Hypertension is a serious public health problem affecting \( \approx 60 \) million Americans, including a disproportionate number of older adults, blacks, and Hispanics. Elevated blood pressure is a major risk factor for a range of cardiovascular events, including heart disease and stroke, the first and third leading causes of death in the United States. In conjunction with lifestyle modification, several classes of medications effectively treat hypertension and lower its associated morbidity and mortality.

Antihypertensive medications have been on the market since 1962. Thiazide diuretics and \( \beta \)-blockers were among the first Food and Drug Administration-approved antihypertensive medications. Angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) entered the market in 1982. Angiotensin-II receptor blockers (ARBs) followed in 1995.

Trends in antihypertensive prescribing practices have been driven by several factors. National clinical guidelines have provided evidence-based recommendations for the treatment of hypertension. Antihypertensive medications have also been influenced by factors such as prices, availability of free drug samples, and drug characteristics. However, concerns about the effectiveness and tolerability of diuretics and \( \beta \)-blockers have also influenced physicians’ decisions to choose newer medications.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) is, to date, the largest antihypertensive trial. We reported previously that the premature termination of the doxazosin arm in ALLHAT resulted in a notable decline in the prescribing of all \( \alpha \)-blockers. The final results comparing the remaining 3 study arms were published in 2002 and concluded that chlorthalidone (a thiazide diuretic) was at least as effective as the more expensive lisinopril (an ACE-inhibitor) and amlodipine (a CCB) in lowering blood pressure, as well as cardiovascular events. Publication of these findings...
was shown to have had an immediate influence on physician practices.24 However, the recommended use of thiazide-type diuretics as first-line therapy for hypertension has not been unequivocally accepted among health providers.25–28 The long-term safety of thiazide-type diuretics has been questioned because of concerns about their adverse metabolic effects, especially new-onset diabetes, hypokalemia, and renal insufficiency.29,30

The literature lacks a complete depiction of trends in antihypertensive prescribing in the recent 2 decades, during which a plethora of clinical evidence regarding the efficacy and safety of various antihypertensive medications and a series of JNC guidelines have come into bearing. To extend past research, we use nationally representative data on medication prescribing by office-based physicians to depict long-term trends in the prescribing of antihypertensive medications from 1990 through 2004, as well as the most recent short-term trends beginning in 2001.

Methods

Data were extracted from the National Disease and Therapeutic Index (NDTI), a continuing physician survey conducted by IMS Health. NDTI provides nationally representative data reported by office-based physicians in the US on patient encounters, including drug prescription information. A random sample of office-based physicians stratified by specialty and geographic location was selected from the master lists of the American Medical Association and the American Osteopathic Association. Approximately 3500 physicians from all specialties involved in direct patient care participated in each calendar quarter. Each physician was randomly assigned 2 consecutive workdays per quarter and reported data on all of the patient encounters during these 2 days. Physicians had no previous knowledge of their date assignments. Physician encounters with patients largely consisted of office visits (>90%), although encounters with patients during telephone calls, as well as hospital and nursing home visits, were also included. Physicians reported all of the diagnoses during a patient encounter and all of the new or continuing medications prescribed to treat each diagnosis. Physicians may report the medications in brand or generic names, and the reporting reflects the physician’s best knowledge of prescription and nonprescription medications taken by the patient. Each reported use of a drug constitutes a drug mention. Multiple drug mentions may occur for a diagnosis during a patient encounter; thus, the sum of drug mentions may exceed 100% of total patient encounters. NDTI does not capture patient adherence to medications or unreported self-medication. Published NDTI data contain aggregates at the individual drug level, as recorded by the percentage of all patient visits with a specific diagnosis.

Our study was based on national estimates for 1990–2004 that were estimated from the NDTI survey sample data. Sample sizes of annual visits for hypertension (International Classification of Diseases, Ninth Revision: 401.0 to 405.9) included in NDTI ranged from 17 318 to 21 885 (mean: 19 602). Data estimation accounts for the 2-stage stratified cluster sampling method used in the NDTI. Annual data are presented as the aggregate of the quarterly surveys conducted within each year. For the sample sizes available for hypertension visits, the 95% CIs around annual national estimates of medication usage rates and patient visits are <6.5%.31

We performed our analyses of trends in the prescribing of antihypertensive medications at the drug class level. Antihypertensive drug classes examined include ACE inhibitors, CCBs, ARBs, diuretics, β-blockers, α-blockers, and central-acting agents. For brand name and combination antihypertensive agents, each generic name (active ingredient) component of the agent was counted separately. Then, each generic name was categorized into its major antihypertensive drug class. The percentage of patient encounters for each antihypertensive drug class prescribed was calculated by dividing the number of hypertension patient visits in which the drug class was mentioned in a calendar year by the number of total hypertension patient visits for that year.

To examine long-term changes in prescribing, we graphically depicted yearly mentions of the antihypertensive drug classes as the percentage of total hypertension patient visits from 1990 through 2004. We hypothesized a priori that there was no significant long-term trend in prescribing for any of the antihypertensive drug classes; we determined significance using 2-tailed Cox and Stuart tests.32 The Cox and Stuart test is a nonparametric test of whether a sequence of observations taken over time exhibits some type of trend. An upward trend is exhibited if the magnitudes of the latter observations tend to be greater than those of the earlier observations, and a downward trend is exhibited if the opposite is true. For greater precision in assessing the most recent changes in antihypertensive prescribing, we depicted quarterly mentions of diuretics (thiazide and other diuretics), ACE inhibitors, CCBs, and ARBs as the percentage of total hypertension patient visits between 2001 and 2004. We performed 1-tailed Cox and Stuart tests to test our hypotheses that the prescribing of thiazide diuretics increased, whereas prescribing of ACE inhibitors, CCBs, and ARBs decreased after the ALLHAT main results were published in December 2002. In addition to the Cox and Stuart test, z tests were used to determine significance of observed differences between 2 proportions.33 Statistical significance was determined at P<0.05.

Results

Long-Term Trends of Antihypertensive Drug Prescribing

Diuretics were the most frequently prescribed antihypertensive medications in 1990 (39% of all hypertension visits) and 1991 (36%), but prescription of diuretics declined successively to 21% in 1998 (P<0.0001; Figure 1). Thereafter, diuretics increased by 7% to 28% of hypertension visits in 2000 (P<0.0001) and became the second most prescribed drug class exceeding CCBs (P<0.01) for the first time since 1991. In 2003, diuretics increased by 5% to 33% of all hypertension visits (P<0.0001) and stabilized at 32% in 2004.

In 1990, CCBs were prescribed in 22% and ACE inhibitors in 28% of all hypertension visits. Since then, prescription of both drug classes had trailed each other very closely through 1997 and exceeded diuretics as the leading antihypertensive drug classes in 1993 (P<0.0001 for both CCBs versus diuretics and ACE inhibitors versus diuretics). CCBs began a gradual decline in 1996 (34%) through 2000 (26%) (P<0.0001) and remained essentially stable thereafter. On the other hand, ACE inhibitors increased markedly from 32% in 1998 to 40% in 2002 (P<0.0001) after being prescribed to a largely stable percentage of hypertension visits between 1992 and 1998. Although ACE inhibitors declined in both 2003 (39%; P<0.05 versus 2002) and 2004 (34%; P<0.0001 versus 2003), they had remained the leading antihypertensive drug class since 1998. Moreover, since the market entry of first ARB (losartan) in April 1995, the use of this particular class of antihypertensive agents increased continuously to 25% in 2004, replacing β-blockers as the fourth most commonly prescribed antihypertensive drug class.

As the fourth most common antihypertensive drug class through 2002, β-blockers were prescribed in 17% of all hypertension visits in 1990. After a slight decline, β-blockers demonstrated a slow gradual increase from 14% in 1993% to 21% in 2001 (P<0.0001) and then stabilized at 19% in 2004.

α-Blockers were constantly prescribed to ~6% of all hypertension visits before they started to decline in 2000 and...
became seldom prescribed after 2001. Similarly, central acting agents declined from 9% of all hypertension visits in 1990 to a negligible level in recent years.

The overall long-term trend in prescribing as determined by the Cox and Stuart test showed a significant increase in the prescribing of ACE inhibitors and β-blockers from 1990 to 2004 and in the prescribing of ARBs from 1995 to 2004. Furthermore, prescribing trends for central acting agents decreased significantly from 1990 through 2004.

**Short-Term Trends of Antihypertensive Drug Prescribing**

Quarterly data from 2001 and 2002 showed that thiazide diuretics were prescribed to a largely stable percentage of hypertension visits, ranging from 19% to 22% (Figure 2).

Prescribing of thiazide diuretics increased notably from 19% in the fourth quarter (Q4) of 2002% to 29% in Q2 2003 but then stabilized at ~26% through Q4 2004 (P<0.001). Use of other diuretics remained essentially unchanged between 2001 and 2004, accounting for 7% of all hypertension visits in each quarter. Prescribing of ACE inhibitors followed a slight ascending slope and peaked at 42% in Q2 2002. Subsequently, a continuous decline was recorded beginning Q2 2003 (41%), and ACE inhibitors were prescribed in 30% of all hypertension visits in Q4 2004 (P<0.0001). The pre-existing pattern of increased prescribing of ARBs continued and peaked in Q4 2004 at 25%. The proportion of hypertension visits in which CCBs were prescribed fluctuated around a mean of 26% without a clear pattern of increasing or decreasing. The Cox and Stuart test for trend found statistical significance only for the upward trend in thiazide diuretics.
Discussion

Physician prescribing practices for hypertension have evolved over the past 15 years. Both long- and short-term trends show a mix of prescribing practices that accorded and dis accorded with clinical recommendations put forward by JNC V, VI, and VII,6,18,19 the JNC reports that were released during the study period.

Recommended as first-line therapy in all 3 of the JNC reports, diuretics ranked among the top 3 antihypertensive drug classes throughout the entire study time span, but they were superseded by both ACE inhibitors and CCBs between 1993 and 1999 and subsequently by ACE inhibitors through 2004. The ALLHAT main results were published in December 2002 suggesting the clinical equivalence of thiazide diuretics to CCBs and ACE inhibitors.23 Prescription of thiazide diuretics increased immediately in the first half of 2003, and prescription of all diuretics significantly surpassed that of CCBs in 2003 as the second most prescribed antihypertensive drug class. Despite being another class of first-line antihypertensive agents recommended in JNC VI, thiazide diuretics were consistently the fourth most common drug class until 2003 when exceeded by ARBs. Nonetheless, prescription of β-blockers was significantly more frequent after 1997, during which JNC VI was released.

As noted, thiazide diuretics increased immediately after the publication of ALLHAT main results in December 2002 and, despite a subsequent decline, stabilized at a level significantly exceeding the pre-ALLHAT level. Similarly, Xie et al24 found a rapid response by physicians to the new clinical evidence from ALLHAT. Furthermore, the ALLHAT main results may be associated with a dampening in the prescription of ACE inhibitors, which generally increased until 2002. After having increased by 13% from 1990, prescription of CCBs began to decline in 1995 continuing through 2000 but showed no significant changes after the release of ALLHAT. This trend coincided with the market entry of ARBs and their increasing popularity, suggesting that ARBs increased at the expense of CCBs and possibly ACE inhibitors because of similar drug action sites.

Interpreted in the context of national guidelines and clinical evidence, our recorded long- and short-term trends suggest that evidence-based recommendations had an impact on antihypertensive prescribing practices in the past 15 years but that the magnitude of this impact may be smaller than desired. Our data and other studies find that thiazide diuretics have significantly surpassed that of CCBs in 2003 as the second most prescribed antihypertensive drug class. Despite being another class of first-line antihypertensive agents recommended in JNC VI and VII,6,18 β-blockers were consistently the fourth most common drug class until 2003 when exceeded by ARBs. Nonetheless, prescription of β-blockers was significantly more frequent after 1997, during which JNC VI was released.

Limitations

Several data limitations exist in our analyses. The results based on NDTI data may differ from those found for the general population, because the data are based on patient visits. Patients making multiple visits are more likely to be sampled. However, the percentage of visits by the same patient is expected to be low in NDTI, because physicians report data on patient encounters during 2 consecutive work days per quarter. As aggregates at the individual drug level, published NDTI data do not support a thorough assessment of treatment appropriateness and physician adherence to guide-
lines for lacking patient-specific clinical detail, such as comorbidities and past drug trials. The data also do not enable use to examine variations in physician prescribing by physician and patient characteristics.

**Perspectives**

Appropriate medication choices are imperative in the treatment of elevated blood pressure and may impact both patient outcomes and health care costs. This study finds that national guidelines and clinical evidence have modest influences on physician prescribing practices. A range of clinical and market factors, such as drug promotion, market competition, media coverage, and purchasing contracts, may balance or even offset the effects of guidelines and clinical evidence on physician prescribing. The sustained preference for ACE inhibitors and the recent popularity of ARBs have increased the cost of treating hypertension without necessarily providing incremental benefits over thiazide diuretics on patient outcomes. In the context of acknowledging the complexity of modern medicine and the vitality of clinical judgment and patient preference, effective strategies are warranted to align practice with the evidence-based recommendation to use thiazide diuretics alone or in combination with other antihypertensive medications for treating most patients with elevated blood pressure.¹⁹

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**Disclosures**

None.

**References**


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