Review Article

A risk–benefit analysis for the treatment of hypertension

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Introduction

A risk–benefit analysis is simply a comparison of the risks of treatment against the benefits. It assumes great importance when the benefits are not dramatic, nor universal and do not obviously outweigh any risk. The treatment of malignant hypertension is an example when the risks are relatively unimportant. In 1961, Pickering, Cranston and Peers provided an overview of the results of treating malignant hypertension.¹ Untreated, 50% die within 6 months and 90% within a year. Treatment ensured that, in 1960, at least 50% survived 2 years. Nevertheless, risks cannot be ignored, and in this condition enthusiasm for immediate pressure reduction with intravenous drugs has given way to a gradual reduction, thus avoiding the rare but real precipitation of stroke events observed with precipitous falls in pressure.

This review is concerned with prevention of the cardiovascular complications of hypertension rather than the treatment of acute life-threatening conditions and these benefits must be considered in the light of the following.

(a) How likely is the complication to occur?

This is only a superficially easy question to answer as the rates vary with age, gender, severity of hypertension, geographic area, race, and the presence and degree of other risk factors. To take an example: if we argue for the treatment of hypertension on the main grounds of reducing coronary heart disease, this may not influence a Japanese doctor whose patients are less likely to experience this problem.

(b) How often is the complication actually due to hypertension?

Cerebral haemorrhage is much more likely than coronary heart disease to be the result of hypertension. However, although the strength of the association (given by the relative risk of something

happening if you are hypertensive compared to not hypertensive) may be greater for cerebral haemorrhage, the importance of treatment may be greater for coronary heart disease in the Western world as this is much more common than cerebral haemorrhage. The *potential* importance of treatment is given by the attributable risk which is the incidence of disease in hypertensives (expressed as a rate/year) less the incidence in non-hypertensives. The problem is that the potential gains from treatment may not match the gains observed in the experimental situation, namely the randomized controlled trial.

(c) To what extent are the potential benefits observed when blood pressure is lowered effectively?

The actual benefit observed divided by the potential benefit gives *fraction of benefit (FOB)*. This varies from almost 100% for stroke to 60% for coronary heart disease.

(d) By how much does blood pressure have to be reduced to achieve the benefit?

This question is very complex as it is probable that the benefits are related both to the untreated pressure and to the pressure achieved by treatment (the reduction in pressure is simply the mathematical difference between the pressures). Moreover, there may or may not be a linear relationship between morbidity and achieved pressure. The possibility that blood pressure can be reduced too far has to be addressed in view of the debate over the J-shaped curve in which cardiac mortality 'increases' somewhat at the lowest levels of diastolic blood pressure.

Providing answers to these four questions is so difficult that the only solution is to examine the results of randomized controlled trials to see what actually happens. In this way we can also examine the risks or down-side of treatment. Unfortunately, the reporting of results is only relevant to the types of patient studied (their age, gender, race, level of

untreated pressure, etc.) and the treatment employed. It may also be claimed that the results are only relevant to a group with a given rate of non-compliance and withdrawal. Thus we are faced with the problem of being unable to predict the possible benefits of so-called 'hygienic' treatments (weight loss, etc.) as these usually have only a small hypotensive effect and have not been employed on their own in trials to determine both morbidity or mortality and the risks of these treatments. Similarly data do not exist for the young or very old and important subgroups such as the middle aged with isolated systolic hypertension. Table I gives an indication of the availability of the data for both sexes and ages 40–59, 60–79 and 80+, with:

1. Diastolic hypertension ($DBP \geq 90$) $\pm$ systolic hypertension ($SBP \geq 160$ mmHg).
2. Isolated systolic hypertension, $SBP \geq 160$ mmHg plus $DBP < 95$ mmHg (or < 90 mmHg).
3. Isolated diastolic hypertension, $DBP \geq 90$ mmHg and $SBP < 160$ mmHg (in the elderly²) or $SBP < 140$ mmHg (in the young).

The trial results will be discussed for the three groups where it is available and the other groups are reviewed subsequently.

Persons aged 40–59, diastolic hypertension $\pm$ systolic hypertension

Benefits—stroke reduction

Collins and his colleagues³ have performed a meta-analysis of the trial data and concluded that anti-hypertensive treatment reduces stroke events by an average of 42% (range 33–50% for the trials). They concluded that epidemiological data would suggest a reduction of 35–40% for the equivalent reduction in blood pressure and therefore the FOB obtained was 100%. Their analysis includes some of the trials in the elderly but the treatment effect was similar in proportional terms for age range 40–59 and 60–79. Collins *et al.* also included the Hypertension Detection and Follow-up Program (HDFP) trial⁴ which included not only more effective treatment of hypertension but also other health care measures that reduced non-cardiovascular deaths. However, the results of this trial tended to reduce the size of the effect on stroke (at least in women) and not to increase it. The consistency of the trial data has led many authorities to assume that it is the blood pressure lowering effect of anti-hypertensive drugs that confers the reduction in stroke incidence and that all drugs should be equally efficacious if they reduce pressure by a given amount. Nevertheless, stroke

Table I Availability of the results of randomized controlled trials (more than one trial must have been performed) according to three types of hypertension, both sexes and three age groups

	Age		
	40–59	60–70	80 +
Diastolic high $\pm$ systolic high			
Men	DA	DA	NA
Women	DA	DA	NA
Systolic high (diastolic low)			
Men	NA	DA	NA
Women	NA	DA	NA
Diastolic high (systolic not high)			
Men	NA	NA	NA
Women	NA	NA	NA

DA = data available; NA = not available.

events were not reduced by propranolol in *smokers* in the first Medical Research Council (MRC) trial in middle-aged subjects,⁵ whereas bendrofluazide did reduce the risk. This interaction between smoking and treatment has not been supported for stroke incidence in the International Prospective Primary Prevention Study in Hypertension (IPP-PSH) trial,⁶ nor in the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial.⁷

Benefits—reduction in coronary events

Collins *et al.*³ also performed a meta-analysis on the reduction in coronary events during the trials. The reduction averaged 14%, range 4–22%, with a FOB of 60%. Thus the gains predicted for coronary heart disease from epidemiological data are not fully realized from anti-hypertensive treatment. Two possible reasons have been widely discussed: that a lag time should be considered before any benefits are realized and secondly that the drugs employed may have an adverse effect on serum lipids and thus prevent the benefits being fully realized. In the MRC trial in younger subjects there was evidence for a reduction in coronary events with propranolol in men who did not smoke. This was not observed in men who smoked nor men who received bendrofluazide.⁵

Benefits—overall

Table II gives the results of the Australian,⁸ MRC (middle age)⁵ and HDFP⁴ trials. For stroke prevention there was a consistent benefit in both men and women with relative risks of 0.51 to 0.71 with treatment and 1% of the hypertensive population

Table II Effects of treatment compared with placebo in the Australian⁸ and MRC (middle age⁵) trials and with controls in HDFP

	<i>Rate/1,000 patient years Treatment</i>	<i>Placebo</i>	<i>Reduction in risk/ 1,000 patient years</i>	<i>Relative risk</i>	<i>95% CI</i>
<i>All strokes</i>					
<i>Both sexes</i>					
Australian	1.9	3.2	1.3	0.58	0.29,1.15
MRC	1.4	2.6	1.2	0.55	0.40,0.75
<i>Men</i>					
MRC	1.7	2.9	1.2	0.57	0.38,0.85
HDFP*	2.9	5.1	2.2	0.57	—
<i>Women</i>					
MRC	1.1	2.1	1.0	0.51	0.31,0.85
HDFP*	3.2	4.5	1.3	0.71	—
<i>Fatal and non-fatal MI</i>					
<i>Both sexes</i>					
Australian	4.7	4.8	0.1	0.98	0.60,1.59
MRC	5.2	5.5	0.3	0.94	0.78,1.13
<i>Men</i>					
MRC	8.3	9.0	0.7	0.92	0.75,1.12
HDFP†	4.8	5.7	0.9	0.83	—
<i>Women</i>					
MRC	1.8	1.7	—	1.10	0.69,1.75
HDFP†	3.9	4.6	0.7	0.86	—
<i>All cause mortality</i>					
<i>Both sexes</i>					
Australian	3.6	5.1	1.5	0.70	0.42,1.17
MRC	5.8	5.9	0.1	0.97	0.81,1.16
<i>Men</i>					
MRC	7.1	8.2	1.1	0.87	0.70,1.08
HDFP*	2.9	3.4	0.5	0.85	—
<i>Women</i>					
MRC	4.4	3.5	—	1.24	0.91,1.70
HDFP*	2.4	2.4	—	0.98	—

Reduction in risk gives the events saved by active treatment. Hypertension Detection and Follow-up Program (HDFP),⁴ intensive treatment compared, not with placebo, but with usual care. Table derived, in the main, from Isles *et al.*¹³

*White only; †includes whites and blacks and additional diagnoses from questionnaire data alone. CI = confidence interval.

being saved a stroke over 10 years. For myocardial infarction (MI) the relative risks on treatment failed to differ significantly from unity but it is possible that, at least in men, up to 1% are saved an MI in 10 years. Benefits appear less likely in women and the fact that MI is relatively rare in younger women means that large benefits cannot be expected to accrue from the prevention of MI in women.

In the HDFP trial, there was some evidence for a reduction in coronary events in women. In this trial, however, although white women had only a 4 mmHg reduction in DBP in the stepped (intensive) care group compared to the usual care group, stroke was reduced by 29%⁹ and myocardial infarction (for all women – black and white) by 14%.¹⁰ The latter effect led to a high reduction in risk but the diagnosis of a non-fatal MI also

depended on responses to a questionnaire, the Rose Questionnaire¹¹ and ischaemic cardiac pain reported in this way may have less clinical significance in terms of mortality than a formal diagnosis of MI.¹² The incidence rates would be reduced by about a half if questionnaire-positive cases were omitted from the HDFP results¹⁰ giving a lower reduction in risk of 0.3 per 1,000 patient years.

The MRC and HDFP data for white women suggest that total mortality is not reduced by the treatment of mild hypertension over a 5 year period.

These data on younger persons do not fit exactly into the age category 40–59, as the age range in this Australian and HDFP trials extended to 69 years, and to 65 years in the MRC trial. However, the benefits appear to apply to the age range 40–59 years as much as for age 60–69.

The question must also be asked whether or not the benefits of treatment are dependent on the type of treatment employed. The treatment compared in two large trials has been a beta-adrenoceptor blocking drug compared with a thiazide; propranolol with bendrofluazide in the MRC trial and atenolol or metoprolol with a thiazide diuretic in the HAPPHY trial.⁷ In the IPPPSH trial oxprenolol was compared with a non-beta-blocker based regime.⁶

Isles *et al.*¹³ have reviewed these trials and concluded 'In the MRC trial the reduction of stroke rate on bendrofluazide was greater than that on propranolol, despite similar reduction of blood pressure. There was a trend towards fewer fatal and non-fatal myocardial infarctions in MRC and IPPPSH patients who received a beta blocker, which was largely a result of lower event rates in men, and was *confined to non-smokers*'.¹³ In other words do not give propranolol to men who smoke. However, Collins *et al.*³ reviewed the data and stated 'it is uncertain whether any worth-while differences between the two treatments exist. . . . too few CHD events have been observed . . . for an overview of the current trial results to have much chance of demonstrating this (previously defined) difference.' The relative risk of a stroke in the MRC trial with propranolol rather than bendrofluazide was 2.3 in men and 2.2 in women¹³ but was less than unity in the IPPPSH and HAPPHY trials.³

The risks

Table III gives the risks observed in the MRC trial expressed in event /1,000 patient years. Rates are those 'attributable' to the drug and may therefore be contrasted with the benefits in Table II. For a saving of one stroke event, one MI event and one

death/1,000 patient years (and not necessarily cumulative) 11 men/1,000 patient years on bendrofluazide and 5/1,000 patient years on propranolol will complain of impotence and 3–5/1,000 of lethargy. Propranolol also produced complaints of Raynaud's phenomenon and dyspnoea in substantial numbers. The problems of impaired glucose tolerance and 'gout' are difficult to assess as we do not know whether or not these problems led to symptoms. For women in this trial a reduction of one stroke/1,000 patient years has to be balanced against similar problems to those experienced by men with the exception of low rates for 'gout' and, as far as we know, no problems with sexual functioning.

Quality of life (QOL) was not formerly measured in the trial and was probably impaired to some extent in the actively treated group owing to the fact that half received propranolol. Propranolol has been shown to reduce quality of life in three different trials.^{14–16} This drug appears to be associated with a number of symptom side effects and adverse effects on mood. However, an impairment in quality of life has not been observed with other beta-blockers such as atenolol^{15,17,18} or acebutolol.¹⁹ However, a non-fatal stroke or severe heart failure would have dramatically reduced QOL in the placebo-treated group.

One would expect that, in survivors with no complication of hypertension, placebo would be associated with the best QOL. However, a recent report from the Treatment of Mild Hypertension Study (TOMHS) stated that two treatments were associated with a statistical improvement in QOL over placebo, namely acebutolol ($P = 0.007$) and chlorthalidone ($P = 0.007$) and that amlodipine, doxazosin and enalapril occupied intermediate positions.¹⁹ This surprising finding, that QOL was

Table III Adverse effects observed in the MRC trial in younger persons⁵ in events/1,000 patient years

	Men		Women	
	Bendrofluazide	Propranolol	Bendrofluazide	Propranolol
Impaired glucose tolerance	4.4	0	3.9	0
Gout or serum uric acid > 500 (men) or 450 μ mol/l (women)	12.1	0	1.5	0
Impotence	11.3	5.0	–	–
Raynaud's	0	5.1	0	4.5
Skin disorder	0	1.2	0	1.1
Dyspnoea	0	6.7	0	6.9
Lethargy	3.1	4.8	1.4	8.0

All entries are significant at the 1% level and represent the difference between the rate on active treatment and the rate on placebo. A zero entry means no statistically significant excess or deficit.

Table IV Percentage change (+ = improvement) in seven aspects of quality of life examined in the Treatment of Mild Hypertension Study (TOMHS)

	<i>Acebutolol</i>	<i>Amlodipine</i>	<i>Chlorthalidone</i>	<i>Doxazosin</i>	<i>Enalapril</i>	<i>Placebo</i>
General Health Index	+ 6.7	+ 2.0	+ 4.6	+ 4.8	+ 3.9	+ 4.1
Energy/fatigue	+ 9.4	+ 4.5	+ 10.0	+ 3.4	+ 5.8	+ 5.2
Mental Health Index	+ 4.7	+ 3.2	+ 4.3	+ 2.2	+ 2.1	+ 2.3
General Functioning Index	+ 2.9	+ 2.1	+ 2.9	- 2.1	- 0.7	- 1.4
Satisfaction with physical abilities	+ 13.6	+ 14.0	+ 13.3	+ 6.7	+ 8.9	+ 8.9
Social functioning	+ 2.8	+ 5.4	+ 2.8	0	+ 5.4	0
Social contacts	0	+ 5.4	- 3.4	0	- 1.7	+ 3.5
Average	+ 5.7	+ 5.2	+ 4.9	+ 2.1	+ 3.4	+ 3.2

least good on placebo may have been due to the subjects being aware of their blood pressure and the fall in blood pressure being least in the placebo group. Nevertheless, the TOMHS is useful in comparing five active treatments and a simple analysis of the QOL data is presented in Table IV. This analysis suggests that QOL may be less acceptable on doxazosin and the authors report that this drug was worse than acebutolol and chlorthalidone for both energy and general functioning ($P < 0.01$ for both comparisons), and also worse than amlodipine for general functioning alone. Enalapril was also no better than placebo. A recent trial comparing prazosin with six other treatments²⁰ found a withdrawal rate due to adverse drug reactions of 14% on prazosin, 10% on clonidine, 6–7% on placebo and diltiazem, 5% on captopril, and 2% and 1% on atenolol and hydrochlorothiazide. Withdrawal rates are related to QOL²¹ and it must be concluded that an impairment of QOL may occur with the alpha-adrenoceptor blocking drugs. Eight drugs have been reported as associated with a good QOL, atenolol, acebutolol, captopril, enalapril, cilazapril, verapamil, amlodipine and hydrochlorothiazide, and three drugs are associated with a less good QOL, methyldopa, propranolol and nifedipine.^{14,21}

It has been assumed that all ACE inhibitors are the same with respect to QOL. However, a recent trial compared captopril and enalapril and concluded that 'patients treated with captopril had more favourable changes in overall quality of life, general perceived health, vitality, health status and emotional control'.²² This was surprising as side effects were similar in the two groups and the withdrawal rates were almost identical on the two drugs. In the event, the statistically significant result occurred mainly with the General Perceived Health Scale (Table V) a subset of the Psychological General Well-being Scale, although there was some support from the emotional control scale and the Side Effects and Symptoms Distress Index.

TOMHS listed 53 symptoms and when considering the five active treatments, enalapril should have had the highest complaint rate, by chance, in 11. In the event enalapril was associated with the highest complaint rate in 19 symptoms, most notably lightheadedness when standing up.¹⁹ However, a preference for captopril over enalapril was not demonstrated in an earlier study¹⁵ where general health (from the Psychological General Well-being Scale) improve more on enalapril than captopril ($P < 0.05$).

Age 40–59, high diastolic conclusions

Malignant hypertension and sustained diastolic pressures over 100 mmHg must be treated. On

Table V Quality of life changes on two ACE inhibitors (Testa *et al.*)²²

	<i>Captopril</i>	<i>Enalapril</i>	<i>P</i>
Psychological Distress Scale			
Anxiety	–	+ 0.11	NS
Depression	–	–	NS
Behavioural or emotional control	+ 0.15	+ 0.10	0.029
Total	–	–	NS
Psychological Well-being Scale			
General positive effect	+ 0.20	–	NS
Emotional ties	+ 0.18	+ 0.14	NS
Life satisfaction	–	–	NS
Total	+ 0.24	+ 0.12	NS
General Perceived Health Scale			
Vitality	+ 0.15	- 0.20	0.007
General health status	–	- 0.20	0.011
Sleep disturbance	–	–	0.015
Total	+ 0.12	- 0.21	<0.001

+ = improvement.

balance, it is probably worth treating mild hypertension, diastolic pressure 90–99 mmHg, in men aged 40–59 but we must be confident that the drug treatment has not impaired QOL. The case has still to be argued for treating very mild hypertension in young women. A possible strategy would be to treat those at higher risk: namely those in their 50s, who smoke, have diabetes mellitus or other cardiovascular risk factors. The risks of stroke or coronary event in non-smoking young women of 40 with a diastolic pressure of 95 mmHg are so low that many may prefer simply to be followed. A proportion will become normotensive, a number will develop moderate to severe hypertension and need treating and others will become more 'at risk'. Eventually all will become older and be considered in the next section. The 'hygienic' methods of reducing blood pressure have not been dealt with owing to lack of data on morbidity and mortality. Nevertheless all hypertensives should stop smoking, irrespective of the effect on blood pressure and obese persons should lose weight. Exercise is usually promoted both in its own right and as a means of lowering pressure. A diet low in saturated fat and salt is also to be recommended.

Persons aged 60–79, diastolic pressure high

Benefits – stroke reduction

A meta-analysis by Amery *et al.*²³ suggested that stroke events in the trials in the elderly were reduced by 40%. Table VI gives the percentage reduction in events in the six trials of anti-hypertensive treatment in the elderly. The consistency of the results is striking with percentage reductions ranging from 25% to 47%. The treatment regimes employed were based on a diuretic regime in the Australian (a subset aged 60–69),²⁴ the European Working Party on High blood pressure in the Elderly (EWPHE),²⁵ and the Sys-

tolic Hypertension in the Elderly Program (SHEP) trial.²⁶ The Hypertension in the Elderly Persons (HEP) trial²⁷ was based on atenolol and the STOP hypertension trial²⁸ was based on either a diuretic or one of several beta-blockers. In the event the vast majority of patients in this trial ended up on a diuretic. The MRC trial in the elderly²⁹ randomized active treatment to be based either on the beta-blocker atenolol or to a hydrochlorothiazide/amiloride diuretic combination. Five of the trials were concerned predominantly with diastolic hypertension but the SHEP trial was concerned exclusively with isolated systolic hypertension and will be considered in a later section.

Table VII gives the results in the MRC trial according to the randomized treatment. Both the diuretic and the beta-blocker lowered stroke rates with a tendency for a lower rate on the diuretic in non-smokers.

Benefits – reduction in cardiac events

In the MRC elderly trial total coronary events were reduced by 44% with a hydrochlorothiazide/amiloride combination but not by atenolol²⁹ (Table VII). In other studies employing a beta-blocker (Table VI) the reductions in total cardiac events were 15% (the HEP trial²⁷), and 13% (the STOP trial²⁸). The corresponding reductions when a diuretic was employed were 19% (Australian trial, age 60–69²⁴), and 20% (EWPHE trial²⁵). In the MRC elderly trial²⁹ the investigators have reported benefits from using a diuretic over and above the effects of lowering blood pressure and a similar finding has been reported in the STOP trial for all active treatment.^{28,30} Any benefits from treatment with a beta-blocker were confined to non-smokers. In view of these findings, Beard *et al.*³¹ recommended diuretics rather than beta-blockers for elderly patients with uncomplicated hypertension. As the earlier MRC trial indicated a doubt concerning the ability of propranolol to reduce stroke events or coronary events in smokers this may be good

Table VI Percentage reduction in stroke and cardiac events, and reduction in total mortality in the six trials of anti-hypertensive treatment in the elderly^{24–29}

	Stroke			Cardiac			Total mortality
	Non-fatal	Fatal	All	Non-fatal	Fatal	All	
Australian ²⁴	– 37	– 1	– 34	– 10	– 75	– 19	– 23
EWPHE ²⁵	– 35	– 32	– 36*	– 9	– 38*	– 20	– 23
Coope and Warrender ²⁷	– 27	– 70*	– 42*	– 26	+ 1	– 15	– 3
STOP ²⁸	– 38*	– 73*	– 47*	–	– 25	– 13	– 43*
MRC ²⁹	– 30	– 12	– 25*	– 13	– 22	– 19	– 3
SHEP ²⁶	– 37*	– 29	– 36*	– 40*	– 20	– 27*	– 13

* $P < 0.05$.

Table VII Events/1,000 patient years in the MRC elderly trial²⁹

	<i>Diuretic group</i>	<i>Atenolol group</i>	<i>Placebo group</i>
Total stroke	7.3	9.0	10.8
Total coronary	7.7	12.8**	12.7
Cancer deaths	7.8	9.3	7.8
All deaths	21.3	26.4*	24.7

***P* = 0.006; **P* = 0.07.

advice. Although the benefits of beta-blockers are fully established in the secondary prevention of MI, the possibility that this action could be translated into a beneficial effect on primary prevention could only be observed in young non-smokers. It would appear wise to avoid beta-blockers in the elderly and this would appear reasonable if we take into account the greater tendency of the elderly to heart failure and chronic obstructive airways disease. In the elderly and the middle-aged male smoker, diuretic treatment may be preferable as first line treatment. Table VII indicates that total mortality was not reduced in the atenolol group of the MRC elderly trial.

The cardiovascular event rate is much higher in the elderly and these persons have more to gain from treatment. Table VIII gives the number of patients that need to be treated for 5 years to prevent one event. The returns from treating the elderly are much greater than for younger persons. In the more hypertensive patients in the EWPHE trial (average untreated pressure 182/101 mmHg) only 10 have to be treated for 5 years to prevent both a stroke event and a cardiac event.

The risks

In the trials the risks of treatment depend on the exact nature of the anti-hypertensive treatment and

range from potentially life-threatening events, to biochemical changes not known to be associated with symptoms, and to adverse effects on quality of life. The risks in the EWPHE and MRC elderly trials are given in Table IX. In the EWPHE trial important consequences of diuretic treatment included gout, 4/1,000/year and diabetes mellitus 9/1,000/year.²⁵ The latter was associated with starting oral hypoglycaemic drugs in 7/1,000/year. Active treatment was also associated with a need for peripheral vasodilators in 7/1,000/year.³² Table IX also indicates that a certain degree of mild hypokalaemia and an elevated serum creatinine will be expected in actively treated patients. As deaths from cardiac causes and renal failure were not increased on active treatment these biochemical changes were presumably, on balance, of little clinical importance. An excess of 12% of patients reported dry mouth and 7% diarrhoea. These symptoms appeared to be mainly due to the methyldopa treatment received by a third of patients on active treatment.

These risks must be contrasted with the benefits. For example, in the EWPHE trial 4/1,000 will get gout in 1 year, nine diabetes and over 120/1,000 will get side effects of drugs. Set against this is the saving of six per 1,000 for fatal strokes, 11/1,000 for non-fatal strokes, 11/1,000 for fatal cardiac events and 8/1,000 for episodes of severe congestive heart failure.

In the MRC trial the adverse events leading to withdrawal have been published and are given in Table IX. The burden of adverse events appear similar to that in the EWPHE trial. The side effects only appear to be less frequent as these adverse events had to be severe enough to cause withdrawal of the patient from the treatment.

These risks have to be compared with the gains in all treated patients of 3/1,000 patient years for all strokes, and 2/1,000 for all coronary events. For diuretic treatment the gains were 4/1,000 and 5/1,000 patient years, respectively.

Table VIII Number of patients needed to be treated for 5 years to save one stroke event and one cardiac event in the MRC trials^{5,29} and the EWPHE trial²⁵

	<i>MRC trials</i>		
	<i>Younger patients</i> <i>(mean age 52)</i>	<i>Older patients</i> <i>(mean aged 70)</i>	<i>EWPHE trial</i> <i>(mean age 72)</i>
<i>Basic treatment</i>			
		<i>Stroke event</i>	
Diuretic	110	60	10
Beta blocker	280	110	–
		<i>Cardiac event</i>	
Diuretic	No benefit	40	10
Beta blocker	No benefit	No benefit	–

Table IX Risks: differences between active and placebo treatment in the EWPHE²⁵ and MRC elderly²⁹ trials (expressed as number/1,000/year)

	<i>EWPHE</i>	<i>MRC</i>	
		<i>Diuretic</i>	<i>Atenolol</i>
Gout	+ 4*	+ 4*	0
Mild hypokalaemia ($K^+ < 3.5$ mmol/l)	+ 71*	—	—
Elevated serum creatinine (≥ 180 μ mol/l)	+ 23*	—	—
Diabetes	+ 9	+ 4*†	+ 3*†
Dry mouth	+ 124*	—	—
Diarrhoea	+ 71*	—	—
Need for hypoglycaemic drugs	+ 7	—	—
Need for peripheral vasodilators	+ 7	—	—
Skin disorders	—	+ 3*	—
Muscle cramp	—	+ 5*	+ 1
Nausea	—	+ 6*	+ 3*
Dizziness	—	+ 6*	+ 9*
Raynaud's	—	+ 1	+ 11*
Dyspnoea	—	+ 1	+ 22*
Lethargy	—	+ 4	+ 17*
Headache	—	+ 3	+ 6*

* $P < 0.05$, for difference between active and placebo rates; †impaired glucose tolerance. The MRC data are reasons for withdrawal. — = data not published.

Conclusions

The risk-benefit analysis in the EWPHE trial is clearly in favour of treatment. In the MRC elderly trial, the results are less convincing but do support a policy of treating the patients entered in the EWPHE trial – those with sustained DBP ≥ 90 mmHg plus SBP ≥ 160 mmHg.

Persons aged 60–79, isolated systolic hypertension

Only one large trial has investigated the effect of treating isolated systolic hypertension, the Systolic Hypertension in the Elderly Program (SHEP) trial.²⁶ This trial only included persons over the age of 60, average age 72 years.

Table X gives the benefits observed in this trial. Fatal cerebrovascular events were little influenced by treatment but non-fatal strokes were reduced by 5/1,000 patient years. Fatal coronary events were reduced by 2/1,000 patient years, non-fatal myocardial infarction also by 2/1,000/year, left ventricular failure by 5/1,000/year and coronary artery bypass grafting by 2/1,000/year. Forty-three per cent of the MRC elderly trial had isolated systolic hypertension and the trial reported 'there is no reason to doubt the applicability of the overall trial results to those with isolated systolic hypertension'.

The risks for treatment in the SHEP trial are also given in Table X. The biochemical adverse effects appear to be qualitatively and quantitatively

similar to those observed in the other trials. In view of the fact that cardiac morbidity and mortality were reduced by active treatment, the increases in serum glucose and cholesterol and reductions in serum potassium did not produce a *net* increase in adverse cardiac events. However, from the patient's point of view the increases in serum uric acid and glucose are likely to have had clinical consequences in some patients, namely those who developed gout or symptoms due to diabetes mellitus.

The SHEP research group reported on 29 symptoms, 27 of which were more frequent in the actively treated group. The exceptions were 'heart beating fast or skipping beats' and 'severe headaches'. The nine symptoms with the greatest excess in the actively treated group are given in Table X. In a separate publication the trial has reported that active treatment increased the time to complete the Reitan Trail Making Test by 3 seconds.³³ This test of psychomotor speed and cognition is compatible with the report of an excess of memory problems in 60/1,000 in Table X. The excess of chest pain and pain in joints is surprising but the complaint of cold hands and swollen ankles may be related to the use of atenolol or other beta-adrenoceptor drugs that were employed in over 20% of actively treated patients.

The risks from treating isolated systolic hypertension appear to be as great as for treating combined systolic and diastolic hypertension, yet the absolute benefits are less, at least for mortal events. In proportional terms the evidence so far

Table X Differences between active and placebo treatment in the SHEP trial²⁶ (numbers are for events occurring any time during the trial)

<i>Benefit</i>	<i>Number/1,000/year</i>
Fatal cerebrovascular events	0.4
Non-fatal cerebrovascular events	5
Fatal coronary events	2
Non-fatal myocardial infarction	2
Left ventricular failure	5
Coronary artery bypass graft	2
<i>Risk</i>	<i>Number/1,000</i>
Serum uric acid > 595 µmol/l	40
Hypokalaemia (K ⁺ < 3.2 mmol/l)	31
Serum sodium < 130 mmol/l	28
Serum glucose > 11.1 mmol/l	17
Serum cholesterol > 7.8 mmol/l	22
Passing out	9
Heart beating slowly	17
Chest pain	76
Cold hands	38
Ankle swelling	39
Memory problems	60
Sexual problems	16
Change in bowel habits	40
Pain in joints	50

suggests a worthwhile benefit from treating isolated systolic hypertension, but in view of the lower absolute gains, more evidence is being accrued in further trials.³⁴ Most importantly the SHEP trial showed that lowering diastolic pressure from 77 mmHg to 68 mmHg was not associated with any increase in cardiac morbidity, making it unlikely that increased cardiac mortality at low diastolic pressures can be attributed to treatment.³⁵

Persons aged 40–59 with isolated systolic hypertension

The prevalence of isolated but sustained systolic hypertension is probably less than 1% at age 50 but rises to about 5% at age 60.^{2,36} Isolated systolic hypertension is therefore not rare in the age group 40–59 years. Epidemiological data would support treatment^{36,37} but a risk–benefit analysis on the basis of a randomized controlled trial is not available.

Persons over the age of 80, any form of hypertension

The EWPHE³⁸ and STOP trials included some patients over the age of 80 but failed to provide any

convincing evidence for efficacy at this age. The epidemiological data do not provide support for treatment over the age of 80³⁹ but in the SHEP trial stroke incidence was lowered by active treatment both under and over the age of 80. Trials are required to evaluate the benefit and risks of treatment over the age of 80.

Isolated diastolic hypertension, all ages

No trial has been specifically designed to provide a risk–benefit analysis for the treatment of isolated diastolic hypertension. Moreover the definition of isolated diastolic hypertension has not been agreed, nor whether or not it would be sensible to concentrate on this condition. Trials with diastolic entry criteria alone, such as the MRC trial in middle-aged subjects must have included a proportion of subjects with DBP > 90 mmHg and SBP < 140 mmHg. However, as the mean entry systolic pressure was 162 mmHg, the trial may not have included many of these subjects. One trial in the elderly allowed entry for a high diastolic alone, the Australian, 60–69 trial²⁴ and the HEP and STOP trial^{27,28} allowed entry for either a high diastolic or a high systolic pressure. These three trials must have included some subjects with isolated diastolic hypertension but with mean entry systolic pressure of 165, 197 and 195 mmHg, respectively, there were not likely to be many such persons included in the trials. The EWPHE²⁵ and MRC, elderly²⁹ trials excluded subjects with a systolic pressure < 160 mmHg.

A risk–benefit analysis as a result of a randomized controlled trial in isolated diastolic hypertension is not available.

Conclusions

The recent publications of management guidelines by the British Hypertension Society⁴⁰ recommended treatment at age 40–59 years for sustained diastolic pressure > 100 mmHg. Treatment at lower pressures (90–99 mmHg) depends on additional factors such as being a man, having diabetes mellitus or other risk factors, or being aged 60–79. The guidelines considered that ‘Convincing evidence of the benefits of treating very old people (over 80 years) is lacking.’ For isolated systolic hypertension the guidelines made an interim recommendation that if SBP remained > 160 mmHg after 3–6 months, then the patient should be treated. The report noted that further trials are in progress to test this recommendation. The British Hypertension Society working group also noted that there are no trial data on the potential benefits of treatment for isolated systolic hypertension at

age 40–59, but recommended treatment for these persons. The Working Party did not specifically consider isolated diastolic hypertension and the

recommendation to treat diastolic hypertension, irrespective of systolic pressure, presumably applies.

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