The Rationale for Differing National Recommendations for the Treatment of Hypertension
Lawrence E. Ramsay, Erica J. Wallis, Wilfred W. Yeo, and Peter R. Jackson

This article examines the rationale for the differences in the guidelines for hypertension management of four national or international bodies: the Joint National Committee (JNC-V), The World Health Organization/International Society of Hypertension (WHO-ISH), the British Hypertension Society (BHS), and the New Zealand guidelines.

These guidelines agree on many aspects of management, but differ on two very important points—the drugs of first choice for hypertension, and the indications for drug treatment of uncomplicated mild hypertension. JNC-V recommends treatment routinely of all people with a sustained blood pressure of 140/90 mm Hg, whereas the BHS guidelines advise treatment routinely at 160/100 mm Hg. Such differences in the threshold for treatment have a major impact on the proportion of the adult population to be treated, and on the benefit from treatment.

JNC-V was heavily influenced by the Hypertension Detection and Follow-up Program (HDFP), which appeared to show a large benefit from the treatment of uncomplicated mild hypertension, whereas the BHS guidelines were influenced by the Medical Research Council (MRC) Trial, which showed a very small benefit. However, the apparent differences in absolute benefit between these, and other, randomized controlled trials is related entirely to differences in the absolute cardiovascular risk of the populations studied. In populations and in individual patients the benefit from antihypertensive treatment is determined by the absolute cardiovascular risk. Blood pressure by itself is a very weak predictor of risk or benefit from treatment.

In uncomplicated mild hypertension the need for drug therapy should be based on the absolute risk of cardiovascular complications, estimated by considering age, sex, serum cholesterol level, diabetes mellitus status, and smoking habits, in addition to blood pressure. Doctors cannot estimate absolute risk accurately informally or intuitively, and the next generation of guidelines should incorporate a simple but accurate method for estimating cardiovascular risk, similar to that in the New Zealand guidelines.

The decision to treat, or not treat, uncomplicated mild hypertension should be based on a formal estimate of absolute cardiovascular risk and not on an arbitrary blood pressure threshold. As regards drugs of first choice, the available evidence supports strongly the stance of JNC-V and JNC VI that diuretics and β-blockers should be preferred unless they are contraindicated, or unless there are positive indications for other drug classes. Am J Hypertens 1998;11:79S–88S © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Antihypertensive treatment, guidelines, randomized controlled trials, absolute cardiovascular risk.
In this review we will discuss three national or international guidelines for hypertension management that may be considered conventional, in that they base the need for antihypertensive drug therapy largely on blood pressure thresholds. These are the United States Joint National Committee (JNC-V),1 the World Health Organization—International Society of Hypertension (WHO-ISH),2 and the British Hypertension Society (BHS)3 guidelines. We will discuss also the New Zealand guidelines,4,5 which have adopted a different approach, in that antihypertensive treatment is targeted at estimated absolute cardiovascular risk rather than blood pressure thresholds.

AGREEMENTS BETWEEN GUIDELINES

Before highlighting the differences between these guidelines, it is important to point out that they have very many points of agreement. They do not differ significantly as regards the clinical assessment of hypertensive patients or the investigation policy recommended. The guidelines all emphasize the importance of nonpharmacologic measures to lower blood pressure, namely weight reduction, alcohol reduction, moderate salt restriction, and regular exercise. They advise attention to cardiovascular risk factors other than blood pressure, particularly smoking and hyperlipidemia. All recommend treatment of isolated systolic hypertension in the elderly. Each emphasizes the importance of indefinite follow-up of blood pressure even if treatment is not initially indicated. As regards drug therapy, all advise the use of lower doses of drugs, particularly diuretics, than were used previously and recognize the importance of observing contraindications, and positive indications, for individual classes of drug. Severe hypertension is to be treated promptly according to each of the guidelines.

A key point of agreement in the conventional guidelines is recognition that certain subgroups of hypertensive patients have a particularly high cardiovascular risk, and that in these groups even very mild hypertension should be treated. High-risk patients include those who already have cardiovascular complications, such as stroke, those with target organ damage, such as left ventricular hypertrophy (LVH), and the elderly (defined as >60 years of age). These high-risk groups are targeted for aggressive treatment because the relative risk reduction by antihypertensive treatment is approximately constant, and the absolute benefit from treatment is therefore determined by the absolute cardiovascular risk.4–6 The absolute benefit from treatment can be summarized conveniently as the number of patients who have to be treated for 5 years for one to benefit by prevention of a cardiovascular complication.7 A low number needed to treat (NNT) indicates a high chance of benefit, and vice versa. Elderly patients with severe hypertension, as in the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial,8 have a very high cardiovascular risk, a large benefit from treatment, and an NNT of only 7.6,9 On the other hand, younger patients with mild hypertension, as in the MRC Mild Hypertension Trial,10 have a much lower risk, gain less from treatment, and have an NNT of 133.6,9 In singling out these high-risk groups for special attention the conventional guidelines are in fact targeting treatment at absolute cardiovascular risk.

To a point the conventional guidelines also agree on the management of uncomplicated mild hypertension (eg, 140 to 170/90 to 105 mm Hg). The emphasis in these patients is to observe and remeasure blood pressure over a prolonged period of 3 to 6 months, during which nonpharmacologic measures to lower blood pressure are implemented. The decision on drug treatment is then based upon the average blood pressure during this period of observation. This is another method of risk stratification that aims to improve the targeting of antihypertensive treatment. In the Australian Trial in Mild Hypertension the average blood pressure at three visits discriminated very poorly between those at high or low risk of cardiovascular complications.11 On the other hand, the average of measurements over a prolonged period identified patients who remained distinctly hypertensive, who had high risk and attained a large benefit from treatment. In many patients blood pressures fall to an average that is normal (<90 mm Hg) or marginally elevated (90 to 94 mm Hg). They have a low risk of cardiovascular complications and very little benefit from treatment.11 This point is emphasized to illustrate again that the principle of treating according to absolute risk is already accepted in all the conventional guidelines.

AREAS OF DISAGREEMENT BETWEEN GUIDELINES

We note in passing that the conventional guidelines differ markedly in their length, from 28 journal pages for JNC-V1 to five journal pages for BHS.3 The point may seem trivial, but guidelines are aimed at busy generalists—how many will wade through 28 or even five journal pages? It may be appropriate to have a detailed discussion document supporting guidelines, but for ordinary practice they should surely be boiled down to one or two pages of key points. Setting aside matters of style, the conventional guidelines differ markedly in two important areas: the drugs of first choice for hypertension, and the recommendations for treating uncomplicated mild hypertension.

Drugs of First Choice Of the conventional guidelines, JNC-V alone gave unequivocal advice: "because
diuretics and beta-blockers are the only classes of drugs used in long-term trials, and shown to reduce morbidity and mortality, they are recommended as first choice agents unless they are contraindicated or unacceptable, or unless there are special indications for other agents. JNC VI again recommended diuretics and beta-blockers as initial therapy. The WHO-ISH guidelines initially recommended treatments in order of proven benefit on morbidity and mortality, with diuretics and beta-blockers apparently preferred to newer drug classes. However, the document then suggests that the choice of initial drug should not be restricted on theoretic or economic grounds to one or two classes of drug. Later the physician is reminded of a responsibility to consider the cost of drugs. The message is far from clear. The BHS guidelines were even less clear. They highlighted the absence of long-term trial data with newer agents, commented that outcome trials were needed and suggested that “if all clinical factors are equal, consider cost.” But there was one fatal sentence—“the committee was divided on the question of prescribing newer drugs instead of diuretics and beta-blockers as first-line treatment.”

Even more remarkable are the shifts in stance from the previous recommendations by the same bodies (Figure 1). JNC moved from a position of advising that several drug classes could be used as first-line treatment to an unequivocal endorsement of diuretics and beta-blockers. The BHS moved from a clear endorsement of thiazides and beta-blockers to no-man’s land. WHO-ISH moved from recommending that several drug classes could be used as first-line treatments to no clear position. Such chaos does little for the reputation of supposedly evidence-based guidelines.

What new evidence had emerged that could (or should) have influenced these recent guidelines? Two major outcome trials, the Systolic Hypertension in the Elderly Program (SHEP) and the MRC elderly trial, had both shown substantial and significant reductions in coronary events by treatment based on low-dose thiazides and beta-blockers. These trials dispelled previous concerns that the metabolic effects of diuretics and beta-blockers might predispose to coronary events—at least for older patients. Additional new evidence had emerged from the excellent Treatment of Mild Hypertension Study (TOMHS)—a large double-blind 4-year study comparing in detail the five major classes of antihypertensive drug. The results could be summarized as showing no important differences between them as regards antihypertensive efficacy, subjective side-effects, quality of life, or numerous surrogate endpoints. The comparison tended to favor thiazides and beta-blockers over the other drug classes, particularly as regards measures of quality of life. Given that thiazides and beta-blockers have proven efficacy in preventing cardiovascular complications, proven safety, at least match other drug classes in all other important respects, and are by far the least expensive drug classes, the endorsements by JNC-V and JNC VI seem obviously correct. The JNC reports score highly on two counts—they took note of important new evidence and, unlike the others, delivered a clear message.

**Treatment Policy for Uncomplicated Mild Hypertension**

Apart from the rather important matter of cost, the debate on first-line treatment probably matters little. Treatment with any effective antihypertensive regimen is likely to prevent cardiovascular complications. The question of who to treat, or not to treat, is much more fundamental. After appropriate nonpharmacologic measures and prolonged observation, JNC-V and VI recommend routinely treating systolic BP of 140 mm Hg or diastolic BP of 90 mm Hg. JNC VI does stress the importance of other risk factors as determinants of the timing of initiation of therapy. A higher risk patient would begin treatment earlier. The BHS guidelines advise routinely treating a systolic BP of 160 mm Hg or a diastolic BP of 100 mm Hg. The equivalent threshold in WHO-ISH is 160/95 mm Hg. The difference of 10 mm Hg in the diastolic BP between JNC-V and VI and BHS may seem trivial, but it has a remarkable impact on the level of cardiovascular risk treated, the NNT, and the proportion of the nonelderly population that will be treated. About 25% of adults would be targeted for treatment in the United States, compared to 8% of adults in the UK. These figures do in fact represent the proportions of the respective populations currently on lifelong antihypertensive treatment. Surprisingly the reasons for such a major difference in policy have never been made explicit or debated.

Their origin can be traced to apparent differences in outcome between major random controlled trials (Ta-
TABLE 1. DIFFERENCES IN OUTCOME BETWEEN MAJOR RANDOM CONTROLLED TRIALS IN MILD HYPERTENSION

<table>
<thead>
<tr>
<th></th>
<th>DBP (mm Hg)</th>
<th>ΔDBP (mm Hg)</th>
<th>NNT-5Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-MRC Mild</td>
<td>90–109</td>
<td>5.0</td>
<td>2000</td>
</tr>
<tr>
<td>Australian Trial</td>
<td>95–109</td>
<td>5.6</td>
<td>133</td>
</tr>
<tr>
<td>HDFP21: no TOD</td>
<td>90–104</td>
<td>4.3</td>
<td>77</td>
</tr>
<tr>
<td>no TOD</td>
<td>90–104</td>
<td>4.3</td>
<td>23</td>
</tr>
<tr>
<td>MRFIT22</td>
<td>90–104</td>
<td>3.8</td>
<td>(1000)*</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure at entry; ΔDBP, difference in diastolic blood pressure between treated and control groups; NNT-5Y, number needed to treat for 5 years to prevent one death; TOD, target organ damage present at baseline; MRC, Medical Research Council; HDFP, Hypertension Detection and Follow-up Program; MRFIT, Multiple Risk Factor Intervention Trial.

* 1 death caused per 1000 patients treated for 5 years.

ble 1). National bodies have understandably tended to base their policy on outcome trials conducted in their own country. UK policy has thus been heavily influenced by the MRC Mild Hypertension Trial, which showed a very small benefit from treatment—an NNT to prevent one death of 2000. The Australian Trial in Mild Hypertension showed a larger benefit, with an NNT of 133. However, the Hypertension Detection and Follow-up Program (HDFP) in the United States showed a much larger benefit from treatment, with an NNT to prevent one death of 77 in uncomplicated mild hypertension (DBP 90 to 104 mm Hg), and an NNT of 23 in those with target organ damage at entry. However, a similar but smaller trial in the United States, Multiple Risk Factor Intervention Trial (MRFIT), showed a small and nonsignificant adverse effect on mortality (NNT to cause one death of 1000). The outcomes in these trials diverge so greatly that they might appear to have been conducted in different species or different planets, not just in different countries. An important question is whether the results of these trials can be reconciled.

CARDIOVASCULAR DEATHS IN THE RANDOMIZED CONTROLLED TRIALS

The differences in outcome in these trials can in fact be explained entirely by differences in the absolute cardiovascular risk of the patients studied. Within HDFP certain subgroups of patients had benefits just as small as was observed in the MRC or MRFIT trials. For example in HDFP the NNT to prevent one death in patients aged <50 was 500, and treatment had a small but nonsignificant adverse effect in white women (NNT to cause one death was 1000). In all subgroups published from HDFP there was a clear relation between absolute risk and absolute benefit from treatment (Figure 2). The small benefit in younger patients and white women was not only explicable, it was inevitable. One cannot prevent cardiovascular complications that are not going to occur. When the outcomes of the MRC Mild, Australian, and MRFIT trials are examined in the same way (Figure 3), it is clear that the small benefit observed in these trials is again not only explained, but inevitable.

The clear message from this analysis is that the level of blood pressure is by itself a remarkably weak predictor of cardiovascular risk or of benefit from treatment. Risk and benefit are predicted much more powerfully by other variables, such as target organ damage, age, sex, smoking, and diabetes mellitus. This was shown by multiple regression analysis within the HDFP population (Table 2). As anticipated, target organ damage, such as renal impairment, previous stroke, or LVH, was a powerful predictor of death. In addition, age, smoking, diabetes mellitus, male sex, and education were all important predictors, but diastolic blood pressure had a very weak predictive value (Table 2).

The clear conclusion is that these randomized controlled trials differed in mortality outcome simply because the populations they studied differed in risk. The relative benefit from treatment was approximately constant in all trials, at approximately 25%. The absolute benefit and NNT in hypertensive popu-

![FIGURE 2](image-url)
When managing hypertension we are concerned not only to prevent death, but to prevent disabling nonfatal complications, such as stroke and myocardial infarction. It is also important to prevent the development of subclinical target organ damage, such as LVH, because once established this confers a high cardiovascular risk that cannot be reversed completely by antihypertensive treatment. There are again important differences between the randomized controlled trials in apparent benefit regarding nonfatal complications, with the benefit in HDFP seemingly much larger than in the other trials. This deserves a detailed examination.

HDFP was designed with all-cause mortality as the principal endpoint. There were several secondary endpoints that are entirely reliable in our opinion, namely fatal coronary, stroke, and cardiovascular events, nonfatal strokes, nonfatal myocardial infarction by electrocardiographic (ECG) criteria, and left ventricular hypertrophy diagnosed by ECG. However, we believe that one secondary endpoint that has been analyzed in detail in secondary publications from HDFP—total nonfatal myocardial infarction—is entirely unreliable, and that this has had a profound effect on perceptions of the overall benefit from treatment in HDFP. The endpoint in question is total nonfatal myocardial infarction. In HDFP nonfatal myocardial infarction was diagnosed in four ways: by ECG alone, by self-reporting, by the Rose questionnaire, and as a composite endpoint "by any method." The 5-year incidence of nonfatal myocardial infarction per 1000 patient-years in the control (RC) group was 8 by ECG alone, 31 by self-reporting, 62 by the Rose questionnaire, and 83 by any method. The very large contribution of self-reporting and the Rose questionnaire to the total should be noted. Because of the study design, the HDFP investigators in these publications quite properly warned that the diagnosis of nonfatal myocardial infarction should be interpreted with some caution, pointing to the possibility of detection, reporting, and observer bias. What they did not discuss was the validity of self-reporting and the Rose questionnaire for diagnosing myocardial infarction. This was examined in a validation study performed as part of the Health Survey for England. The diagnosis of myocardial infarction and other cardiovascular conditions by self-reporting and by the Rose questionnaire was compared to actual diagnoses in the medical records. Self-reporting inflated diagnoses of myocardial infarction by 72%. The Rose questionnaire inflated the prevalence even more, by a factor of 3.5 in men and 4.2 in women. Furthermore, overestimation was not uniform at different ages. In those aged <45 years overreporting was substantial, whereas at ages >65 years there was actually a slight underreporting.

Armed with this information, we examined the pattern of myocardial infarction reported from the control group (RC) in HDFP (Table 3). Fatal myocardial infarction (a reliable endpoint) increased sevenfold from age 30 to 49 years to age 60 to 69 years, as expected. For self-reports of myocardial infarction the

FIGURE 3. Regression of absolute benefit on absolute risk in the Hypertension Detection and Follow-up Program (HDFP) subgroups with 95% confidence intervals showing also the mean data from the Australian Therapeutic Trial in Mild Hypertension (AUST), British Medical Research Council (MRC), and Multiple Risk Factor Intervention Trial (MRFIT) trials. Within the HDFP, $r = 0.89, P < .001$; benefit $= -0.534 + 0.229$ risk. This equation predicts no benefit when the initial risk is 2.3% per 5 years. Closed circles indicate HDFP subgroups. Reproduced from Ramsay with permission. © 1997 American Medical Association.

<table>
<thead>
<tr>
<th>Target Organ Damage</th>
<th>RR</th>
<th>Other Factors</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>High creatinine</td>
<td>2.8</td>
<td>Age (10 years)</td>
<td>1.9</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.8</td>
<td>Smoking</td>
<td>1.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.6</td>
<td>Diabetes mellitus</td>
<td>1.7</td>
</tr>
<tr>
<td>Major left ventricular hypertrophy</td>
<td>1.6</td>
<td>Male sex</td>
<td>1.4</td>
</tr>
<tr>
<td>Claudication</td>
<td>1.4</td>
<td>Education*</td>
<td>1.4</td>
</tr>
<tr>
<td>Angina</td>
<td>1.3</td>
<td>Diastolic blood pressure (10 mm Hg increase)</td>
<td>1.03</td>
</tr>
</tbody>
</table>

*Education to less than high school versus high school and above.
age gradient was much less. For Rose questionnaire myocardial infarctions, the age gradient was actually reversed, so that nonfatal myocardial infarction was considerably more common in those aged 30 to 49 years than those aged 60 to 69 years (Table 3). Because of the contribution of Rose questionnaire diagnoses to total nonfatal myocardial infarctions, total nonfatal infarcts were more frequent in young than in old subjects (Table 3). Note also that the apparent case fatality rate of myocardial infarction was only 8% at age 30 to 49 years, compared to 39% at age 60 to 69 years.

These data are of course entirely implausible, and the reason is evident from the Health Survey of England validation. Younger patients reported large numbers of myocardial infarctions that would not have been found in their medical records, and which presumably did not in fact occur.

The effects of these “nonfatal myocardial infarctions” on the benefits of treatment in HDFP are shown in Table 4. In patients aged 30 to 49 years treatment was associated with a small excess of fatal myocardial infarctions but a massive reduction in supposed nonfatal infarcts. No less than 5% of these young patients supposedly had a nonfatal infarct prevented by antihypertensive treatment. Compare this to the data for those aged 60 to 69 years (Table 4). They had a substantial reduction in fatal myocardial infarctions, but a much smaller reduction in nonfatal infarcts. Again, this pattern of benefit is entirely implausible. Also shown in Table 4 is the effect of this apparent benefit on the NNT. In those aged 30 to 49 years the NNT for prevention of cardiovascular death or nonfatal stroke (reliable endpoints) was 250—a very small benefit. When “nonfatal myocardial infarctions” are included, the NNT falls to 30, implying a very large benefit from treatment. Note that in older patients (60 to 69 years) the NNT only moves from 31 to 20 with the inclusion of nonfatal myocardial infarction.

We have to conclude that the endpoint “nonfatal myocardial infarction” in the secondary HDFP publications is entirely unsafe. Estimates of a treatment benefit should be based on those endpoints that were ascertained reliably. In the age range 30 to 49 years one would have to treat 883 patients for 5 years to prevent one death from any cause, 556 to prevent one fatal stroke, and 244 to prevent the new development of LVH on the ECG of one. Taking as a composite endpoint death, nonfatal stroke, or LVH, the NNT to prevent any one of these would be 123. This is a small benefit from treatment, and it is essential to remember that included in this group were patients with diastolic pressures >115 mm Hg and patients who already had target organ damage or cardiovascular complications at entry to the trial. Young patients with mild hypertension and free of target organ damage likely had a very much smaller benefit from treatment. The inclusion of “nonfatal myocardial infarctions” diagnosed by self-reporting or the Rose questionnaire has inadvertently but seriously exaggerated the benefits of antihypertensive treatment in HDFP. The large benefits claimed for treatment in young subjects and in women are entirely due to this. When these spurious diagnoses are stripped out, the benefits from antihypertensive treatment in young patients with uncomplicated mild hypertension are very small—as they have been in other random controlled trials.10,19,22 It should be noted that the risk of developing LVH in such patients is also extremely small. About 250 young patients would need treatment with antihypertensive drugs for 5 years to prevent development of left ventricular hypertrophy in one. Prevention of LVH is certainly highly desirable, but this hardly seems a worthwhile return when set against the disadvantages of treating so many.

### Table 3. Pattern of Myocardial Infarction (MI) Reported in the Control Group (Referred Care) of the Hypertension Detection and Follow-Up Program.29 Rates Are 5 Year Incidence Per 1000 Patients

<table>
<thead>
<tr>
<th></th>
<th>30–49 years</th>
<th>50–59 years</th>
<th>60–69 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal MI</td>
<td>8.4</td>
<td>31.4</td>
<td>58.0</td>
</tr>
<tr>
<td>Self reported MI</td>
<td>22.4</td>
<td>38.2</td>
<td>51.2</td>
</tr>
<tr>
<td>MI by Rose Questionnaire</td>
<td>73.4</td>
<td>71.7</td>
<td>49.5</td>
</tr>
<tr>
<td>All non-fatal MI</td>
<td>90.3</td>
<td>98.8</td>
<td>89.6</td>
</tr>
<tr>
<td>Case fatality rate of MI</td>
<td>8%</td>
<td>24%</td>
<td>39%</td>
</tr>
</tbody>
</table>

### Table 4. Events Prevented by Stepped Care (Active Treatment) in the Hypertension Detection and Follow-Up Program

<table>
<thead>
<tr>
<th>Number of events prevented per 1000 patients in 5 years</th>
<th>30–49 years</th>
<th>50–59 years</th>
<th>60–69 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal MI</td>
<td>–1.9</td>
<td>3.4</td>
<td>13.1</td>
</tr>
<tr>
<td>“Nonfatal MI”</td>
<td>25.2</td>
<td>15.8</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Number needed to treat for 5 years to prevent one event

| Cardiovascular death | 476 | 112 | 48 |
| Cardiovascular death + stroke | 250 | 60 | 31 |
| Cardiovascular death + stroke + LVH | 123 | 38 | 22 |
| Plus “non-fatal MI” | 30 | 24 | 20 |

LVH, left ventricular hypertrophy; MI, myocardial infarction.
CONSEQUENCES OF TREATING HYPERTENSION IN PATIENTS AT VERY LOW RISK

Given that some hypertensive subjects, such as young women with uncomplicated mild hypertension, have a very low risk of cardiovascular complications, might there by harm in treating them? To examine this question we look first to an excellent analysis of the cost-effectiveness of antihypertensive treatment by Johansson.33 They examined cost-effectiveness according to absolute cardiovascular risk, calculated by the Framingham risk function, and using long-term average blood pressure, as recommended in all the guidelines. It assumed relative risk reductions for stroke of 38% and for coronary events of 16%, derived from a metaanalysis of all randomized controlled trials.34 The cost per life-year gained by treatment was based on the least expensive drugs, thiazides and β-blockers, and healthcare costs for Sweden. The findings are shown in Table 5. The key point in this analysis is that the cost-effectiveness of antihypertensive treatment varies hugely in different patient groups. In older patients there are actually healthcare savings by treatment. In young patients with mild hypertension, however, treatment is remarkably expensive. Consider, for example, women aged <45 years with diastolic blood pressures of 90 to 94 mm Hg. The cost per life-year gained is over $400,000, a cost much higher than that of chronic dialysis. This is for treatment with thiazides and β-blockers, and routine use of more expensive drugs, such as calcium antagonists or ACE inhibitors, in such patients will easily top $1,000,000 per life-year gained.

The main lesson from this analysis is not really the cost of treatment. The extremely poor cost-effectiveness reflects the vanishingly small risk in these patients, and the even smaller chance of benefit from treatment. Could there be a downside to treating these low-risk patients other than the cost? The antihypertensive drugs now available are undoubtedly very safe, well-tolerated, and have no measurable adverse effect on quality of life.18,39 However Hoes et al35 have presented evidence that treatment may adversely affect the prognosis of those at very low risk. Their analysis has been criticized,36 but unless antihypertensive drugs are 100% safe there must inevitably be some point where treatment will do more harm than good. Perhaps a more important concern is that people do not like taking drug treatments, as Freis pointed out. In the 1980s there was a considerable literature on the adverse effects of “labeling” people as hypertensive.38 Some studies, but not all, suggested that the diagnosis or treatment of hypertension could lead to perceived ill-health and psychological morbidity. This concern has resurfaced in recent reports of a worrying excess of psychiatric symptoms in hypertensive patients. There is a remarkably high incidence of panic attacks and panic disorder39,40 and anxiety39,41 in hypertensive patients. When considering the treatment of uncomplicated mild hypertension the potential for causing harm should not be underestimated.

CAN ANTIHYPERTENSIVE TREATMENT BE TARGETED MORE EFFECTIVELY?

It is instructive to examine in Table 5 the consequences of the recommendations in current conventional guidelines. Strict adherence to JNC-V or JNC VI will lead to unthinkably expensive treatment of people with virtually no cardiovascular risk. On the other hand, the BHS advice to treat routinely only diastolic pressure ≥100 mm Hg may fail to treat subjects at relatively high risk who ought to be treated, for example middle-aged men with diastolic pressures of 95 to 99 mm Hg. The WHO-ISH guideline would overtreat some at very low risk, and fail to treat some at relatively high risk. Because blood pressure alone is a very weak predictor of cardiovascular risk, treatment targeted at blood pressure thresholds is inevitably inefficient.

The concept of targeting treatment at absolute cardiovascular risk rather than blood pressure threshold is not new, and was perhaps first set out most clearly by Madhavan and Alderman in 1981.42 They argued that blood pressure alone was a poor predictor of risk
and benefit, recommended targeting treatment at absolute cardiovascular risk, and suggested risk estimation using multiple risk factors, such as age, sex, smoking habit, diabetes mellitus, and lipid levels. The New Zealand guidelines\(^4,5\) have developed this concept into a practical method. In the initial version,\(^4\) the guidelines assumed that relative risk reduction by treatment was constant at 33%, and targeted for treatment a cardiovascular event risk of 2.0% per year, estimated by a simplified form of the Framingham risk function. Using this, the outcome of treatment would be an NNT (5 years) of 50, but the authors suggested that the level of benefit targeted needed public debate. Recent New Zealand guidelines\(^5\) include a simple, elegant and accurate colored chart that allows ordinary doctors to estimate absolute cardiovascular risk readily. In our view the next generation of management guidelines for hypertension will be deficient if they do not incorporate a simple, accurate aid to cardiovascular risk assessment similar to this. JNC VI\(^12\) has moved in that direction but perhaps not far enough.

**PROBLEMS OF TARGETING ABSOLUTE RISK**

Certain difficulties have emerged when targeting absolute cardiovascular risk for treatment. The first is a conceptual difficulty. We are accustomed to targeting for treatment threshold levels of single risk factors, such as blood pressure or cholesterol, and it is therefore difficult to leave untreated “high” levels that were treated previously. It is essential that those not treated immediately, because their absolute risk is very low, are followed up indefinitely. Their risk will increase with age, and they may come to need treatment in old age. A second difficulty is the overwhelming effect of age on absolute cardiovascular risk.\(^43\) Intuitively many doctors would prefer to treat more aggressively young rather than elderly hypertensives, yet the benefit from treatment is directly related to older age. Perhaps society values more highly the prevention of a complication or death in a young subject, and, if so, the level of absolute risk targeted should be lower in the young. However, to date no satisfactory method of adjusting the level of risk for age has emerged. Above all there has been a failure to address a fundamental question—what level of benefit, or NNT, should be required from our treatment? Should we be targeting antihypertensive treatment for an NNT of 20, 40, 100, or what? The policy chosen should depend on the balance between harm and benefit from treatment, the cost-effectiveness of treatment, the views of society, and, above all, the wishes of patients. According to present guidelines, hypertensive patients in the United States are considered much more willing to take treatment, and to accept a smaller benefit, than are similar patients in Britain. What is not clear is whether ordinary people in the United States and Britain differ—or is it just their experts who differ? We ought to find out.

**CONCLUSIONS**

It is evident that targeting treatment at a blood pressure threshold alone is inefficient, and that treatment is targeted much more accurately at a specified level of absolute cardiovascular risk. Doctors cannot assess risk intuitively,\(^44\) and some formal method of counting and weighting the factors that determine cardiovascular risk is needed. For ordinary practice the method has to be simple and accurate, and the next generation of hypertension management guidelines ought to include such methods for estimating absolute cardiovascular risk. It has been suggested that the benefit (NNT) desired from treatment ought to be debated.\(^4\) We believe that it should not simply be debated, it ought to be studied. It is time to explore what benefit hypertensive patients would wish from their treatment, and whether there are indeed differences between countries in the level of benefit that is acceptable.

Concerns have been expressed that targeting absolute risk and use of the NNT may lead to rationing and a restriction of clinical freedom. Knowledge of the NNT simply informs doctors about the benefit that they are offering, and patients about the benefit they are likely to obtain from treatment. Informed choice provides real freedom.

When drug therapy is indicated, the evidence available strongly supports the use of thiazides and \(\beta\)-blockers as first-line drugs unless they are contraindicated, ineffective, or poorly tolerated, or unless there are positive reasons in the individual patient for choosing an alternative class of drug.

**REFERENCES**

5. Ministry of Health: Guidelines for the Management of Mildly Raised Blood Pressure in New Zealand. Core
Services Committee, Ministry of Health; Wellington, New Zealand, 1995.


