Process Versus Outcome in Hypertension: A Positive Result


SUMMARY. We studied the association between the outcome of antihypertensive care and three items of that care among 230 hypertensive steelworkers who were referred to 83 physicians. The first item was the decision to treat some patients but not others: 63% of the patients were treated antihypertensive drugs and the mean decrease in their diastolic blood pressure (DBP) was greater than that among untreated patients (12.2 ± 0.84 vs 7.8 ± 0.83 mm Hg [±SEM], p < 0.001). The second item was the vigor of prescribed medication: Patients prescribed more vigorous treatments had lower DBP (p < 0.005). Third, patient compliance was related to achieving a goal DBP of less than 90 mm Hg (p < 0.05) and the product of prescribed vigor and compliance was highly associated with DBP response (p < 0.0001). These results stand in contrast to those of previous studies that failed to detect associations between various other items of the care process and the outcome of antihypertensive care.

A PARADOX exists in the management of hypertension. Medical practitioners strive to translate the positive results of randomized therapeutic trials in hypertension into effective treatment programs for their patients. However, control of high blood pressure in our communities remains far from optimal, and two important studies of the management of hypertensive patients have not identified elements of the process of care that affect blood pressure control. Brook and Appel reviewed the clinical records of 173 hypertensive patients who had been discharged from the hospital. Five months after discharge, 44% of the patients had not attained blood pressure control. Five methods of peer review were applied to assessment of the quality of care provided to patients. In none of the assessments was the process of care found to be correlated with blood pressure response. Similarly, Nobrega et al. found no positive correlations between lowering of blood pressure and 23 items of clinical history, 26 items of physical examination, 13 initial laboratory tests, nine special diagnostic tests, eight treatment procedures and 10 follow-up procedures. The only statistically significant observations in this investigation were contrary to expectation: Increases in the number of special diagnostic tests or the number of treatment processes administered to patients were associated with worse blood pressure control.

From a clinical perspective, these studies failed to investigate at least three important factors. First, they were limited to patients who were already receiving therapy for hypertension, thus ignoring the initial decision to treat some but not other hypertensive patients. Second, no assessment was made in these studies of the relative pharmacologic “vigor” of the regimens that were prescribed. Thus, patients who were treated with insufficient doses of antihypertensive drugs were lumped with those on more potent regimens. Finally, no accurate measures of medication compliance were available in these studies.

We report here the results of a study in which strategies were incorporated for measuring these three factors.

Methods

Recruitment, Initial Assessment, and Referral of Patients

The patients in this investigation were participants in a series of randomized trials of strategies to improve compliance with antihypertensive therapy that have been described in detail. In brief, a random two-thirds (5400) of the male employees of the Dominion Foundries and Steel Limited of Hamilton, Canada, were screened for hypertension. Two hundred forty-five men met the following criteria: average fifth-phase diastolic blood pressure (DBP) > 95 mm Hg (average of the second and third of three readings taken with the patient sitting quietly at rest for 5 minutes on each of two occasions over a 3-month period), no antihypertensive therapy for at least 6 months before screening, no daily medications and no remediable secondary form of hypertension. After the study was explained to them, 230 men (94%) consented to participate. Each participant underwent a standardized comprehensive history, a physical examination and laboratory tests, including chest x-ray, ECG, hemoglobin, white blood count, electrolytes, cholesterol and urinalysis. Special investigations, such as endocrine tests, i.v. pyelography and renal angiograms, were ordered only if indicated by history, physical or initial laboratory work-up. By random allocation, patients were then referred, along with a summary of their work-up, to their family physician or to a plant physician for further assessment and care. All 230 patients were successfully referred through making an initial appointment and following patients until at least one appointment had been kept.

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The decision to start treatment was left up to the 83 participating physicians to whom the patients were referred.

Follow-up Assessments

Before entry, each participant consented to be visited at home during the course of the study. Twelve months after entry, arrangements to visit were made by telephone, usually on the same day that the visit took place, for the ostensible purpose of assessing blood pressure at home. At the home visit, the blood pressure was measured and the patient’s treatment status determined. Patients taking antihypertensive drugs were asked to present all medications to bring the visitor “up to date” on the patient’s current prescription. The patient was asked if he kept any of his medication elsewhere and, if so, how much was there. He was also asked whether he began taking pills from the container on hand on the dispensing date or, if not, when he had started the medication. The patient was then asked to provide a urine specimen and, during his absence, the tablets were counted. In addition, the prescribed regimen, dispensing pharmacy and dispensing date were recorded. The pharmacy was subsequently contacted for any missing or ambiguous prescribing information and the prescription was verified with the attending physician. Compliance was calculated by dividing the number of pills missing from all containers by the number of pills that would have been missing if the patient had taken all his medicine as prescribed.

Assessment of the Vigor of Prescribed Medication

To compare the vigor of the various regimens prescribed for patients in the study, an empirical scale of relative potency of antihypertensive drugs was derived (table 1). The scale was established by setting 50 mg of chlorthalidone per day as 1 “unit of vigor” and culling the relative potency of other drugs from controlled clinical trials in which the various drugs were compared with each other. This scale treats multiple doses of a given drug as if they were additive, but only to the maximal dose documented or recommended in the literature, and treats the effects of different drugs as if they were additive. The scale was constructed without knowledge of the blood pressure response of patients in the study described here. Using the scale, the vigor of each patient’s regimen after 12 months in the study was calculated. For ease in analysis, patients were grouped into three levels of prescribed vigor: those prescribed less than 1 unit, those prescribed 1–1.9 units, and those prescribed 2 or more units of vigor.

Statistics

Statistical analyses were performed using chi-square for proportions, the two-tailed unpaired t test for comparison of continuous data for two groups and one-way analysis of variance for comparison of continuous data for more than two groups. Results were accepted as statistically significant if the probability that an observed difference was due to chance alone was less than 5% (p < 0.05). Values are given as mean ± SEM.

Results

Patient Characteristics and Follow-up

By design, all 230 participants were male. Other relevant entry characteristics are displayed in table 2. Eighteen men (8%) were lost to follow-up through leaving employment at the plant. There were no statistically significant differences in the entry characteristics of those who began the study and those who completed it.

The Decision To Treat

The 83 participating physicians originally prescribed antihypertensive drugs to 144 of the 230 referred patients (63%). Twelve months after entry, 131 of the remaining 212 men (62%) were taking antihypertensive drugs. The other 81 patients were either untreated or were prescribed regimens that did not include blood-pressure-lowering medication (for example, tranquilizers, weight reduction, salt restriction or exercise).

Figure 1 shows the blood pressure reductions for treated and untreated patients. Treated patients had an average decrease in blood pressure (systolic/diastolic) of 22.1 ± 1.14/12.2 ± 0.84 mm Hg over the 12 months, compared with only 12.2 ± 1.21/7.8 ± 0.83 mm Hg for untreated patients (p < 0.001 for both systolic and diastolic pressures).

The decision to treat appears to have been influenced by the entry blood pressure of patients and their age. Patients who were subsequently treated had significantly higher entry systolic and diastolic pressures than patients who remained untreated and were also significantly older. Despite their higher initial blood pressure, slightly more treated patients reached

<table>
<thead>
<tr>
<th>Code</th>
<th>Drug</th>
<th>Size of 1 unit of vigor (daily dose in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Chlorthalidone</td>
<td>50</td>
</tr>
<tr>
<td>Ib</td>
<td>Hydrochlorothiazide</td>
<td>50</td>
</tr>
<tr>
<td>Ic</td>
<td>Chlorothiazide</td>
<td>500</td>
</tr>
<tr>
<td>II</td>
<td>Spironolactone</td>
<td>200</td>
</tr>
<tr>
<td>III</td>
<td>Reserpine</td>
<td>0.125</td>
</tr>
<tr>
<td>IV</td>
<td>Hydralazine</td>
<td>50</td>
</tr>
<tr>
<td>V</td>
<td>Methyl dopa</td>
<td>500</td>
</tr>
</tbody>
</table>

Rules for incremental doses and combinations:
1. Within code I, II, or III, the maximal effect is 2 units.
2. Across codes I and II, the maximal effect is 2 units for each, for a total of 4 units.
3. Across codes I and III, the maximal effect is 2 units for each, for a total of 4 units.
4. Within code IV, the maximal effect is 4 units.
5. Within code V, the maximal effect is 6 units.
6. Across codes I, III and IV, these drugs may be combined with maximal effects of 2, 2 and 4 units, respectively, for a total of 8 units.
7. Across codes I and V, the maximal effects are 2 and 6 units, respectively, for a total of 8 units.

Table 1. A System for Classifying the Vigor of Antihypertensive Regimens
TABLE 2. Entry Characteristics of Patients Beginning and Completing the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients beginning study (n = 230)</th>
<th>All patients (n = 212)</th>
<th>Treated patients (n = 131)</th>
<th>Untreated patients (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>40.9 ± 0.63</td>
<td>41.2 ± 0.66</td>
<td>42.2 ± 0.87</td>
<td>39.5 ± 0.99†</td>
</tr>
<tr>
<td>Height (cm)*</td>
<td>172.3 ± 0.51</td>
<td>172.2 ± 0.54</td>
<td>172.3 ± 0.65</td>
<td>172.0 ± 0.95</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>87.1 ± 0.86</td>
<td>87.1 ± 0.89</td>
<td>87.2 ± 1.16</td>
<td>86.9 ± 1.37</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)*</td>
<td>152.4 ± 0.88</td>
<td>152.5 ± 0.91</td>
<td>155.1 ± 1.23</td>
<td>148.4 ± 1.21‡</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)*</td>
<td>103.1 ± 0.47</td>
<td>103.2 ± 0.50</td>
<td>104.4 ± 0.69</td>
<td>101.1 ± 0.61‡</td>
</tr>
<tr>
<td>Married (%)</td>
<td>90</td>
<td>91</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Ethnic origin (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>46</td>
<td>45</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Italian</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Yugoslavian</td>
<td>15</td>
<td>16</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>26</td>
<td>27</td>
<td>23</td>
</tr>
</tbody>
</table>

*Mean ± SEM.
†p < 0.01 for treated vs untreated patients.
‡p < 0.0001 for treated vs untreated patients.

a DBP of < 90 mm Hg than untreated patients (37% vs 31%, p = 0.39).

Thus, the clinical decision to treat some patients but not others does have a clear impact on the outcome of blood pressure control among hypertensive patients. Although the prescription of antihypertensive medication is a necessary step in treating hypertension, the finding of an effect on treatment outcome for all patients is more complex than it seems. A treatment effect would not be observed if, for example, physicians had withheld treatment only from patients whose blood pressure had dropped naturally, or had prescribed inadequate treatment to those with elevated blood pressures, or had failed to continue therapy for the period of observation, or had failed to gain their patient’s cooperation with therapy.

The Vigor of Prescribed Medication

The empirical scale of vigor in table 1 was applied to the regimens of 128 of 131 patients on medication 12 months after referral. The remaining three patients were on treatments such as metolazone, for which we could not find appropriate potency comparisons. Using 50 mg of chlorthalidone or its equivalent as 1 unit of vigor per day, 18 patients (14%) were prescribed less than 1 unit of vigor per day, 43 patients (34%) 1–1.9 units and 67 patients (52%) 2 or more units (fig. 2). DBPs for the three groups were highly significantly different overall (p < 0.005). However, patients prescribed less than 1 unit of vigor or 1–1.9 units had very similar average changes in DBP, whereas patients prescribed 2 or more units of vigor experienced a more substantial decrease in DBP over the same period of time. A potential confounding factor is that the pretreatment DBPs of the three groups were different: 102.5 ± 1.36 mm Hg, 101.9 ± 0.77 mm Hg and 106.3 ± 1.14 mm Hg for the low-, medium-
and high-vigor groups, respectively \((p < 0.01)\). To adjust for this, a multiple regression analysis was performed; the initial diastolic blood pressure and the prescribed vigor were each related, in a highly statistically significant fashion, to the reduction in DBP. Thus, this second process item, the pharmacologic vigor of the prescribed regimen, exerted an important effect on the lowering of blood pressure.

Compliance with Prescribed Medication

Careful pill counts were conducted to measure the compliance of all patients taking medication. These measures afforded two further analyses. First, treated patients were dichotomized into those whose compliance was less than 80\% and those whose compliance rate was 80\% or better (fig. 3). The 56 patients with low compliance had a mean DBP reduction over 12 months of 10.9 ± 1.42 mm Hg, whereas the 75 patients with high compliance had a reduction of 13.2 ± 1.00 mm Hg for the same period. Although there is no statistically significant difference between the mean DBP reduction of these two groups, a comparison of the two groups in terms of achieving a DBP < 90 mm Hg was significant: Only 27\% of the low-compliance subjects achieved this level, whereas 44\% of the high-compliance subjects achieved the level \((p < 0.05)\).

The combination of prescribed vigor and compliance permitted the final analysis. A new variable was computed by multiplying each patient's prescribed vigor by his medication compliance, thereby providing a measure of the vigor of the antihypertensive drug regimen actually consumed by the patient. Thus, 50 patients consumed less than 1 unit of vigor per day, 40 consumed 1–1.9 units, and 38 consumed 2 or more units. The DBP changes over 12 months for the three groups are shown in figure 4. The differences between the three groups are highly statistically significant \((p < 0.0001)\). This dramatic difference in DBP reduction as a function of consumed vigor can be seen in comparing the high with the low consumed-vigor groups. The reduction in DBP among patients who consumed 2 or more units was more than twice that among patients who consumed less than 1 unit. Further, the gradient between vigor and DBP change is greater for consumed vigor than for prescribed vigor; although only 42\% of the patients prescribed a high-vigor antihypertensive regimen achieved a DBP < 90 mm Hg, 47\% of men who actually consumed a high-vigor regimen achieved this level of blood pressure control. Thus, the product of a patient’s compliance with his prescribed regimen — his consumed vigor — is an important measure of the blood pressure response.

Discussion

We have shown the importance of three elements of the process of managing hypertensive patients. First is the decision to treat some but not other hypertensives. The primary care physicians in our study chose to forego pharmacologic treatment for 37\% of patients referred to them. Although this decision was related to the initial DBP, patients at any level of blood pressure who were not treated showed smaller blood pressure reductions on the average and were less likely to reach a DBP less than 90 mm Hg than were treated patients. As the evidence mounts that the treatment of mild hypertension is beneficial, physicians must reduce the level of DBP at which they intervene with pharmacologic treatment. Thus, assessments of the quality of care provided to hypertensive patients must include all hypertensive patients, not merely those for whom treatment has been prescribed.

The second process of importance is the vigor of the prescribed antihypertensive drug regimen. It is not enough to consider merely whether medication has been prescribed. The vigor of the drug regimen has an important influence on lowering of blood pressure, and studies of the quality of antihypertensive care must recognize that many patients will remain inade-
quately controlled because they have not been pre-
scribed enough medication.

Finally, the vigor of the regimen actually consumed
is important. Even when adequate amounts of medica-
tion are prescribed, many patients will fail to benefit
from it because they do not take enough. This finding
also emphasizes the clinical importance of several re-
cent trials that have shown that patient compliance
with antihypertensive therapy can be improved.7, 10–24
Because patients’ acceptance of therapy can be in-
creased by their clinicians, quality-of-care studies that
include accurate measures of compliance among their
process variables will reflect this important process.

Our study was not designed to describe the effects of
the more commonly assessed process variables, such as
history, physical examination and laboratory work-
up, because all patients underwent a standardized
evaluation before referral to care. Thus, we cannot
compare findings on these processes with previous in-
vestigations.8–7 Rather, our results complement those
of the earlier studies. Brook and Appel6 and Nobrega
et al.7 found many aspects of the process of care that
do not bear a clinically important relationship to the
success of blood pressure control (and perhaps merit
less emphasis in the care of patients), whereas we have
identified three items of care that do influence out-
come (and warrant more attention by practitioners
and those who would assess the quality of their anti-
hypertensive care).

We propose three cautions in interpreting our find-
ings. First, they may not be broadly generalizable,
because all of our patients were steelworkers from a
single nonunion Canadian worksite. However, they
were representative of all plant employees (94% par-
ticipation in screening; 92% follow-up at 1 year) and
all family physicians of these patients cooperated fully
with the project.

The second caution concerns the scale of vigor
applied in the study. It is a first attempt, and can no
doubt be improved by including more drug com-
parisons, by testing the assumptions of addictivity
of multiple doses and drugs, and by including new anti-
hypertensive drugs. We predict that any improve-
ment in the assessment of vigor will increase the strength
of the association between prescribed vigor and lower-
ing of blood pressure.

Finally, although the pill count method of measur-
ing compliance in our study is more accurate than
other methods,26 it is expensive in personnel and
awkward in logistics. Thus, it is unlikely to be used for
assessing compliance in usual clinical settings.
Further, it does not provide information concerning
the pattern or cadence in which medications are con-
sumed and assumes that medications removed from
the pill containers have been consumed by the patient
rather than discarded or shared with others. Thus,
although our pill count showed the importance of
compliance as variable in antihypertensive care, better
and easier measures of compliance are needed.

Despite the crudeness of our tools, we could detect
important relationships between the outcome of care
and the decision to treat, the vigor of treatment, and
patient acceptance of the treatment. In retrospect, one
is less surprised that these processes are important
than that their importance was not documented much
earlier.

These findings raise additional questions. What in-
fluences the clinician’s decision to treat only some
hypertensive patients? How do physicians select the
level of vigor of medication they prescribe? With the
plethora of drugs now available for treating hyperten-
sion, is there an optimal method to achieve appro-
priate vigor (and is the stepped-care approach8–4 the
optimal method)? Finally, can independently practic-
ing clinicians modify their management of hyperten-
sion in response to new knowledge on effective
management? A great deal of work remains for the
many investigators involved in studying the clinical
application of the dramatic results of explanatory
trials of the treatment of high blood pressure.

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sive Agents: Double blind control study on antihypertensive
Response of the Systemic and Pulmonary Circulation to Converting-enzyme Inhibition (Captopril) at Rest and During Exercise in Hypertensive Patients

ROBERT FAGARD, M.D., CHRISTOPHER BULPITT, M.D., PAUL LIJNEN, PH.D., AND ANTOON AMERY, M.D.

SUMMARY Twenty sodium-replete patients with hypertension were allocated either to a placebo or to a captopril treatment group. Each patient was investigated in rest-recumbent (RR) and rest-sitting (RS) positions and during an uninterrupted, graded, submaximal exercise test (up to the anaerobic threshold) before treatment, and with a similar protocol 75 minutes after treatment with captopril or placebo on the same morning. Captopril decreased brachial intraarterial pressure by 7/4 mm Hg at RR, by 16/10 mm Hg at RS, and by 19/10 mm Hg during exercise (p < 0.001), based on a decrease of systemic vascular resistance (p < 0.001). Slight increases of cardiac output and of heart rate were noted at rest; cardiac output was not significantly affected during exercise, but the increase of heart rate of 2.4 beats/min was significant (p < 0.01). Captopril decreased pulmonary artery (p < 0.05) and capillary wedge pressures (p < 0.001), with unchanged pulmonary vascular resistance.

The data indicate that the action of captopril is characterized by arteriolar and possibly venous dilatation both at rest and during exercise. Pulmonary vascular resistance, however, is not affected.

INTERFERENCE with the renin-angiotensin system by either angiotensin II antagonists or converting-enzyme inhibitors indicates that the role of angiotensin II in maintaining arterial pressure depends on the prevailing plasma levels of renin or angiotensin II, which vary with sodium state and physical activity. The role of angiotensin II appears to be insignificant in recumbent, sodium-replete normotensive persons, but angiotensin II does seem to contribute to the arterial pressure of some normal subjects in the sitting position, and during exercise. During sodium restriction of sufficient degree, angiotensin II antagonists and converting-enzyme inhibitors lower arterial pressure at any level of physical activity. In hypertensive patients, plasma renin levels vary widely and do determine the response to angiotensin antagonists and converting-enzyme inhibitors, which is enhanced by sodium depletion. The hypotensive effect of these agents is based on a decrease of systemic vascular resistance in most subjects; cardiac output usually is not changed, but increases with converting-enzyme inhibitors and decreases with angiotensin antagonists have been reported. These effects have not been studied during exercise.

We report the hemodynamic effects of captopril (2-D-methyl-mercaptopropionic-L-proline; SQ 14225; Squibb Institute for Medical Research) at rest and during exercise in hypertensive patients. The study was restricted to sodium-replete patients because a single dose of sodium may produce adverse hypotension after sodium depletion.
Process versus outcome in hypertension: a positive result.
R B Haynes, E S Gibson, D W Taylor, C D Bernholz and D L Sackett

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