to men on alpha-methyldopa, was 0·64 (95% confidence interval: 0·41 to 0·98; $P<0·05$) and 0·74 (95% confidence interval: 0·47 to 1·16) compared with men on other treatments. For mortality from coronary heart disease, the corresponding relative risks were 0·55 (95% confidence interval: 0·30 to 1·00; $P=0·05$) and 0·77 (95% confidence interval: 0·41 to 1·46). In women, the lowest rates were observed in subjects on alpha-methyldopa, but the confidence limits for the risk ratios were wide. A subgroup analysis showed that the reduction in total mortality and mortality from coronary heart disease associated with beta-blockers was mainly due to the effect of the drug in non-smoking men.

Primary prevention in adult hypertensive patients

The MRC trial in middle-aged subjects

In the single-blind Medical Research Council's (MRC) trial, first published in 1985, 17 354 adult patients with

Key Words: Blood pressure, cardiovascular complications, coronary heart disease, hypertension, primary prevention, secondary prevention.

Revision submitted 17 April 1998, and accepted 29 April 1998.

Correspondence: Jan A. Staessen, MD, PhD, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

0195-668X/99/010011+20 $18.00/0

© 1999 The European Society of Cardiology

Table 1 Bendrofluazide and propranolol in the prevention of cardiovascular complications in the MRC trial in younger adults[17,18]

End-point	Bendrofluazide		Propranolol		Placebo	
	n†	Rate†	n	Rate	n	Rate
All cardiovascular events (p, 116)‡	140	6·6*	146	6·7*	352	8·2
Smokers#	65	10·6	84	14·0	157	13·2
Non-smokers	75	5·0	61	3·9*	193	6·3
Stroke (p, 103)‡	18	0·8*	42	1·9***	109	2·6
Smokers#	6	1·0*	26	4·3	48	4·0
Non-smokers	12	0·8*	16	1·0*	60	1·9
Coronary events (p, 111)	119	5·6	103	4·8	234	5·4
Smokers#	57	9·3	57	9·5	102	8·5
Non-smokers	62	4·1	45	2·9*	131	4·3
Sudden death (p, 114)	33	1·6	16	0·7**	45	1·1
Silent myocardial infarction (p, 81)¶	353	22·7*	271	16·8*,****	626	19·8
Overt coronary events plus silent myocardial infarction§	456	27·4	352	20·4*,****	814	23·9

†Number of events and age-adjusted rates (events per 1000 patient-years).
‡From Miall and Greenwood (p=page number[18]).
#Results for smokers and non-smokers were extracted from the first MRC report[17], and are given only if the interaction between smoking status and treatment was significant ($P \leq 0{\cdot}05$). Number of events in smokers and non-smokers do not always add up to the total, because smoking habits were not recorded at randomization in 76 people.
¶Electrocardiographic evidence of transmural myocardial infarction (Minnesota codes 1.1–1.3[19,20]).
§Data extracted[23].
Significance of differences: *$P \leq 0{\cdot}05$ vs placebo; **$P<0{\cdot}05$; ***$P<0{\cdot}01$; ****$P<0{\cdot}001$ vs bendrofluazide.

mild hypertension[17,18] were randomized to active treatment with either propranolol (up to 240 mg per day) or bendrofluazide (10 mg per day), or to placebo. Eligible patients were from 35 to 64 years old. At screening, their diastolic blood pressure ranged from 90 mmHg to 109 mmHg and their systolic blood pressure was lower than 200 mmHg. Active treatment reduced the incidence of all cardiovascular complications (286 vs 352 events; 6·7 vs 8·2 events per 1000 patient-years; $P<0{\cdot}05$) and stroke (60 vs 109 strokes; 2·6 vs 1·4 strokes per 1000 patient-years; $P<0{\cdot}001$). Active treatment, however, made no difference to the occurrence of coronary events (222 vs 234 events; 5·2 vs 5·5 events per 1000 patient-years).

Further post hoc and subgroup analyses were carried out, but require cautious interpretation[17]. Comparison of the two active drugs showed that the stroke rate was reduced in both smokers and non-smokers taking bendrofluazide, but only in the non-smokers of the propranolol group (Table 1). The difference between bendrofluazide and propranolol in this regard was statistically significant ($P=0{\cdot}03$). On the other hand, the rates of coronary and cardiovascular events were not significantly affected in smokers and non-smokers on bendrofluazide or in smokers randomized to propranolol. However, in non-smokers on propranolol, the latter complications diminished significantly in comparison with the non-smokers randomized to placebo (Table 1).

Further analyses[18] focused on the electrocardiographic changes compatible with transmural myocardial infarction[19,20], including silent as well as overt events (Table 1). As in the Framingham study[21] both types of infarctions were associated with poorer prognosis[22,23]. Compared with placebo, propranolol significantly reduced the incidence of silent myocardial infarction by 15%, while in patients randomized to bendrofluazide the rate increased by 15%. Sudden death was also significantly higher on the diuretic, with a trend for reduction on propranolol. If overt coronary events and silent myocardial infarction were pooled, their combined incidence in the propranolol group was 15% and 26% lower than in the patients randomized to placebo or bendrofluazide, respectively[23].

The IPPPSH trial

The International Prospective Primary Prevention Study in Hypertension (IPPPSH)[24] was a randomized double-blind trial conducted in 6357 men and women, aged 40 to 64 years, with uncomplicated hypertension (diastolic blood pressure: 100–125 mmHg). At the start of the study, 3185 patients received antihypertensive treatment based on oxprenolol (retard tablets of 160 mg), a non-selective beta-blocker with intrinsic sympathomimetic activity[25], while in the remaining 3172 patients oxprenolol was replaced by placebo. The study medication could be increased; other open-label non-beta-blocking antihypertensive drugs could also be added to the study medication with the aim of reducing the diastolic blood pressure to the target level of 95 mmHg or less.

Table 2 Cardiac events on antihypertensive treatment starting with oxprenolol or placebo in the IPPPSH trial[24]

Subgroup	Oxprenolol		Placebo	
	n†	Rate†	n	Rate
Men				
Smokers	34	18·1	25	14·5
Non-smokers	20	5·4	39	11·6
Women				
Smokers	8	6·6	8	8·0
Non-smokers	17	4·1	9	2·1

†Number of events and rates (events per 1000 patient-years). The value of *P* for the interaction between treatment and smoking status was 0·007 in men and 0·32 in women. The overall effect of treatment was nonsignificant in both sexes.

Table 3 End-points observed on antihypertensive treatment starting with thiazide or beta-blocker in the HAPPHY trial[26]

End-point	Thiazides		Beta-blockers	
	n†	Rate†	n	Rate
Coronary heart disease	116	9·5	132	10·6
Smokers‡	61	14·7	70	16·3
Non-smokers	54	6·9	60	7·6
Stroke	41	3·4	32	2·6
Smokers	20	4·8	17	4·0
Non-smokers	20	2·6	14	1·8
Total mortality	101	8·2	96	7·7
Smokers	58	14·0	52	12·1
Non-smokers	40	5·1	43	5·5

†Number of events and rates (events per 1000 patient-years).
‡Number of events in smokers and non-smokers do not always add up to the total, because smoking habits were not recorded at randomization in 72 people. The interaction terms between treatment and smoking were non-significant.

Additional drugs prescribed in the oxprenolol and placebo groups were either diuretics (34%), sympatholytic agents (2%) or vasodilators (1%) used in monotherapy, or various combinations of these drugs (41%). Total diuretic use was 67% in the oxprenolol patients and 82% in the control group.

The patients were followed for 3 to 5 years. Compared with the control group, the patients randomized to oxprenolol fared equally well with respect to sudden death (relative risk: 1·08; 95% confidence interval: 0·68 to 1·72), myocardial infarction (relative risk: 0·83; 95% confidence interval: 0·59 to 1·16) and cerebrovascular accidents (relative risk: 0·97; 95% confidence interval: 0·64 to 1·47). In patients smoking at randomization, the cardiac event rate was twice as high as in non-smokers[24]. Further analysis suggested that in men, but not women, the prevention of cardiac events by beta-blockade depended on smoking status (Table 2). Compared with the group started on placebo, the incidence of sudden death and fatal and non-fatal myocardial infarction was reduced in non-smoking men, but not in smoking men randomized to oxprenolol[24].

The HAPPHY trial

The Heart Attack Primary Prevention in Hypertension (HAPPHY) trial[26] had an open randomized design with blinded end-point evaluation. Initially, the patients were randomized to metoprolol (200 mg per day) or a thiazide diuretic (hydrochlorothiazide 50 mg per day or bendroflumethiazide 5 mg per day). The first patients were randomized in March 1976. Two years later, the protocol of the ongoing trial was changed, so that centres wishing to randomize patients to either the beta-blocker atenolol or to one of the two thiazide diuretics could also take part. Of the 184 centres, 70 used metoprolol. The first-line drugs, either a beta-blocker or a thiazide, were not to be crossed over or to be given together. However, for ethical reasons, at the discretion of the physician in charge, patients with non-fatal myocardial infarction in the diuretic group qualified for treatment with a beta-blocker, and patients with heart failure randomized to a beta-blocker were entitled to be started on diuretics. If the first-line antihypertensive drugs did not achieve blood pressure control, defined as a diastolic blood pressure of less than 95 mmHg, hydralazine (75–150 mg per day) and spironolactone (75–100 mg per day) could be started as second-line and third-line medications. In resistant patients, other drugs could also be employed.

The HAPPHY trialists recruited 6569 men, from 40 to 64 years old, with untreated diastolic blood pressure averaging between 100 and 130 mmHg (four readings on two different occasions). Patients with a history of myocardial infarction, angina pectoris or stroke were not eligible for recruitment. Follow-up averaged nearly 4 years. Of the patients randomized to diuretics (n=3272) and beta-blockers (n=3297), 83·4% and 85·9% remained on the scheduled treatment, 24·2% and 21·0% were prescribed hydralazine as second-line drug, and 5·2% in both groups had spironolactone as third-line treatment. About 4% in both the diuretic and the beta-blocker group were on the opposite drug, and 3% were on drugs other than those foreseen by the protocol.

Compared with diuretics, beta-blockers showed similar effects on the incidence of fatal and non-fatal coronary heart disease (relative risk: 0·88; 95% confidence interval: 0·68 to 1·14), fatal and non-fatal stroke (relative risk: 1·29; 95% confidence interval: 0·82 to 2·04), total mortality (relative risk: 1·06; 95% confidence interval: 0·80 to 1·41) and all trial end-points combined (relative risk: 1·00; 95% confidence interval: 0·83 to 1·21)[26]. The percentage of patients withdrawn due to side effects was similar in both treatment groups. Subgroup analyses did not detect any differences in the effects of beta-blockers compared with diuretics in smokers as opposed to non-smokers (Table 3).

Table 4 Total mortality on antihypertensive treatment starting with thiazides or metoprolol in the MAPHY trial[27]

Follow-up time	Thiazides		Metoprolol		*P*-value#
	n†	Rate†	n	Rate	
842 days	27	7·3	15	4·1	0·073
Smokers	16	13·5	5	4·1	0·020
Non-smokers	11	4·6	10	4·2	0·83
Median follow-up (4·2 years)	54	9·3	28	4·8	<0·01
Smokers	31	16·9	15	7·9	0·016
Non-smokers	23	6·1	13	3·4	0·093
End of study	83	10·3	65	8·0	0·028¶
Smokers	50	19·7	35	13·2	0·013¶
Non-smokers	33	6·3	30	5·7	0·40

†Number of events and rates (events per 1000 patient-years).
#Significance of the difference between the metoprolol and thiazide group.
¶*P*-values reported[27]; the other *P*-values were calculated by comparing the death rates as described[113].

The MAPHY trial

The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial[27] was published after the HAPPHY study[26], but both trials shared 3234 patients. Indeed, when the HAPPHY trial closed on 31 December 1985, 66 of the 70 centres using metoprolol, decided to continue follow-up of their patients with the aim of collecting more data on the possible cardiovascular protective effects of metoprolol. No information about end-points was available at the time of the decision to continue the trial.

In the MAPHY trial[27], eligible (see HAPPHY[26]) patients were randomized to metoprolol, a beta$_1$-selective agent or a thiazide diuretic. The 3234 patients were followed for at least 842 days or until they died. Median follow-up was 4·2 years with a maximum of 10·8 years. The daily dose of metoprolol averaged 174 mg and those of hydrochlorothiazide and bendroflumethiazide 46 mg and 4·4 mg, respectively. At the last follow-up visit, 11·6% of the patients randomized to diuretics were reported to be receiving beta-blockade; the corresponding proportion using diuretics in the metoprolol group was 6·3%.

Total mortality (65 vs 83 deaths; $P=0·028$; Table 4) and cardiovascular mortality (42 vs 57 deaths; $P=0·012$) were significantly lower in the metoprolol group than in the patients randomized to diuretics[27]. In addition, in the metoprolol group, fewer patients died from coronary heart disease (36 vs 43; $P=0·048$) or stroke (two vs nine; $P=0·043$). Non-cardiovascular mortality was similar in the metoprolol and the diuretic group (23 vs 26 deaths). Results on non-fatal end-points or combined fatal and non-fatal complications were not presented. Total mortality was significantly ($P=0·013$) lower in smokers randomized to metoprolol than in smokers randomized to diuretics (Table 4). However, at median follow-up, the same trend ($P=0·09$; Table 4) was also observed in non-smokers.

Further analysis[28] demonstrated that the reduction of cardiovascular mortality in the metoprolol group could, to a large extent, be explained by a decrease of sudden cardiovascular deaths, occurring within 24 h after the onset of symptoms. At median follow-up the number of such events was 12 (2·1 per 1000 patient-years) in the metoprolol group and 28 (4·8 per 1000 patient-years) in the patients randomized to diuretics. At the end of follow-up, these numbers were 32 (3·9 per 1000 patient-years) and 45 (5·6 per 1000 patient-years), respectively ($P=0·17$).

The HAPPHY[26] and MAPHY[27] trials shared a substantial proportion of the collected patient-years. However, the HAPPHY steering committee was of the opinion that the two studies were separate trials[29], because in MAPHY end-points were in part redefined, collected separately, and evaluated by a different and independent end-point committee. In addition, the HAPPHY steering committee underscored that in the HAPPHY trial the patients were not randomized to atenolol or metoprolol, but to one of two beta-blockers or a diuretic. This firmly militated against any direct comparison between the two beta-blockers or the two thiazide diuretics used in the HAPPHY trial[29].

Meta-analyses

Both the MRC trial[17,18] and the IPPPSH[24] study showed a tendency in men for beta-blocker therapy to be associated with a lower incidence of coronary events as compared with placebo[17,18] diuretic-based treatment[17,18] or antihypertensive drug treatment not including a beta-blocker[24]. The combined results in men showed an 18% reduction in total mortality and a 21% reduction in the pooled incidence of fatal and non-fatal coronary events[30,31].

In a second meta-analysis[29], the results of the MRC[17,18], IPPPSH[24] and HAPPHY[26] trials, with

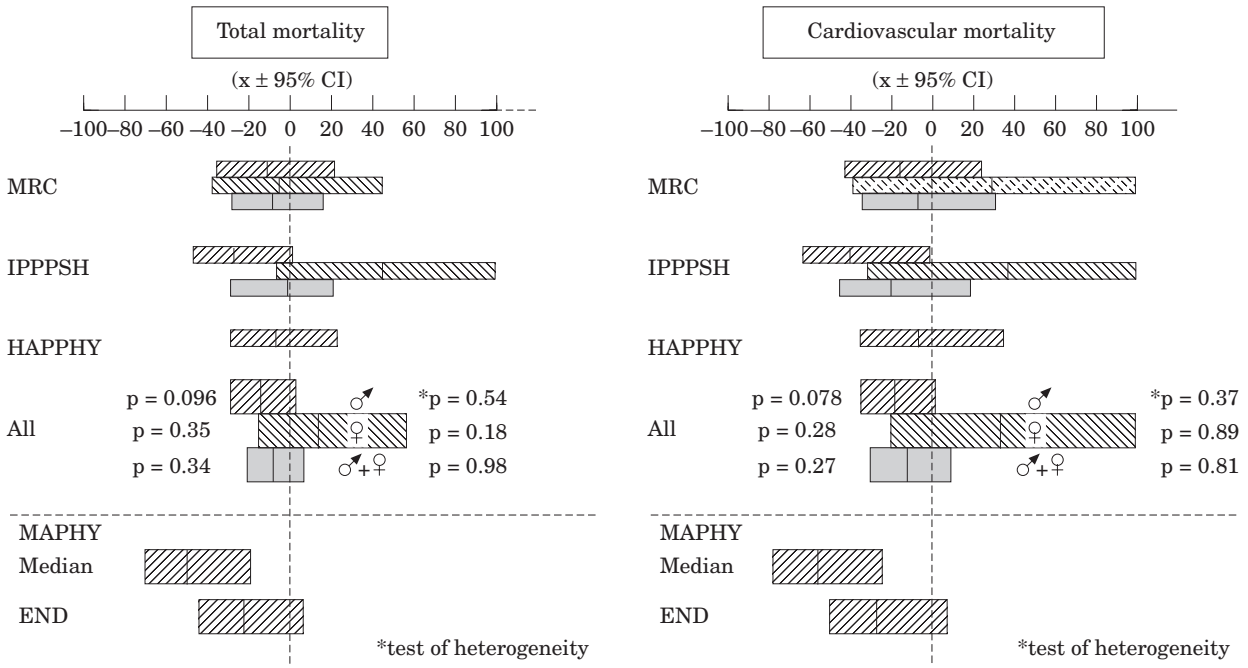

Figure 1 **Percentage difference (point estimates and 95% confidence intervals) in total (left) and cardiovascular (right) mortality between beta-blocker-based and diuretic-based antihypertensive treatment in various trials and in two sexes. For the Medical Research Council (MRC) study[17,18], the placebo group was not considered. For the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study[27], statistics refer to median and total (end of study) follow-up. In the meta-analysis (ALL), the results of three trials were combined (the MRC trial[17,18], the International Prospective Primary Prevention Study in Hypertension [IPPPSH][24], and the Heart Attack Primary Prevention in Hypertensives [HAPPHY] trial[26]). Reproduced with permission[29].**

regard to total and cardiovascular mortality, were pooled (Fig. 1). In men, antihypertensive treatment initiated with beta-blockade compared with a regimen mainly based on diuretics, tended to decrease total mortality by 14% (95% confidence interval: −28% to +3%; $P=0{\cdot}096$) and cardiovascular mortality by 19% (95% confidence interval: −36% to +2%; $P=0{\cdot}078$). In women, the relative changes in total and cardiovascular mortality in the beta-blocker group amounted to +16% (95% confidence interval: −15% to +56%; $P=0{\cdot}35$) and +32% (95% confidence interval: −20% to +119%; $P=0{\cdot}28$), respectively.

Primary prevention in elderly hypertensive patients

The HEP trial

Coope and Warrender recruited for the HEP (Hypertension in the Elderly Prevention) trial 884 older (60–79 years) hypertensive patients from 13 general practices in England and Wales[32,33]. Eligible patients maintained a blood pressure of at least 170 mmHg systolic or 105 mmHg diastolic at three consecutive run-in visits. According to an open design, the patients were randomized to active treatment or untreated follow-up. The antihypertensive agents were stepwise adjusted to reduce the blood pressure below 170 mmHg systolic and 105 mmHg diastolic. The first-line agent was atenolol 100 mg in the morning. In a second step, 5 mg bendrofluazide could be added. If atenolol and bendrofluazide failed to lower blood pressure, 500 mg alpha-methyldopa could be given in a single dose in the evening. Patients on active treatment, who did not respond or who developed unacceptable side-effects, could be started on any other recognized antihypertensive agent. During the last 2 years of the trial, treatment-resistant patients received nifedipine, usually prescribed as nifedipine retard 20 mg twice daily. Patients in the control group who developed sustained blood pressures above 280 mmHg systolic or 120 mmHg diastolic or who suffered strokes or cardiac complications, such as left ventricular failure, could be treated.

The blood pressure at entry averaged 196 mmHg systolic and 99 mmHg diastolic. Of the patients randomized to active treatment (n=419), 70% were on atenolol, 60% on bendrofluazide, 7% on bendrofluazide only, and 5% were on no treatment throughout most of the study. In the control group (n=465), 2% were put on antihypertensive drugs because of a rise in blood pressure above 280 mmHg systolic or 120 mmHg diastolic, and 7% were started on diuretics because of left ventricular failure. There was a consistent blood pressure difference of about 18 mmHg systolic and 11 mmHg diastolic between the two groups. Active treatment reduced the incidence of fatal stroke by 70% (95% confidence

Table 5 Bendrofluazide or atenolol in the prevention of cardiovascular complications in the MRC trial in older adults[34]

End-point	Bendrofluazide		Atenolol		Placebo	
	n†	Rate†	n	Rate	n	Rate
All cardiovascular events‡	107	17·4§	151	24·6	309	25·2
Smokers	37	29·6	55	44·4	84	32·2
Non-smokers	70	14·3	96	19·6	225	23·3
Stroke‡	45	7·3**	56	9·0	134	10·8
Smokers	17	13·5	17	13·5	29	10·9
Non-smokers	28	5·7	39	7·9	105	10·7
Coronary events	48	7·7****	80	12·8	159	12·7
Smokers	13	10·1	28	21·9	46	17·4
Non-smokers	35	7·1	52	10·5	113	11·4
Total mortality#	134	21·3	167	26·4	315	24·7
Smokers	39	30·0	68	52·3	98	36·2
Non-smokers	95	19·1	99	19·7	217	21·6

†Number of events and rates (events per 1000 patient-years).
‡Interaction ($P \leq 0{\cdot}04$) between active treatment (bendrofluazide and atenolol groups combined) and smoking status.
#Interaction ($P = 0{\cdot}04$) between type of active treatment and smoking status.
Significance of differences versus placebo: **$P<0{\cdot}05$; ****$P<0{\cdot}001$.

interval: −89% to −16%; $P<0{\cdot}025$) and that of all strokes by 42% (95% confidence interval: −65% to −4%; $P<0{\cdot}03$). In contrast, active treatment did not influence the incidence of coronary attacks (+3%; 95% confidence interval: −37% to +67%), non-fatal heart failure (−37%; 95% confidence interval: −65% to +11%) or cardiovascular mortality (−22%; 95% confidence interval: −49% to +20%).

The MRC trial in older hypertensive patients

The MRC trial in older adults[34] included 4396 patients from 65 to 74 years old, who were recruited at general practices and randomized to receive beta-blockade, diuretic treatment, or placebo. Eligible patients had mean systolic blood pressures ranging from 160 mmHg through 209 mmHg and mean diastolic blood pressures of less than 115 mmHg during an 8-week run-in period while not taking antihypertensive treatment.

An early substudy assessed blood pressure control and biochemical effects of two different dose regimens of diuretics, either hydrochlorothiazide 50 mg per day combined with 5 mg amiloride, or hydrochlorothiazide 25 mg per day combined with 2·5 mg amiloride. As a result, all patients randomized to diuretic treatment were eventually transferred to the lower dose. The daily dose of atenolol was 50 mg, but was doubled to 100 mg in 20% of the patients. When further blood pressure control was necessary, the alternative trial drug was used to supplement the active drug allocated by randomization. After this, the calcium channel blocker nifedipine in doses of up to 20 mg daily or other supplementary drugs could be prescribed.

After randomization, systolic and diastolic blood pressures fell promptly in all groups, with the greatest systolic fall in the first 3 months occurring in the diuretic group. After 2 years, however, the two groups on active treatment had similar systolic and diastolic blood pressures, which were approximately 20 mmHg and 10 mmHg lower than in the placebo group. More patients randomized to the beta-blocker required supplementary drugs than those randomized to the diuretic (52% vs 38%). Overall, the beta-blocker group had significantly more withdrawals than the diuretic group, both for suspected major side-effects and for inadequate blood pressure control. Patients randomized to atenolol, compared with the bendrofluazide group, were withdrawn significantly more because of Raynaud phenomenon (11·3 vs 0·6 withdrawals per 1000 patient-years), dyspnoea (22·9 vs 0·8), lethargy (19·1 vs 4·1), headache (7·2 vs 2·5), or low pulse rate (28·0 vs 0·0)[34].

Compared with the placebo group, the diuretic and beta-blocker groups combined experienced a 25% reduction in stroke (95% confidence interval: −42% to −3%; $P=0{\cdot}04$), a 19% reduction in coronary events (95% confidence interval: −36% to +2%; $P=0{\cdot}08$), and a 17% reduction in all cardiovascular events (95% confidence interval: −2 to −29%; $P=0{\cdot}03$). After adjusting for the baseline characteristics, the diuretic group had significantly reduced risks of stroke (−31%; 95% confidence interval: −3% to −51%; $P=0{\cdot}04$), coronary events (−44%; 95% confidence interval: −21% to −60%; $P<0{\cdot}001$), and cardiovascular events (−35%; 95% confidence interval: −17% to −49%; $P<0{\cdot}001$). In contrast, the beta-blocker group showed no significant decrease in these end-points (Table 5). However, these findings are difficult to interpret, because 38% of the diuretic group and 52% of the beta-blocker group received the alternative active drug.

The rates of every end-point were raised in smokers compared with non-smokers (Table 5). Smokers and non-smokers differed in their response to active

treatment with respect to the prevention of stroke ($P=0{\cdot}04$) and all cardiovascular events ($P=0{\cdot}03$). In both groups, the decrease in end-points in patients receiving active treatment was confined to the non-smokers. Furthermore, the association between beta-blocker treatment and deaths from all causes was significantly modified by smoking when compared with the corresponding association in the diuretic group ($P=0{\cdot}04$; Table 5). However, conclusions about possible interactions between smoking status and type of antihypertensive treatment should be considered with caution. In this single-blind trial, 53%, 48% and 63% of randomized patients withdrew or were lost to follow-up in the placebo, diuretic and beta-blocker arm, respectively. These losses may bias any of the results reported, in particular the subgroup analyses, for which the patients had not been randomized.

The STOP-Hypertension trial

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension)[35] was a randomized double-blind intervention study, set up to compare the effects of beta-blockade, diuretic treatment or both drug classes with those of placebo on the combined incidence of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction and other cardiovascular mortality in patients from 70 to 84 years old. During a 1-month run-in period on masked placebo, at three separate measurements in the supine position eligible patients maintained a systolic blood pressure between 180 and 230 mmHg with a diastolic blood pressure of at least 90 mmHg, or a diastolic blood pressure between 105 and 120 mmHg, irrespective of the systolic blood pressure. A total of 1627 patients were randomized.

All study medications were given once daily. In the active treatment group, treatment consisted of atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2·5 mg. If the supine blood pressure, as defined above, was 160 mmHg systolic, or 95 mmHg diastolic, or higher after at least 2 months of treatment, the diuretic was added to any of the beta-blockers, or vice versa. In the placebo group, matching placebos were employed similarly. Each centre was free to choose any of the four basic active drug regimens, which had then to be maintained throughout the trial. If the supine blood pressure exceeded 230 mmHg systolic or 120 mmHg diastolic on two subsequent visits, the patient was changed to open-label antihypertensive drug treatment. However, after a non-fatal end-point, patients could continue on double-blind treatment.

Two-thirds of the actively treated patients received combined treatment. At the last evaluation before a primary end-point, death, or study termination, supine blood pressure averaged 186 mmHg systolic and 96 mmHg diastolic in the placebo group and 167 mmHg and 87 mmHg, respectively, in the active treatment group. The differences in systolic and diastolic blood pressures between the two groups were therefore 19·5 mmHg and 8·1 mmHg. At that time, 77% of the placebo group and 84% of the actively treated patients were still taking the double-blind medication.

Compared with placebo, active treatment reduced all primary end-points by 40% (95% confidence interval: −57% to −15%), all strokes by 47% (95% confidence interval: −67% to −14%), fatal strokes by 73% (95% confidence interval: −94% to −16%) and total mortality by 43% (95% confidence interval: −63% to −13%). In contrast, fatal myocardial infarction (−2%; 95% confidence interval: −74% to +266%) and fatal combined with non-fatal myocardial infarction (−13%; 95% confidence interval: −51% to +56%) were not significantly reduced in the patients randomized to active treatment. Furthermore, the older subgroup of patients randomized to active treatment, compared with the control group, experienced less reduction of stroke, myocardial infarction and cardiovascular mortality. The upper 95% confidence limit of the relative risk crossed unity at 73 years[35].

Trial in isolated systolic hypertension in the elderly

The patients randomized in the double-blind placebo-controlled Systolic Hypertension in the Elderly Program (SHEP) trial had a blood pressure of at least 160 mmHg systolic and less than 90 mmHg diastolic[36,37]. Active treatment consisted of 12·5 to 25 mg chlorthalidone per day with the possible addition of atenolol (25–50 mg . day^{-1}) or reserpine (0·05–0·1 mg . day^{-1}). At the 5-year visit, 46% of the actively treated patients were on diuretic treatment, but 23% were also taking atenolol alone or in combination with chlorthalidone.

In spite of the low entry diastolic blood pressure, which has been postulated to enhance the risk of coronary events[38], the SHEP investigators found that active treatment reduced the incidence of non-fatal myocardial infarction by 33% (95% confidence interval: −53 to −4%) and that of coronary heart disease (fatal and non-fatal myocardial infarction, sudden and rapid cardiac death and coronary artery bypass graft or angioplasty) by 25% (95% confidence interval: −40 to −6%). In the active treatment group, fatal and non-fatal stroke combined, the primary trial end-point, decreased by 36% (95% confidence interval: −50% to −18%; $P=0{\cdot}0003$) and non-fatal stroke alone by 37% (95% confidence interval: −51% to −18%). None of the fatal end-points, however, was significantly influenced by active treatment[36,37].

Evidence from other studies

Secondary prevention in postmyocardial infarction patients

The role of beta-blockers in the secondary prevention after acute myocardial infarction is well established. A meta-analysis[39] of 12 early (1972–1982) studies[40–51]

demonstrated that the results of each trial were compatible with a reduction of total mortality by beta-blockade of 20% to 30%. The benefit was mainly related to a decrease in cardiac mortality, in particular sudden death, while the incidence of reinfarction was also diminished. Subsequent quantitative reviews of 65[52] to 71[53] randomized short-term and long-term clinical trials confirmed that chronic (one year) beta-blockade after myocardial infarction reduced total mortality and non-fatal reinfarction by about 25% and sudden death by approximately 30%.

The meta-analyses also suggested that the early intravenous beta-blockade resulted in decreased mortality[52,53]. Studies in patients admitted to coronary care units with the suspected diagnosis of myocardial infarction demonstrated that the immediate intravenous administration of 5 to 10 mg atenolol, followed by 50 mg orally, if no undue hypotension or bradycardia developed, and subsequently by 7[54] to 10[55] days of oral treatment with 100 mg atenolol once daily, reduced enzyme release by 30%[55], significantly enhanced R-wave preservation[55], and reduced cardiovascular mortality by 15%[54].

In a retrospective cohort study including 5332 elderly ($\geq$65 year) survivors of myocardial infarction only 21% of the eligible patients received beta-blocker therapy[4]. Controlling for other predictors of survival, the mortality rate was 43% less (95% confidence interval: 31% to 63%) in the recipients of beta-blockers than in the non-recipients. Recipients of beta-blocker were also 22% less likely to be re-hospitalized (95% confidence interval: 10% to 33%)[4].

Beta-blockers still improve outcome in acute myocardial infarction when combined with interventions, such as coronary artery bypass surgery, percutaneous transluminal angioplasty or thrombolysis. However, high-risk patients may possibly benefit more from deferred beta-blockade, whereas low-risk patients may gain more from immediate intravenous treatment[56]. The benefit of beta-blockade is probably not only limited to patients with a recent history of myocardial infarction. Indeed, among the patients with chronic coronary heart disease, who have been screened for participation in the Bezafibrate Infarction Prevention study, 2723 had non-insulin dependent diabetes mellitus[57]. Of these, 911 (33·5%) were on beta-blocker treatment and 1812 (66·5%) did not receive such treatment. After adjustment for confounders, beta-blocker therapy was significantly and independently associated with a prolonged survival. The risk reduction in the beta-blocker group was 42% (95% confidence interval: 26% to 54%). Within the diabetic group, the largest benefit was observed in older patients, in those with a history of myocardial infarction and in patients with limited functional capacity[57].

Silent ischaemia

Asymptomatic or silent ischaemia detected by ambulatory electrocardiographic recording during routine daily life, is the most common form of coronary ischaemia[58]. Patients with silent ischaemia, in comparison with people without such symptom, are at increased risk[59–61]. The Atenolol Silent Ischemia Trial (ASIST)[62] was a double-blind, placebo-controlled trial, mounted to test the hypothesis that drug treatment would reduce the adverse outcome of patients with preexisting coronary heart disease and silent ischaemia. A total of 306 outpatients with mild or no angina (Canadian Cardiovascular Society class I or Il), abnormal exercise tests, and ischaemia on ambulatory monitoring were randomized to receive either atenolol, 100 mg daily, or placebo. Their mean (SD) blood pressure at entry was 139 (17) mmHg systolic and 81 (10) mmHg diastolic. These values suggest that the study group included a substantial number of hypertensive patients. The primary outcome measure was event-free survival at 1 year by Kaplan–Meier analysis. Events were death, resuscitated ventricular tachycardia or fibrillation, myocardial infarction, hospitalization for unstable angina, aggravation of angina, or revascularization. The secondary outcome was ischaemia during ambulatory electrocardiographic monitoring at 4 weeks.

After 4 weeks of treatment, the number (1·7 vs 3·1 events per 48 h; $P=0{\cdot}002$) and the average duration (16·4 vs 30·0 min per 48 h) of ischaemic episodes were less in the atenolol than the placebo group[62]. Event-free survival improved in atenolol-treated patients ($P<0{\cdot}007$), who had an increased time to onset of the first adverse event (120 vs 79 days) and fewer total first events compared with placebo (relative risk: 0·44; 95% confidence interval: 0·26 to 0·75; $P=0{\cdot}001$). There was a non-significant trend for fewer serious events (death, resuscitation from ventricular tachycardia or fibrillation, non-fatal myocardial infarction, or hospitalization for unstable angina) in atenolol-treated patients (relative risk: 0·55; 95% confidence interval: 0·22 to 1·33; $P=0{\cdot}18$)[62]. The most powerful univariate and multivariate correlate of event-free survival was the absence of ischaemia on ambulatory monitoring at 4 weeks. Thus, beta-blockade reduced daily life ischaemia and was associated with reduced risk for adverse outcome in asymptomatic and mildly symptomatic patients with coronary heart disease.

Beta-blockade in trials of antiarrhythmic drugs

The Cardiac Arrhythmia Suppression Trial (CAST)[63–65] showed that antiarrhythmic drug suppression of asymptomatic or mildly symptomatic ventricular arrhythmias in survivors of myocardial infarction was harmful. A retrospective analysis[66] of the CAST trial[63–65] demonstrated that at 30 days and at 1 and 2 years of follow-up, patients receiving optional beta-blocker treatment had a reduced overall mortality and experienced fewer arrhythmic deaths or non-fatal cardiac arrests. In a multivariate analysis, beta-blockade was independently associated with a one-third reduction in arrhythmic death and cardiac arrest ($P=0{\cdot}036$).

The European Myocardial Infarct Amiodarone Trial (EMIAT)[67] was a randomized double-blind placebo-controlled trial, which assessed whether amiodarone reduced all-cause mortality (primary end-point), cardiac mortality or arrhythmic death (secondary end-points). The median follow-up was 21 months. All-cause and cardiac mortality did not differ between the two groups, but in the amiodarone group arrhythmic deaths decreased by 35%. Of the 1486 patients, 44·2% were on beta-blocker treatment at randomization. With regard to cardiac mortality, there was a strong tendency towards a favourable interaction ($P=0·06$) between the use of a beta-blocker and amiodarone, which was independent of left ventricular function[67]. Furthermore, all-cause mortality, analysed by intention-to-treat, was reduced on amiodarone in patients on beta-blocker treatment, in those with an ejection fraction lower than 30%, with arrhythmia on the initial Holter registration, or with an initial heart rate higher than 75 beats per minute[68]. A multivariate analysis confirmed that these univariate effects were mutually additive[68].

The double-blind placebo-controlled Canadian Amiodarone Myocardial Infarction Trial (CAMIAT)[69] recruited 1202 survivors of acute myocardial infarction with frequent or repetitive ventricular premature depolarizations. The median follow-up was 21 months. Amiodarone reduced the incidence of resuscitated ventricular fibrillation and arrhythmic deaths. At randomization, 59·5% of the enrolled patients were on beta-blocker treatment. As in the EMIAT trial[67], there was a positive interaction between amiodarone and beta-blockade ($P=0·008$), suggesting that compared with placebo, amiodarone conferred benefit only in patients who also took beta-blockers[69].

Beta-blockade in heart failure trials

In CAST[63–65] patients with a history of congestive heart failure, beta-blocker treatment was independently associated with longer time to occurrence of new or worsened congestive heart failure ($P=0·015$)[66]. In a retrospective analysis of data[70] from the Survival and Ventricular Enlargement (SAVE) Study[71], with adjustments for baseline imbalances applied, beta-blocker use was associated with a 30% reduction of cardiovascular mortality (95% confidence interval: 12% to 44%) and a 21% decrease in the incidence of heart failure (95% confidence interval: 12% to 44%)[70]. These reductions were independent of the intake of captopril. In contrast, beta-blockade did not significantly influence the incidence of recurrent infarction[70].

The Cardiac Insufficiency Bisoprolol Study (CIBIS) was a double-blind placebo-controlled trial of bisoprolol in patients with chronic heart failure of various origins and a left ventricular ejection fraction below 40%. Bisoprolol is a cardioselective $beta_1$-blocker devoid of partial agonist or membrane stabilizing activity and possessing both lipophilic and hydrophilic properties[72]. The 641 randomized patients were in New York Heart Association functional classes III (95%) or IV (5%). Mean follow-up was 1·9 years. All patients received background treatment with diuretics and angiotensin converting enzyme inhibitors (90%) or other vasodilators. There were no differences between both groups in total mortality, sudden death, or death related to documented ventricular tachycardia or fibrillation. However, bisoprolol significantly improved the functional status of the patients. Fewer patients in the bisoprolol group required hospitalization for cardiac decompensation, and more patients improved by at least one New York Heart Association functional class by the end of the follow-up period. These findings are in line with earlier studies with metoprolol[73–75].

Sudden death

In an exhaustive evaluation of more than 400 original and review articles, of all therapies available for the prevention of sudden cardiac death, none was found to be more established or more effective than the use of beta-blockers[5]. The reviewers graded the evidence that beta-blockers exert a cardioprotective effects as compelling[5]. Moreover, based on their review of the literature, they concluded that beta-blockade probably reduces the rate of atheroma formation, decreases the risk of ventricular fibrillation in animal models of ventricular fibrillation, reduces cardiac mortality in primary prevention trials, and reduces mortality, particularly from sudden death, in patients with a history myocardial infarction.

Cardiac necrosis in patients with head injury

In a multicentre study[76], 114 haemodynamically stable patients with acute head injury were randomized to placebo or atenolol given intravenously (10 mg every 6 h) for 3 days and then orally (100 mg per day) for a further 4 days. Both groups were equally stressed as shown by raised arterial norepinephrine levels.

In patients receiving placebo, but not in those of the beta-blocker group, there was a significant ($P<0·01$) positive correlation between arterial norepinephrine and the levels of the myocardial isoenzyme of creatine kinase[76]. Fewer patients in the atenolol group showed circulating creatine kinase levels compatible with myocardial damage (7·4% vs 30·0%; $P<0·05$) or infarction (0% vs 16·7%; $P=0·05$). Furthermore, atenolol not only significantly reduced the likelihood of supraventricular tachycardia and ST-segment and T-wave changes, but also prevented cardiac necrosis observed at autopsy.

Ancillary properties of beta-blockers

Intrinsic sympathomimetic activity

In the secondary prevention trials in patients with myocardial infarction, the benefit appeared to be less in trials

with beta-blockers with intrinsic sympathomimetic activity than in studies with drugs without such activity (10% vs 30% reduction of total mortality; $P<0{\cdot}01$)[52,53]. Intrinsic sympathomimetic activity may accelerate heart rate[77,78] and increase blood pressure[78], especially at night when sympathetic tone is low. For these reasons, beta-blockers with intrinsic sympathetic activity may provide less protection against myocardial ischaemia[77] and cardiac mortality[52,53]. Nevertheless, in the Secondary Prevention after High-Risk Myocardial Infarction (ASPI) trial with acebutalol[79] (607 patients) and in the Multicenter International Study with practolol[80] (3053 patients) the administration of cardioselective $beta_1$-blockers with intrinsic sympathomimetic activity led to a 48% and 38% reduction in mortality, respectively. One could therefore speculate that intrinsic sympathomimetic activity may have deleterious effects in patients with myocardial infarction only if it is exerted at the level of the $beta_2$-receptors. The ensuing vasodilation could activate the baroreflex and stimulate the sympathetic nervous system. However, no comparative trials among various types of beta-blockers are available so that the latter hypothesis should be interpreted with restraint.

Lipophilicity vs hydrophilicity

The reduction of myocardial ischaemia and cardiac sympathetic activation are effects common to most beta-blockers. Furthermore, some investigators hypothesized that attenuation of stress-induced vagal withdrawal, and hence a beneficial increase in cardiac vagal tone, could play a role in preventing cardiac events, in particular sudden death[5,81]. According to this concept, lipophilic beta-blockers would be more effective in reducing cardiac mortality and sudden death, because they penetrate easily into the brain. Along similar lines, a recent meta-analysis proposed that lypophilicity would be associated with a greater reduction of cardiovascular risk[53]. However, for the 1-week mortality results in clinical trials with early intravenous administration of the beta-blocker, for total mortality in short-term and long-term clinical trials, and for reinfarction and sudden death in the long-term trials, the point estimates of the combined results for lipophilic compared with hydrophilic beta-blockers were largely similar and the widely overlapping confidence intervals seemed to exclude rather than to reveal differences among these two types of beta-blockers[53].

The hypothesis that lipophilicity would be required to protect against cardiac mortality and sudden death is also not substantiated by individual trial data. Indeed, the MIS trial[80] with practolol, a strongly hydrophilic compound, demonstrated a 38% reduction in cardiac mortality ($P<0{\cdot}01$) and a 44% reduction in sudden death ($P<0{\cdot}01$). Furthermore, a recent Chinese trial[82] in 1103 patients with myocardial infarction showed that the hydrophilic $beta_1$-blocker atenolol decreased sudden death by 68% ($P<0{\cdot}05$).

Parasympathetic cardiovascular modulation in human subjects may be measured through power spectral analysis of heart variability[83–85]. Several studies[85–91] with hydrophilic beta-blockers, in particular atenolol, demonstrated a significant increase in heart rate variability and its high frequency component. Four comparative trials[85–87,91] did not show any difference in this respect between atenolol and metoprolol, a lipophilic $beta_1$-blocker. One recently published trial actually revealed a significant difference in favour of the hydrophilic $beta_1$-blocker[87]. On balance, these findings[85–91] suggest that the parasympathetic cardiac protection ascribed to beta-blockade may well be peripherally mediated through direct interaction between the adrenergic and cholinergic receptors.

Cardioselectivity

In the secondary prevention trials in patients with recent myocardial infarction, cardioselectivity did not seem to confer any advantage over and above that of non-selective beta-blockade according to one meta-analyst[52], whereas the opposite conclusion was reached by a second reviewer[53]. However, these conclusions must be interpreted with great caution, because in the post-myocardial infarction trials patients were randomized to beta-blockade or placebo, but never to different classes of beta-blockers. Thus, the pooled estimates may reflect random variability among the trials rather than true therapeutic effects.

Comparisons between non-selective beta-blocking agents, such as propranolol[25], oxprenolol[92,93] and nadolol[92] and $beta_1$-selective agents, such as atenolol[94,95], metoprolol[96] and acebutolol[92,97,98], have demonstrated close similarities in their blood pressure lowering characteristics. However, $beta_1$-selective drugs may offer some advantages in hypertensive patients with concurrent conditions, such as obstructive airway disease, peripheral vascular disease and hyperlipidaemia[93]. At lower doses $beta_1$-blockers inhibit the cardiac $beta_1$-receptors, but not the bronchial and vascular $beta_2$-receptors, which mediate bronchodilatation and vasodilatation. Glycogenolysis and glucose release from the liver are also partially mediated via $beta_2$-receptor stimulation. For this reason, $beta_1$-selective agents seem to be preferred in diabetic patients, especially if they are using insulin or oral antidiabetic drugs, because the $beta_1$-selective drugs do not significantly delay recovery from hypoglycaemia[97,98].

Conclusions

The compelling reason for treating hypertension is to prevent the associated cardiovascular complications, in particular stroke, myocardial infarction, sudden death and heart failure. Before the publication of the Shangai Trial of Nifedipine in the Elderly (STONE)[99] and the Systolic Hypertension in Europe (Syst-Eur) trial[100], evidence from prospective randomized clinical trials

only favoured the use diuretics and beta-blockers as first-line agents in this therapeutic indication.

The evidence supporting the role of beta-blockers in the primary prevention of the cardiovascular complications of hypertension, stems mainly from randomized clinical trials in middle-aged[17,18,24,26,27] or older[32–37] hypertensive patients. Four trials showed that treatment largely based on beta-blockers with the possible addition of diuretics[17,18,32,33,35] or vice versa[36,37] was significantly better than placebo or no treatment. In other trials, beta-blockers were equally effective as diuretics[26] or therapy to a large extent based on diuretics or other sympatholytic agents[24]. In one trial[27,28], metoprolol was found to be more effective than a thiazide in reducing cardiovascular and total mortality and sudden death. With regard to the latter findings, the HAPPHY steering committee concluded that any apparent differences between atenolol and metoprolol were consistent with the play of chance[101]. The death rates in the HAPPHY study were lower in patients receiving atenolol than in those given metoprolol (6·9 vs 7·9 deaths per 1000 patient-years). However, the death rates in the diuretic arm randomized against atenolol were inexplicably lower than those in the diuretic arm randomized against metoprolol (5·5 vs 9·9 deaths per 1000 patient-years)[102]. In the MRC trial in older hypertensive patients[34], the beta-blocker conferred less protection than the diuretic. However, in the latter study[34] a larger proportion of the patients randomized to the beta-blocker was lost to follow-up or withdrawn, many of them because of a low pulse rate, a marker of effective beta-blockade (28·0 vs 0·0 withdrawals per 1000 patient-years). Patients with a history of myocardial infarction within 3 months before possible enrolment or patients treated for angina pectoris, who could especially profit from beta-blockade, were not eligible for randomization. In addition, 38% of patients in the diuretic group received beta-blockers, and 52% of the beta-blocker group were on diuretic treatment.

In some studies[17,18,24,34] the beneficial effects of beta-blockade seemed limited to non-smokers (Tables 1, 2 and 5), whereas in other trials they were either similar[26] (Table 3) in smokers and non-smokers or tended to be even greater[27] in smokers than non-smokers (Table 4). Several mechanisms have been proposed to explain the apparently lesser reduction of cardiovascular complications by non-selective beta-blockade in hypertensive smokers. The catecholamines released by nicotine[103,104] may increase heart rate and cardiac output and exert an increased pressor effect, when non-selective beta-blockers, such as propranolol, inhibit the vasodilating $beta_2$-receptors, but leave the vasoconstricting alpha-receptors unopposed. In a per-protocol analysis limited to the first year of follow-up in the MRC trial[105], systolic blood pressure fell less in smokers than in non-smokers randomized to placebo ($P=0·002$) or propranolol ($P\leq 0·01$), but not in the bendrofluazide group ($P\geq 0·37$). After adjustment for age, body weight and pulse rate at randomization, the difference in the systolic blood pressure fall between smokers and non-smokers tended to be approximately 2·0 mmHg ($P=0·06$) greater in the propranolol than in the bendrofluazide group[105]. Smoking also induces hepatic enzymes involved in the metabolism of propranolol[106,107], so that this beta-blocker is cleared to a greater extent in smokers than non-smokers. However, the contradictory findings according to smoking status in the controlled clinical trials with beta-blockers[17,18,24,26,27,32–37] are more likely to reflect random variability or confounding in subgroup analyses. Lower protection in smokers has been found not only with non-selective beta-blockers[17,18,24], but also with selective beta-blockers[34], thiazides[27] and a calcium channel blocker[108]. For these reasons, until proof to the contrary, the preventive effects of beta-blockade should be considered as established regardless of smoking status. On the other hand, the bronchial symptoms associated with smoking may urge clinicians to prescribe only selective $beta_1$-blockers or no beta-blockers at all to smokers.

In keeping with the evidence from the trials, expert committees advised that beta-blockers should be accepted as suitable first-line therapy for the vast majority of hypertensive patients[1,109,110], mainly because they are effective for the primary prevention of stroke, myocardial infarction and sudden death[111]. Secondary prevention of cardiac mortality and sudden death in patients with a history of coronary heart disease, myocardial infarction or heart failure may provide additional indications to use beta-blockers. Furthermore, the co-existence of conditions that respond well to beta-blockers also constitute a reason for choosing such agents. These disorders include stress- or exercise-induces arrhythmias, chronic anxiety or stress, migraine, glaucoma, portal hypertension, hypertrophic cardiomyopathy, thyrotoxicosis, or tremor[112].

The expert assistance of Mrs Sylvia Van Hulle and Mrs Renilde Wolfs is gratefully acknowledged.

J. A. STAESSEN*
J. G. WANG*
W. H. BIRKENHÄGER†
R. FAGARD*
**Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, University of Leuven, Leuven, Belgium*
†Erasmus University, Rotterdam, The Netherlands

References

[1] The Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157: 2413–46.

[2] Kawano Y, Minami J, Ishimitsu T, Hirohata K, Mishima M, Takishita S. Use of antihypertensive drugs and levels of office and home blood pressure in elderly patients with hypertension. Ther Res 1996; 17: 140–3.
[3] Siegel D, Lopez LM. Trends in antihypertensive drug use in the United States. Do the JNC V recommendations affects prescribing? JAMA 1997; 278: 1745–8.
[4] Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of β-blockers in elderly survivors of acute myocardial infarction. JAMA 1997; 277: 115–21.
[5] Kendall MJ, Lynch KP, Hjalmarson Å, Kjekshus J. β-blockers and sudden cardiac death. Ann Intern Med 1995; 123: 358–67.
[6] Kennedy HL, Rosenson RS. Physician use of beta-adrenergic blocking therapy: a changing perspective. J Am Coll Cardiol 1995; 26: 547–52.
[7] Philipp T, Anlauf M, Distler A *et al*. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. Br Med J 1997; 315: 154–9.
[8] Psaty BM, Smith NL, Siscovick DS *et al*. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997; 277: 739–45.
[9] Psaty BM, Koepsell TD, LoGerfo JP, Wagner EH, Inui TS. β-blockers and the primary prevention of coronary heart disease in patients with high blood pressure. JAMA 1989; 261: 2087–94.
[10] Stewart IMG. Compared incidence of first myocardial infarction in hypertensive patients under treatment containing propranolol or excluding β-receptor blockade. Clin Sci Mol Med 1976; 51: 509s–11s.
[11] Berglund G, Sannerstedt R, Andersson O *et al*. Coronary heart disease after treatment of hypertension. Lancet 1978; i: 1–5.
[12] Trafford JAP, Horn CR, O'Neal H, McGonigle R, Halford-Maw L, Evans R. Five year follow-up of effects of treatment of mild and moderate hypertension. Br Med J 1981; 282: 1111–3.
[13] Beevers DG, Johnston JH, Larkin H, Davies P. Clinical evidence that beta-adrenoceptor blockers prevent more cardiovascular complications than other antihypertensive drugs. Drugs 1983; 25: 326–30.
[14] Cruickshank JM, Pennert K, Sörman AE, Thorp JM, Zacharias FM, Zacharias FJ. Low mortality from all causes including myocardial infarction in well-controlled hypertensives treated with a beta-blocker plus antihypertensive. J Hypertens 1987; 5: 489–98.
[15] Fletcher A, Beevers DG, Bulpitt C *et al*. Beta-adrenoceptor blockade is associated with increased survival in male but not female hypertensive patients; a report from the DHSS Hypertension Care Computing Project (DHCCP). J Hum Hypertens 1988; 2: 219–27.
[16] Casiglia E, Spolaore P, Mazza A *et al*. Effect of 2 different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly. Jpn Heart J 1994; 35: 589–600.
[17] Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. Br Med J 1985; 291: 97–104.
[18] Miall WE, Greenberg G, on behalf of The Medical Research's Council's Working Party on Mild to Moderate Hypertension. Mild Hypertension: Is There Pressure to Treat? Cambridge, United Kingdom: Cambridge University Press, 1987.
[19] Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings -Standards and Procedures for Measurement and Classification. Littleton, Massachusetts, USA: John Wright PSG Inc, 1982.
[20] Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation 1960; 21: 1160–75.
[21] Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham Study. N Engl J Med 1984; 311: 1144–7.
[22] Medical Research Council Working Party. Stroke and coronary heart disease in mild hypertension: risk factors and the value of treatment. Br Med J 1988; 296: 1565–70.
[23] Green KG. British MRC trial of treatment for mild hypertension — a more favorable interpretation. Am J Hypertens 1991; 4: 723–4.
[24] The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Primary Prevention Study in Hypertension (IPPPSH). J Hypertens 1985; 3: 379–92.
[25] Ahlquist RP. Propranolol in clinical medicine. Am Heart J 1979; 97: 137–40.
[26] Wilhelmsen L, Berglund G, Elmfeldt D *et al*. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. J Hypertens 1987; 5: 561–72.
[27] Wikstrand J, Warnold I, Olsson G *et al*. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. JAMA 1988; 259: 1976–82.
[28] Olsson G, Tuomilehto J, Berglund G *et al*. Primary prevention of sudden cardiovascular death in hypertensive patients: mortality results from the MAPHY Study. Am J Hypertens 1991; 4: 151–8.
[29] Wilhelmsen L, Staessen J, Fagard R *et al*. Primary prevention with metoprolol in patients with hypertension. JAMA 1988; 260: 1713–16.
[30] Wikstrand J. Beta-blockers and cardioprotection — is there any good news from the recent trials? J Clin Pharmacol Ther 1987; 12: 347–50.
[31] Wikstrand J. Reducing the risk for coronary events and stroke in hypertensive patients: comments on present evidence. Clin Cardiol 1991; 14 (Suppl III): III25–III35.
[32] Coope J. Hypertension in the elderly. J Hypertens 1987; 5 (Suppl 3): S69–S72.
[33] Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J 1986; 293: 1145–51.
[34] MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. Br Med J 1992; 304: 405–12.
[35] Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991; 338: 1281–5.
[36] The Systolic Hypertension in the Elderly Program Cooperative Research Group. Implications of the systolic hypertension in the elderly program. Hypertension 1993; 21: 335–43.
[37] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265: 3255–64.
[38] Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. Lancet 1987; i: 581–3.
[39] Staessen J, Bulpitt C, Cattaert A, Fagard R, Amery A. Secondary prevention with beta-adrenoceptor blockers in post-myocardial infarction patients. Am Heart J 1982; 104: 1395–9.
[40] Hansteen V, Mcinichen E, Lorentsen E *et al*. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. Br Med J 1982; 284: 155–60.
[41] A Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoceptor blockade using practolol. Br Med J 1975; 3: 735–40.
[42] Hjalmarson Å, Elmfeldt D, Herlitz J *et al*. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet 1981; ii: 823–7.

[43] Julian DG, Prescott RJ, Jackson FS, Szekely, P. Controlled trial of sotalol for one year after myocardial infarction. Lancet 1982; i: 1142–7.
[44] The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304: 801–7.
[45] Baber NS, Wainwright Evans D, Howitt G *et al*. Multicentre post-infarction trial of propranolol in 49 hospitals in the United Kingdom, Italy and Yugoslavia. Br Heart J 1980; 44: 96–100.
[46] Reynolds JL, Whitlock RML. Effects of a beta-adrenergic receptor blocker in myocardial infarction treated for one year from onset. Br Heart J 1972; 34: 252–9.
[47] Wilcox RG, Roland JM, Banks DC, Hampton JR, Mitchell JRA. Randomised trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. Br Med J 1980; 280: 885–8.
[48] Wilhelmsson C, Vedin A, Wilhelmsen L, Tibblin G, Werkö L. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 1974; 2: 1157–60.
[49] Andersen MP, Bechsgaard P, Frederiksen J *et al*. Effect of alprenolol on mortality among patients with definite or suspected acute myocardial infarction. Lancet 1979; ii: 865–88.
[50] The Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trial in post infarction patients. Eur Heart J 1988; 9: 8–16.
[51] Burley DM. Secondary prevention studies with oxprenolol in coronary heart disease. 2. Long-term effects — eight weeks to seven years. In: Burley DM, Birdwood GFB, eds. The Clinical Impact of Beta-Adrenoceptor Blockade. Proceedings of an International Symposium, Berlin, May 1980. Horsham, England, UK: Ciba Laboratories, 1980: 173–83.
[52] Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985; XXVII: 335–71.
[53] Soriano JB, Hoes AW, Meems L, Grobbee DE. Increased survival with β-blockers: importance of ancillary properties. Prog Cardiovasc Dis 1997; XXXIX: 445–56.
[54] ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986; ii: 57–64.
[55] Yusuf S, Sleight P, Rossi P *et al*. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. Circulation 1983; 67 (Suppl I): I-32–I-41.
[56] Roberts R, Rogers WJ, Mueller HS *et al*. Immediate versus deferred β-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. Circulation 1991; 83: 422–37.
[57] Jonas M, Reicher-Reiss H, Boyko V *et al*. Usefulness of beta-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary heart disease. Am J Cardiol 1996; 77: 1273–7.
[58] Deanfield JE, Shea M, Ribiero P *et al*. Transient ST-segment depression as a marker of myocardial ischemia during daily life. Am J Cardiol 1984; 54: 1195–1200.
[59] Yeung AC, Barry J, Orav J, Bonassin E, Rabyu KE, Selwyn AP. Effects of asymptomatic ischemia on long-term prognosis in chronic stable coronary disease. Circulation 1991; 83: 1598–604.
[60] Langer A, Minkowitz J, Dorian P *et al*. Pathophysiology and prognostic significance of Holter-detected ST segment depression after myocardial infarction. J Am Coll Cardiol 1992; 20: 1313–17.
[61] Bonaduce D, Petretta M, Lanzillo T *et al*. Prevalence and prognostic significance of silent myocardial ischemia detected by exercise test and continuous ECG monitoring after myocardial infarction. Eur Heart J 1991; 12: 186–93.
[62] Pepine CJ, Cohn PF, Deedwania PC *et al*. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). Circulation 1994; 90: 762–8.
[63] The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406–12.
[64] Echt DS, Liebson PR, Mitchell LB *et al*. Mortality and morbidity in patients receiving encainide, flecainide or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324: 781–8.
[65] The Cardiac Arrhythmia Suppression Trial-II Investigators. The effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992; 327: 227–33.
[66] Kennedy HL, Brooks MM, Barker AH *et al*. Beta blockade, ventricular arrhythmias, and sudden death. Am J Cardiol 1997; 80: 29J–34J.
[67] Julian DG, Camm AJ, Frangin G *et al*. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997; 349: 667–74.
[68] Janse MJ, Malik M, Camm AJ *et al*. Identification of post acute myocardial infarction patients with potential benefit from prophylactic treatment with amiodarone. A substudy of EMIAT (The European Myocardial Infarct Amiodarone Trial). Eur Heart J 1998; 19: 85–95.
[69] Cairns JA, Connolly SJ, Roberts R, Gent M, for the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Lancet 1997; 349: 675–82.
[70] Vantrimpont P, Rouleau JL, Wun CC *et al*. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the survival and ventricular enlargement (SAVE) study. J Am Coll Cardiol 1997; 29: 229–36.
[71] Pfeffer MA, Braunwald E, Moyé LA *et al*. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992; 327: 669–77.
[72] Lancaster SG, Sorkin EM. Bisoprolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in hypertension and angina pectoris. Drugs 1988; 36: 256–85.
[73] Waagstein F, Caidahl K, Wallentin I, Berg C, Hjalmarson Å. Long-term betablockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989; 80: 551–63.
[74] Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Beneficial effects of long-term betablockade followed by withdrawal in patients with congestive cardiomyopathy. Br Heart J 1980; 44: 117–33.
[75] Waagstein F, Bristow MR, Swedberg K *et al*. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993; 342: 1441–6.
[76] Cruickshank JM, Neil-Dwyer G, Degaute JP *et al*. Reduction of stress/catecholamine-induced cardiac necrosis by beta1-selective blockade. Lancet 1987; ii: 585–9.
[77] Quyyumi AA, Wright C, Mockus L, Fox KM. Effect of partial agonist activity in beta-blockers in severe angina pectoris: a double-blind comparison of pindolol and atenolol. Br Med J 1984; 289: 951–3.
[78] Parati G, Pomidossi G, Casadei R *et al*. Evaluation of the antihypertensive effect of celiprolol by ambulatory blood pressure monitoring. Am J Cardiol 1988; 61: 27C–33C.
[79] Boissel JP, Leizorovicz A, Picolet H, Peyrieux JP, study-group Acebutolol et Prevention Secondaire de l'Infarctus (APSI). Secondary prevention after high-risk acute myocardial infarction with low dose acebutolol. Am J Cardiol 1990; 66: 251–60.

[80] Multicenter International Study: Supplementary Report. Reduction in mortality after myocardial infarction with long-term β-adrenoceptor blockade. Br Med J 1977; 2: 419–21.
[81] Åblad B, Bjurö T, Björkman JA, Edström T, Olsson G. Role of central nervous beta-adrenoceptors in the prevention of ventricular fibrillation through augmentation of cardiac vagal tone. J Am Coll Cardiol 1991; 17 (Suppl): 165.
[82] Wu N, Fan Z, for Beijing Collaborative Study Group. Secondary prevention of cardiac events following myocardial infarction. Chin Med J 1997; 110: 602–6.
[83] van Ravenswaaij-Arts CMA, Kollée LAA, Hopman JCW, Stoelinga GBA, Van Geijn HP. Heart rate variability. Ann Intern Med 1993; 118: 436–47.
[84] Moser M, Lehofer M, Sedminek A *et al*. Heart rate variability as a prognostic tool in cardiology: a contribution to the problem from a theoretical point of view. Circulation 1994; 90: 1078–82.
[85] Tuininga YS, Crijns HJGM, Brouwer J *et al*. Evaluation of importance of central effects of atenolol and metoprolol measured by heart rate variability during mental performance tasks, physical exercise, and daily life in stable post-infarct patients. Circulation 1995; 92: 691–5.
[86] Lurje L, Wennerblom B, Tygesen H, Karlsson T, Hjalmarson Å. Heart rate variability after myocardial infarction in patients treated with atenolol and metoprolol. Int J Cardiol 1997; 60: 157–64.
[87] Kardos A, Long V, Singh J, Sleight P, Casadei R. Lipophilic versus hydrophilic b_1 blockers and the cardiac sympathovagal balance during stress and daily activity in patients after acute myocardial infarction. Heart 1998; 79: 153–60.
[88] Bittiner SB, Smith SE. β-adrenoceptor antagonists increase sinus arrhythmia, a vagotonic effect. Br J Clin Pharmacol 1986; 22: 691–5.
[89] Guzzetti S, Piccaluga E, Casati R *et al*. Sympathetic predominance in essential hypertension: a study employing spectral analysis of heart rate variability. J Hypertens 1988; 6: 711–17.
[90] Cook JR, Bigger Jr JT, Kleiger RE, Fleiss JI, Steinman RC, Rolnitzky LS. Effect of atenolol and diltiazem on heart period variability in normal persons. J Am Coll Cardiol 1991; 17: 480–4.
[91] Niemelä MJ, Airaksinen KEJ, Huikuri HV. Effect of beta-blockade on heart rate variability in patients with coronary artery heart disease. J Am Coll Cardiol 1994; 23: 1370–7.
[92] Frishman WH. β-adrenoceptor antagonists: new drugs and new indications. N Engl J Med 1981; 305: 500–6.
[93] Frishman WH. Clinical significance of beta-1-selectivity and intrinsic sympathomimetic activity in a beta-adrenergic blocking drug. Am J Cardiol 1987; 59: 33F–37F.
[94] Frishman WH. Atenolol and timolol, two new systemic β-adrenoceptor antagonists. N Engl J Med 1982; 306: 1456–62.
[95] Heel RC, Brogden RN, Speight TM, Avery GS. Atenolol: a review of its pharmacological properties and therapeutic efficacy in angina pectoris and hypertension. Drugs 1979; 17: 425–60.
[96] Koch-Weser J. Drug therapy. Metoprolol. N Engl J Med 1979; 301: 698–703.
[97] Newman RJ. Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycemia. Br Med J 1976; 2: 447–9.
[98] Deacon SP, Karunansyska A, Barnett D. Acebutolol, atenolol and propranolol and metabolic responses to acute hypoglycemia in diabetics. Br Med J 1977; 2: 1255–7.
[99] Gong L, Zhang W, Zhu Y *et al*. Shanghai trial of nifedipine in the elderly (STONE). J Hypertens 1996; 14: 1237–45.
[100] Staessen JA, Fagard R, Thijs L *et al*. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension [correction published in Lancet 1997, volume 350, November 29, p 1636]. Lancet 1997; 350: 757–64.
[101] Holme I, Olsson G, Tuomilehto J, Wikstrand J, for the MAPHY Steering Committee. MAPHY and the two arms of HAPPHYC. JAMA 1989; 262: 3272–3.
[102] Cruickshank JM. Treatment of hypertension in older adults. Br Med J 1992; 304: 984.
[103] Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976; 295: 573–7.
[104] Trap-Jensen J, Carlsen JE, Svendsen TL, Christensen NJ. Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta adrenoceptor blockade in humans (propranolol, atenolol). Eur J Clin Pharmacol 1979; 9: 181–3.
[105] Greenberg G, Thompson SG, Brennan PJ. The relationship between smoking and the response to antihypertensive treatment in mild hypertensives in the Medical Research Council's trial of treatment. Int J Epidemiol 1987; 16: 25–30.
[106] Vestal RE, Wood AJJ, Branch RA, Shand DG, Wilkinson GR. Effects of age and cigarette smoking on propranolol disposition. Clin Pharmacol Ther. 1979; 26: 8–15.
[107] Gardner SK, Cady WJ, Ong YS. Effect of smoking on the elimination of propranolol hydrochloride. Int J Clin Pharmacol Ther Toxicol 1980; 18: 421–4.
[108] Staessen JA, Fagard R, Thijs L *et al*. Subgroup and per-protocol analysis of the randomized European trial on isolated systolic hypertension in the elderly. Arch Intern Med 1998; 158: 1681–91.
[109] The Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. 1993 Guidelines for the Management of Mild Hypertension. Memorandum from a World Health Organization/International Society of Hypertension Meeting. Hypertension 1993; 22: 392–403.
[110] Zanchetti A. Guidelines for the management of hypertension: the World Health Organization/International Society of Hypertension view. J Hypertens 1995; 13 (Suppl 2): S119–S122.
[111] Kaplan NM. Beta blockade in the primary prevention of hypertensive cardiovascular events with focus on sudden death. Am J Cardiol 1997; 80: 20J–22J.
[112] Cruickshank JM, Prichard BNC. Beta-blockers. In: Swales JD, ed. Textbook of Hypertension. Oxford, England, UK: Blackwell Scientific Publications, 1994: 1059–88.
[113] Amery A, Birkenhäger W, Brixko P *et al*. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; i: 1349–54.

European Heart Journal (1999) **20,** 25–30

Diuretics, beta-blockers, and gin and tonic

See page 5 for the Editorial comment on this article

Introduction

In 1993 the Fifth Joint National Committee (JNC-V) established new guidelines for the treatment of hypertensions[1]. Unlike its previous version in which all four drug classes, i.e., diuretics, beta-blockers, calcium antagonists, and angiotensin converting enzyme (ACE) inhibitors were deemed equally acceptable as first-line therapy, the 1993 version stated that 'because diuretics and beta-blockers have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials, these two classes of drugs are preferred for initial drug therapy.' Although numerous epidemiological studies attest to the safety and efficacy of diuretics in this regard, the data for beta-blockers are sketchy and unconvincing. In fact, closer scrutiny of the available data suggest that the clinical benefits of beta-blockers are poorly documented and that they may be inefficacious or even harmful in the elderly, who account for a large segment of the hypertensive population.

Effects of beta-blockers on morbidity and mortality

Although beta-blockers have been used for the treatment of hypertension for more than three decades[2], no study shows that their monotherapeutic use in the elderly reduces morbidity and mortality compared with placebo. On the contrary, in a recent meta-analysis we documented that although blood pressure was lowered significantly by beta-blockers, they were ineffective in preventing coronary heart disease, and cardiovascular and all-cause mortality (odds ratio 1·01, 0·98, and 1·05, respectively) (Fig. 1)[3]. Not only was beta-blocker monotherapy not effective, but patients who received the combination of beta-blockers and diuretics fared consistently worse than those on diuretics alone. In contrast, diuretic therapy was superior to beta-blockade with regard to all end-points and was effective in preventing coronary heart disease, fatal strokes, cardiovascular events, and cardiovascular and all-cause mortality. This meta-analysis was based on 10 trials involving a total of 16 164 elderly patients (aged 60 and older). About 66% of the patients assigned to diuretics were well controlled on monotherapy, compared to less than one third of the patients assigned to beta-blockers.

Thus, despite their having a 'beneficial' effect on the surrogate end-point, i.e., blood pressure, beta-blocker therapy failed to favourably affect the real end-point, i.e., heart attack, death from strokes, cardiovascular events and all causes. Similarly, in a recent case control study, the risk of sudden cardiac death was higher in elderly patients receiving either beta-blocker as monotherapy or in combination with a thiazide diuretic than in patients receiving other therapy (calcium antagonists, ACE inhibitors, potassium-sparing diuretics)[4]. This would indicate that beta-blocker therapy exposes millions of elderly hypertensive patients (6·4 million in the United States alone) to adverse effects and cost while not conferring any benefit whatsoever.

The absence of a primary cardioprotective effect by beta-blockers was most recently acknowledged by Furberg and colleagues, who stated[5], 'Perhaps the most interesting finding from the beta-blocker component of the meta-analysis[6] is the fact that . . . β-blockers do not appear to prevent coronary events in the primary prevention trials in patients with high blood pressure.' However, a few months later the authors recant their thoughts with this statement[7], 'The treatment of hypertension is based on . . . multiple well-designed, randomized trials[6] showing the effectiveness of low-dose diuretics and β-blockers in preventing stroke, congestive heart failure, coronary events, and all-cause mortality.' Both of these contradictory statements give the same reference[6].

Of note, in the MRC-0 study the diuretic was associated with a lower risk of cardiovascular events compared with beta-blockers, even after adjustment for the decrease in blood pressure[8]. This indicates either that the diuretic confers a specific benefit irrespective of the decrease in arterial pressure or, more perturbingly, that the beta-blocker confers an ill effect on the cardiovascular system that overrides the beneficial effects of the decrease in arterial pressure.

Gin and tonic studies

In all studies in the geriatric population in which beta-blockers were implied to reduce morbidity and mortality, they were used in combination with a

Manuscript submitted 21 July 1998, and accepted 29 July 1998.

Correspondence: Franz H. Messerli, MD, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, U.S.A.

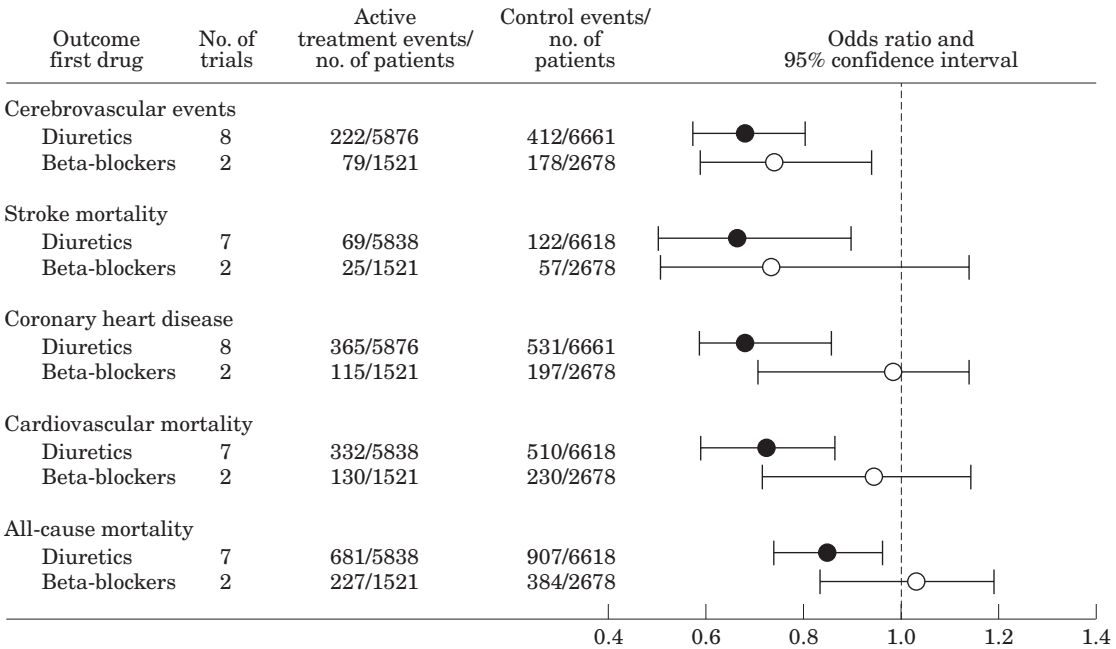

Figure 1 **Meta-analysis of prospective clinical trials in elderly patients with hypertension according to first-line treatment strategy. (Reproduced with permission from Messerli FH, *et al.* JAMA 1998; 279: 1903–7.)**

diuretic. Thus, in the Swedish STOP trial[9] more than two thirds of the patients were receiving combination therapy, and no information was available regarding the effects of beta-blocker monotherapy. In the SHEP study[10], only 21% of patients were receiving atenolol, and almost all of these in combination with a diuretic. In the study of Coope and Warrender[11], which demonstrated a significant reduction in the rate of strokes, 70% of patients in the treatment group were receiving atenolol and 60% were receiving bendrofluazide[2]. It is difficult to prove convincingly that tonic water causes cirrhosis of the liver in a study in which a water-drinking group of people are compared to a group in which people either drink tonic water, gin, or gin and tonic — yet this is exactly what was concluded from these data. In both of these studies over 60% of the patients in the treatment group were receiving a combination of a diuretic and a beta-blocker, and the effects of the beta-blocker were not assessed separately. In fact Coope and Warrender[11] clearly stated: 'Since patients were not randomized to treatment groups it is impossible to compare response to the beta-blockers and the diuretics.' None of these studies allows us to draw the conclusion that either a beta-blocker alone or the addition of the beta-blocker to the diuretic regimen significantly affected morbidity and mortality. There is, nevertheless, some indirect evidence suggesting that beta-blockers may have benefits in middle-aged and younger patients, as pointed out by Staessen *et al.*[12].

Beta-blockers in the elderly hypertensive: A pathophysiological/pharmacological mismatch

High blood pressure is no doubt a powerful risk factor for heart attack, stroke, sudden death and other cardiovascular morbidity and mortality. Ever since the pioneering observation of Freis[13], we have been led to believe that a reduction of blood pressure (achieved by a diuretic alone or in combination) will per se reduce high-blood-pressure-related cardiovascular morbidity and mortality. However, since the unexpected findings of the above meta-analysis, should we not conclude that this reduction is not necessarily related to the reduction of millimeters of mercury per se regardless of the means by which it is achieved? Yes, beta-blockers do reduce blood pressure but so do leeches, snake poison, etc. The following discussion covers some of the points that may possibly account for the failure of beta-blockers to reduce morbidity and mortality in the elderly hypertensive patient.

Effects of beta-blockers on systemic haemodynamics

Except in the early or borderline phase, the haemodynamic profile of established essential hypertension

is characterized by normal cardiac output and high systemic vascular resistance[14]. In the elderly patient with essential hypertension, cardiac output has been reported to be low, and systemic vascular resistance greatly elevated[15,16]. The provocative work of Fries[17] and Folkow[18] has well documented that systemic vascular resistance parallels hypertensive vascular disease. Antihypertensive therapy should therefore aim to diminish vascular resistance, by affecting it either functionally or structurally, and to preserve systemic blood flow, i.e., cardiac output. Most antihypertensive agents including the diuretics produce a fall in vascular resistance while sparing systemic flow. The only notable exception to this rule is the beta-blocker as a class. Numerous studies have attested to the fact that beta-blockers (with the exception of the few vasodilating compounds) lower arterial pressure by decreasing cardiac output, while systemic vascular resistance increases. In fact, Lund-Johansen has reported that even after 5 years of atenolol therapy, cardiac output remained depressed and systemic vascular resistance increased when compared with pretreatment levels[19].

A review of 85 studies on 10 different blockers showed an increase in peripheral resistance and a decrease in cardiac output with short-term treatment, whereas with long-term treatment, cardiac output remained depressed although total peripheral resistance fell somewhat but remained distinctly above normal levels[20]. Thus, while lowering arterial pressure, beta-blockers produce a haemodynamic effect exactly the opposite to that desirable in the patient with essential hypertension. By shifting the haemodynamic profile from a normal-cardiac-output, high-vascular-resistance pattern to a low-cardiac-output, high-vascular-resistance pattern, beta-blockers make the hypertensive patient haemodynamically older and thereby may well accelerate the biological clock[15,16].

Effects of beta-blockers on the heart

The common or garden variety of hypertensive heart disease is characterized by left ventricular hypertrophy, most often of the concentric type (i.e., thickening of the wall at the expense of chamber volume), the consequences or sequelae of which are impaired filling and contractility, ventricular arrhythmias, and impaired coronary reserve[21]. Beta-blockers have been documented to reduce left ventricular hypertrophy to some extent, but they seem to be less efficacious than most other drug classes[22–24]. In the elderly, Schulman *et al.*[24] in a thorough double-blinded study reported that atenolol failed to reduce left ventricular hypertrophy, whereas verapamil produced a fall in left ventricular mass in parallel with a reduction in arterial pressure. One might argue that by improving left ventricular filling and reducing heart rate, beta-blockers may have a beneficial effect on hypertensive heart disease. However, heart rate decreases spontaneously with age, and, in most elderly patients, the negative inotropic effect of beta-blockers is undesirable. A decrease in left ventricular contractility has been documented very early in the course of hypertensive heart disease[25,26], and in the patient with impaired contractility, beta-blockade in doses to treat hypertension should be avoided.

Effects of beta-blockers on vascular disease

Hypertensive vascular disease, the common denominator of hypertensive target organ involvement, is characterized by functional and structural changes of all layers in the arterial wall[18]. Unlike the ACE inhibitors and the calcium blockers, beta-blockers (with the exception of the vasodilating compound) do not reduce pulse pressure, arterial compliance, pulse-wave reflections or shear stress.

In a very thorough double-blind randomized trial, Schiffrin *et al.*[27] showed that media–lumen ratios of subcutaneous resistance arteries were reduced with an ACE inhibitor (cilazapril), whereas no significant change was observed after 1 year of beta-blocker therapy. In both treatment groups, blood pressure decreased to the same extent. In a 2-year follow-up, the same group of investigators reported progressive normalization of the structure of the resistance artery of patients with essential hypertension who were treated with an ACE inhibitor and with a calcium antagonist, whereas there was no change in patients treated with beta-blockers, despite the fact that arterial pressure was lowered to the same extent in both treatment groups[28,29].

Effects of beta-blockers on hypertensive renal disease

Hypertensive renal disease in the early stages is characterized by a decrease in renal blood flow, a relatively well-preserved glomerular filtration rate, and an increase in filtration fraction[30–33]. With a few notable exceptions, beta-blockers have been reported to further diminish renal blood flow and thereby to increase filtration fraction[33]. In some instances, even a decrease in glomerular filtration rate has been reported with beta-blockade[34]. Microproteinuria has been shown, to some extent, to parallel renal disease, particularly in hypertensive patients with diabetes[35–38]. Data assessing the effects of beta-blockade on microproteinuria are inconsistent. Whereas with short-term therapy microproteinuria

diminishes under beta-blockade, prolonged beta-blocker therapy fails to reduce microproteinuria compared with therapy with either ACE inhibitors or non-dihydropyridine calcium antagonists, despite equal antihypertensive efficacy[35].

Of note, in a recent randomized controlled trial in hypertensive patients with chronic renal failure, enalapril significantly slowed the progression toward end-stage renal failure when compared with beta-blockers[39]. The fact that blood pressure control was similar in both treatment groups indicates that the effect on renal function was not mediated through blood pressure, suggesting that either enalapril has a blood-pressure-independent beneficial effect or the beta-blocker has a blood-pressure-independent detrimental effect on renal function.

Metabolic effects of beta-blockers

The reports on the effects of beta-blockers on serum lipoprotein and carbohydrate metabolism are conflicting. Several thorough review studies conclude that beta-blockers increased triglyceride levels and decreased high density lipoprotein (HDL)-cholesterol levels[40–44]. Beta-blockers with intrinsic sympathomimetic activity have a lesser effect on triglycerides and HDL than beta-blockers without intrinsic sympathetic activity. Kasiske *et al*., in a recent review of 474 studies, showed that cardioselectivity diminished the increase in triglyceride levels and that the effects of beta-blockers on HDL cholesterol appeared to diminish with duration of treatment[44].

Non-diabetic hypertensive patients may be at a higher risk for developing diabetes when treated with beta-blockers[45–48]. However, in the elderly the effects of beta-blockers on both lipid and carbohydrate metabolism may be of less a concern than in the younger patient who will be exposed to them for a much longer period of time.

Beta-adrenergic responsiveness and age

Several experimental and human studies have documented that normative ageing is accompanied by a progressive decrease in cardiovascular responsiveness to beta-adrenergic stimulation[43,49–52]. The age-associated changes in cardiovascular findings are accompanied by increased plasma catecholamine levels[15,53], similar to the effects observed with beta-blocker therapy. In an elegant study assessing the effects of acute beta-adrenergic receptor blockade on age-associated changes in cardiovascular performance with exercise, Fleg and collaborators[54] have shown that the age-associated declines in maximal heart rate and left ventricular contractility with exercise are probably manifestations of a reduced beta-adrenergic responsiveness. This would indicate that 'physiological beta-blockade' accounts for the attenuated cardiac acceleration and myocardial contractility in the elderly. Not surprisingly, the hypertensive elderly patient will very poorly tolerate a pharmacological beta-blockade that is superimposed on the intrinsic physiological one.

The effects of beta-blockers on exercise capacity

Elderly subjects respond to exercise with a blunted increase in heart rate and ejection fraction and a greater use of the Frank-Starling mechanism when compared with the younger patient. Exercise capacity progressively diminishes with age, more so in the hypertensive than in the normotensive population. By exerting a negative chronotropic and negative inotropic effect, beta-blockers further diminish exercise capacity in the elderly and are, therefore, particularly ill-tolerated in those patients who remain physically active.

Effects of beta-blockers on co-morbidity in the elderly

Hypertension is rarely an isolated disorder in the elderly patient. Chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, depressive disorders, and sexual dysfunction are co-morbid conditions frequently encountered in the geriatric population. Although none of these co-morbid conditions is a direct contraindication to using beta-blockers, their presence not only makes beta-blockers less desirable as first-line antihypertensive drugs, but they are also prone to diminish the patient's tolerability for beta-blockers.

Conclusions

Beta-blockers have been used for the treatment of hypertension for more than three decades. Despite their well-documented potential for lowering millimeters of mercury, no study is available that shows that beta-blockers, either in monotherapy or when added to diuretic therapy, diminish cardiovascular morbidity and mortality. Quite to the contrary, a recent meta-analysis in the elderly reported little if any benefits of beta-blocker therapy when compared

with placebo or other therapy, despite the fact that blood pressure was lowered in the blocker group. In this context it must be remembered that blood pressure is a surrogate end-point that often, but not always, correlates with real end-points, i.e., heart attack, strokes, sudden death, etc. By favourably affecting the surrogate end-point (blood pressure) without
reducing the real end-points (heart attacks and death), beta-blockers are prone to lull physicians and patients into a sense of false security. The reason for the inefficacy of beta-blockers may lie in their inherent unfavourable effect on systemic haemodynamics and on pathophysiological findings in the arterial tree, the heart, the kidneys, and the brain, and to a lesser extent on the metabolism of lipids and carbohydrates. Thus, antihypertensive therapy with beta-blockade needlessly exposes the elderly to the cost and adverse effects of these drugs without conferring any benefits. The irony is that the very studies that demonstrate inefficacy of beta-blockers in the elderly was used as an argument by the JNC-V to promote them to a 'preferred' status. Until proven otherwise, beta-blockers should no longer be considered appropriate for monotherapy of essential hypertension in the elderly.

F. H. MESSERLI*
E. GROSSMAN†
**Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana, U.S.A.*
†*Internal Medicine D, The Chaim Sheba Medical Center, Tel-Hashomer, Israel*

References

[1] The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. The Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V). Arch Intern Med 1993; 153: 154–83.
[2] Prichard BNC, Gillam PMS. Use of propranolol (Inderal) in treatment of hypertension. Br Med J 1964; 2: 725–7.
[3] Messerli FH, Grossman E, Goldbourt U. Are β-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998; 279: 1903–7.
[4] Hoes AW, Grobbee DE, Lubsen J, Man in't Veld AJ, van der Does E, Hofman A. Diuretics, β-blockers, and the risk for sudden cardiac death in hypertensive patients. Ann Intern Med 1995; 123: 482–7.
[5] Psaty BM, Smith NL, Koepsell TD, Furberg CD. In reply (letter). JAMA 1997; 277: 1759–60.
[6] Psaty BM, Smith NL, Siscovick DS *et al*. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997; 277: 739–45.
[7] Furberg CD, Psaty BM. JNC VI: timing is everything. Lancet 1997; 350: 1413–6.
[8] MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. Br Med J 1992; 304: 405–2.
[9] Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester P-O. Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-Hypertension). Lancet 1991; 338: 1281–5.
[10] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265: 3255–64.
[11] Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J 1986; 293: 1145–51.
[12] Staessen J, Fagard R, Amery A. Letter to the Editor. JAMA 1988; 260: 1713–4.
[13] Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 1970; 213: 1143–52.
[14] Frohlich ED, Tarazi RC, Dustan HP. Re-examination of the hemodynamics of hypertension. Am J Med Sci 1969; 257: 9–23.
[15] Messerli FH, Ventura HO, Glade LB, Sundgaard-Riise K, Dunn FG, Frohlich ED. Essential hypertension in the elderly: haemodynamics, intravascular volume, plasma renin activity and circulating catecholamine levels. Lancet 1983; 2: 983–6.
[16] Lund-Johansen P, Omvik P. Hemodynamic patterns of untreated hypertensive disease. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology, Diagnosis, and Management, Vol. 1, 2nd edn. New York: Raven Press, 1995: 323–42.
[17] Fries ED. Hemodynamics of hypertension. Physiol Rev 1960; 40: 27–55.
[18] Folkow B. Physiological aspects of primary hypertension. Physiol Rev 1982; 62: 347–504.
[19] Lund-Johansen P. Hemodynamic consequences of long-term beta-blocker therapy: a 5-year follow-up study of atenolol. J Cardiovasc Pharmacol 1979; 1: 487–95.
[20] Man in't Veld AJ, Van Den Meiracker AH, Schalekamp MA. Do beta-blockers really increase peripheral vascular resistance? Review of the literature and new observations under basal conditions. Am J Hypertens 1988; 1: 91–6.
[21] Messerli FH. Combination therapy in hypertension. J Hum Hypertens 1992; 6 (Suppl 2): S19–S21.
[22] Cruickshank JM, Lewis J, Moore V, Dodd C. Reversibility of left ventricular hypertrophy by differing types of antihypertensive therapy. J Hum Hypertens 1992; 6: 85–90.
[23] Dahlöf B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. Am J Hypertens 1992; 5: 95–110.
[24] Schulman SP, Weiss JL, Becker LC *et al*. The effects of antihypertensive therapy on left ventricular mass in elderly patients. N Engl J Med 1990; 322: 1350–6.
[25] Grossman E, Oren S, Messerli FH. Left ventricular mass and cardiac function in patients with essential hypertension. J Hum Hypertens 1994; 8: 417–21.
[26] Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995; 26: 195–202.
[27] Schiffrin EL, Deng LY, Larochelle P. Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. Hypertension 1994; 23: 83–91.
[28] Schiffrin EL, Deng LY, Larochelle P. Progressive improvement in the structure of resistance arteries of hypertensive patients after 2 years of treatment with an angiotensin I-converting enzyme inhibitor: comparison with effects of a β-blocker. Am J Hypertens 1995; 8: 229–36.

[29] Schiffrin EL, Deng LY. Structure and function of resistance arteries of hypertensive patients treated with a β-blocker or a calcium channel antagonist. J Hypertens 1996; 14: 1247–55.
[30] Hollenberg NK, Epstein M, Basch RI, Merrill JP. 'No man's land' of the renal vasculature. An arteriographic and hemodynamic assessment of the interlobar and arcuate arteries in essential and accelerated hypertension. Am J Med 1969; 47: 845–54.
[31] London GM, Safar ME, Sassard JE, Levenson JA, Simon AC. Renal and systemic hemodynamics in sustained essential hypertension. Hypertension 1984; 6: 743–54.
[32] Schmieder RE, Schächinger H, Messerli FH. Accelerated decline in renal perfusion with aging in essential hypertension. Hypertension 1994; 23: 351–7.
[33] de Leeuw PW, Gaillard CA, Birkenhäger WH. Renal hemodynamic patterns in essential hypertension. In: Laragh JH, Brenner BM, eds. Hypertension: Pathophysiology Diagnosis, and Management, Vol 2, 2nd edn. New York: Raven Press, 1995: 1857–67.
[34] Bauer JH, Brooks CS. The long-term effect of propranolol therapy on renal function. Am J Med 1979; 66: 405–10.
[35] Maki DD, Ma JZ, Louis TA, Kasiske BL. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995; 155: 1073–80.
[36] Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 1993; 118: 129–38.
[37] Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. N Engl J Med 1984; 310: 356–60.
[38] Bauer JH. Diabetic nephropathy: can it be prevented? Are there renal protective antihypertensive drugs of choice? South Med J 1994; 87: 1043–53.
[39] Hannedouche T, Landais P, Goldfarb G *et al*. Randomised controlled trial of enalapril and β-blockers in non-diabetic chronic renal failure. Br Med J 1994; 309: 833–7.
[40] Weidmann P, Ferrier C, Saxenhofer H, Uehlinger DE, Trost BN. Serum lipoproteins during treatment with antihypertensive drugs. Drugs 1988; 35 (Suppl 6): 118–34.
[41] Grimm Jr RH. Antihypertensive therapy: taking lipids into consideration. Am Heart J 1991; 122: 910–8.
[42] Roberts WC. Recent studies on the effects of beta blockers on blood lipid levels. Am Heart J 1989; 117: 709–14.
[43] van Brummelen P, Buhler FR, Kiowski W, Amann FW. Age-related decrease in cardiac and peripheral vascular responsiveness to isoprenaline: studies in normal subjects. Clin Sci 1981; 60: 571–7.
[44] Kasiske RL, Ma JZ, Kalil RSN, Louis TA. Effects of antihypertensive therapy on serum lipids. Ann Intern Med 1995; 122: 133–41.
[45] Skarfors ET, Lithell HO, Selinus I, Åberg H. Do antihypertensive drugs precipitate diabetes in predisposed men? Br Med J 1989; 298: 1147–52.
[46] Bengtsson C, Blohmé G, Lapidus L, Lissner L, Lundgren H. Diabetes incidence in users and non-users of antihypertensive drugs in relation to serum insulin, glucose tolerance and degree of adiposity: a 12-year prospective population study of women in Gothenburg, Sweden. J Intern Med 1992; 231: 583–8.
[47] Pollare T, Lithell H, Selinus I, Berne C. Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. Br Med J 1989; 298: 1152–7.
[48] Lithell H, Pollare T, Vessby B. Metabolic effects of pindolol and propranolol in a double-blind cross-over study in hypertensive patients. Blood Press 1992; 1: 92–101.
[49] Lakatta EG, Gerstenblith G, Angell CS, Shock NW, Weisfeldt ML. Diminished inotropic response of aged myocardium to catecholamines. Circ Res 1975; 36: 262–9.
[50] Guarnieri T, Filburn CR, Zitnik G, Roth GS, Lakatta EG. Contractile and biochemical correlates of beta-adrenergic stimulation of the aged heart. Am J Physiol 1980; 239: H501–8.
[51] Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJ. Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta-adrenergic sensitivity in the elderly. N Engl J Med 1984; 310: 815–9.
[52] Stratton JR, Cerqueira MD, Schwartz RS *et al*. Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. Circulation 1992; 86: 504–12.
[53] Vlachakis ND, Aledort L. Hypertension and propranolol therapy: effect on blood pressure, plasma catecholamines and platelet aggregation. Am J Cardiol 1980; 45: 321–5.
[54] Fleg JL, Schulman S, O'Connor F *et al*. Effects of acute β-adrenergic receptor blockade on age-associated changes in cardiovascular performance during dynamic exercise. Circulation 1994; 90: 2333–41.