Effect of Risk Status on Treatment Criteria
Implications of Hypertension Trials
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When deciding whether to treat a patient with hypertension, clinicians must balance the benefit of treatment against its adverse effects. In the absence of an interaction, the multiplicative model of risk implies that the absolute benefit of treatment is related to the underlying risk of an adverse outcome. Thus, each additional risk factor multiplies the absolute benefit of treating hypertension. Analyses of data from subgroups in clinical trials of hypertension treatment suggest that this model is usually valid. In contrast, the adverse effects of treatment are usually unrelated to other risk factors. Thus, the cutoff point for treatment differs in different individuals: setting a single treatment threshold and goal for the entire population is not appropriate. Patients who are at high absolute risk because of prior coronary artery disease or other risk factors have a greater potential absolute benefit, and such patients deserve a low threshold and goal, such as a diastolic blood pressure of 90 mm Hg. Conversely, persons at low risk, such as white women without other risk factors, do not require such aggressive management. (Hypertension 1989;13(suppl I):I-51–I-56)

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n deciding whether to treat a patient with hypertension, a practitioner must estimate the likelihood that treatment will be beneficial for that individual. This likelihood is different in different patients, so the question becomes, for example, what is the likely benefit from controlling hypertension in a 50-year-old white male smoker?

The direct research approach to answering this question would be to undertake a clinical trial of hypertension treatment in a sample of middle-aged white men who smoke. Similarly, the benefits and the costs of treatment in patients with other characteristics could be studied in other trials, and the effects of treatment could be measured in every subgroup of the population that is of potential interest. The scientific advantages of this strategy, however, are outweighed by its logistic problems—the number of such studies and the number of subjects required would be impossibly large.

In another approach to the problem, subjects with a wide variety of baseline characteristics could be enrolled in a single trial. The effect of the intervention would then be estimated in various subgroups in that trial, classified, for example, by age, race, sex, and smoking status. These subgroups, however, would likely be too small to allow a reliable determination of the intervention effect in any particular subgroup like middle-aged white male smokers. This unreliability is due to the fact that clinical trials are designed to have just enough power to answer the research question for the entire study sample.

In this article, we discuss the only practical option, which is to model the effects of treatment in the subgroups of interest by combining observational and experimental data. We compare the predictions of the model with the actual results of several hypertension trials, suggest guidelines for making judgments about when the model may not be appropriate, and discuss the implications of the model when setting thresholds and goals for hypertension treatment.

Multiplicative Model in Observational Studies
Our approach is based on the multiplicative model of risk relations, which has produced the best fit for cardiovascular risk factor data. The model specifies that the absolute risk that an individual will have for a particular outcome, such as death, depends on the number and strength of the risk factors that the individual has. The absolute risk equals the baseline risk of the outcome in someone with no risk factors multiplied by the relative risk (RR) associated with each of the patient’s independent risk factors. The more risk factors, the greater the absolute risk

Absolute risk = baseline risk × RR₁ × RR₂ × RR₃ × . . .

For any particular risk factor, such as hypertension, the model specifies that the relative risk is
similar in all individuals. Observational results in subjects screened for the Multiple Risk Factor Intervention Trial (MRFIT)2 confirm this assumption (Table 1). The relative effects of each risk factor were similar in all subgroups; hypertension consistently increased 6-year mortality by about 1.4 times, smoking by about two times, and hypercholesterolemia by about 1.3 times. Thus, mortality in the highest-risk subgroup (hypertensive smokers with hypercholesterolemia) was 70.7 deaths/1,000, about four times (1.4 x 2 x 1.3) greater than the mortality of 19.3/1,000 in the lowest-risk subgroup (normotensive nonsmokers with “normal” serum cholesterol).

Another implication of this model is that, although the relative effect of any single risk factor is similar in different subgroups, the absolute effect should be greater in subgroups with other risk factors. Again, results in subjects screened for the MRFIT2 confirm these predictions (Table 1): the absolute effect of hypertension was about three times greater among smokers with hypercholesterolemia (20.1 additional deaths/1,000) than among nonsmokers with normal cholesterol levels (6.5/1,000), despite similar relative risks (about 1.4) in the two subgroups. This absolute effect of a risk factor, which is sometimes called the excess risk, is more relevant to clinical decisions than the relative risk because the former indicates the potential reduction in risk that can be achieved by modifying that risk factor.

**Applying the Multiplicative Model to Clinical Trials**

We have assumed that the same principles also apply to interventions that reduce disease risk: the relative benefit of an intervention should be similar in all subgroups. This relative benefit can be estimated most precisely from the overall result of a clinical trial because the overall result is based on the largest number of observations. For example, since the Hypertension Detection and Follow-up Program (HDFP) intervention reduced 5-year mortality by 16.3% compared with controls,2 the assumption is that 16.3% is also the best estimate of the relative benefit in every subgroup.

The absolute benefit of an intervention in a subgroup, however, depends on the absolute risk of the disease, which in turn depends on the presence or absence of other risk factors including age and sex. The multiplicative model predicts that each risk factor (e.g., smoking) multiplies the potential absolute benefit of modifying any other risk factor (e.g., hypertension)

$$\text{Absolute benefit} = \text{absolute risk} \times \text{relative benefit} \times \left( \text{baseline risk} \times \text{RR} \times \text{RR}^2 \times \ldots \right) \times \text{relative benefit}$$

In the example of middle-aged male smokers, the absolute benefit of hypertension treatment on (6-year) mortality would be estimated as the absolute risk of about 71 deaths/1,000 (observed in MRFIT screenees) multiplied by the relative benefit of 16.3% (as in the HDFP), for a benefit of 12 deaths prevented/1,000 men treated.

**Empirical Tests of the Model**

*As Predicted, Relative Benefit Is Constant in all Subgroups, and Absolute Benefit Is Greater in Those at Higher Risk*

The estimated effect of modifying a risk factor, as predicted by this model, can be compared with the actual results among subgroups in clinical trials. As noted, smokers have approximately twice the mortality rate of nonsmokers. Thus, if the multiplicative model is valid, the relative benefit from treatment of hypertension (comparing the intervention group with the control) should be the same in smokers and nonsmokers, but the absolute benefit should be twice as great in smokers.

Figure 1 shows the overall results of the HDFP,4 and the results among smokers and nonsmokers are displayed on a graph comparing absolute mortality (ordinate) with the relative effect of the intervention (abscissa). The arrows point from the mortality rate in the referred-care control group to that in the special-care intervention group; arrows pointing down indicate a benefit from the intervention. As predicted by the model, the relative benefits of the intervention were similar in the subgroups (the arrows line up vertically), whereas the absolute benefit was greatest in the smokers (the arrow is longer in that subgroup).
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Figure 1. Graph showing absolute and relative effect of hypertension treatment on 5-year mortality in the Hypertension Detection and Follow-up Program among smokers (n=4,239), nonsmokers (n=6,701), and overall. Arrows point from mortality in the referred-care control group to that in the special-care treatment group. The width of the arrows is proportional to sample size.

Another example of this pattern predicted by the model, that is, a similar relative benefit but a greater absolute benefit in the higher-risk subgroup, is shown in Figure 2. The subgroup of HDFP subjects with preexisting heart disease as determined by electrocardiographic (EKG) or historical evidence of a previous myocardial infarction have the same relative benefit from hypertension treatment as those without such evidence, but the higher-risk subgroup has an absolute benefit that is almost three times greater. These results provide empirical support for the model and emphasize the importance of absolute risk in estimating the effect of hypertension treatment.

Relative Benefit Is Occasionally Not Constant

Many (perhaps most) subgroup analyses, however, do not fit the model as well. By chance alone, some differences in the relative benefit in various subgroups in a clinical trial are expected. Sometimes, the magnitude of the difference in relative benefit between two subgroups is so large that the validity of the model in that subgroup must be questioned, and a decision must be made as to whether that difference is real.

A finding in the HDFP, for example, that did not confirm the assumption of equal relative benefit in all subgroups is the analysis by age groups (<50 years or ≥50 years) shown in Figure 3. The arrows do not line up vertically because the relative magnitude of the benefit differed in the two subgroups (1% compared with 19%). The question is whether this observed difference means that the intervention would have no effect in the population among hypertensive persons younger than age 50 years. The answer is probably not. First, the difference between subgroups is not statistically significant; the number of events observed in the younger age group was small, and it is reasonable to conclude that the differences observed in the HDFP may have been due to chance. Second, the difference has not been observed in other trials; the Australian Therapeutic Trial in Mild Hypertension, for example, found that the relative benefits of treatment were slightly greater in the younger age group. We believe that the study-wide HDFP relative benefit is the best estimate of the treatment effect in each of these two age groups.

Only if the relative benefits in subgroups differ markedly from each other is it necessary to decide...
TABLE 2. Criteria for Evaluating the Possibility of an Interaction in Subgroups in a Clinical Trial

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do observational results conform to the expected results based on previous studies?</td>
<td>Higher-risk subgroups (e.g., smokers) should have a greater event rate than lower-risk subgroups (e.g., nonsmokers) in the intervention and control groups.</td>
</tr>
<tr>
<td>Is the difference in relative benefit between subgroups substantial?</td>
<td>The difference in relative benefit should be qualitatively large (e.g., a benefit from the intervention in one subgroup and harm in the other) and significant.</td>
</tr>
<tr>
<td>Is the interaction biologically plausible?</td>
<td>Although this is a necessary condition, it is easy to formulate reasonable explanations for most phenomena.</td>
</tr>
<tr>
<td>Is the interaction seen consistently in other studies?</td>
<td>This is the most important criterion.</td>
</tr>
</tbody>
</table>

whether such an inconsistency means that the intervention really would have a different effect in that subgroup in the population. Interactions, as such inconsistencies are usually termed, are vexing.6-7 Planners of clinical trials usually exclude subjects from a particular subgroup if they anticipate an interaction, so most apparent interactions are unexpected and therefore are unlikely to represent real phenomena in the population. Because of the large number of potential subgroups in any trial, however, finding a few possible interactions that are “significant” is likely. For these reasons, it is essential to regard all apparent interactions skeptically. Before projecting that an interaction observed in a sample will also be present in the population, we suggest applying the criteria listed in Table 2.

No interactions in hypertension treatment have been unequivocally established although there are a number of possibilities. One candidate interaction is the notorious finding in the MRFIT among hypertensive subjects with certain baseline EKG abnormalities.8 MRFIT participants in the special-intervention (SI) group had a higher coronary heart disease mortality than those in the usual-care (UC) control group (i.e., there was a substantial net harm from the intervention in the special-intervention subgroup, which was mainly treated with hydrochlorothiazide). Hypertensive subjects without these baseline EKG abnormalities, on the other hand, showed a benefit from the MRFIT intervention.8

Figure 4. Graph showing absolute and relative effect of multiple risk factor intervention on 6-year coronary artery disease mortality in the Multiple Risk Factor Intervention Trial among hypertensive subjects with normal (n=5,593) and abnormal (n=2,418) resting electrocardiograms at baseline.8 Arrows point from mortality in the usual-care control group to that in the special-intervention treatment group.

Figure 5. Graph showing absolute and relative effect of hypertension treatment on 5-year coronary artery disease mortality in the Hypertension Detection and Follow-up Program among ‘‘MRFIT-like’’ subjects (see text for details) with normal (n=1,522) and abnormal (n=631) resting electrocardiograms at baseline.8 MRFIT, Multiple Risk Factor Intervention Trial.
white man who smokes, a practitioner must balance the estimated absolute benefit of treatment against the estimated adverse effects. In the absence of an interaction, that absolute benefit is a function of the relative benefit of the treatment, which is determined in clinical trials, and of the patient’s absolute risk before treatment, which depends on the presence of other risk factors. Thus, the absolute benefit of treatment is greater in individuals with several risk factors or who already have coronary artery disease. In contrast, the adverse effects of treatment, including drug toxicities and economic costs, are usually unrelated to the presence or number of other risk factors. Thus, the point at which the costs and the benefits of treatment are balanced will often differ in different individuals.11,12

These implications can be illustrated with the findings for the four major race-sex subgroups of the HDFP (Table 3). To decide whether to treat hypertension in the same way in each of these subgroups (e.g., should white women, in whom there was no observed benefit, be treated at all?), we must evaluate whether an interaction may be present by applying the criteria in Table 2. First, the observational results in the referred-care control are in the expected direction: blacks and men are at higher risk. Second, although the differences in the relative benefit in the four subgroups are substantial, ranging from -5.5% to 32%, the results in white women were not statistically different from the other groups. Third, given that the intervention was beneficial in some whites (among men) and in some women (among blacks), it is difficult to find a biologic reason why it would be selectively harmful in white women. Thus, especially without confirmation of this potential interaction in other trials, it seems reasonable to assume that the best estimate of the relative benefit in white women is the same as the overall relative benefit of 16.3%.

Even with the assumption that the relative benefit is constant, however, the differences in the estimated absolute benefit suggest that hypertension treatment will be substantially more beneficial in some subgroups than others (Table 4). As an example, for every 1,000 black men with hypertension who are treated for 5 years, about 21 lives will be saved, white women.

### Table 3. Observed 5-Year Mortality in the Hypertension Detection and Follow-up Program by Major Race-Sex Subgroups (Referred Care Compared With Stepped Care)*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Mortality* per 1,000 in RC</th>
<th>Mortality* per 1,000 in SC</th>
<th>Relative benefit (RC-SC)/RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black women</td>
<td>2,700</td>
<td>77.6</td>
<td>52.8</td>
<td>32.0%</td>
</tr>
<tr>
<td>Black men</td>
<td>2,150</td>
<td>127.7</td>
<td>107.8</td>
<td>15.6%</td>
</tr>
<tr>
<td>White women</td>
<td>2,330</td>
<td>43.6</td>
<td>46.0</td>
<td>-5.5%</td>
</tr>
<tr>
<td>White men</td>
<td>3,760</td>
<td>67.7</td>
<td>58.9</td>
<td>13.0%</td>
</tr>
<tr>
<td>Overall</td>
<td>10,940</td>
<td>76.7</td>
<td>64.2</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

*Mortality was directly adjusted for age distribution of the entire Hypertension Detection and Follow-up Program sample. RC, referred care and SC, stepped care.

This potential interaction meets three of the four criteria listed in Table 2. First, the difference is substantial and significant; the arrows for the subgroups with and without EKG abnormalities are widely separated horizontally and even point in opposite directions (Figure 4). Second, the phenomenon is biologically plausible and may be related to diuretic-induced changes in serum and intracellular electrolytes. Finally, the finding has been observed in other studies. In subjects similar to those enrolled in the MRFIT (white men initially free of end-organ disease), the results of the HDFP show a similar horizontal pattern (Figure 5) as do those of the Oslo Study (not shown). In both of these studies, the subgroups with baseline EKG abnormalities did worse (comparing intervention with control groups) than those without such EKG changes. However, the interaction fails to meet the first criterion, in that an abnormal EKG was associated with a lower mortality, rather than the expected higher mortality, in the MRFIT control group. Thus, the evidence is not definitive that the MRFIT finding represents a real interaction in the population. The clinical implication is that it may be prudent to avoid using hydrochlorothiazide in patients with abnormal EKGs while awaiting further evidence from other trials.

### Implications for Clinical Policy

When deciding whether to treat an individual patient for hypertension, such as a 50-year-old

### Table 4. Projected Absolute Benefit, Assuming That Overall Relative Benefit of 16.3% Applies to all Subgroups*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observed mortality without treatment† (per 1,000)</th>
<th>Projected mortality with treatment‡ (per 1,000)</th>
<th>Projected lives saved per 1,000§ treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black women</td>
<td>77.6</td>
<td>65.0</td>
<td>12.6</td>
</tr>
<tr>
<td>Black men</td>
<td>127.7</td>
<td>106.9</td>
<td>20.8</td>
</tr>
<tr>
<td>White women</td>
<td>43.6</td>
<td>36.5</td>
<td>7.1</td>
</tr>
<tr>
<td>White men</td>
<td>67.7</td>
<td>56.7</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Lives saved per 1,000 persons treated for 5 years.
†Based on age-adjusted mortality in Hypertension Detection and Follow-up Program referred-care subgroups.
‡Projected mortality=observed mortality×(100−16.3%).
§Projected lives saved=observed mortality−projected mortality.
three times the number projected for hypertensive white women. The implication is that treatment for white women should be less vigorous, for example, setting a treatment threshold and goal of 100 mm Hg if the one for black men is 90 or 95 mm Hg.

Conclusion
When generalizing the results of a clinical trial to a population, the relative benefit in every subgroup is the same as the overall relative benefit observed in the trial, except in the rare event that subgroup results strongly and consistently suggest that an interaction is present. The absolute benefit, on the other hand, is greater in higher-risk subgroups and should be estimated as the overall relative benefit times the absolute risk in a subgroup.

Setting a single treatment threshold and goal for treating hypertension, such as a diastolic blood pressure of 95 mm Hg, is therefore not appropriate. Clinicians should take into account absolute benefit when determining thresholds and goals for treatment in individual patients. Those who are at high absolute risk because of prior coronary artery disease or other risk factors have a greater potential absolute benefit, and such patients deserve a lower threshold and goal. Conversely, persons at low risk, like white women without other risk factors, do not require such aggressive management.

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