From Clinical Trials to Clinical Practice
Why the Gap?

Theodore A. Kotchen

Based on an analysis of National Health and Nutrition Examination Survey data, the prevalence of hypertension in the United States increased from 25.0% in 1988 to 1991 to 28.7% in 1999 to 2000. Despite compelling evidence for the cardiovascular and renal benefits of hypertension control, during that same decade, hypertension control rates increased from 24.6% to only 31.0%. At a time when he was director of the National Heart, Lung, and Blood Institute, Claude Lenfant expressed the concern that the potential benefits of clinical research are lost in the translation into clinical practice. Others have also pointed out the slow pace of diffusion of new scientific knowledge into health care and have recommended strategies for decreasing the gap between knowledge and clinical practice.

In this issue of Hypertension, Stafford et al describe prescription patterns for antihypertensive agents and suggest that prescriptions for specific classes of agents do not reflect incorporation of lessons learned from clinical trial outcomes. Based on data extracted from the National Disease and Therapeutic Index, which is a continuing survey of a national sample of US office-based physicians, between 1990 and 2004, overall, the most frequently prescribed agents were angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs); diuretics were the third most frequently prescribed agents. After publication of the results of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) in 2002, diuretic prescriptions increased by early 2003 and surpassed CCBs. However, by 2004, although the use of diuretics exceeded pre-ALLHAT levels, their use had declined from their peak use in early 2003. The authors concluded that thiazide diuretics are underprescribed despite clear evidence that they are the most cost-effective antihypertensive agent.

ALLHAT was a randomized, double-blind clinical trial, involving >40,000 high-risk hypertensive patients, that compared cardiovascular outcomes in patients treated with diuretics as first-step therapy with outcomes in patients treated with an ACEI (lisinopril), a CCB (amlodipine), or an α-antagonist (doxazosin). The intended follow-up was 4 to 8 years, although the doxazosin arm was terminated early, because the incidence of combined cardiovascular events, particularly congestive heart failure, was significantly higher for the doxazosin-treated than the chlorthalidone-treated patients. The primary end point of the study, the combination of fatal coronary heart disease and nonfatal myocardial infarction, was identical in the chlorthalidone, amlodipine, and lisinopril groups. Other large clinical trials have also failed to detect an overall cardiovascular advantage for different classes of antihypertensive agents. The ALLHAT investigators concluded that, “Thiazide type diuretics are superior in preventing one or more major forms of cardiovascular disease and are less expensive. They should be preferred for first-step antihypertensive therapy.” Similarly, for ≈3 decades, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommendations for initial drug treatment have included a diuretic (Table). With the increasing availability of generic drugs, although the cost differential between diuretics and other agents has lessened, it has not been obliterated.

Similar to the observations of Stafford et al, previous studies of the trends of antihypertensive drug use in the United States also point out that JNC recommendations and ALLHAT have had relatively little long-term impact on prescribing patterns. A number of factors may contribute to the gap between these recommendations and the prescribing patterns of practicing physicians who are responsible for the care of individual patients. These include the following: (1) the newer and more expensive antihypertensive agents have been aggressively marketed to physicians and consumers by the pharmaceutical industry; (2) different comorbidities may influence the selection of an antihypertensive agent; (3) different agents may have cardiovascular and renal protective effects beyond their capacity to lower blood pressure in select groups of high-risk patients; (4) the ALLHAT conclusion that diuretics are superior to other agents in preventing cardiovascular disease has been overstated, because it is based on an analysis of secondary end points and because the potential long-term consequences of the metabolic side effects of diuretics remain unknown; and (5) in apparent contrast to the ALLHAT results, in an Australian randomized trial of ≈6000 older subjects, ACEI-based antihypertensive therapy resulted in fewer cardiovascular events or death from any cause than diuretic based therapy.

A recent meta-analysis suggests essentially equivalent blood pressure–lowering effects of thiazide diuretics, β-blockers, ACEIs, angiotensin receptor blockers, and CCBs when used as monotherapy. Earlier JNC reports advocated a stepped care approach, whereby before adding a second agent, the recommendation was to gradually increase the dose of the initial agent until goal blood pressure was attained, side effects became intolerable, or the maximum dose was reached. However, for most agents, blood pressure reductions at half-standard doses are only ≈20% less than at standard doses. The most recent JNC report

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JNC Recommendations for an Initial Antihypertensive Agent

<table>
<thead>
<tr>
<th>Committee</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 1</td>
<td>1977</td>
<td>Thiazide-type diuretic</td>
</tr>
<tr>
<td>JNC 2</td>
<td>1980</td>
<td>Diuretic</td>
</tr>
<tr>
<td>JNC 3</td>
<td>1984</td>
<td>Thiazide-type diuretic or BB</td>
</tr>
<tr>
<td>JNC 4</td>
<td>1988</td>
<td>Diuretic or BB or CCB or ACEI</td>
</tr>
<tr>
<td>JNC 5</td>
<td>1993</td>
<td>Diuretic or BB</td>
</tr>
<tr>
<td>JNC 6</td>
<td>1997</td>
<td>Diuretic or BB</td>
</tr>
<tr>
<td>JNC 7</td>
<td>2003</td>
<td>Thiazide-type diuretic, either alone or in combination with ACEI, ARB, BB, or CCB</td>
</tr>
</tbody>
</table>

BB indicates β blocker, ARB, angiotensin receptor blocker.

recommends initiating therapy with either a diuretic alone or a diuretic in combination with another agent. This is based on the recognition that most hypertensive patients will require two or more antihypertensive medications to achieve blood pressure goals. Appropriate combinations of agents at lower doses have additive or almost additive effects on blood pressure with a lower prevalence of side effects. With increasing emphasis on the use of combinations of antihypertensive agents, generally including a diuretic, it will be of interest to determine whether there continues to be a gap between these newer recommendations and future prescription patterns. Consistent with these recommendations, between 1988–1994 and 1999–2002, multiple antihypertensive drug use increased, whereas monotherapy with a diuretic or β blocker decreased.

The high rate of uncontrolled hypertension, despite the availability of effective antihypertensive agents, represents a more disturbing gap than the selection of an initial agent in the translation of scientific knowledge into clinical practice. Strategies to improve blood pressure control should be our number one priority for the treatment of hypertension.

Disclosures

None.

References

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