

## Are We Overtreating Hypertension

– CP Venter



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### Curriculum vitae

Professor Chris Venter is professor in Pharmacology and Therapeutics at Medunsa. He matriculated in Krugersdorp, obtained a MBChB at the University of Pretoria (1953) and then a BSc (Hons) (1969) and MSc (1973) in Pharmacology at Potchefstroom. He then changed to Medunsa where a MD was awarded to him in 1985. His professional career includes some years as a GP in Kestell, Medical Superintendent in Bethlehem, Specialist Anaesthetist in Durban and Johannesburg, several years with a pharmaceutical firm in Johannesburg before taking up his present post at Medunsa in 1982. He has a good list of publications to his credit. Chris is married and has 4 children.

### Summary

*With so many drugs available today, the danger of treating too soon too much is a real one. A few reasons why doctors overtreating are discussed: an incorrect diagnosis, inappropriate choice of drug, neglect of non-pharmacological methods, treating too much too fast and age factors. Referring to clinical trials at Medunsa, practical guidelines and suggestions are given and the final question always is: are the effects of the treatment not worse than the consequences of the treatment?*

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### KEYWORDS:

Hypertension; Drug Therapy; Drug Evaluation.

Blood pressure values are influenced by a number of factors such as emotions, physical exercise, body build, sex and also age. Shortly after birth, blood pressure is 80/45 mmHg, at the age of 4 years about 100/65 mmHg and in normal adults about 120/80 mmHg. With increasing age in adult life, the elasticity of arteries gradually decreases, which leads to a gradual increase in systolic values up to the age of 70 years whereafter it may decrease somewhat. Diastolic pressure though, in healthy individuals, increases to the age of 50-60 years, when it stabilises between 80-90 mmHg, whereafter it is inclined to decrease a little with increasing age.<sup>1,2</sup>

From the numerous clinical trials and studies that were conducted in hypertensive patients, it would appear that the cut-off point between normal

blood pressure and hypertension, lies between 90-95 mmHg in the case of diastolic pressure, and between 140-160 mmHg (depending on age) in systolic pressure. Persistent elevations above these levels are epidemiologically found to be associated with an increase in morbidity and mortality.<sup>3</sup>

It is therefore advocated that hypertension should ideally be detected as early as possible and treated aggressively to avoid target organ damage and all its consequences. Since at least 10% of our adult population is allegedly hypertensive, this policy has gained a great deal of support and public acclamation.

With the modern drugs that are available for the treatment of hypertension, it is, in the majority of patients, possible to lower blood pressure to virtually any level that may be desired. Lowering of blood pressure is however not an innocuous procedure for it may effect the quality of life adversely and may even have serious consequences on mortality and morbidity, if it is not done discreetly and carefully. Great care should therefore be taken, firstly in making the diagnosis of hypertension and secondly in the planning and monitoring of the treatment of the condition.

Hypertension can be overtreated in various ways:

- (a) By making an incorrect diagnosis

We generally teach students that it is wrong to label a patient as hypertensive on the strength of only a single measurement of blood pressure, but that the diagnosis

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should be confirmed by at least three different recordings that had been conducted on three different occasions at least one week apart. It is furthermore emphasised that patients should be completely restful and relaxed during the recordings. This is in fact the way we go about it when we screen patients and volunteers for

BP values are also influenced by emotions, exercise, body build, sex and age

prospective studies that we conduct in our hypertension clinics at Medunsa. After we have "diagnosed" patients as hypertensive on the basis of a persistent elevation of diastolic pressure above 95 mmHg on three occasions, they are entered into the first or placebo phase of a clinical trial (Figure 1). During this phase these patients receive (without their knowledge) placebo for a period of 4 weeks before they are randomised and entered in the second phase of the study. Only those patients whose diastolic blood pressures are constantly elevated above 95 mmHg are elected to continue with the trial. In our experience between 12-30% of prospective participants are eliminated from further participation in clinical trials because their diastolic pressures have fallen below 95 mmHg while they were receiving placebo.<sup>4,5</sup>

After completion of a clinical trial, a washout phase usually follows during which patients once again receive placebo prior to the commencement of a new study. Theoretically blood pressure values should return to pretreatment or baseline values

during this phase. We have however frequently observed that blood pressures of a certain proportion of patients remain within normal limits for prolonged periods (and perhaps indefinitely) after cessation of pharmacological treatment. The dictum "once hypertensive, always hypertensive", is not always true.<sup>6</sup>

It is therefore suggested that the diagnosis of hypertension should only be made with great circumspection and that the administration of placebo may be of value to establish an accurate and reliable diagnosis. It may furthermore be recommended that patients should not be kept on antihypertensive medication for indefinite periods, but that they should perhaps intermittently be subjected to "drug free periods" with the objective to assess whether they are indeed still hypertensive or not. Care should be taken though in patients who are on

centrally acting drugs like clonidine where an abrupt cessation of treatment may culminate in a severe rebound hypertension which may have disastrous consequences. In patients who have been on drugs with

Completely restful and relaxed during recordings

a long duration of action like thiazide diuretics, a considerable period of time, even several months may elapse after cessation of treatment, before they become hypertensive again.<sup>7</sup>

(b) By applying inappropriate treatment

Before embarking on pharmacological treatment of hypertension it is mandatory to assess

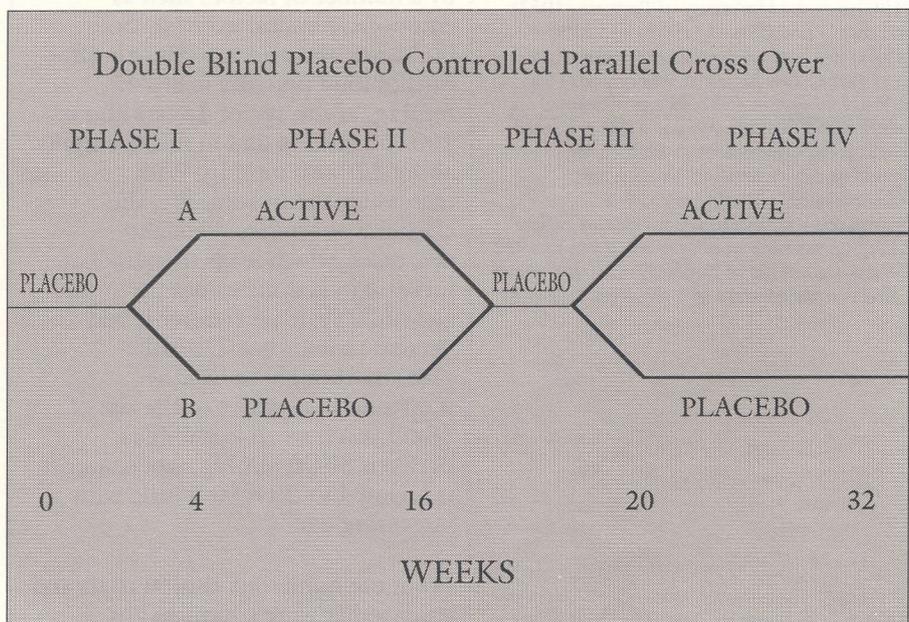


Figure 1: Design of an Anti-hypertensive Study

## ... Hypertension

whether non-pharmacological methods such as reduction in body mass, abstinence from or reduction in alcohol consumption, restriction in sodium intake, exercise in moderation... etc, may not reduce blood pressure significantly. It is furthermore of great importance to

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Lowering of BP may effect the quality of life adversely and even have consequences on morbidity and mortality

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realise that certain drugs eg non-steroidal anti-inflammatory agents, carbenoxolone, cyclosporin A, cortisone and its analogues, hormonal contraceptives and sympathomimetic amines should ideally be discontinued before it is justified to embark on the administration of antihypertensive drugs.

### (c) By using the wrong drugs

During the last four decades research has made a large number and a great variety of anti-hypertensive agents available for clinical use. On the South African pharmaceutical market about 45 mono-compounds and 25 combination products are currently available for use in hypertension. Many of these drugs which include Diuretics, Adrenergic blockers, ACE-Inhibitors, Calcium antagonists, Vasodilators and Centrally acting agents are potent and extremely effective and may cause rapid and dramatic reductions in blood pressure within a comparatively short period of time. Patients do not however respond equally well to

antihypertensive drugs, but various factors may exert an influence on the efficacy of these drugs, eg

#### *Age:*

Young patients generally respond better to betablockers or ACE-Inhibitors, while older patients respond better to calcium antagonists or alfablockers.<sup>8</sup>

#### *Race:*

Black hypertensives usually respond better to diuretics, calcium antagonists or alfablockers,<sup>9</sup> but less favourably to betablockers<sup>10</sup> and very poorly to ACE-Inhibitors.<sup>11</sup>

#### *Tobacco Smoking*

Thiazide diuretics may prevent strokes in men above the age of 40 years who indulge in tobacco smoking. On the other hand, smoking may inhibit the antihypertensive effects of betablockers.

It is thus advisable that abovenamed factors should be taken into consideration when treating hypertensive patients.

Patients should ideally receive the most effective drug in the smallest effective dosage. This would ensure that the optimum hypotensive effect

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“Once hypertensive, always hypertensive” – not always true!

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is achieved with the minimum of side effects. Using relatively ineffective drugs necessitates an unrealistic increase in dosage which is often of no avail but may only lead to an

increase in adverse effects. In cases where monotherapy is unsuccessful, or in whom severe and unacceptable side effects are encountered, it is advisable to change to suitable alternate therapy as outlined in stage 1 of the individualised approach (Fig 2). When monotherapy fails, combination therapy is indicated; not

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Adverse effects of anti-hypertensive drugs are numerous, and may even be worse than the disease itself

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only do most antihypertensive drugs act synergistically, but they frequently counter certain unwanted effects of each other, for instance:

Betablocker + Thiazide diuretic combination, where the betablocker may counter the hypokalaemia and the increased release of renin caused by the diuretic.

### (d) By lowering the blood pressure too much and/or too fast

Excessive lowering of the blood pressure is usually caused by too high doses of drugs, especially the more potent ones. The clinical effects of antihypertensive drug therapy are influenced by various factors, including:

- the level to which blood pressure is reduced.
- the rate and degree of reduction
- the age of the patient
- the drug(s) that are used
- the functional status of the patient's organs

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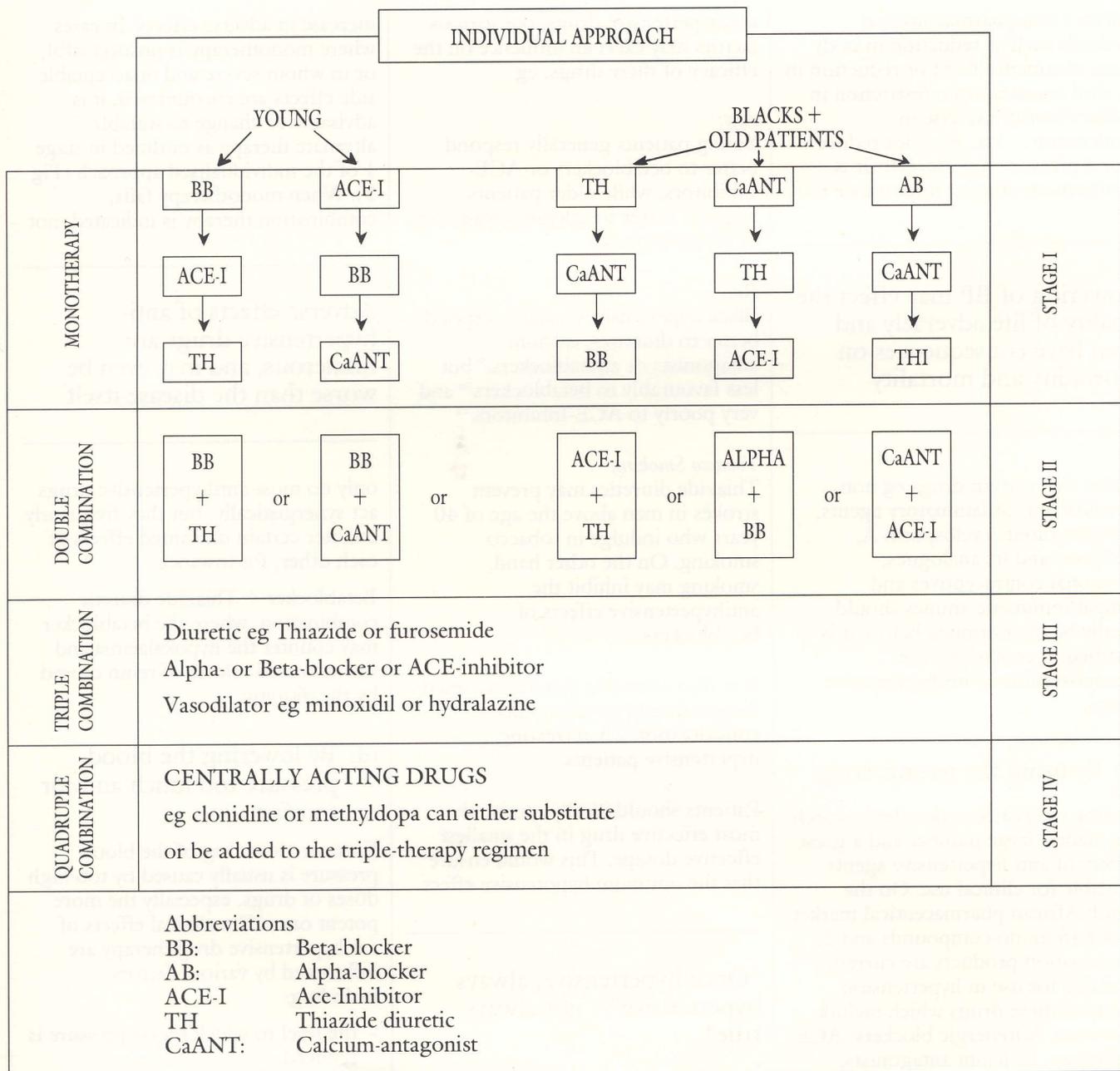


Fig 2: The Individual Approach in Anti-hypertensive treatment

(From Venter CP, Pharmacotherapy. Pretoria: MC Publishers 1989.)

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Adverse effects of antihypertensive drugs may be due to:

- (i) *The effects of the lowering of blood pressure per sé:*

This is usually encountered when blood pressure is lowered too fast and too much, especially in elderly patients. Generally speaking it may be said that diastolic blood pressure should not be reduced more than 25% in

### Lowering BP too much or too fast can be disastrous

any one week and never lower than 85-90 mmHg.<sup>13</sup> Even in emergencies the diastolic pressure should not be lowered more than 25%.<sup>14</sup> It has been shown that lowering the blood pressure in mild to moderate hypertension reduces the incidence of strokes significantly, but it has also been proven that lowering of the diastolic pressure below 85-90 mmHg leads to an increase of the incidence of myocardial infarction in patients with coronary arterial disease.<sup>15</sup>

- (ii) *The side effects of the antihypertensive drugs:*

The adverse effects of antihypertensive drugs are numerous and manifold.<sup>16</sup> They do not only vary from one drug to another and from one patient to the other, but are also influenced by age and their intensity is usually dose-related. The following are commonly encountered adverse effects of antihypertensive drugs: Sexual

dysfunction, Upper GIT-symptoms, Lethargy and Weakness, Mental depression, Dizziness and Syncope, Headache, Hypokalaemia and Orthostatic hypotension. These effects may influence the quality of life to such an extent that the treatment of hypertension may be worse than the disease and its consequences itself and it may thus have negative effects on compliance.

Dosages of drugs thus seem to be of cardinal importance in the treatment of hypertension. This was perhaps best proven in the instance of thiazide diuretics where it has been convincingly shown that relatively low doses may still exert acceptable antihypertensive effects but may cause less or even no disturbances of serum potassium, uric acid and glucose metabolism.<sup>17</sup> It may furthermore be advisable to commence treatment with fairly high doses of thiazides but to titrate them downwards after satisfactory reductions in blood pressure had been achieved.<sup>18</sup> With

### The most effective drug in the smallest effective dosage

betablockers<sup>19</sup> it also appears that a ceiling effect is reached beyond which an increase in dosage will not lower the blood pressure any further but may only aggravate their adverse effects.

- (e) *By treating hypertension in the elderly*

It is fairly generally accepted that all grades of hypertension should be

treated up to the age of 60-70 years of age. Hereafter the decision to treat or not to treat hypertension becomes controversial. It seems rather superfluous to treat uncomplicated mild to moderate essential hypertension after the age of 70-75 years and after the

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Especially with the aged always ask: are the effects of treatment not worse than the disease?

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age of 80 years little or no benefit can be derived from antihypertensive therapy.<sup>20</sup> At this stage of life lowering the blood pressure by drugs cannot really contribute much as far as reducing morbidity or mortality in these patients. The drugs per sé will certainly not improve the quality of life, but may in fact make life pretty miserable for some of those patients anyway.

In the final analysis in any hypertensive patient, and especially the elderly, the question should be asked whether the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction, or in simple language: whether the effects of treatment are not worse than the consequences of treatment? In this respect, general practitioners could play an extremely important role.

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