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The Relationship Between Hypertension and Coronary Heart Disease: Is Treatment for Better or for Worse?

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## INTRODUCTION

Hypertension is a major risk factor for the development of coronary heart disease (CHD) and its complications, angina pectoris, heart attack, and sudden cardiac death, along with other types of cardiovascular morbidity and mortality. (P1, K1, K2, K3, K4 ). Data from the Pooling Project (P1), a pooling of 5 epidemiologic studies which include the results of 7065 men from age 40-59, are shown in Table 1. These men were free of definite coronary heart disease upon entry into the study. The rate of deaths from all causes, the death rate from coronary heart disease, and the rate of coronary events, non-fatal MI plus coronary heart disease deaths are shown with respect to diastolic blood pressure at the study baseline. Mild hypertension, with a diastolic blood pressure of $90-104 \mathrm{~mm}$ Hg increases coronary event rate $75 \%$ compared to men with diastolic blood pressure less than 80 mm Hg . Moderate hypertension, with a diastolic blood pressure of $105-114 \mathrm{~mm} \mathrm{Hg}$ increases the coronary event rate by $88 \%$. If hypertension is complicated by left ventricular hypertrophy (LVH) as judged by highly specific but not very sensitive ECG criteria (LVH-ECG) the prognosis for coronary heart disease is ominous. LVH-ECG including repolarization abnormalities (ST-segment and Twave changes) is associated with a six-fold increase in mortality from coronary heart disease. (K5,K6). Increased left ventricular voltage alone, without repolarization abnormalities, triples the risk for coronary events. (K6). Detection of LVH by echocardiography (LVH-ECHO) has proved to be an excellent means of detecting $L V H$ and $a \operatorname{valuable}$ adjunct to the ECG. ( $\mathrm{R} 1, \mathrm{D} 1, \mathrm{D} 2, \mathrm{D} 3, \mathrm{~S} 1, \mathrm{~W} 1$ ). In a recent study of 140 hypertensive men followed for a mean of 4.8 years, detection of LVH-ECHO was associated with an incidence of coronary events ( $14 \%$ ) almost 3 times as high as in hypertensive men without

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LVH-ECHO (5\%). (C1). The prevalence of hypertension in the US is high, afflicting $30 \%$ of the population. Mild-to-moderate diastolic hypertension, from 90 to 114 mm Hg , is the commonest, afficting about $20 \%$ of the population. (J2).

One would predict, on the basis of these overwhelming epidemiological data, that treatment of hypertensive patients should be associated with a clear-cut decrease in morbidity and mortality from coronary heart disease along with a decrease in the overall toll from other cardiovascular complications including development of LVH, stroke, cerebrovascular deaths, congestive heart failure, and accelerated hypertension. But such an effect on coronary heart disease endpoints from anti-hypertensive therapy has been hard to show. The results of clinical trials have often been perplexing and sometimes have seemed to be contradictory. Different interpretations of the data have led to differing, sometimes contradictory, conclusions and recommendations. Considerable new data have been presented in the last two years. The purpose of this review is to take a fresh look at the status of coronary heart disease and anti-hypertensive treatment. I will look for answers to three questions:

1. Does anti-hypertensive therapy of mild-to-moderate hypertension reduce mobidity and mortality from coronary heart disease?
2. Which hypertensive patients should be treated with the aim of reducing the toll from coronary heart disease?
3. Does the type of antihypertensive therapy matter?

For this review, I have limited consideration of the large clinical trials to those studies that included at least several hundred subjects and that had a mean follow-up period of at least 3 years. There are 10 such studies. One of them, the Heart Attack Primary Prevention in Hypertension or HAPPHY Study, was just presented at a meeting in the fall of 1986. A full
report has not been published. Therefore, the data that $I$ will discuss are derived for the most part from nine clinical trials. Six trials were controlled with a placebo or no-treatment group. Two trials compared the results of carefully conducted antihypertensive treatment with usual care in the community. Two trials, one with a placebo group as well, compared therapy based on diuretic therapy with therapy based on beta-blockers.

## CLINICAL TRIALS WITH PLACEBO OR NO-THERAPY CONTROLS

Table 2 outlines the design features of the six trials that compared anti-hypertensive therapy with placebo administration or with no therapy. The first of these, the Veterans Administration Cooperative Study (VA), that was first published in 1970, is the classic well-designed study on the efficacy of treatment of mild-to-moderate hypertension. (V1, V2). It came three years after the report from the same group of investigators on the remarkable effectiveness of treatment of severe hypertension. (V3). The most recent reports, from the European Working Party on High Blood Pressure in the Elderly (EWPHE) (Al) and the study supported by the Medical Research Council of the United Kingdom (MRC) (M1), were published just over a year ago.

With the single exception of the EWPHE trial, the subjects studied were predominantly middle-aged, the mean age ranging from 44.4 in the Public Health Service Hospitals Cooperative Study (PHS) (S2), to 52.8 in the VA trial. The EWPHE trial enrolled only patients aged 60 and older. The mean age was 72.

All the patients in the VA and Oslo (Hl) trials were male. Men comprised 80\% of the PHS trial, $63 \%$ of the Australian Therapeutic Trial in Mild Hypertension (Australian) (M2), and $52 \%$ of the MRC trial. In only one trial, the EWPHE trial, were men in the minority, making up $30 \%$ of the total. The sex ratio is important in analyzing the trials, for even in hypertensive patients, coronary heart disease endpoints are far commoner in men than women.
 ABBREVLATIONS: DB = double blind, SB=single blind, HCTZ = hydrochlorthiazide, HDRZ - Hydralazine, CrZ -
 1. These data should be used cautiously because there was no uniform definition of LVH among the studies
2. Patients vith blood glucose higher than 7.2 mmol/L were given only a Phase II drug. 72 patients vere
$\begin{array}{llll}\begin{array}{lll}\text { Met change in DBP, } \\ \text { Treated-control }(\text { minh })\end{array} & -19 & -10 & -10\end{array}$


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The greater the proportion of men in such studies, the greater power it has for examining the differences in the rates of coronary events.

With the exception of the Oslo trial, subjects were enrolled with blood pressure elevations that ranged from mild to moderate with the lower limit of diastolic blood pressure ranging from 90 to 95 mm Hg and the upper limit from 109 to 119 mm Hg . The 0 slo trial was confined to a somewhat milder group of hypertensives entering only patients with diastolic pressures of 95 to 99 mm Hg or systolic pressures of 150 to 179 mm Hg .

The VA trial was the most liberal in entering patients with existing cardiac disease. Only patients with severe cardiac involvement were excluded. The other trials excluded patients with any active cardiac disease. The PHS and 0slo Studies excluded patients with any cardiac disease except left ventricular hypertrophy. The degree of cardiac damage at the study baseline is also an important issue to keep in mind when analyzing these studies. One would expect a larger number of coronary endpoints during follow-up in patients with pre-existing cardiac disease than in patients without it.

The VA, PHS, Oslo, and EWPHE Studies were moderate in size, each en rolling several hundred patients. The Australian trial was much larger, enrolling almost 3.5 thousand subjects. The MRC trial was huge, enrolling over 17,000 hypertensives.

The time of active follow-up was only moderately long in all of these studies. Follow-up ranged from a mean of 3.8 years in the VA study to over 7 years in the PHS Study. In the other studies mean follow-up was 4 to 5.5 years.

All but the PHS study utilized a step-care approach to treatment. In that study all patients received diuretic and sympatholytic therapy. The VA study utilized a step-care approach only in a limited sense. All patients
received diuretic, sympatholytic and vasodilator therapy. The second step was merely an increase in vasodilator dose. Three studies utilized a step-care approach similar to that commonly used in clinical practice now: diuretic therapy as step 1 and addition of sympatholytic therapy as step 2. The Australian trial had a third step allowing addition of vasodilator or switch to yet another sympatholytic agent. The MRC trial had two separate treatment modes. In the first, step one was beta-blocker and step two was addition of a central sympatholytic. In the other active treatment group, step one was diuretic and step two was addition of a peripheral or central sympatholytic agent.

The net decrease in diastolic blood pressure in the treated group, that is the drop in the treated group less the drop in the control group, was greatest by far in the VA trial, -19 mm Hg . It was -10 mm Hg in the PHS and Os lo trials, -8 mm Hg in the EWPHEtrial, -6 mm Hg . In the Australian trial and only -5.5 mm Hg in the huge MRC trial. This rather small net treatment effect in the MRC trial has been the subject of discussion and criticism. There is a dual reason. The drop in blood pressure in the treatment groups was less than hoped for and the drop in the placebo group was greater than expected. A detailed analysis of the findings of these studies other than on coronary heart disease is beyond the scope of this review, but a brief discussion of these findings is necessary to put the coronary heart disease findings into proper perspective. Protection against stroke, congestive heart failure, accelerated hypertension, and development of left ventricular hypertrophy have been found rather uniformly. The Australian and EWPHE trials also showed a statistically significant reduction in all cardiovascular disease deaths. There was a strong trend in that direction in the VA trial.

Table 3 outlines the results of these six trials on coronary heart

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disease endpoints, non-fatal MI, coronary heart disease death, and the combination of these two, referred to as coronary events. The results on coronary heart disease endpoints are much more difficult to analyze. In these six trials, there were only two endpoints that were statistically significant or nearly so. In the EWPHE trial, coronary heart disease deaths were decreased $37 \%$ by antihypertensive therapy $(p=0.036)$. The same endpoint was reduced $55 \%$ in the Australian trial $(p=0.051)$. (The Australian trial was stopped at that point because total mortality, all cardiovascular causes of death, and all cardiovascular endpoints were significantly reduced by antihypertensive therapy). There were similar strong trends in the VA and PHS studies. In reviewing these six studies, there is no apparent trend favoring a reduction in non-fatal $M I$. Therefore, in reviewing the coronary event rate, only a trend favoring a rather small, perhaps $10 \%$ reduction emerges, which owes largely to a reduction in the coronary death rate.

## CLINICAL TRIALS HITH CUSTOMARY CARE IN THE COMNURITY CORTROLS

In the early $1970^{\prime}$ s, the National Heart, Lung, and Blood Institute assembled panels to make recommendations on the need and feasibility of trials to address risk factors for cardiovascular disease. One of the major issues was whether risk factor modification could lower mortality and morbidity from coronary heart disease. From the recommendations of these panels came two very large studies that compared special intervention in special clinical centers with customary care in the community. The first of these, the hypertension detection and follow-up program (HDFP) (H2,H3,H4,H5), restricted their efforts to correction of hypertension. The second, the Multiple Risk Factor Intervention Trial (MRFIT) (M3,G1), was designed to treat hypertension, and to make efforts to diminish tobacco smoking and to lower serum cholesterol by nutritional changes. The aim was to identify men in the highest decile of

TABLE 4
MIID-TD-MODERATE HYPERTENSION ARD CORONARY HEART DISEASE
DESIGN FRATURES OF TWO TRIALS WITH COMNINITY CARE CONIRTLS

risk for development of coronary heart disease. Sixty-two percent of all patients en rolled were hypertensive. Table 4 outlines some of the design features of these two trials. Like most of the six studies just described, the subjects were mostly middle-aged. The mean age at entry was 51 for HDFP and 46 for MRFIT. Slightly over half of the subjects in HDFP and all of the MRFIT subjects were men. MRFIT limited enrollment to patients with mild to moderate hypertension. HDFP had no upper limit, but there were relatively few patients enrolled with diastolic blood pressure 115 mm Hg or higher. HDFP, like the earlier VA study, excluded subjects with cardiac damage only when it was severe. MRFIT was more conservative; it excluded men with angina or known MI. Both studies were huge. There were almost 11,000 subjects in HDFP and just over 8,000 hypertensive subjects in MRFIT.

The more aggressively treated groups, called stepped care (SC) in HDFP and special intervention (SI) in MRFIT were treated with very similar regimens. The first steps were diuretic therapy. The second steps were addition of sympatholytic therapy. MRFIT, but not HDFP, included a betablocker as a choice along with reserpine and alpha methyl DOPA (AMD). The third steps were addition of vasodilator and the fourth addition of another sympatholytic agent, guanethidine. HDFP had a fifth step of other approved drugs for the few who did not respond to steps 1-4. Bothtrials succeded in lowering the absolute levels of blood pressure. But the control patients who received customary care in the community [referred care (RC), HDFP; usual care (UC), MRFIT] had a greater drop in blood pressure than had been anticipated when the study was designed, so the net reduction in blood pressure between treatment and control groups was rather small, 5 mm Hg for HDFP and 4 mm Hg for MRFIT. The results of these two trials on coronary heart disease endpoints are shown in Table 5. So far, MRFIT has published only


mortality data. The death rate was practically identical in SI and UC groups. There were some positive results from $H D F P$. There were 15 fewer deaths in the SC group than there were in the RC group, a $20 \%$ reduction that was not statistically significant. The decline in the incidence of myocardial infarction and coronary events was presented in this study based upon how the information was determined. Sensitive, yet specific detection of MI in a study such as this is quite difficult. Detection of new pathologic $Q / Q S$ change on occasional ECGs is very specific but insensitive. Adding cases based upon medical histories and a standardized questionaire (the Rose Questionaire) is likely to be fairly sensitive but less specific. Presumably, however, in a large study such as this, the errors in both groups would be comparable allowing the judicious use of subjective as well as objective analysis for MI detection. There was only one fewer MI by Q/QS criteria on ECG. But when the data are analyzed using subjective criteria for MIs, statistically significant reductions in the MI rate from 16 to $23 \%$ were detected. The number of coronary events is similarly affected depending on the way of reckoning MI. With pathologic $Q / Q S$ changes on ECG, there were 19 fewer events, a statistically insignificant reduction of $9 \%$ but adding subjective MI detection, the reduction of coronary events ranges from 16 to $21 \%$ and was statistically significant.

The HDFP also looked at the incidence of angina in the $S C$ and $R C$ groups. The prevalence of angina at the study baseline in the SC group, $7.6 \%$, was slightly higher than the $7.2 \%$ incidence observed in the RC group. But at each of the three blood pressure strata of mild, moderate, and severe hypertension, there were significantly fewer patients experiencing angina in the SC than in the RC groups. The reduction was $15 \%$ for mild hypertension, $43 \%$ for moderate hypertension, and $54 \%$ for severe hypertension. The total reduction was $28 \%$.

There is certainly no entirely satisfactory way to pool the results of these eight trials to get a better overview. Nevertheless, recognizing the hazards, I have simply summed the incidences of non-fatal MI, CHD death, and coronary events in Table 6. Using this approach, there were $10 \%$ fewer deaths with therapy and either $8 \%$ or $12 \%$ fewer coronary events, the former using the HDFP MI incidence limited to $Q / Q S$ changes, the latter using all criteria for MI in that trial.

If the angina data from the $H D F P$ were included along with MI as a morbidity endpoint, the overall results favoring therapy would be even stronger.

These are the data available to address the question: Does antihypertensive therapy of mild-to-moderate hypertension reduce morbidity and mortality from coronary heart disease? There is not now a consensus on the answer to that question and debate will doubtless continue. I amprepared, however, to cautiously conclude that the answer is probably positive. I base that conclusion on the following:

1. The simultaneous overview of all the trials showing an overall benefit, even if a small one.
2. The statistically significant positive findings in the HDFP and the EWPHE trial, and the nearly significant positive findings of the Australian trial.
3. The lack of any statistically significant negative findings.

But the benefit a rather disappointingly small one. Assuming that the patients enrolled in these studies were like those of the Pooling Project and had a doubled likelihood of a coronary event, complete amelioration of the excess risk would reduce coronary events by $50 \%$, roughly five times what was found.

## MILD-TO-MODERATE HYPPRTENSION AND COROTARY HEART DISEASE

## SIAPRD RESULTS OF ETGHT TRTAIS OF ANTIHYPERTENSIVE THRRAPY TO PRGVENT CORONARY

HFART DISFASE ENDPOINIS

|  | No. CHD Deaths $\mathrm{T} \quad \mathrm{C}$ |  | No. Coronary Events |  | No. Subjects |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  | T | C | T | C |
| Trial |  |  |  |  |  |  |
| VA | 6 | 11 | 11 | 13 | 186 | 194 |
| PFIS | 2 | 4 | 9 | 10 | 193 | 196 |
| OSLO | 6 | 2 | 14 | 10 | 406 | 379 |
| AUSTRALIAN | 5 | 11 | 33 | 33 | 1721. | 1706 |
| EWPHE | 29 | 47 | 48 | 59 | 416 | 424 |
| MRC | 106 | 97 | 2.22 | 234 | 8700 | 8654 |
| MPFIT | 80 | 79 | - | - | 4019 | 3993 |
| HDFP | 85 | 100 | 431(125)* | 513(141)* | 4973 | 4949 |
| TOTAL DFATHS | 319 | 351 |  |  | 20614 | 20495 |
| \% | 1.5\% | 1.7\% |  |  |  |  |
| TOTAL CORONARY EVENTS |  |  | 768(462)* | 872(500)* | 16595 | 16502 |
| \% |  |  | 4.6\%(2.8\%)* | 5.3\%(3.0\%)* |  |  |
| $\begin{aligned} & \text { \% CHANGE, } \\ & \text { C-T/C } \end{aligned}$ |  | -9.6\% | $-12.4 \%(-8.1 \%)$ |  | $\cdot$ |  |

* Numbers in parentheses are values if only the MIs objectively documented by pathologic O/OS changes on ECG are included from the HDFP .

ABRREVIATIONS: $\mathrm{C}=$ Control, $\mathrm{T}=$ Treatment

## WHY IS THE REDUCTION IN CORONARY EVENTS WITH ANTIHYPERTENSIVE THERAPY ONLY ONE-FIPTH THE MAXIMUM EXPECTED BENEFIT

A consideration of why the demonstrated reduction in coronary events with antihypertensive therapy is only about one-fifth the maximum expected benefits is a necessary and interesting digression.

There are three major possibilities:

1. Anti-hypertensivetherapyisonly minimally effectivein decreasing coronary events.
2. The studies, as designed, did not have sufficient power to more frequently detect,with statistical significance differences between the treatment and control groups.
3. Treatment, at least in some subgroups, may have been deleterious and thereby masked beneficial effects in other subgroups.

## Diminished Power of the Studies to Detect CHD Endpoints with Statistical Significance

Four of the eight studies discussed above were very large. Their size was planned to give them the power to detect, with statistical significance, small changes and two of those studies did so and one almost did. Several things happened to frustrate the plans for the studies' designs and reduced the power of the studies. The mortality and morbidity rates of the control groups were lower than had been anticipated. Blood pressure in the control groups fell more than was anticipated in some studies. It would have made for more powerful studies to include more men and older subjects but the cost of such design would be to make the studies less relevant to women and a younger population.

The complexities of the interactions of the risk factors for coronary heart disease, especially male sex, hypertension, tobacco smoking, hypercholesterolemia and diabetes mellitus also affect the power of trials such as these. The other major complications of hypertension are less
affected by the other risk factors. But to design an intervention trial in the 1970s or even now in an attempt to unravel these complex interactions is impractical and much too costly.

## Could Treatment in Some Patients be Deleterious? Atherogenic Effects on Serum Lipids

The possibilities of deleterious treatment effects deserves detailed discussion. The first possibility, adverse treatment effects on serum lipids - causing a more atherogenic pattern - has received wide attention (W5). Diuretic therapy and also beta-blocker therapy - at least beta-blockers without intrinsic sympathomimetic activity - do this. This raises the question that a more atherogenic lipid profile might accelerate the atherosclerotic process and diminish or counterbalance a protective effect of lowering blood pressure. There is no clear resolution of this issue available but there is a consensus that the changes in lipids are much too modest and the treatment periods studied too short to believe that accelerated atherosclerosis was a major confounding influence in these eight clinical trials. Nevertheless, since antihypertensive therapy is often necessary for decades, this issue is an open one and deserves further investigation.

Diuretics. Hypokalemia. and VPD's
A second possible deleterious influence of therapy has also received wide attention. Diuretic therapy with thiazide or thiazide-1ike diuretics was a fundamental part of anti-hypertensive therapy in each of the studies discussed above except for the group in the MRC trial treated principally with betablockers, and $34 \%$ of that group also received supplementary therapy with diuretics. This results in reduced serum potassium levels and increased frequency and complexity of ventricular premature depolarizations (VPDs). The

MRC trial explored this issue extensively (M4, G2). Long-term bendrofluazidetreated patients had significantly more VPDs and more complex VPDs and significantly lower serum potassium levels than placebo patients. Magnesium losses as well as hypokalemia during long-term diuretic therapy have also been suggested to be associated with VPDs. ( $\mathrm{H} 6, \mathrm{H} 7$ ). A causal role of hypokalemia for the increased VPDs in the MRC study cannot be claimed, but the weight of literature regarding VPDs and hypokalemia in patients with heart disease certainly favors a causal role. The relationship between frequent and complex VPDs and sudden death in patients with heart disease is well-established. (R3). Again, we have insufficient data to reach any firm conclusions regarding the power of more frequent or more complex VPDs to diminish or counterbalance beneficial effects of lowering blood pressure in hypertensive patients. Again, there is a consensus that increased VPDs do not have that power, but this issue also remains open and will require more investigation for a firm conclusion. Comparison of beta-blocker-based and non-beta-blockerbased therapy in hypertension speaks to this issue to some degree and is discussed below.

## Is Antihypertensive Therapy In Patients <br> with ECG Abnormalities Potentially Deleterious

A third possible deleterious effect of therapy in a subset of patients was first raised by MRFIT. In this trial, a post hoc analysis of subgroups showed that men with abnormal ECGs at the study baseline who were in $t$ he $S I$ group had more CHD deaths than subjects in the UC group. On the other hand, men without ECG abnormalities at the study baseline in the SI group fared better than men in the UC group. (G1). (Table 7). The principal ECG abnormalilty (observed in $41 \%$ of cases) was tall R-waves. Atrioventricular or intraventricular conduction defects (observed in $29 \%$ of cases), and
$\mathrm{T}=$ Treatment, $\mathrm{C}=$ Control . * EVENTS = Coronary Heart Deaths for MRFIT and HDFP. Coronary heart disease deaths, myocardial infarction, and angina + abnormal
EOG during exercise for Oslo.
IRate $=$ Events per 1000 patients.
ABBREVIATIONS = SC = Stepped Care, $\mathrm{RC}=$ Referred Care, $\mathrm{SI}=$ Special Intervention, UC = Usual Care, CFD = Coronary Heart Disease,

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-40.5
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repolarization abnormalities (ST-segment deviation or T-wave inversion, observed in $26 \%$ of cases) (H8) were the commonest abnormalities. Note that in these subjects, hypertensive heart disease (especially left ventricular hypertrophy) is likely the chief cause of these ECG abnormalities followed by CHD or both disorders.

These findings prompted $\operatorname{HDFP}$ to perform a similar post hoc analysis of their data. (H8) They were able to identify 5173 men and women who, other than inclusion of women, were like the subjects of MRFIT. The major ECG abnormalities at the study baseline were similar: tall R waves in $49 \%$ of cases, conduction defects in $23 \%$ of cases, and repolarization abnormalities in $45 \%$ of cases. The overall findings in HDFP, unlike MRFIT, favor antihypertensive therapy in the $S C$ over $R C$ in patients with these ECG abnormalities at the study baseline, but the results, limited to CHD deaths, are similar to although less marked than, those of MRFIT; subjects with baseline ECG abnormalities do worse with SC than do their RC counterparts, but subjects without ECG abnormalities at the study baseline do much better with SC than with RC. (Table 7).

The 0slo study has also carried out a post hoc analysis of their data along somewhat similar lines. (H9). Since that study had a much smaller number of participants, the investigators had to compare the pooled occurrence of several CHD endpoints instead of only CHD death. These endpoints were CHD death, MI, and angina pectoris with an abnormal ECG during exercise. Recall that of all of the eight studies, the 0slo trial had the most negative results. Even with this analysis, there were no trends favoring therapy, even in the group without ECG abnormalities at baseline, but in the group with ECG abnormalities at baseline, the treatment group fared much worse than the placebo group. (Table 7).

There seems to be consensus that there may be some substance to this issue and that it deserves further investigation. These observations, if correct, certainly beg for reasons why. Again the issue of diuretic therapy, hypokalemia, and VPDs arises. It is quite likely that patients with ECG abnormalities at entry into the study had more advanced cardiac disease than did their counterparts without ECG abnormalilties. It has been observed that VPDs in the presence of heart disease are associated with a greater risk of sudden death than VPDs in its absence. (B5).

Diminished Coronary Arterial Elow Reserve in Left Ventricular Hypertrophy and CHD. Could this be Related to Possible Deleterious Effects of Antihypertensive Therapy?

I would like to propose another possible mechanism that has been little considered, namely that rapid lowering of blood pressure in patients with left ventricular hypertrophy or coronary heart disease or both may, in some circumstances, be deleterious by compromising coronary perfusion.

Under normal circumstances, oxygen extraction from the coronary arteries is nearly maximal at rest. The principal means of increasing mocardial oxygen delivery is by increased flow. Therefore, in health, coronary flow can increase about five-fold. Increased myocardial oxygen demand promptly leads to a decrease in coronary vascular resistance and a corresponding increase in flow. This normal autoregulatory capacity is referred to as normal coronary reserve. (H14). In coronary heart disease, myocardium that is downstream from a hemodynamically significant narrowing of a large epicardial vessel has already signaled for a decrease in coronary arteriolar tone. Coronary reserve in that bed is diminished or even obliterated. Coronary reserve is also diminished in LVH. (B2,M6,P2,S3). The number of capillaries do not increase
to match the increased myocardial mass. Therefore, to maintain normal oxygen delivery, flow through the existing vessels must be increased. ( $\mathrm{Bl}, \mathrm{R} 2, \mathrm{M} 5, \mathrm{M} 6, \mathrm{P} 2$ ). Furthermore, blood flow during maximal vasodilation may be diminished as a result of changes in the walls of the vessels. (M7,S4). In addition, distribution of blood flow between endocardium and epicardium is disturbed (M5). These pertubations in coronary reserve and blood flow characteristics favor development of myocardial ischemia and infarction, (M8) and when infarction occurs, larger size. (K7). In a canine model, infarction in the presence of $L V H$ was more apt to result in ventricular fibrillation than in its absence. (K7).

In the presence of $L V H$ or $C H D$, a certain coronary bed or the entire left ventricular myocardium might be dependent on a higher-than-normal perfusion pressure to maintain adequate oxygen delivery. Rapid lowering of the perfusion pressure without regression of LVH or amelioration of coronary stenoses could theoretically cause myocardial ischemia or infarction.

## ARE ALL MEANS OF EQUAL BLOOD PRESSURE LOWERING OF EQUAL BENEFIT

IN PREVENTING CHD MORTALITY AND MORBIDITY?
A number of findings in recent years have raised the question of whether all means of lowering blood pressure to an equal degree are of equal benefit in preventing complications of hypertension, especially CHD endpoints. The two issues raised earlier about agents that alter serum lipids to more atherogenic pattern and the relationship of diuretic therapy and VPDs are both germane to this discussion. A third important observation is that betablockers, at least those without intrinsic sympathomimetic activity, reduce the incidence of subsequent coronary events in survivors of MI ( $\mathrm{B} 3, \mathrm{H} 10, \mathrm{~N} 1$ ). A fourth finding is that $L V H$ regression can be effected by some regimens, but not by others. It is a reasonable hypothesis that a treatment regimen that
leads to regression of $L V H$ will be more effective in reducing coronary events than one that does not. Regression of LVH in man was shown as early as 1957 (H11) and has been confirmed many times. The effect on LVH regression is somewhat hard to sort out because many studies in man used multi-drug regimens. Nevertheless, animal and human investigations indicate that LVH regression can be effected by centrally active sympatholytics such as alpha methyl DOPA, (S5,S6,F1), peripherally active sympatholtics such as guanethidine ( 01 ), beta-blockers (W2,H12,T1,T2,C2), calcium antagonists (M9), and angiotensin-converting enzyme inhibitors. (N2,D4,S8,L1). Monotherapy with vasodilators does not cause LVH regression. (D5). Most of the data with diuretic therapy are a part of multi-drug regimens. It appears that monotherapy with diuretics also does not effect LVH regression. (D6,W3). It is noteworthy that there is a dissociation between the amount of blood pressure depression and the degree of LVH regression. (F1).

Comparison data in clinical trials to date are limited to beta-blockerbased therapy versus non-beta-blocker-based therapy (principally diuretics) in studies begun in the late 1970s. The possibility of a protective effect of beta-blockers against CHD endpoints in hypertension was given a stimulus by some observational findings in 1978 by the Gothenberg Primary Prevention Trial. (B4). A group of men with diastolic blood pressure greater than 115 mm Hg and who were treated in the hypertension clinic - mostly with betablockers as primary therapy followed by diuretics, vasodilators, and sympatholytics - had fewer coronary heart disease events than a control group of men with less severe hypertension who were not followed in hypertension clinic and whose hypertension was not treated, but who received the same anti-smoking and anti-hypercholesterolemic measures as the treated hypertensive cohort.

Table 8 shows the design features for the two trials for which extensive results have been published, the Medical Research Council of the U.K. trial (MRC) (M1) and the International Prospective Primary Prevention Study in Hypertension (IPPPSH). (I2). The MRC trial also had a placebo group (see above). The two studies were similar in several ways. The mean ages were identical, 52 years, and the age ranges were very close. Men composed about half of both trials. Both excluded advanced cardiac disease. IPPPSH was more conservative towards coronary heart disease; it excluded any such known disease altogether. The MRC admitted men with remote MI without angina. On the other hand, IPPPSH enrolled $18 \%$ of their patients with LVH-ECG compared to less than $1 \%$ in the MRC trial. This probably reflects the higher diastolic blood pressures in the IPPPSH subjects, $100-125 \mathrm{mmHg}$, than those of the MRC trial, 90-109 mm Hg. Both studies were very large. The MRC study included 8700 patients and 42,911 patient - years who received a beta-blocker-based or diuretic-based regimen. There were 6,557 patients and 25,651 patient - years in IPPPSH. The treatment protocols differed. Both had a beta-blocker based group, propranolol in the MRC and oxprenolol, a beta-blocker with intrinsic sympathomimetic activity, in IPPPSH. Secondary therapy for the beta-blocker group in the MRC trial was limited to alpha methyl DOPA but could be any other non-beta-blocker drug in IPPPSH. Sixty-seven percent received diuretics. Non-beta-blocker therapy in the MRC trial was the thiazide diuretic, bendrofluazide, as a first step. A sympatholytic could be added as a second step. In $I P P P S H$, only $15 \%$ received monotherapy with the placebo resembling oxprenolo1. Supplementary drugs could include any non-beta-blocker agent. Eighty-two percent received diuretic therapy. As noted above, blood pressure reduction in the MRC trial was a bit disappointing. Thirty to forty percent of treatment patients had diastolic blood pressures above 90 mm Hg at each of

TABLE 8

## MIID-TO-MODERATE EYPFRTENSION AND COROMARY HEART DISEASE



FRC
1985
Polulation
age, range, mean
\% men
Blood Pressure
Cardiac Disease
Exclusions

LVH, Prevalence
Size, No.
Patient years

Years follow-up,
range, mean
Beta-Blocker Regimen

Non Beta-Blocker
Regimen
52
0.3\%

8700*

42911*

35-64, 52

90-109, D
CHF, MI within
3 mos., Angina
$?-5,4.9$
I. Propranolol, up to 240
II. ADD AMD, ?
I. Bendrofluazide, 10
II. Add AMD, ?
or
add Guanethidine, ?

Change in Diastolic BP with Treatment:
Beta-Blocker
Non Beta-Blocker
ca.-9
ca. -10

IPPPSH
1985
40-64, 52

50

100-125, D
CAF, MI, Angina
$18 \%$
6557

25651

3-5,?
I. Oxprenolol, 160
as monotherapy, $30 \%$
II. Supplementary Drugs: diuretic $34 \%$; sympatholytic
$1.7 \%$; vasodilator $1.3 \%$; diuretic + sympatholytic $14 \%$; diuretic + vasodilator $10 \%$; diuretic + sympatholytic + vasodilator $9 \%$; sympatholytic + vasodilator $0.6 \%$.
I. Placebo
as monotherapy, $15 \%$
II. Supplementary Drugs:
diuretics 34\%; sympatholytic
$2 \%$; vasodilator $0.9 \%$; diuretic + sympatholytic $21 \%$; diuretic +vasodilator 11\%; diuretic + sympatholytic + vasodilator $16 \%$; sympatholytic + vasodilator $0.8 \%$ 。
$-20$
$-17$

* = These figures exclude the patients in this study on placebo.
\| = All doses given in mg.
ABBREVIATIONS: Same as for Table 2.
the anniversary visits. Nevertheless, diastolic blood pressure was dropped an average of about 9 mm Hg with beta-blocker-based therapy and about 10 mm Hg with diuretic-based therapy. Diastolic blood pressure reduction was greater in $\operatorname{IPPPSH}$, reflecting in part the higher average blood pressures at entry into the study. There was a 20 mm Hg drop with beta-blocker-based therapy and a 17 mm Hg drop with non-beta-blocker therapy.

The results of these trials in reducing CHD endpoints are outlined in Table 9. The results of both are remarkably similar. Overall, there was no significant difference between the two types of treatment, although there may be a slight trend favoring beta-blocker-based therapy. There is a difference between the sexes, however. There is no apparent difference between the two treatments for women, but there appears to be a trend favoring beta-blocker based therapy in men. Combining the results of men in both studies, all CHD endpoints were lower in the beta-blocker-based therapy: non-fatal MI by $15 \%$, CHD death by $21 \%$, and coronary events by $18 \%$. The answer to the questions raised by the differences between the sexes appears to lie in interesting post hoc sub-group analyses of the results of smokers versus non-smokers. The MRC trial found that in non-smokers, the coronary event rate was reduced overall by a beta-blocker-based regimen compared to placebo but was not reduced at all by the diuretic-based-regimen compared to placebo. The protective effect was almost totally restricted to male non-smokers. Coronary events were rare and almost equal in non-smoking women regardless of treatment regimen. Similarly, in IPPPSH, male non-smokers fared significantly better on a regimen based on a beta-blocker than on one not including a beta-blocker. The trend favoring beta-blockers overall and especially in men cang therefore, be accounted for by a protective effect of beta-blockers against CHD endpoints in non-smoking, hypertensive men. These observations point out again the complexities of the interactions of the risk factors for CHD. An additional
$\%=$ Rate per 1000 patient years．
ABBREVIATIONS：$\quad B B=$ beta blocker
Non－Fatal MI
IPPPSH
NRC
Cardiac Death
IPPPSH
NRC
Total Coronary Event
IPPPSH
MRS
No．of Subjects
IPPPSH
MRS
Patient－Years
IPPPSH
PRC


FINDINGS OF THO TRIALS COMPARING REAMERS WITH AND WITHOUT BETA－EXOCXER
MILD TO MODERATE HYPERTENSION AND CORONARY HEART DISEASE
Z6912
$\stackrel{N}{N}$
L6で
LIE
$\stackrel{\oplus}{\sigma}$
$\begin{array}{lll}0 & 8 & 9 \\ 0 & 9\end{array}$
$9^{\circ} \mathrm{G}$
$7^{\circ} 8$
$8^{\circ}$ 亿
$I^{\circ} \varrho$
$8^{\circ} \zeta$
$Z^{\circ} \zeta$
名

observation of the IPPPSH was that LVH-ECG resolved more quickly in the betablocker group than in the non-beta-blocker group.

## FUTURE DIRECTIONS

In the next few years, it seems likely that the most rapid advances in our knowledge of cardioprotective effects of various antihypertensive regimens will come from anatomic, physiologic, and biochemical studies. In man, echocardiography, Doppler ultrasonography, and radionuclide ventriculography are being used with considerable success in studying the anatomical and physiological responses of the heart to hypertension and the results of treatment on the heart. I have already mentioned the use of echocardiography as a sensitive means of detecting left ventricular hypertrophy and its regression. In recent years, attention has been given to systolic and diastolic function of the heart in hypertension. Diastolic dysfunction appears to be the earliest detectable abnormality. (Q1,H13,F2,I3,D7,S1). Systolic dysfunction appears later and the earliest response of the heart to hypertension seems to be an enhanced contractile state. Investigation in the next few years should vastly increase our knowledge of the beneficial and deleterious effects on cardiac anatomy and function of different therapeutic interventions in different subsets of patients in the evolution of hypertensive heart disease. (Q1,H13,F2,I3,D7,S1,F3,S9,D8,H15,A2,F4,B6)。 Perhaps the best example of this so far is the recent discription of a syndrome in elderly hypertensive patients of extraordinary concentric LVH, supernormal systolic function, and marked diastolic dysfunction.(T3). A11 patients who received beta-blockers or calcium blockers obtained symptomatic relief, whereas half of the patients who received vasodilators experienced hypotensive complications, including one death.

Future research in both animal and human subjects should be able to
clarify several important issues, especially: (1) The rate of LVH regression with various pharmacologic interventions and (2) Whether various treatments that effect resolution of LVH are associated with resolution of diastolic dysfunction and improvement in coronary reserve and at what rate.

## A CONCISE SUMMARY

Briefly summarized, considerable strides have been made in the last 20 years in our understanding of the relationship of hypertension to CHD endpoints. The major observations and conclusions, in my view, are as follows:

1. Hypertension approximately doubles the risk of coronary events; hypertension plus LVH increases the risk about six-fold.
2. Treatment of mild-to-moderate hypertension reduces CHD end-points, but the observed reduction is rather small, about $10 \%$, and thus difficult to demonstrate conclusively, even in large trials. The observed reduction, about one-fifth of the expected maximum benefit probably somewhat underestimates the real benefit, since the controlled intervention trials were of relatively short duration (1-8 years) and blood pressure reduction in the control groups was often greater than expected.
3. Reduction of $C H D$ endpoints with treatment of hypertension is considerably less prominent than reduction in other hypertensive complications such as stroke, congestive heart failure, development of LVH, and accelerated hypertension. This probably owes in part to the dependency of coronary heart disease on multiple risk factors with complex interactions, while hypertension alone is the major risk factor for the other complications.
4. While part of the problem of demonstrating a positive effect on coronary events conclusively may lie in inadequate power of the studies, possible deleterious effects of antihypertensive therapy must be considered and include: (a) atherogenic changes in serum lipids with diuretics and many beta-blockers; (b) diureticinduced hypokalemia and increased VPDs; (c) increased coronary events in patients with abnormal ECGs, especially LVH, receiving antihypertensive therapy, especially high-dose diuretics. I propose that this
last possibility may be due to decreased coronary flow reserve and dependency of coronary perfusion on a certain critical perfusion pressure.
5. A11 means of equal blood pressure lowering are not equally cardioprotective. Prevention of LVH development and regression of established LVH is effected by betablockers, sympatholytics, calcium antagonists, and angiotension converting enzyme inhibitors, but not by vasodilators alone and probably not by diuretics alone. An antihypertensive regimen including beta-blocker reduces the likelihood of coronary events in non-smoking men more than a regimen that does not include a betablocker, but does not clearly do so in women or men who smoke. Major advances in this area should come in the next few years in hypertensive subjects with noninvasive study of cardiac anatomy and systolic and diastolic function.

## CONCLUSIONS AND RECOMMENDATIONS

In formulating recommendations, I have relied heavily on the 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. (J1, J2). But that report was prepared in final form in February, 1984 and many of the data reviewed here have been published since then. Therefore, $I$ will take the reviewers perogative to differ on some points. In view of the limited scope of this review, my recommendations will be largely restricted to treatment of hypertension for prevention of CHD mortality and morbidity.

My first conclusion, a cautious one, is that antihypertensive therapy for patients with mild-to-moderate hypertensiong probably does reduce CHD mortality and morbidity, but only slightly by approximately $10 \%$.

A second conclusion, also a cautious one, is that antihypertensive therapy appears to be substantially more effective in preventing CHD endpoints if therapy is begun before rather than after cardiac damage, especially LVH. Such an interpretation of the data are inconsistent with the recommendations favored by some, that therapy for mild-to-moderate hypertension be held until there is evidence of end-organ damage.

The Joint National Committee recommended pharmacological therapy for patients with persistent elevation of diastolic blood pressure above 95 mm Hg and for those with diastolic blood pressures of $90-94 \mathrm{~mm} \mathrm{Hg}$ aged 50 or older or with other risk factors present for CHD or any evidence of target organ damage. For low-risk patients younger than 50 years and with pressures 90-94 mm Hg , they recommended initial non-pharmacological therapy such as weight reduction, a prudent isotonic exercise program, salt restriction, and biofeedback therapy. They noted the current controversies about initiating pharmacological therapy in patients in this least group when non-pharmacologic therapy fails to lower the blood pressure below 90 mm Hg . It would require a study of enormous magnitude and cost to specifically address this issue for an effect on CHD endpoints. I find it hard to reach a conclusion on this issue. Data from HDFP and overall data suggesting better results for preventive rather than remedial therapy favor beginning drug treatment. But in a group with low risk for $C H D$, if one chooses drug therapy it is imperative to choose a regimen very carefully, avoiding one that would increase the risk of CHD endpoints as much or more than slight blood pressure depression would decrease them. Patients not receiving drug therapy should be observed carefully. Many will progress to higher blood pressures.

A fourth conclusion is that an antihypertensive regimen chosen to prevent CHD endpoints should be one that has been shown to prevent LVH and cause its regression, and therefore should include a beta-blocker or other sympatholytic agent, angiotensin converting enzyme inhibitor, or calcium blocker.

A fifth conclusion is that an antihypertensive regimen should include a beta-blocker in non-smoking men, unless otherwise contraindicated.

A sixth conclusion is that high-dose diuretics should be avoided whenever possible to avoid increases in frequency and complexity of VPDs, especially in
patients with known or suspected cardiac disease.
A final conclusion is that it may be prudent to commence treatment in patients with LVH-ECG very carefully and with frequent observation, lowering the blood pressure gradually over a number of months and initiating therapy with a well-selected regimen for each given patient including an agent that can effect regression of LVH. It is not yet been proved that regression of LVH is a beneficial goal, but such an outcome seems likely and there is no cogent reason to think regression of LVH is deleterious. Therefore, in my view, regression of LVH in therapy of hypertension should be a goal of current therapy for patients with LVH. Similar care appears prudent for commencing therapy for the patient with coronary heart disease, especially those with ECG abnormalities. Their regimen should include agents that also prevent or mitigate myocardial ischemia, such as beta-blockers or calcium blockers. During initiation of therapy, careful follow-up is prudent to watch for any evidence of worsened ischemia.

The clinical trials reviewed this morning did not unambiguously answer all the questions that they raised, but they raised several additional new hypothesis as often happens with such trials. These trials were conducted concurrent with development of new technologies to study the heart and new antihypertensive drugs. Work in the next few years should greatly enhance our understanding of how to protect hypertensive patients from the toll of coronary heart disease.

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