Opening remarks

The risk-benefit equation: when to initiate treatment

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The proceedings of the second session of the conference are devoted to a critical look at the use of angiotensin converting enzyme (ACE) inhibitors, and particularly enalapril, in the treatment of hypertension. Here, I will introduce the proceedings by giving a review of what has been called the risk-benefit equation in hypertension treatment.

It is now well known that if we take a random sample of any adult Western or Westernised population, we shall come up with a distribution of blood pressure values, as are shown in Figure 1 (Robertson, 1983). Although this distribution of blood pressure values is continuous, we are interested in the people whose blood pressures lie towards the upper end of that range because we know they are at risk of a variety of cardiovascular complications. We therefore seek to identify these people, and possibly bring them under antihypertensive treatment in an attempt to prevent the occurrence of adverse events.

Specifically, the lesions which occur more frequently and at an earlier age in those with above-average blood pressures are strokes, cardiac failure, coronary heart disease and progressive impairment of renal function. The

risk of those complications is in proportion to the blood pressure, even when measured in quite casual circumstances.

There have been, over the last 20 years, a number of placebo-controlled trials of antihypertensive drug therapy, and an assessment has been made of the ability of blood pressure lowering agents to prevent the occurrence of complications (Robertson, 1983). Figure 1 is a schematic diagram of the distribution of diastolic blood pressure such as is seen in an adult Western population and indicates the values of pressure above which a protective effect of antihypertensive therapy has been seen. Antihypertensive drug trials really began with the pioneering work of Hamilton and his colleagues in the UK in 1964 (Hamilton *et al.*, 1964). What Hamilton *et al.* (1964) showed was that protection was conferred by antihypertensive drug therapy with presenting diastolic pressures of 110 mm Hg and above.

The succeeding years have seen progressive refinement of the drug trials, and a progressive lowering of the presenting diastolic pressure above which antihypertensive drug therapy can demonstrate a protective effect against adverse cardiovascular complications. We have seen the various Veterans' Administration trials (1967, 1970), and the Australian trial, which has probably been the best of the placebo-controlled trials conducted to date. The early analysis of the Australian study in 1979 (Australian Therapeutic Trial in Mild Hypertension, 1979) suggested to the authors that a protective effect was demonstrable with presenting diastolic pressures of 100 mm Hg and upwards; subsequent analysis in more detail (Australian Therapeutic Trial in Mild Hypertension, 1980) of the Australian trial has suggested to the organisers that they can recommend antihypertensive drug therapy in adults whose diastolic pressure remains at or above 95 mm Hg. That means we now have some justification, some

Figure 1 Blood pressure values where treatment shows benefit (placebo-controlled trials). Published with permission (Robertson, 1983).

would say indication, for antihypertensive prophylactic drug therapy in a substantial proportion of what is an apparently normal, and certainly symptomless, adult population.

I have not plotted the outcome of the American Hypertension Detection and Follow-Up Program (HDFP, 1979)—a very big study that has been the subject of a considerable amount of controversy. The controversy has centred on the fact that it was not a strictly controlled placebo-matched study. In that trial people were allocated either to a special stepped-care programme in a hospital clinic, or were referred back to their regular form of medical care. In a sense, the neighbourhood physician was acting as a placebo, and not everyone has accepted that as an appropriate way of conducting a trial.

The proponents of the HDFP study would certainly suggest that the results indicate that we could take an even bigger proportion of an apparently normal adult population and recruit them for antihypertensive drug therapy. Dr Marvin Moser of New York, speaking last year (Peart, 1983), said that the results of the HDFP study suggested that we should treat adults whose diastolic pressures remained at or above 90 mm Hg. Not everyone, however, accepts the results of this trial. One of the more stern critics is Hampton of Nottingham, UK. In his view the HDFP study ought to be rejected because it was not a proper trial of the treatment of hypertension (Hampton, 1983). It was large and it involved a lot of expense, but according to Hampton its value is very limited.

Another critic, Beevers of Birmingham, UK, has called the HDFP a strange study, containing plenty of data but not much information (Beevers, 1982). However, in rebuttal, Maxwell of Los Angeles claims that the HDFP is not a strange study (Maxwell, 1982).

We do not have space to go into the ramifications of this controversy here, entertaining though that might be. I simply want to make the point that if we do accept the HDFP findings, then we are obliged to recruit an even bigger proportion of symptomless mildly hypertensive people and bring them under antihypertensive care.

The Australian study was a placebo-controlled trial and it continued for 2000 days (Australian Therapeutic Trial in Mild Hypertension, 1980). In the course of the trial there was a highly significant reduction in all hypertension-related complications in those who received active antihypertensive drug therapy as against placebo. Deaths from all causes in the course of that trial were also significantly reduced if the subjects got active treatment. It is also worthy of some emphasis that the elderly in the Australian trial

also showed benefit if they got active therapy. There were quite a number of over-60s at entry into the Australian trial: nearly 600 in all (Australian Therapeutic Trial in Mild Hypertension, 1981). In the 2000 days of the study, a significant reduction in all hypertension-related complications in the elderly getting active antihypertensive therapy was recorded.

It is important to recognise that the principal benefits that have been seen in all those studies in terms of response to antihypertensive drugs have been a prevention of stroke, a prevention or correction of cardiac failure, and an arrest of the progression of renal functional deterioration. Of great interest and no little concern is that the trials have not shown any convincing benefit in preventing deaths from coronary heart disease, although there is no doubt that hypertension is a very powerful risk factor for coronary heart disease. One of the things that we have to address in the next few years is why that has been so; why it is that despite very powerful antihypertensive drugs, we have not made much impact on deaths from coronary heart disease. A number of possibilities have been raised. I shall consider just three.

One explanation is that the controlled studies of antihypertensive drug therapy were necessarily brief. Treatment may not have been begun in them early enough, or may not have continued for long enough, for any benefit in regard to coronary heart disease to have been demonstrated, although it was demonstrable in relation to stroke prevention (Robertson, 1983).

A second possibility—one that will be central to the first papers in this session—is that some of the drugs on which we have relied for treatment of hypertension may carry, as well as some very beneficial effects, some adverse effects, especially in relation to the heart. The thiazides have come under particular suspicion in this respect in recent years.

There is a third possibility, a theoretical one, which has been argued quite cogently by Doyle (1983): that although hypertension and coronary heart disease are related, they may not stand in a causal relationship one to another.

It is with the second of these possibilities that I would like to be concerned mainly in this brief introduction.

The idea that the thiazides may not be wholly good if administered to hypertensive patients is by no means new. The possibility was raised by Doyle as long ago as 1976 (Doyle, 1976) in a meeting of the World Health Organisation, when he suggested that we should consider whether or not the use of diuretics, by inducing hypokalaemia and a reduction of total body potassium, might increase the risk of arrhythmia,

and hence of sudden death, if they were used in hypertensives who had associated coronary heart disease, as many hypertensives would. That notion was not particularly well received by the WHO at that time. Some two years later, at a meeting of the New York Academy of Sciences devoted to the therapy of mild hypertension, I again raised this question (Robertson, 1978). I suggested that we ought to address the possibility that thiazides, when used in the treatment of hypertension might well predispose to arrhythmias, and hence to sudden death. I thought also we should consider the converse proposition, that the increasing use of β -adrenoceptor blockers in the treatment of hypertension might, as well as lowering high blood pressure, possibly protect against myocardial infarction and sudden death. I can certainly vouch for the fact that this was a notion that was received with extreme coolness in New York at that time.

These ideas nevertheless have persisted and they are now the subject of at least polite conversation. A good deal more evidence has accumulated since 1978. Some of that evidence comes from an interim report of the Medical Research Council Trial of antihypertensive drug treatment still going on in the UK. As part of that trial, a study was made of 24-h electrocardiographic (ECG) ambulatory monitoring (MRC Working Party, 1983). In the study a substantial number of people, 74 allocated to thiazide and 81 allocated to placebo, were compared. They were well matched in terms of sex distribution and for age, and in both groups the duration of therapy was two years. Not surprisingly, there was a significant reduction in serum potassium in those who had been taking thiazide for two years.

On 24 h ECG monitoring it was found that in those who were receiving long-term bendrofluzide there was a distinct excess of ventricular ectopic activity, and quite a number of those ventricular ectopics were of complex form: multiform ectopics, couplets, the R-on-T phenomenon and bigeminy were seen in no less than 38% of those who were taking bendrofluzide. The precise prognostic significance of these events is by no means agreed, but I would suggest that these are hardly reassuring phenomena, and they are at least consistent with the idea that we should begin to consider whether we are doing entirely good things by giving thiazides long-term in big doses to people who may well have coronary heart disease.

There is also a pervasive rumour that one of the reasons why the Multiple Risk Factor Intervention Trial (1982) in the United States did not show distinct benefit may also have been due to the use of big doses of hydrochlorothiazide or chlorthalidone. Those participants who did have

multiple risk factors modified in that study did not show any overall benefit in terms of mortality as compared with those who did not have such formal intervention of risk factors. It has been reported that excess mortality was seen in that trial in hypertensives who had ECG abnormalities at entry if they were given hydrochlorothiazide or chlorthalidone.

I shall now turn to the converse proposition, whether or not β -adrenoceptor blockers can carry a protective effect against myocardial infarction if they are used prophylactically in the treatment of hypertension? It is obvious that if they could be shown to carry such benefit, this would put the β -adrenoceptor blockers in a very strong position in terms of primary selection for antihypertensive drug therapy. There is not as yet any direct evidence relating to that of which I am aware, but there are some encouraging signs, particularly from the secondary prevention trials where β -adrenoceptor blockers have been used after myocardial infarction. Of course this latter is not necessarily concerned with hypertensive subjects.

One of the earliest studies, and perhaps the most convincing to date, is the Norwegian trial of timolol (Norwegian Multicentre Study Group, 1981), given post myocardial infarction. After people had stabilised following a myocardial infarction, they were randomly allocated double-blind to receive either matching placebo or timolol. After three years from entry there was a 40% reduction in all deaths in those who got a β -adrenoceptor blocker as against those who got matching placebo. Not only was there a reduction in deaths from all causes, there was a reduction in all cardiac deaths, all sudden deaths, and also in reinfarction. These findings have subsequently been supported by a number of other trials of β -adrenoceptor blockers post myocardial infarction.

We are less sure, indeed we have no firm evidence, whether or not β -adrenoceptor blockers given prophylactically in the treatment of hypertension will protect against a first myocardial infarction. We have, however, some hints from retrospective work. One such study was conducted by Stewart and reported in 1976 (Stewart, 1976). This was a trial in patients with severe, and initially uncomplicated hypertension. Whether they were given a β -adrenoceptor blocker as part of their treatment depended on their response to therapy and whether or not they were getting side-effects. At the end of 5¼ years, Stewart (1976) found that those whose treatment did include a β -adrenoceptor blocker had a significant reduction in first myocardial infarctions as compared with those whose treatment did not include a β -adreno-

ceptor blocker. Of course we cannot accept this other than as an indirect hint that β -adrenoceptor blockers may be helpful.

One of the aspects which the ongoing Medical Research Council trial (1983) of the treatment of mild hypertension in the UK is designed to illuminate is precisely that. Adults with mild hypertension are initially allocated at random to receive a thiazide, placebo or propranolol. In this way it is hoped to reveal whether or not there is any differential benefit, particularly in relation to coronary heart disease, between those who receive a thiazide as against a β -adrenoceptor blocker. At the moment this remains speculative.

What is the present mould or pattern of treatment of hypertension? Is it likely that the ACE inhibitors, and particularly the newer generation of ACE inhibitors, will succeed in breaking or modifying that mould? Most people are now agreed that the initiation of therapy should be either with a β -adrenoceptor blocker or a thiazide, and for the reasons which I have put forward here, I would personally, other things being equal, favour a β -adrenoceptor blocker over a thiazide as initial therapy at present. If either of those alone were not sufficient to control arterial pressure, it is logical, and I think appropriate, to combine a β -adrenoceptor blocker with a thiazide and give the two together.

What should be added as a third drug if the combination of β -adrenoceptor blocker and thiazide were not enough has not been studied perhaps as much as it might. We have just completed a trial in Glasgow and Sheffield (McArdavey *et al.*, 1984) where we examined five different agents added on to a β -adrenoceptor blocker plus thiazide combination when that combination itself was not sufficient to control arterial pressure. Of the drugs we studied, hydralazine and prazosin came out best. We did not in that trial include a calcium antagonist. Calcium antagonists are becoming very popular, and many would suggest that a drug such as nifedipine could very well challenge hydralazine or prazosin at that stage of therapy. That remains to be evaluated.

Any drug that is to be considered as challenging established therapy has to pass certain very stringent tests. If the ACE inhibitors are to make any serious inroads in the treatment of hypertension, we have to know first how well they work. Are they effective agents, and are they effective agents if they are used initially on their own in the treatment of mild to moderate hypertension? If they are, we need to know accurately the most appropriate dose. We are well aware of a number of misfortunes where inappropriately high doses have been given of various drugs,

including the ACE inhibitors (Hodsman & Robertson, 1983), as therapy for hypertension.

If ACE inhibitors work, is their use in any way likely to be constrained or precluded because they carry a risk of serious toxic effects? If they can pass that test, we then have to consider whether they impair, even in a mild way, the ability to enjoy life: what has been termed in the jargon of the day, the 'quality of life'. It is precisely these issues which I hope will be covered in the following pages. It is evident that we can accept, and we can ask the patients to accept, a wider range of side-effects and a greater risk of toxic reactions, if we are treating a disease which carries a poor prognosis and involves a lot of symptoms, for example, cardiac failure or severe complicated hypertension. But if we are proposing to treat, often for many years, people with mild, symptomless, and initially uncomplicated hypertension, then obviously we do need drugs which are very clean and which do not impair the ability to enjoy life.

There is one other aspect of the ACE inhibitors which I should mention. We did a study in Glasgow a number of years ago, in which we combined captopril with frusemide in the treatment of previously intractable hypertension (Atkinson *et al.*, 1980). The combination of captopril with a loop diuretic was effective in controlling blood pressure in these previously unresponsive people. Despite the big doses of diuretic, the combination was capable of producing sustained reduction of circulating angiotensin II, and probably because of that reduction in angiotensin II there was also sustained reduction in plasma aldosterone. This is, I think, a very important aspect of the action of ACE inhibitors: they do produce a lowering of aldosterone, and when they are used in the treatment of hypertension, even with big doses of diuretics, we do not usually require to give potassium supplements or potassium-conserving diuretics in order to maintain potassium or magnesium balance.

In the study reported in this issue by Dr Henry Dargie (Cleland *et al.*, 1984) we looked double-blind at captopril against placebo in the treatment of cardiac failure on a fixed background of diuretic therapy with digitalis. The ACE inhibitor, captopril, in this context corrected a deficiency of total body potassium, and it also corrected a lowering of serum potassium. In association with that correction of potassium there was a significant reduction of ventricular ectopic rhythms as assessed on 24-h ECG monitoring: a reduction of ventricular couplets, salvos and ventricular tachycardia. That, of course, is the exact converse of what the MRC study (1983) showed in the treatment of mild

hypertension with thiazides. If this can also be observed when ACE inhibitors are used in the treatment of hypertension, it would obviously be very important.

It is difficult to break established patterns. When we are considering breaking the mould of antihypertensive drug therapy, we need to look at any new agents in a very stringent fashion.

This next section examines the ACE inhibitors in the treatment of hypertension. Do they work, and what is the right dose at which they work? Does the new generation of ACE inhibitors, such as enalapril, lack serious side-effects? Will

the use of these agents help protect against arrhythmias when we use them in conjunction with diuretics in treating hypertension? If they pass these various tests, we shall also need to look much more critically in the future at very subtle ways in which these drugs may interfere with quality of life (Callender *et al.*, 1983). We hope we may have agents here which are well accepted by people who are initially symptomless and who will have to take them for long periods. Any drug which permits the subject to enjoy his life to the full will be a valuable one indeed.

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