The Benefit, Risks and Cost of Primary Stroke Prevention with Antihypertensive Drugs

Christopher J. Bulpitt

The benefits of treatment with anti-hypertensive drugs not only include a reduction in stroke incidence of 40% but also a reduction in cardiac deaths, severe congestive heart failure, severe retinal changes and almost certainly a reduction in the incidence of angina. The risks depend on the drug employed and include gout and diabetes mellitus for diuretics and symptom side effects with all drugs. Certain drugs have been proven to impair the quality of life of treated patients. The cost of an extra year of life gained is lower in men, in the elderly and at higher levels of diastolic pressure. It is desirable to adjust the years of life gained by their quality (a cost-utility analysis) but such methods await good data. (*Hypertens Res* 1994; 17 Suppl. I: S115-S119)

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The best definition of hypertension is "the level of blood pressure above which treatment does more good than harm". This definition has to be qualified by stating the level of systolic or diastolic pressure, the fact that the level should be a sustained and not transient reading, and a statement made as to whether or not the definition applies to both sexes and all ages. In order to define the benefit and risks of antihypertensive treatment we have to look at the results of randomised controlled trials.

Benefits

Collins and his colleagues (1) have performed a meta-analysis of the trial data and concluded that antihypertensive 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 Fraction of Benefit (FOB) obtained was 100%. In the elderly a meta-analysis by Amery *et al.* (2) suggested that stroke events in the trials were associated with a 40% reduction, thus confirming a similar efficacy of treatment in the elderly. 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 confirms the reduction in stroke incidence and that all drugs should be equally efficacious if they reduce pressure by a given amount. Nevertheless, stroke events were not reduced by propranolol in smokers in the first Medical Research Council trial in middle aged subjects (3), whereas bendrofluazide did reduce the risk.

This interaction between smoking and treatment has not been supported for stroke incidence in the International Prospective Primary Study in Hypertension (IPPPSH) trial (4), nor in the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial (5).

When considering the benefits of antihypertensive treatment for strokes it is also important to consider other benefits that may accrue. Collins *et al.* (1) 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 realised from antihypertensive treatment. Two possible reasons have been widely discussed, that a lag time should be considered before any benefits are realised and secondly that the drugs employed may have an adverse effect on serum lipids and thus prevent the benefits being fully realised. 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 (3). In the elderly, the MRC trial found a reduction in cardiac events of 19% (6) and other trials reported a benefit ranging from a reduction of 13% to 27% (7). The smallest reductions were observed when a beta blocker was employed as first line treatment.

In the MRC elderly trial coronary events were reduced by 44% with a hydrochlorothiazide/amiloride combination but only by 3% with atenolol (6). In other studies employing mainly a beta blocker the

reductions in cardiac event were 15% (the HEP trial, 8), and 13% (the STOP trial, 9). The corresponding reductions when a diuretic was employed were 19% (Australian trial, 10), 20% (EWPHE trial, 11) and 27% (SHEP trial, 12). In view of these findings, Beard *et al.* (7) recommended diuretics rather than beta blockers for elderly patients with uncomplicated hypertension.

The other benefits of treatment are less easy to quantify. In younger subjects accelerated hypertension with retinal haemorrhages and exudate is prevented by active treatment. Similarly it is expected that renal failure, hypertensive heart failure and multi-infarct dementia may be prevented by anti-hypertensive treatment. These events are infrequent and therefore the benefits of treatment are difficult to establish, especially within narrow quantitative boundaries. In the EWPHE trial (11) severe congestive heart failure was reduced by 8/1,000 patient years, severe retinal changes by 4/1,000 patient years (Table 1). Pulmonary embolus was not reduced by treatment and renal failure was rare, only one death occurring in the trial (this patient was taking active treatment). Anti-hypertensive treatment may also be expected to reduce angina and the need for a beta blocker was reduced by 4/1,000 patient years by active treatment (11). The prescription of a beta blocker, however, may not always have been for angina. The benefits of treatment for the EWPHE trial are summarised in Table 1.

Risks

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 trial are also given in Table 1. Important consequences of diuretic treatment included gout 4/1,000 patient years and diabetes mellitus 9/1,000 patient years (13). The latter was associated with starting oral hypoglycaemic drugs in 7/1,000 patient years. Active treatment was also associated with a need for peripheral vasodilators in 7/1,000 patient years (14). Table 1 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 of no clinical importance. An excess of 12% of patients reported dry mouth and 7% diarrhoea. This appeared to be mainly due to the methyldopa treatment received by a third of patients on active treatment. Examining Table 1, most would agree that the prevention of cardiac and stroke deaths and prevention of non fatal stroke and severe congestive heart failure were benefits that far out-weigh the disadvantages or risks of treatment.

Quality of life (QOL) was not formerly measured in the EWPHE trial and was probably impaired to some extent in the actively treated group owing to the fact that a third received methyldopa. 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 (15). This surprising finding, that QOL was 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 2. 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 treatments (16) 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 QOL (17) and it must be concluded that a impairment of QOL may occur with the alpha adrenoceptor blocking drugs. Five drugs have been associated with a good QOL, atenolol, captopril, enalapril, cilazapril and verapamil and two drugs are associated with a less good QOL, propranolol and nifedipine (17). In Table 3, three drugs are

Table 1. Differences between Active and Placebo Treatment in the EWPHE Trial (11)

Benefit	Numbers/1,000/year
Fatal cardiac events	-11*
Fatal cerebrovascular events	-6
Non-fatal cerebrovascular events	-11*
Severe congestive cardiac failure	-8*
Severe retinal changes	-4
Need for beta blocker	-4
Risk	
Gout	+4*
Mild hypokalaemia [$K^+ < 3.5$ mmol/l]	+71***
Elevated serum creatinine [≥ 180 μ mol/l]	+23**
Diabetes	+9
Dry mouth	+124**
Diarrhoea	+71*
Need for hypoglycaemic drugs	+7
Need for peripheral vasodilators	+7

* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$, difference between active and placebo rates.

Table 2. Percentage Change (+, Improvement) in 7 Aspects of Quality of Life Examined in the Treatment of Mild Hypertension Study (TOMHS)

	Acebutolol	Amlodipine	Chlorthalidone	Doxazosin	Enalapril	Placebo
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

Table 3. Relationship between Some Anti-Hypertensive Drugs and Measures of Quality of Life (QOL)

Drugs associated with a good QOL	
Atenolol, acebutolol (beta blockers)	
ACE inhibitors: captopril, enalapril, cilazapril	
Verapamil, amlodipine (calcium channel blockers)	
Diuretics	
Drugs that have been proven to impair certain aspects of QOL	
Methyldopa	(centrally acting drug)
Propranolol	(beta blocker)
Nifedipine	(calcium channel blocker)
? Doxazosin	(alpha blocker)

added, as a result of the TOMHS, acebutolol, amlodipine and diuretics for their association with a good QOL. Methyldopa is also added as a drug associated with poor QOL (18). In this table it is assumed that all ACE inhibitors are the same. 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" (19). This was surprising as side effects were similar in the two groups (Table 4) and moreover, 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 5) although there was some support from the emotional control scale and the Side Effects and Symptoms Distress Index (Table 6). 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. However, a preference for captopril over enalapril was not demonstrated in an earlier study (20) where general health (from the Psychological General Well-being scale) improved more on enalapril than captopril ($p < 0.05$).

Costs

The costs of primary stroke prevention are mea-

Table 4. Side Effects and Withdrawal Rates on Two ACE Inhibitors (Testa *et al*, 19)

	Captopril	Enalapril
Headache (%)	15	16
Asthenia (%)	9	10
Dizziness (%)	8	7
Cough (%)	5	6
Withdrawal due to		
adverse events (%)	9	8
Total withdrawals (%)	21	20

sured by cost-effectiveness, where the costs are divided by a health effect; or by cost utility where costs are divided by quality of life adjusted units of survival (QALYS). The most important health effect that has been studied is the number of years of life gained by the expenditure of money. There are no health effects that have been studied that are specifically concerned with benefits derived solely from stroke prevention. Most studies have utilised data from Western societies and thus the prevention of death from ischaemia heart disease has had a major effect on the calculations. In societies where stroke is more common than heart disease, the cost-effectiveness analysis would be more relevant to stroke prevention *per se*.

The major difficulty in cost-effectiveness analysis has been in determining the life years gained. Extrapolation from epidemiological studies has not provided the correct denominator. However, the estimates of cost-effectiveness are improving with the recent meta-analysis of the major trials providing estimates of the Fraction of Benefit (FOB) to be achieved. It does now appear possible to calculate the cost of an extra year of life, although these costs do vary according to health care system and the drugs used. The cost of an extra year of life are lower at higher levels of pressure, in men rather than women and at older ages (21). It is very difficult to examine other conditions to see if the treatment of, say, hypercholesterolaemia or non-insulin dependent diabetes mellitus costs less to achieve one extra year of life. Those who have considered the costs of treating mild hypertension have guessed whether we get "value for money" or not. The cost-effectiveness of treating diastolic pressures over

Table 5. Quality of Life Changes on Two ACE Inhibitors (Testa *et al*, 19)

	Captopril	Enalapril	<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

Table 6. Quality of Life Changes on Two ACE Inhibitors (19)

	Captopril	Enalapril	<i>p</i>
Well-being at work or in daily routine scale	0	-0.15	0.082
Sexual symptom distress	-0.19	-0.18	NS
Side effects and symptoms distress index	+0.10	-0.08	0.068
Overall quality of life	+0.11	-0.11	<0.05

100mmHg appears not to be excessive (21). A measure of cost-effectiveness does not take into account the QOL during treatment and this adjustment has been essential with certain anti-hypertensive treatments employed in the past. It is obviously important to consider both quantity and quality of life and QOL can be measured by collecting standard data on many aspects of well-being (physical and psychological) and activity. However, such measures have to be aggregated to give a Health Status Index which is utilised to adjust the years of survival and give the required QALYS. This is sensible in a hierarchical sense but does not necessarily allow us to compare, say, hip replacement with anti-hypertensive treatment. Firstly the studies have not been performed to compare such disparate conditions and secondly the numeric results will depend heavily on what is included in any assessment and the weightings given to various aspects of life. The corrections for QOL with anti-hypertensive treatment can render treatment undesirable. Although this may be true in certain circumstances, it would appear intuitively unlikely for severe hypertension. Fletcher has stated "there are sufficient problems with the current methodology to suggest we should not be using QALYS to determine treatment options" (22). Acceptance of this view does not imply that QOL cannot be measured and compared with-in, for example, a double blind randomised controlled trial. If such a trial includes an overall measure

of QOL, such as a HSI, mortality as an outcome, costs and different randomised treatments then the trial would generate QALYS which could be employed to decide on treatment options. Unfortunately no trial has measured both survival and QOL carefully enough to allow this comparison. Long term randomised trials with mortality as an outcome should include a measure of QOL and costs and provide cost-effectiveness and cost-utility comparisons. In the meantime we can only assume that the drugs are similar in their effects on survival and then calculate the cost of obtaining an extra QALY. However we already know that drugs are not similar and that, in the elderly, diuretics may be preferred to beta blockers (7). In the meantime some argue that diuretics have the most favourable cost-utility, others that this is an attribute of selective beta blockers, calcium channel blockers, alpha blockers or ACE inhibitors. Cost-utility analysis await good data, information that is unlikely to be available for at least five years.

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