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 19501 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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**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.14,17

**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 ANTIHYPTERTENSIVE 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
of antiulcer or neurotropic agents and previous visits to a cardiologist were negatively associated with ACEI use at treatment initiation relative to β-blockers. Previous use of NSAIDs or neurotropic or antiulcer agents, as well as previous visits to a cardiologist, decreased the risk of starting antihypertensive treatment with multiple agents, whereas respiratory illness and diabetes were positively associated with that initial choice. Older age and male sex also increased the likelihood of using multiple agents at treatment initiation compared with β-blockers.

**MODIFICATIONS TO THERAPY**

**Incidence of Modifications to Therapy**

During the period of observation, 11.5% of study subjects had no treatment modification or interruption. The overall rate of treatment modification was 58.1 per 100 subjects per year. Treatment interruptions and addition of 1 or several agents were the most frequent types of modification (30.1 and 27.9 per 100 subjects per year, respectively), whereas the rate of switching across therapeutic classes was rather low (5 per 100 subjects per year). Predictors of the frequency of switching or adding drugs belonging to another therapeutic class were found to be older age, male sex, and overt heart failure or angina. Also, the rates of such modifications to therapy were significantly higher among subjects who started treatment with an ACEI (adjusted relative risk, 1.29; 95% confidence interval, 1.24-1.34), a CA (adjusted relative risk, 1.11; 95% confidence interval, 1.06-1.16), and combination therapy (adjusted relative risk, 1.45; 95% confidence interval, 1.37-1.55), compared with β-blockers.

**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 to therapy was ascribed 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.

**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 β-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.
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 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 common...
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, we found that only 11.5% of study subjects continuously used the agent with which they initiated treatment. Caro et al.\(^*\) reported earlier that a surprisingly high number of patients discontinued therapy early after treatment initiation. Our study confirms this finding. In addition, we found this to be more of a problem among \(\beta\)-blocker users, who tend to stop using antihypertensive agents earlier and in a higher proportion. It is also interesting to note that patients receiving combined therapy were less likely to modify their treatment regimen.

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 NSAIDs, nonsteroidal anti-inflammatory agents. \(^{22,23}\) While contributing to the increased use of CAs and ACEIs

### Table 3. Baseline Characteristics of Study Subjects in Relation to Initial Drug Class (vs \(\beta\)-Blockers)\(^*\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prevalence, %†</th>
<th>Adjusted RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BBL (n = 5147)</td>
<td>ACEI (n = 7291)</td>
</tr>
<tr>
<td>Year of treatment initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>30.4</td>
<td>24.1</td>
</tr>
<tr>
<td>1991</td>
<td>26.3</td>
<td>25.5</td>
</tr>
<tr>
<td>1992</td>
<td>21.7</td>
<td>26.4</td>
</tr>
<tr>
<td>1993</td>
<td>21.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>34.1</td>
<td>20.2</td>
</tr>
<tr>
<td>50-59</td>
<td>26.3</td>
<td>27.0</td>
</tr>
<tr>
<td>60-69</td>
<td>24.0</td>
<td>30.1</td>
</tr>
<tr>
<td>70-79</td>
<td>15.6</td>
<td>22.7</td>
</tr>
<tr>
<td>Social assistance</td>
<td>4.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>43.3</td>
<td>50.7</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>3.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>12.8</td>
<td>9.7</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>27.9</td>
<td>26.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Neurotropic agents</td>
<td>27.7</td>
<td>16.0</td>
</tr>
<tr>
<td>Visits to cardiologist</td>
<td>27.7</td>
<td>31.9</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>18.6</td>
<td>18.9</td>
</tr>
</tbody>
</table>

†Because of rounding, percentages may not total 100.
‡All risk ratios are adjusted simultaneously for every listed factor. Separate models were run for each agent with \(\beta\)-blockers as the reference.
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

<p>| Table 4. Types and Frequency of the First 2 Modifications to Therapy, According to Initial Drug Class* |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Pattern</th>
<th>ACEI (n = 7291)</th>
<th>BBL (n = 5147)</th>
<th>CA (n = 5355)</th>
<th>Multitherapy (n = 1708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never modified</td>
<td>13.1</td>
<td>7.9</td>
<td>9.3</td>
<td>22.3</td>
</tr>
<tr>
<td>Discontinued therapy without having modified before</td>
<td>14.8</td>
<td>31.8</td>
<td>25.6</td>
<td>18.7</td>
</tr>
<tr>
<td>Added or switched once and did not modify afterward</td>
<td>17.5</td>
<td>8.9</td>
<td>11.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Added or switched once and then discontinued therapy</td>
<td>3.5</td>
<td>4.1</td>
<td>4.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Added or switched twice</td>
<td>12.0</td>
<td>7.4</td>
<td>8.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Added or switched, interrupted, and started a new course of therapy later on</td>
<td>9.9</td>
<td>6.8</td>
<td>8.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Interrupted treatment and came back to initial treatment</td>
<td>17.7</td>
<td>18.7</td>
<td>17.0</td>
<td>13.3</td>
</tr>
<tr>
<td>Interrupted treatment and started a new course of therapy using different agents</td>
<td>11.5</td>
<td>14.3</td>
<td>15.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

*ACEI indicates angiotensin-converting enzyme inhibitor; BBL, β-blocker; and CA, calcium antagonist.
†Because of rounding, percentages may not total 100.

Figure 3. Cumulative proportion of patients continuing to receive initial therapy, according to initial agent. ACEI indicates angiotensin-converting enzyme inhibitor; BBL, β-blocker; and CA, calcium antagonist.
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, 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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