Antihypertensive Drug Therapy in Saskatchewan

Patterns of Use and Determinants in Hypertension

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Background: The benefits of continuous treatment of hypertension have been extensively documented in randomized controlled trials. However, clinical trials may not reflect actual drug use in the population.

Objective: To examine the distribution and determinants of patterns of use of antihypertensive agents in the first 5 years of hypertension treatment in Saskatchewan.

Methods: Patterns of use and modifications to therapy were derived from a careful examination of medication use in a cohort of 19,501 subjects aged 40 to 79 years, without recognized cardiac disease and initiating therapy with an angiotensin-converting enzyme inhibitor, a calcium antagonist, or a β-blocker in Saskatchewan between 1990 and 1993.

Results: Angiotensin-converting enzyme inhibitors (37.4%), followed by calcium antagonists (27.5%) and β-blockers (26.4%), were the most commonly prescribed agents to initiate treatment in our study population. Patients with diabetes were less likely to be dispensed a β-blocker, as were younger and female patients. Previous visits to a cardiologist decreased the likelihood of receiving combination therapy or angiotensin-converting enzyme inhibitors but increased that of using calcium antagonists. Apart from dose adjustment, 89% of study subjects underwent at least 1 modification to their initial regimen, at a median time of 134 days. After 1 year, only 33.8% of patients were still using their initial drug. An early decrease in the proportion of patients continuing to receive initial therapy was noted, especially among β-blocker users.

Conclusions: Erratic drug-taking behaviors were observed in this Saskatchewan population. In addition, initial drug use does not seem to be in accordance with the stepped-care approach to hypertension therapy recommended in the Canadian guidelines.

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Suboptimal treatment of uncomplicated hypertension constitutes a major barrier to effective therapy. Early discontinuation and erratic drug use manifested by frequent interruptions and switches to different treatment regimens have been shown to be associated with the progression of cardiovascular and renal diseases, and to increase the risk of a readmission to the hospital.¹⁻⁸

Clinical guidelines on the management of hypertension are based on scientific evidence obtained from randomized controlled trials that are not designed for evidence gathering on actual drug use in the clinical practice. Several attempts have been made to document the management of hypertension in the general population. However, few studies have examined longitudinally the patterns of antihypertensive drug use, including treatment interruptions and modifications in treatment regimens.⁵⁻⁶,⁹⁻¹¹ Several of these studies did not use a cohort of newly treated hypertensive subjects but rather included patients at different times in the course of their disease.⁵⁻¹¹ Indeed, patients with established hypertension, compared with newly diagnosed subjects, may present different characteristics, such as severity of hypertension and coexisting conditions that may affect patterns of drug use. In addition, these studies were restricted to no more than 1 year of follow-up⁵⁻¹¹ or included only continuous users or compliers.⁶

Recent publications by Caro et al¹²⁻¹⁵ focused on persistence with therapy in association with initial treatment among single-drug users. Although the authors presented an interesting algorithm to identify changes in treatment such as additions, switches, and deletions, they only reported on persistence rates of antihypertensive therapy and did not provide any insight as to the incidence or timing of such modifications to therapy. Hence, despite these previous attempts, an important information gap exists with regard to the patterns of use of antihypertensive agents in the population, from treatment initiation onward.

In this study, we documented the management of uncomplicated hypertension by examining the distribution and de-
PATIENTS AND METHODS

SOURCE OF DATA
Data were obtained from the Saskatchewan Health data files developed in the context of the universal health insurance program provided to 95% of all residents of this Canadian province. These data files provided drug-related information (drug type and dispensing date), demographic data (date of birth, sex, coverage initiation and termination dates, date of death, and receipt of social assistance), and information concerning hospital admissions and medical visits. Information on the indication for drug use was not available. The accuracy of these data for use in a research setting has been documented.16,17

STUDY POPULATION
A cohort of 35631 subjects initiating therapy with angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, or calcium antagonists (CAs) between January 1, 1990, and December 31, 1993, was first identified. Treatment initiation was the date of the first dispensing of 1 or several of these agents. To ensure that study subjects were initiating treatment, those dispensed any antihypertensive agent (including diuretics, α-blockers, or centrally acting agents) in the year preceding treatment initiation were excluded from the cohort. Because incidence rates of hypertension are low in these age groups, we excluded 6881 subjects younger than 40 years. We also excluded 2793 subjects older than 80 years because of short follow-up and the very high prevalence of comorbidity in that group.

Several criteria were used to identify subjects for whom the most likely indication for antihypertensive treatment was uncomplicated essential hypertension. We first restricted the cohort to subjects without evidence of overt cardiovascular disease as indicated by hospital admissions with heart disease as a discharge diagnosis (International Classification of Diseases, Ninth Revision, code 402, 404, 410-416, 420-429, or 745.4-746.9) in the year preceding cohort entry. We also excluded subjects who, in the same period, were pharmacologically treated for conditions for which antihypertensive medications are also indicated. These conditions include migraine, hyperthyroidism, and arrhythmia (for which β-blockers are indicated), angina (β-blockers and CAs), and congestive heart failure (ACEIs and diuretics). Subjects who used any cardiovascular agent (anticoagulants, loop diuretics, or other cardiac agents) in the year before initiation of hypertension therapy were also excluded. Overall, slightly more than 7000 subjects were excluded from the initial cohort because of overt cardiovascular disease. An additional 89 users of thyroid drugs and 969 subjects who used ergot preparations were excluded because of the possible use of antihypertensive agents as an adjuvant to the treatment of hyperthyroidism or migraine. We assumed the remaining subjects to be treated for uncomplicated hypertension and followed them up until the earliest of March 31, 1997, date of death, emigration from the province, or end of coverage of the insurance plan.

ANTIHYPERTENSIVE DRUG USE
Patterns of use of the major antihypertensive drug classes were examined. Both initial treatment and subsequent modifications to therapy were documented.

Initial Therapy
Initial treatment regimen was defined as the first antihypertensive agent dispensed. Initial regimens were divided into terminants of selected patterns of antihypertensive drug use in Saskatchewan from treatment initiation onward during up to 7 years of observation. More specifically, we examined the factors associated with specific choices of initial therapy, the incidence and timing of treatment modifications during the course of therapy, and their correlates.

RESULTS

PATIENT CHARACTERISTICS
Study subjects were aged 60 years on average, and almost half of them were male (Table 2). Slightly more than 4% of them received social assistance at initiation of therapy. Slightly more patients were included earlier during the study period (27% in 1990 and 22% in 1993).

INITIAL ANTIHYPERTENSIVE THERAPY
Distribution of Antihypertensive Drugs at Treatment Initiation
Of the 4 treatment regimens under study, ACEIs were the most commonly dispensed at treatment initiation (37.4%), followed by CAs (27.5%) and β-blockers (26.4%). Of the 1708 patients starting combination therapy (8.8%), 86.8% received a diuretic in addition to 1 of the 3 main agents. Only 64 patients received more than 2 different agents to initiate therapy.

Time Trends
Examination of the rates of use of these agents at treatment initiation over time showed ACEI use to have significantly increased between 1990 and 1993 (P<.001 by χ2 test). The use of CAs and β-blockers as single agents and prescription of multiple drug therapy seemed more stable (Figure 1).

Factors Associated With Initial Therapy
Men, older subjects, users of antidiabetic medications or respiratory agents, and subjects who visited a cardiologist in the preceding year were more likely to initiate therapy with an ACEI or a CA than with a β-blocker (Table 3). Later initiation of therapy also increased the probability of being prescribed CAs, whereas previous use of neurotropic agents was negatively associated with filling a first prescription for CAs. However, previous use
single-drug use (ACEI, \(\beta\)-blocker, or CA only) or combination therapy, defined as either the dispensing of more than 1 drug class or a fixed-combination product containing drugs from different classes (eg, ACEI-diuretic combination) (Table 1). Subjects initiating therapy with diuretics were not included.

**Modifications to Therapy**

Any change to the initial drug class was considered a modification to therapy. A treatment interruption was defined as a failure to fill a prescription for any of the studied agents in the 120 days after the filling date of the last prescription, assumed to last 30 days. The 90-day cutoff point for drug holidays was based on the ground that, with an 80% threshold for compliance, 2.5 months without using any antihypertensive drugs would be required during a 1-year period for a patient to be considered not compliant enough to benefit from therapy. When the last treatment regimen included more than 1 agent from the same drug class, possible stockpiling of medications was considered by treating them as sequential prescriptions and assuming continuing therapy, providing the prescriptions were dispensed within 15 days of each other.

To differentiate between a switch and the addition of a second or third drug, an algorithm similar to that used by Caro et al\(^\text{23}\) was constructed by using, for each prescription, information pertaining to the subsequent dispensing dates. Two types of modifications to therapy were considered: (1) switching from a therapeutic drug class to another (if at least 1 agent belonging to a different therapeutic drug class was encountered in the following trimester without renewal of the index one) and (2) adding a second drug class (if at least 1 prescription that belonged to a different therapeutic class was encountered in the following trimester in addition to the index one). Dropping 1 or several drugs from treatment was not considered in the algorithm. For a switch or a drug addition to occur, a gap of up to 119 days was allowed between 2 dispensing dates. Otherwise, the modification was considered to be a treatment interruption if a new course of therapy occurred before the end of follow-up and a discontinuation of therapy if not. Hence, a subject discontinuing therapy did not use any antihypertensive agents until the end of follow-up. Dosage adjustments were not considered to be modifications to therapy.

**STATISTICAL ANALYSIS**

Simple contingency tables for proportions were used to provide descriptive data on the patterns of use of antihypertensive agents. Logistic regressions were used to examine the correlates of initial treatment, with \(\beta\)-blockers as the reference. Time to the first modification to therapy was assessed by means of multivariate Cox proportional hazards models, and the rates of modifications to therapy were modeled by means of Poisson regression for rates accounting for between-subject variation. Factors potentially associated with any of these patterns of use included patient characteristics (age, sex, and social assistance), physician visits and hospitalizations in the year preceding treatment initiation, and drug markers for comorbid conditions during that same period (nonsteroidal anti-inflammatory drugs, glucocorticoids, neurotropic [lithium carbonate, benzodiazepines, antidepressants, and major tranquilizers] and antilipemic agents, drugs used for respiratory illness, and antiulcer medications). The year of treatment initiation and the duration of follow-up were also controlled for to account for possible time trends in medication use. Diabetes and the onset of heart failure or angina were also included as predictors of treatment modifications, along with the drug class used at treatment initiation.

**Types of Modifications**

Of the first episodes of treatment modification, the most common were interrupting treatment (31.5%) and discontinuing therapy (22.6%) (Figure 2). Agents belonging to a different drug class were added for 20.1% of the study subjects, whereas 14.3% switched to another therapeutic drug class. Of those who added a drug to their initial treatment regimen, 47.6% did not subsequently modify their treatment, whereas 20.9% underwent another drug addition or switch. Among those who switched first, these figures were 24.4% and 36%, respectively. More than half of the stoppers came back to their initial treatment after the interruption. For 6940 subjects (35.6%), the first modification was the only one to occur during the entire period of observation.
Timing and Predictors of the First Modification to Therapy

One year after starting treatment, only 33.8% of patients were still using the drug they were dispensed at treatment initiation, ie, did not yet undergo any modification to initial therapy. Overall, the median time to the first treatment modification was 134 days. A rapid early decrease in the proportion of patients continuing to receive initial therapy was shown (Figure 3; P<.001 [log-rank test]). The first modification to therapy arose considerably later for patients who started with combination therapy or ACEIs, with median times to the first modification of 202 and 208 days, respectively. This compares with 75 days for patients who initiated treatment with β-blockers and 105 days for CAs. Timing of treatment modifications also differed according to the type of the first modification, with discontinuation of therapy and treatment interruptions occurring earlier than drug switches and additions (not shown). Overall, 50% of subjects discontinuing therapy did so within 37 days of initiation of therapy. Median time for a treatment interruption was 86 days, whereas this figure was 146 and 218 days for patients who started with combination drugs and treatment interruptions occurring earlier than drug switches and additions, respectively.

Predictors of a first modification to therapy did not differ in a clinically important way across modification types, all relative risks lying between 0.85 and 1.2. As a general rule, younger subjects were found to be more likely to experience any type of modification to therapy, as were men. Patients initiating therapy with a β-blocker were also found to have higher rates of modifications than others, even after statistical adjustment for other potential predictors. Finally, subjects starting treatment with a com-

Table 1. Antihypertensive Drug Classes Used at Treatment Initiation*

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>Specific Agents</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>Captopril, enalapril maleate, lisinopril, lisinopril sodium, quinapril hydrochloride, benazepril hydrochloride, cilazapril, ramipril</td>
<td>7291 (37.4)</td>
</tr>
<tr>
<td>CA</td>
<td>Nifedipine, diltiazem hydrochloride, verapamil hydrochloride, nicardipine hydrochloride, felodipine, amiodipine besylate, nifedipine PA, diltiazem SR, verapamil SR</td>
<td>5355 (27.5)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Acebutolol hydrochloride, atenolol, propranolol tartrate, pindolol, metoprolol, nadolol, labetalol hydrochloride, oxprenolol hydrochloride, timolol maleate, propranolol SR, metoprolol SR, oxprenolol SR</td>
<td>5147 (26.4)</td>
</tr>
<tr>
<td>Combination drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic-based Fixed ACEI-diuretic combinations (enalapril-HCTZ, lisinopril-HCTZ), fixed β-blocker-diuretic combinations (pindolol-HCTZ, timolol-HCTZ, propranolol-HCTZ, metoprolol-HCTZ), atenolol-chlorthalidone, any other diuretic-based combinations</td>
<td>1483 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>ACEI + β-blocker,† ACEI + CA†</td>
<td>225 (1.2)</td>
</tr>
<tr>
<td></td>
<td>β-blocker + CA,† ACEI + β-blocker + CA†</td>
<td></td>
</tr>
</tbody>
</table>

*ACEI indicates angiotensin-converting enzyme inhibitor; CA, calcium antagonist; PA, prolonged action; SR, sustained release; and HCTZ, hydrochlorothiazide.
†Could include diuretics.

Figure 1. Time trends in initial treatment according to antihypertensive drug class. ACEI indicates angiotensin-converting enzyme inhibitor; BBL, β-blocker; and CA, calcium antagonist.

Table 2. Characteristics of the Study Population at Treatment Initiation

<table>
<thead>
<tr>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
</tr>
<tr>
<td>40-49</td>
</tr>
<tr>
<td>50-59</td>
</tr>
<tr>
<td>60-69</td>
</tr>
<tr>
<td>70-79</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Social assistance at treatment initiation</td>
</tr>
<tr>
<td>Year of treatment initiation</td>
</tr>
<tr>
<td>1990</td>
</tr>
<tr>
<td>1991</td>
</tr>
<tr>
<td>1992</td>
</tr>
<tr>
<td>1993</td>
</tr>
</tbody>
</table>

*Mean ± SD, 59.9 ± 11.0 years.
bination therapy were less likely to experience a modification to therapy.

This study represents one of the first attempts to describe the patterns of use of antihypertensive agents in Saskatchewan, from treatment initiation onward, during a long period of observation. Our study confirms that those patterns are highly variable, with a high frequency of treatment interruptions and modifications. First, it appears that ACEIs and CAs are increasingly used as initial therapy. Second, many patients discontinued therapy early after treatment initiation. Our study confirms that, because of the high prevalence of treatment modifications and interruptions, this may not be the case.

Both US and Canadian guidelines on the treatment of hypertension advise the use of either diuretics or \( \beta \)-blockers as first-line agents, unless there are special indications for the use of other drug classes.18-21 The high prevalence of treatment initiation with ACEIs and CAs in our study suggests that either adherence to clinical guidelines in Saskatchewan is not very high or our study did not succeed in identifying special indications for the use of other drug classes. Despite efforts to include modifications to therapy, treatment interruptions, and general adherence to treatment regimens in effectiveness analyses, randomized controlled trials are hardly comparable with what actually happens at the population level. Still, it is assumed that the positive results of large-scale randomized controlled trials would be translated into effective treatment regimens in clinical practice. Our study shows that, because of the high prevalence of treatment modifications and interruptions, this may not be the case.

Commercial influences may have contributed to decreasing the use of older agents such as \( \beta \)-blockers22,23 while contributing to the increased use of CAs and ACEIs.
at treatment initiation. Characteristics of the patients such as age, sex, and the presence of risk factors or markers of complicated hypertension should also influence hypertension management. Such factors did indeed emerge in our study as predictors or correlates of initial drug choice. Surprisingly, however, none of them emerged as predictors of the rates of treatment modification.

We found that patients who started treatment with β-blockers had higher discontinuation rates that occurred earlier in time. One likely hypothesis to explain this result is that patients with less severe hypertension or without specific comorbid conditions were more likely to receive these agents, which would be consistent with clinical guidelines. We may assume as well that modifications to treatment regimens may be indicative of poor blood pressure control, lack of tolerance of the drug, or the onset of concomitant conditions. Failure to achieve blood pressure control or the presence of concomitant diseases may prompt treating physicians to step up the treatment regimen by (1) prescribing a higher dose of the same agent, (2) substituting a more potent medication, or (3) adding another antihypertensive agent. Side effects of the drugs, although not documented in this study, are also a possible reason for stopping treatment. Also, the use at that time of nonselective β-blockers as well as the formerly often used high starting doses may have resulted in many such changes.

Patients initiating therapy with combination drugs are probably considerably different from other patients with newly diagnosed hypertension. First, it is contrary to every clinical guideline to initiate therapy with multiple drugs. These atypical patients represent only 8.8% of our study population, which would represent around 3.5% of all patients with newly diagnosed hypertension if patients starting treatment with diuretics were included. We hypothesize that they represent sicker patients, more prone to use health services (including drugs) and consequently more compliant with therapy, which would explain the lower incidence of modifications to therapy in that group.

Computerized databases of prescription claims offer major advantages for drug use studies, including the possibility of documenting the entire history of drug use. Records of dispensed medications offer the possibility of investigating patterns and timing of drug exposure and assessing determinants and consequences of different patterns of use. Also, the large number of study subjects allows a detailed description of the frequency of these patterns in the population.

The degree of detail with regard to drug dispensing and a 7-year period of observation constitute 2 major strengths of this study. Modifications to therapy are hard to measure with accuracy. Previous drug use studies and examination of drug-taking behaviors have mostly focused on measures of compliance averaged over a short period (usually 12 months). Also, 22% of the study subjects modified their treatment regimens for the first time after the first year of observation. Hence, limiting the latter to 1 year would result in a considerable loss of information.

However, the use of computerized records also carries some limitations, a major one being the lack of information about the indication and the specific directions for use of the prescribed agents. Despite the fact that drug markers have been used previously with good correlations with the diagnosis of hypertension, antihypertensive agents may have been used in some study subjects to treat other conditions. Also, the average duration of an antihypertensive drug prescription in Saskatchewan had to be used as a proxy. Finally, drug data represents dispensed medications, and actual drug-taking behaviors remain unknown. We suggest, however, that the likelihood of a patient not actually taking medications that have been filled continuously is probably low.

An important limitation of our study pertains to the definition of the source population. First, because our
initial study proposal did not address patterns of drug use in patients who started treatment with diuretics, those were not included in the cohort. This considerably limits the applicability of our study findings. On the basis of external sources,13 diuretic use at treatment initiation could represent 38% of all prescriptions for an antihypertensive agent. However, providing that the reported prevalence data are interpreted in relative rather than absolute terms in our study, this should not be a major threat to the validity of the study. The results would also have benefited from an age-stratified analysis to assess whether the patterns of use of antihypertensive agents vary across age groups, especially among the very elderly population. Unfortunately, our sample size was insufficient to allow such an analysis. Also, drug dosage adjustments were not included in our definition of a modification of therapy, and drug dropping was not documented. This means that our reported rates of modification to therapy are probably conservative. Finally, these results describe the use of prescribed drugs in Saskatchewan between 1990 and 1997 and may not reflect actual drug use in other settings or time frames.

Despite all the progress in the field of hypertension management, selecting the most appropriate agent for the individual patient remains a challenge. Guidelines are based on efficacy results obtained from randomized controlled trials, which may not reflect the actual population that eventually uses these agents. Also, the relative value of antihypertensive agents should not be measured solely by their ability to lower blood pressure or by their beneficial effect on intermediate variables. Evidence of their ability to deliver better cardiovascular protection and to improve survival should be available for the entire population of potential users, not only for highly selected groups of subjects such as those participating in randomized controlled trials. Hence, high degrees of variability in drug-taking behaviors should be taken into account when drug effects are assessed at the population level, and adherence to therapy should be strongly encouraged.

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