Feature Article

Raised blood pressure in the aged — to treat or not to treat*

— J C Brocklehurst

Summary
There is still doubt in the over 65s as to what constitutes hypertension and whether or not it should be treated. With advancing age there is a gradual increase in systolic blood pressure in both sexes. The first difficulty is to decide what is normal; if only modest improvements in morbidity and mortality can be shown from normalising high blood pressure, the benefits cannot be regarded as certain unless side effects of the therapeutic agents are less hazardous than the anticipated risks of the untreated state. The reaction to hypotensive drugs may vary because of age effects on the regulation of blood pressure through the baroreceptor reflex. Ageing also affects pharmacokinetics and pharmacodynamics. A few studies of the treatment of hypertension in the elderly are discussed.

S Afr Fam Pract 1088;9:256-61

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Curriculum vitae
Prof Brocklehurst is Professor of Geriatric Medicine at the University of Manchester. He obtained his MBChB at the University of Glasgow in 1947, his MD with Honours in 1950 and has been awarded FRCP Edinburgh and Glasgow and an Honorary MSc from the University of Manchester in 1974. He has been very involved in the geriatric field for the last two decades, and his present appointment (since 1970) is Professor of Geriatric Medicine of the University of Manchester and a Director of the Unit for Biological Ageing Research, University of Manchester, since 1974. In January 1988 he was knighted by Queen Elizabeth. He has published nine text books on Geriatrics and has contributed chapters to twenty text books written by others. He also has over 50 scientific papers, mainly in relation to the ageing bladder and incontinence, vitamins and nutrition in the elderly, the structure of geriatric care, stroke, and the geriatric day hospital.

KEYWORDS: Blood Pressure; Hypertension; Age Factors

*Paper presented at the 6th General Practitioners Congress

While it is well established that hypertension in the under 65s should almost always be treated, there is less agreement as to its management in patients above this age and particularly those over 75. This is because blood pressure, as measured in normal populations, shows an increase with age. This has been recorded in many studies with a considerable range of difference, but in general there is a rise in systolic pressure but little change in diastolic pressure (Fig 1). There is also some difference between the sexes. Figure 2 gives an illustration of one such
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Figure 1
Mean arterial pressures by age and sex. Rhondda Fach and Vale of Glamorgan. Pooled data from four surveys. (Miall WE & Brennan PJ.)

study and since it indicates that 33% of men aged 75 have a systolic blood pressure of 190 mm Hg, which in younger people would be regarded as abnormal, the question of treating one third of the population of this age group raises real problems. This is particularly so when the side effects of the drugs involved are borne in mind. In women the case is even more striking since the mean systolic blood pressure at age 75 is about 190 mm Hg. Any effective treatment of hypertension may produce postural hypotension leading to falls and fractures in the very old. The most benign form of treatment with thiazides may produce secondary gout and elevations of serum creatinine and glucose. The drugs required for more advanced treatment have additional hazards. Therefore the case has to be strongly made in favour of hypotensive therapy in old people before it may be generally recommended.

Malignant hypertension is rare in old age and it is the complications which commonly arise from benign hypertension that are important. These include stroke, congestive heart failure and myocardial infarction.

Before proceeding to analyse the trials that have been carried out, a word or two on the measurement of blood pressure is appropriate. Everyone recognises that blood pressure is relatively labile and, indeed, that there may be some diurnal variation. The actual measurement is not always easy and it is important to distinguish which level is regarded as the diastolic blood pressure - Korotkov 4 (that is when muffling appears) or Korotkov 5 (disappearance of all sound). The latter is usually accepted as the diastolic blood pressure but difficulties may arise in patients with atrial fibrillation and in occasional others. The normal indirect method of measurement under-estimates systolic and over-estimates diastolic blood pressure when compared with direct readings from the radial artery. However, this difference is the same in the old as in the young and thus the conventional method of measurement is acceptable at all ages.

The work of the Framingham Study has shown beyond doubt that the reduction of high blood pressure in the under 65s diminishes the incidence of strokes and heart disease. Unfortunately this study has not dealt extensively with the over 65s although the most recent information does extend to those aged up to 74 and similar conclusions are reached that not only should high systolic and diastolic pressure be normalised, but that high systolic pressure alone is a risk factor in older as in younger subjects.

Rajala and colleagues from Tampere in Finland fired off a lively correspondence in the Lancet in 1983 when they published findings of hypertension in subjects aged 85 and over, based on a population study of 83% of the population of that age in Tampere. They indicated that systolic and diastolic hypertension was negatively associated with mortality in the following two years and those most at risk had a systolic blood pressure less than 110 and a diastolic blood pressure less than 70. Lindholm from Dalby in Sweden had evidence from a cohort of 174 people aged 70 and

The first difficulty in hypertension in the elderly, is to decide what is normal.
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Figure 3
Age changes in systolic blood pressure among two African tribes with contrasting ecologies: the Kikuyu, sedentary agriculturalists, and the Samburu, nomadic cattle herders. (Bourliere F & Vallery-Masson J.)*

over living in the community in which they found no difference in mortality or in cardiovascular morbidity in those with hypertension in a ten-year prospective study (Fig 3). Fry* also reported no difference in mortality in 70-year-old hypertensives. Mitchell† reported on elderly residents in old people's homes in whom hypertensives treated with methyl-dopa did worse than controls. They divided their series of 549 individuals into tertiles according to diastolic blood pressure and found that in men aged 75 to 94 and women aged 85 to 94, those in the top tertile (highest diastolic blood pressure) had the best prognosis. This study was criticised by Langford and Abernethy§ who indicated that for significant conclusions to be drawn, a sample ten times greater than that used (that is a sample of 5,000) would be needed. They suggested that the fact of admission to a residential home was itself a marker for impending death (although this would not explain the difference between the hypertensive and the non-hypertensive subjects).

Levels of blood pressure in older people may also relate to their ethnic and ecological backgrounds. For instance, a difference between two African tribes has been illustrated by Bourliere and Vallery-Masson* (Fig 4) who show a lifelong difference in systolic blood pressure levels between the Kikuyu and Samburu. In the former, systolic blood pressure rose from the age of 35 to 40 whereas in the latter it only began to rise at the age of 60. There was no difference in diastolic blood pressure. It showed no increase with age in either tribe. The Kikuyu are sedentary agriculturalists and the Samburu nomadic cattle-herders.

Complications which commonly arise from benign hypertension, especially in the aged, are important.

An attempt to dissociate the cardiovascular adaptations to high blood pressure from those simply due to ageing was made by Messerli et al† who compared a group of matched older patients with hypertension and a group of younger hypertensive patients. The mean ages were 73 and 32 years respectively, the mean systolic and diastolic blood pressures were 182/81 and 153/93. These differences gave an identical mean arterial pressure of 114 ± 16,7 for the old and 113 ± 16,2 for the young. They found significant differences between the two age groups in relation to many indices of haemodynamic and endocrine effects (eg cardiac output, stroke volume, renal blood flow, plasma renin

Figure 4
Survival rate of male and female pensioners who reached the age of 70 and had the diagnosis of hypertension (Ht) in comparison with pensioners without hypertension at that age (NHT). (Lindholm L, et al§)
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activity) and on this basis they concluded that "essential hypertension is a pathophysiological process that accelerates the physiological haemodynamic fluid volume and endocrine processes of ageing...".

The ultimate answer to the question as to when to treat lies in a study of the beneficial effects, if any, of hypotensive treatment in comparative trials in old people. A number of these have been published and I should like to consider two in some detail. The first study by Coope and Warrender is a trial within a large number of general practices of the treatment of hypertension identified on a community screening programme. The trial compared treated and untreated groups on the basis of random assignment after a number of exclusion criteria were applied. It was not, however, a placebo nor a double-blind trial for practical reasons. The blood pressure levels chosen for treatment were either a systolic of 170 or a diastolic of 105, or both. The first line of treatment was atenolol 100 mg in the morning. If necessary, bendrofluazide 5 mg daily was added and if further treatment was needed metyldopa 500 mg was added. In cases where such treatment was inappropiate, atenolol was diminished to 50 mg or withdrawn altogether.

A total of 884 subjects entered the trial, 419 being randomised to intervention and 465 as control. The average length of follow-up was three and a half years. The age range at entry was 60 to 79 years. Once patients reached the age of 80 and had been in the study for five years they were excluded from further analysis. The total study time was eight years and the mean age 69. One chance difference which arose in the randomisation was that 28% of the treatment group were smokers compared to only 21% of the control group and this will be referred to below.

On analysis there were two significant differences in outcome between the treatment and control groups, namely the higher incidence of fatal strokes and of total strokes (including transient ischaemic attacks) in the control group (see Table 1). There was no significant difference in the incidence of myocardial infarction nor in ventricular failure although there was a reduction of non-fatal ventricular failure in the treated group.

The difference in all strokes on the basis of 1000 patient years was 8.9 — which is equivalent to 112 patient years of treatment for every stroke prevented or 112 patients treated for one year to prevent one stroke. There were no important side effects in the treatment compared to the control group although there were significant biochemical changes with elevation of blood urea, serum creatinine, blood sugar and serum uric acid at both one and two years of treatment. The total death rate for the two groups was the same and there was no difference in all causes of mortality except stroke. When the subjects were divided by age into 60-69 and 70-79 (at entry) there was no significant difference between treatment and control groups in either of these two age cohorts although in the 60-69 group there were more than twice as many strokes per 1000 patient years (see Table 2).

When the smokers and non-smokers were considered separately (Table 3) there was no statistical difference in the incidence of stroke between the treatment and control group among the smokers and the difference lay, therefore, among the non-smokers. The second important study is that of the "European Working Party Trial on high blood pressure" in which physicians from nine European countries collaborated. Results were published in 1985 and 1986. This trial differed from the general practice trial of Coope and Warrender, inasmuch as the patients treated were those referred to hospital clinics and discovered to be significant in the incidence of stroke at initial screening — rate per 1000 patient years (Coope & Warrender, 1986)11

Table 2 All strokes according to age at initial screening (rate per 1000 patient years) (Coope and Warrender, 1986).11

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>X²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69</td>
<td>7.5 (9)</td>
<td>14.3 (20)</td>
<td>NS</td>
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</tr>
<tr>
<td>70-79</td>
<td>18.7 (14)</td>
<td>34.4 (24)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12.5 (23)</td>
<td>21.4 (44)</td>
<td>&lt;.03</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 All strokes according to smoking at initial screening — rate per 1000 patient years (Coope & Warrender, 1986).11

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>X²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>17.4 (9)</td>
<td>23.1 (10)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>10.5 (14)</td>
<td>20.9 (34)</td>
<td>&lt;.03</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12.5 (23)</td>
<td>21.4 (44)</td>
<td>&lt;.03</td>
<td></td>
</tr>
</tbody>
</table>
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hypertensive. The general practice trial was carried out on a random screening of a population which was not reporting illness. The minimum blood pressure measurements at entry were different inasmuch as blood pressure had to be equal to or greater than both systolic of 160 and diastolic of 90. The minimum age at entry was 60 years. The initial treatment was by hydrochlorothiazide 25 mg and triamterene 50 mg daily increasing this to twice daily if necessary and thereafter adding 500 mg of methyl-dopa, again if necessary. A total of 840 patients were entered, 416 in the treatment group and 424 in the control group, with an average period of treatment of just over four and a half years.

The ultimate answer to the question when to treat, lies in the beneficial effects, if any, of hypotensive treatment.

The findings were analysed in three ways — fatal events, non-fatal events requiring termination of the trial and non-fatal events not requiring termination of the trial. These are shown in Tables 4, 5 and 6.

In non-fatal terminating events, severe congestive heart failure occurred more than twice as often in the control group and again there was a significant difference in the total number of cardiovascular events including sudden death. In the number of non-fatal, non-terminating events, there was a significant difference in the incidence of cerebral thrombosis.

The side effects, apart from biochemical changes, were considered not important.

... another study gave evidence that there was little or no benefit in treatment beyond 80.

The second paper (European Working Party, 1986) made a separate analysis by age and blood pressure level of the data and gave some evidence that treatment benefit decreased with advancing age and that there was little or no benefit in treatment beyond the age of 80. In addition, the cardiovascular mortality and terminating events were significantly related to systolic but not to diastolic blood pressure at the time of entry.

It is concluded from this trial that the treatment of 1 000 patients each for one year, would lead to 18 fewer cardiovascular deaths, including six fewer deaths from stroke, and 25 fewer non-fatal cardiovascular events including 12 fewer strokes and eight fewer cases of severe congestive heart failure.

A comparison between these two trials indicates that while 112 patient treatment years are required to

| Table 4 Fatal events per 1000 patient years (European Working Party, 1985) |
|----------------------|---------------|---|
| **Treatment Group** | **Control Group** | X² |
| Stroke             | 9 (12)        | 15 (19)       | NS |
| Myocardial infarct. | 5 (7)         | 13 (16)       | .043 |
| Total cardiac      | 12 (17)       | 23 (29)       | .048 |
| Total cardiovascular| 30 (42)       | 48 (61)       | .023 |

| Table 5 Non-fatal terminating events per 1000 patient years (European Working Party, 1985) |
|------------------|--------------|---|
| **Treatment Group** | **Control Group** | X² |
| Severe CCF       | 5 (7)        | 13 (17)      | .014 |
| Cerebral haemorrhage | 3 (4)   | 2 (3)        | NS |
| Papilloedema, retinal haemorrhage or exudates | 5 (0) | 4 (5) |
| Total cardiovascular | 8 (11)     | 20 (25)      | .0064 |

| Table 6 Non-fatal non-terminating events per 1000 patient years (European Working Party, 1985) |
|-------------------|--------------|---|
| **Treatment Group** | **Control Group** | X² |
| Cerebral thrombosis | 4 (5)        | 10 (12)      | .026 |
| Total cerebrovascular | 9 (13)   | 20 (24)      | .053 |
| Total cardiac      | 32 (42)      | 31 (37)      | NS |

SA FAMILY PRACTICE JULY 1988 260 SA HUISARTSPRAKTYK JULIE 1988
SCHEDULING STATUS
PROPRIETARY NAME:
RENITEC* Tablet

COMPOSITION
Each RENITEC Tablet contains 5 mg enalapril maleate. Each RENITEC 20 Tablet contains 20 mg enalapril maleate.

PHARMACOLOGICAL CLASSIFICATION
A.1.3 Vascular mediators - other hypertensives

PHARMACODYNAMIC ACTIVATION
RENITEC (enalapril maleate) is the maleate salt of an angiotensin II converting enzyme inhibitor, L-arginine, followed by oral absorption, is converted to the active dihydrate form, which is a selective, long-acting, non-sodium-potassium occupying converting enzyme inhibitor.

INDICATIONS
RENITEC is indicated at all grades of essential hypertension.

CONTRA-INDICATIONS
Pregnancy and lactating mothers.

HYPERSENSITIVITY TO THIS OR ITS COMPONENTS.

DOSEAGE AND DIRECTIONS FOR USE
ORAL: Since its absorption is not affected by food, RENITEC can be administered before, during or after meals. The usual daily dosage ranges from 10 to 40 mg in all indications. RENITEC may be administered once or twice a day. The maximum dose studied in man is 80 mg daily.

In the presence of renal insufficiency, lower doses and/or less frequent administration of RENITEC may be required (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

ESSENTIAL HYPERTENSION
The initial dose is 10 to 20 mg depending on the degree of hypertension. With this dose, the patient's systolic blood pressure should be reduced by at least 10 mm Hg. If no response is obtained, the dose may be increased to 30 mg daily. The usual maintenance dose is 20 mg taken once daily. The dosage should be adjusted according to the needs of the patient.

CONGESTIVE HEART FAILURE
In the presence of renal insufficiency, lower doses and/or less frequent administration of RENITEC may be required (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

SYMPATHETIC HYPERTENSION
Sympathetic hypertension may occur following the initial dose of RENITEC. The patient should be monitored closely and the dose should be reduced before beginning treatment. If a hypotensive crisis occurs following the initial dose of RENITEC, it may not be necessary to discontinue therapy since this form of hypertension may recur during chronic therapy when RENITEC and diuretics are combined to achieve optimal blood pressure control.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Diuretics and other vasodilator therapy may be used in special situations. The combination of RENITEC with other antihypertensive drugs may increase the antihypertensive effect, especially in combination with diuretics. The combination of RENITEC with beta-blockers and methyldopa improves the efficacy of lowering blood pressure. Because of less experience, concomitant treatment of RENITEC with calcium antagonists is not recommended.

Most likely to occur in the presence of bilateral renal artery stenosis, especially in patients with renal insufficiency.

Renova'sular Hyperlsion
Hypersensitivity to the product or its components.

Pregnancy and lactating mothers.

Concomitant therapy with RENITEC and diuretics is recommended. The initial dose of RENITEC should be comprised of 10 mg or less of enalapril maleate and should be administered once daily. The dose should be increased to 20 mg daily and then according to the needs of the patient. If renal function is impaired, lower doses and/or less frequent administration may be required (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

The final conclusions to be drawn from all the evidence presented above is still uncertain in relation to the treatment of hypertension in the over 70s. It seems clear that treatment is not indicated in patients over 80 and in patients with diastolic blood pressure levels below 95. Systolic blood pressure, on the other hand, seems to be the important index for treatment as suggested from the Framingham study, and treatment should be seriously considered in asymptomatic patients with a systolic blood pressure over 190 or symptomatic patients with a systolic blood pressure over 170.

References:

SCHEDULING STATUS
PROPRIETARY NAME:
RENITEC*20 Tablet

DOSEAGE AND DIRECTIONS FOR USE
RENITEC*20 Tablet taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended. (See SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Dosage in Renal Insufficiency
Generally, the interval between the administration of enalapril should be prolonged and/or the dosage reduced.

Renal Status
Creatinine Clearance
Initial Dose/ mg/day
Mild impairment
< 80 < 30 5
Moderate impairment
30-50 20-30 10
Severe impairment
< 10 5-10 15

Side Effects
Enalapril is a dihydride, dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Congestive Heart Failure
Diuretics and other vasodilator therapy should be monitored closely and be given before and after treatment with enalapril (see PRECAUTIONS) because hypotension and consequent renal failure have been reported in patients with CHF, the usual maintenance dose is 20-30 mg daily, given in single or divided doses. The initial dose of RENITEC in patients with CHF especially renally impaired or sodium- and/or volume-depleted patients should be lowered to 10 mg and should be administered under close medical supervision to determine the initial effect on the blood pressure. If possible, the dose of diuretics should be reduced before beginning treatment. The appearance of hypotension after the initial dose of RENITEC does not imply that hypotension will recur during chronic therapy with RENITEC and does not preclude concomitant use of the drug.

Dialysis
In patients on regular hemodialysis or peritoneal dialysis who are maintained on RENITEC, plasma concentrations of enalapril are not increased. Enalapril should be administered as scheduled or when/if possible, the dose or diuretics should be reduced before starting treatment. If hypotension is anticipated, the dose should be reduced to 10 mg or less.

SIDE EFFECTS AT D SPECIAL PRECAUTIONS
Essential Hypertension
The initial dose is 10 to 20 mg depending on the degree of hypertension. With this dose, the patient's systolic blood pressure should be reduced by at least 10 mm Hg. If no response is obtained, the dose may be increased to 30 mg daily. The usual maintenance dose is 20 mg taken once daily. The dosage should be adjusted according to the needs of the patient. If renal function is impaired, lower doses and/or less frequent administration may be required (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Concomitant Therapy
Diuretics and other vasodilator therapy may be used in special situations. The combination of RENITEC with other antihypertensive drugs may increase the antihypertensive effect, especially in combination with diuretics. The combination of RENITEC with beta-blockers and methyldopa improves the efficacy of lowering blood pressure. Because of less experience, concomitant treatment of RENITEC with calcium antagonists is not recommended.