Antihypertensive Drug Therapy
The Effect of JNC Criteria on Prescribing Patterns and Patient Status Through the First Year
Michael H. Alderman, Shantha Madhavan, and Hillel Cohen

This study was designed to evaluate the impact of the protocol-driven antihypertensive therapy on outcomes guided by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of high blood pressure. In a systematic hypertension control program for union employees conducted in New York City, untreated patients who began treatment on monotherapy guided by JNC recommendations during three representative periods: I—pre-JNC IV (1986–1987); II—post-JNC IV (1990–1991); and III (JNC V)—period of application of what were later published as JNC-V guidelines (1992) were observed during 1 year of treatment. A total of 550 presumably untreated patients were prescribed either diuretics, β-blockers, calcium channel blockers, or angiotensin converting enzyme inhibitors. These were 231 in period I, 213 in II, and 106 in III. The patient composition over time became more predominantly female and Hispanic (I to III: 28% to 34%, and 35% to 45%, respectively). The main outcome measures were type of drug first prescribed and the outcomes at the end of 1 year—changes in blood pressure, clinical chemistry measures and therapy, and clinic attendance and dropout rate. The pattern of first drug prescription changed from 85% to 90% of patients given diuretics or β-blockers in I to 90% begun on calcium channel blockers or angiotensin converting enzyme inhibitors in II and finally, to an even distribution of drugs in III. Blood pressure response was similar across the three periods, 135/89 mm Hg (I), 138/89 (II), and 140/89 (III). Proportion of patients remaining on their initial drug in each period was fairly similar (60%, 67%, and 69%). Scheduled clinic visits fell significantly from 7.4 visits in I, 6.9 in II, and 6.4 in III (1 vs III P = .004). Dropouts diminished significantly from 17% in I, to 10% in II, and 9% in III (1 vs II or III P = .045). Modest positive changes in cholesterol and fasting blood sugar level occurred over time. In this general community setting, dramatic shifts in the choice of initial drug based upon application of JNC guidelines had little discernable impact on short term patient outcomes. Am J Hypertens 1996;9:413–418

KEY WORDS: Antihypertensive drug therapy, JNC criteria, calcium channel blockers.

Since orally effective antihypertensive agents first became available in the 1950s, an active search for new and better pharmacological agents has yielded no less than six classes of effective agents. Since then, patterns of drug use have shifted dramatically. Now, for example, diuretics and beta blockers, which had been the mainstays of therapy through the 1970s, have been largely eclipsed by...
calcium channel blockers (CCB) and angiotensin converting enzyme (ACE) inhibitors, which were introduced in the 1980s. These changes may have been stimulated, in part, by the recommendations of the 1988 report of the Fourth Joint National Committee (JNC) on the Detection, Evaluation, and Treatment of Hypertension. In this report, four classes of antihypertensive agents were viewed as equal choices for initial therapy. That position was reversed in 1993, when the Fifth JNC report identified diuretics and β-blockers as preferred choices for initial antihypertensive therapy in cases where there was no particular contra-indication to their use, or specific indication for the use of another drug.

These sequential recommendations have been applied in a standardized protocol-driven, worksite-based treatment program. We now report, by year, first drug prescription patterns and patient experience during 1 year for 531 new untreated patients who entered treatment between 1986 and 1992.

**MATERIAL AND METHODS**

**Setting** A systematic, occupationally-sponsored program to detect and treat hypertension among employed union members, which was started in 1973, enrolls new patients as they are identified through ongoing union-sponsored screening. A protocol-driven care system begins with standardized screening to establish eligibility, and is followed by clinical evaluation culminating in the prescription of initial therapy by the supervising physician. Follow-up care is provided by the nurse guided by the protocol, with the physician available for consultation. At interval visits, averaging six to seven during the first year, interval history, response to therapy, and blood pressure readings are recorded. The nurse may, with limits defined by the protocol, and in response to the clinical situation, alter therapy. All patient information is recorded on standardized forms for computer storage.

Until 1988, the potential choices in the protocol were diuretics, β-blockers, and α-blockers. In 1988, guided by JNC-IV, ACE inhibitors and CCBs were added to the list of approved drugs for first use. In January, 1992, the selection of first drug was again altered to match what became JNC-V guidelines in the 1993 report. Patients were to be started on diuretics or β-blockers unless a specific indication for another agent existed, or if there was a contraindication to the preferred drugs. The indications for another agent included asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure, or history of bypass surgery. Contraindications were coexisting conditions such as diabetes mellitus, hyperlipidemia, COPD / asthma, congestive heart failure, gout, bradycardia and impotence, for one or both drug classes. Plasma renin activity was estimated for each patient to further direct initial drug therapy. In general, low renin patients were begun on either a diuretic or calcium channel blocking agent. High renin subjects began with a β-blocker or converting enzyme inhibitor. Demographic characteristics guided the choice for the majority whose renin profile was in the normal range.

**Study Design and Subjects** Study subjects were all eligible patients who entered the treatment program in 1986 and 1987 (pre-JNC IV period: I), 1990 and 1991 (post-JNC IV period: II), and 1992 (JNC V period: III). Eligible subjects were those who entered without therapy, began treatment with a single drug, and could have been in treatment for at least 1 year (ie, entered before 31 December 1992 to permit 1 year analysis). Of 591 eligible patients, those (n = 550) whose first drugs were one of the four classes (diuretics, β-blockers, CCB and ACE) were grouped according to the period of entry, excluding 40 patients on other drugs in all three periods and the single patient on ACE in period I.

During the initial nurse visits, baseline demographic, historical, clinical, and laboratory data prior to therapy were obtained. At the end of 1 year of treatment, the final blood pressure level was established by averaging the last two readings out of the three taken at that visit, similar to the procedure at initial and visits.

**Data Analysis** Univariate analysis was performed to describe the experience of patients by period of entry as the primary unit of analysis. For comparison of characteristics according to drug between periods, ANOVA (analysis of variance) and Student’s t test for continuous variables and χ² test for categorical variables were used, adopting P ≤ .05 as the level of statistical significance.

All patient information was recorded on standardized forms for regular transfer to computer storage. The data set was retrieved from the master file and all analyses were performed using SPSS / WIN.

**RESULTS**

Table 1 presents the pattern of first drug prescription over time. The yearly entry cohort of untreated patients was rather constant (100 to 150) and reflected about 30% of total annual entrants. Others entered already taking drugs. In the pre-JNC IV period I (1986–1987), 85% to 90% of patients were first given diuretics or β-blockers. The pattern changed in the post-JNC IV period II (1990–1991), when 90% of patients were begun on CCBs or ACE inhibitors. In 1992 (JNC V period III), the four drugs were evenly distributed.

The baseline characteristics of 550 patients, whose first drugs were one of the four classes, in the three entry periods (Table 2) revealed that the patient composition of the treatment program changed modestly over time to become increasingly female (I: 28% to
TABLE 1. DISTRIBUTION OF PATIENTS BY FIRST DRUG AND PERIOD OF ENTRY

<table>
<thead>
<tr>
<th>First Drug</th>
<th>Period of Entry*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (N) (%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>146 (54.9)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>85 (31.9)</td>
</tr>
<tr>
<td>CCB**</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>ACE**</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other drugs</td>
<td>34 (12.8)</td>
</tr>
<tr>
<td>Total</td>
<td>266 (100.0)</td>
</tr>
</tbody>
</table>

* I, Pre-JNC IV Period (1966–87); II, Post-JNC IV (1990–91); III, JNC V (1992); + CCB, Calcium Channel Blockers; ** ACE, Angiotensin Converting Enzyme Inhibitors.

III: 34%) and Hispanic (I: 35% to III: 45%). Initial blood urea nitrogen, cholesterol, and blood pressure did not differ over time, except that fasting blood sugar was the lowest in period I. Age at entry and body mass index, and initial systolic and diastolic blood pressure of patients in all three periods were similar.

Outcomes in Therapy Blood Pressure Control Overall, blood pressure response, measured by mean final pressure was not substantially distinguishable clinically across the years. Blood pressure levels achieved at the end of 1 year of treatment in the three periods showed no significant differences for diastolic pressure, although systolic pressure for period I was significantly lower by 4.2 mm Hg compared with that of period III (Table 3).

The percent of patients remaining on their initial drug were similar in the three periods I, II and III respectively (60.0%, 66.7, 66.9). Furthermore, roughly similar fractions needed an additional drug in periods I (15.6%) and III (12.3%), although significantly fewer did in period II (8.9%). Switching to an alternate drug or discontinuing medication were similar in the three periods.

Clinical Attendance and Dropout The mean number of scheduled visits over time fell from 7.4 in I, 6.9 in II, to 6.4 in III (I vs III, P = .004). Patients who failed to have a visit at the end of 1 year (dropouts) diminished from 17% in I to 10% in II and 9% in III. The differences in proportion of dropout between period I and II or III were significant (P = .045).

Clinical Chemistry Measures Mean initial cholesterol levels (I:221, II:219, III:221 mg/dL) and the mean levels at the end of the first year (II, 215, 214) in the three entry periods were very similar in magnitude, although the final level for period I was significantly higher by 10 mg/dL (Table 4). For fasting blood sugar levels...
TABLE 3. BLOOD PRESSURE ACHIEVED, PRESCRIPTION, NUMBER OF CLINIC VISITS AND DROP-OUT BY PERIOD OF ENTRY

<table>
<thead>
<tr>
<th>Period of Entry</th>
<th>I (N = 231)</th>
<th>II (N = 213)</th>
<th>III (N = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mm Hg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final systolic</td>
<td>135.3 ± 13.4</td>
<td>138.3 ± 15.7</td>
<td>139.5 ± 16.7</td>
</tr>
<tr>
<td>Final diastolic</td>
<td>89.3 ± 7.5</td>
<td>89.3 ± 8.5</td>
<td>89.0 ± 7.9</td>
</tr>
<tr>
<td>Prescription in First Year:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Add</td>
<td>60.2</td>
<td>66.7</td>
<td>68.9</td>
</tr>
<tr>
<td>Switch</td>
<td>15.6</td>
<td>8.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Off medication</td>
<td>10.8</td>
<td>9.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Number of Visits (mean ± SD)</td>
<td>7.4 ± 2.8</td>
<td>6.9 ± 2.5</td>
<td>6.4 ± 1.9</td>
</tr>
<tr>
<td>Drop-Out (%)</td>
<td>16.9</td>
<td>10.1***</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Level of significance at P = .05.
* I v II, P = .03; † I v III, P = .01; ‡ Differences in % between periods not significant; ‡‡ I v II, P = .02, ‡‡‡ I v III, P = .008; *** I v II, P = .045.

DISCUSSION

During the late 1980s, given free choice, physicians in this systematic treatment program made sharp shifts away from older drugs toward newer ones. In 1992, imposition of practice guidelines, aimed at implementing national recommendations, dramatically reversed these recently adopted prescription patterns. The salient finding has been that patient outcomes, despite seismic shifts in drug use, measured by aspects of BP control, persistence in therapy, and clinical chemistry results, did not vary by period of entry. In fact, choice of drug did not importantly influence any measurable aspect of treatment.

It is reasonable to believe that experience in this well-defined treatment program during the 1980s accurately reflected changing patterns of antihypertensive therapy throughout the country.

Pharmaceutical sales data and surveillance information suggest widespread abandonment of diuretics and β-blockers during the 1980s in favor of the newer drugs. The reasons for this vast change are not immediately apparent. Newer drugs had not been shown to be more effective hypotensive agents, nor was there any evidence of greater capacity to prevent cardiovascular morbidity, nor were they less expensive. Reasons for their popularity must lie elsewhere. Perhaps physicians were drawn to them either because they believed either that the new drugs were more tolerable or that avoiding the metabolic disadvantages of diuretics and β-blockers would improve outcomes. It is also possible that effective marketing by the pharmaceutical manufacturers convinced physicians that their products were superior.

Not surprisingly, since metabolic factors influence choice of drug, when newer drugs that did not adversely affect cholesterol and fasting blood sugar were
available, those levels were lower than had been the case when these options did not exist. During the period when nearly universal diuretic and β-blocker was the pattern, there was a tendency for glucose and cholesterol to rise over the year. The 1992 protocol guided patients with hyperlipidemia and hyperglycemia away from diuretics and β-blockers. The happy result was that mean levels of both of these measures fell over the year. These declines were greater for patients begun on converting enzyme inhibitors and CCBs than diuretics and β-blockers. The mean fasting blood sugar of patients started on p-blockers rose minimally over the year. Thus, it would appear that reasoned avoidance of diuretics and beta blockers in patients with elevated lipids or fasting blood sugar, may have produced satisfactory metabolic consequences for the entire group.

The 1992 experience suggests that the JNC V recommendations do not deny patients access to the full range of drugs. Despite preferred use of diuretics and β-blockers, one half of all patients still began with a CCB or ACE. Roughly one quarter of all patients then developed a compelling reason either to add (12%) to the preferred drugs, or to switch (14%) from the preferred drugs in favor of another agent. Another 5% (5/106) did not need drug at the end of first year. In sum, by the end of the first year of therapy, distribution of drug use approximated that at the beginning of the year. For those patients who entered following JNC V, and were in treatment, 53/101 were on diuretics or β-blockers, while a similar proportion 57/101 were taking either CCB or ACE. α-Blockers were used infrequently. Interestingly, this shift in drug use towards diuretics and β-blockers mandated here. also appeared to occur in the general community. Recently, it has been suggested that trends may reflect the influence of clinical trials.

The finding here that initial drug choice had such an imperceptible effect on short term outcomes is wholly consistent with the recently reported randomized comparisons of these agents. In both TOMHS (Treatment of Mild Hypertension Study)8 and Veterans Affairs Cooperative Study Group on Antihypertension Agents,9 parallel comparison of representatives of the drug classes used here demonstrated only small and inconsistent differences in outcomes. BP control and drug persistence was similar across classes, and adverse metabolic consequences with diuretics and β-blockers were unusual. Of note, in both these studies, no agent exceeded diuretics in ability to reverse left ventricular hypertrophy.

As for blood pressure, it is clear that more than 50% of all patients will respond successfully to any agent.10 It is not, however, the same set of individuals who will respond to each drug. Thus, as seen here, by sequential application of various agents it is possible to control the pressure of the vast majority of patients with minimal therapy. Drug use here might not mirror experience when the same guidelines are applied in hospital clinics or physician offices where sicker patients seeking care might congregate. It is likely, however, that the findings here reflect what might be expected if JNC V guidelines were implemented for the majority of mild, uncomplicated hypertensive patients.

The strength of this study is that participants were drawn from the general community. Their pattern of care was standardized. The union/management sponsor paid full drug cost, thus price did not influence selection by either physician or patient. However, since the final protocol change was introduced in January, 1992, it was only possible to examine patient experience for one year. Moreover, the numbers were insufficient to draw reliable inferences regarding either side effects or laboratory use. No effort was made to examine the economics of the experience here, although the protocol guided other resource consumption. Clinic visits and laboratory tests were similar for all patients regardless of drugs so costs other than drugs were likely to be roughly equal.

The fascinating unanswered question is why physicians were so willing to abandon drugs that had been successfully used, in the case of diuretics, for decades, and that had produced cardiovascular protection. Experience here and elsewhere suggests that hopes for greater tolerance and superior blood pressure control that physicians and pharmaceutical representatives may have harbored, do not stand up to careful experimental scrutiny. Furthermore, there is inadequate evidence that the newer agents are as safe over the long term as older agents, nor was there (or is there) information about the relative cardioprotective capacity of these newer agents. ALLHAT (The Antihypertensive and Lipid Lowering Treatment for Heart Attacks Trial)12 is a major, prospective randomized trial designed to compare cardiovascular morbidity and mortality in older, high risk hypertensive patients prescribed a diuretic, calcium channel blocker, or converting enzyme inhibitor. In sum, the findings here suggest that vast changes can occur in the choice of initial antihypertensive drug without measurable impact on short term outcomes. These findings, in a general community setting, are consistent with the results of formal randomized clinical trials. Moreover, it is clear that application of JNC V guidelines produced results that confirmed neither the fears of its opponents nor the hopes of its advocates. The use of newer drugs was hardly eliminated. Instead, they tended to be targeted to situations where there is reason to believe that they may offer advantage sufficient to justify replacement of drugs whose cardiovascular benefits have already been demonstrated.
REFERENCES