The Risk of Hip Fracture After Initiating Antihypertensive Drugs in the Elderly

Debra A. Butt, MD, MSc, CCFP, FCFP; Muhammad Mamdani, PharmD, MPH; Peter C. Austin, PhD; Karen Tu, MD, MSc, CCFP, FCFP; Tara Gomes, MHSc; Richard H. Glazier, MD, MPH, CCFP, FCFP

Background: Initiating antihypertensive drugs in the elderly has been associated with an immediate increased risk of falls. However, it is unknown whether initiation of antihypertensive drugs (eg, thiazide diuretics, angiotensin II converting–enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, or β-adrenergic blockers) is associated with an immediate increased risk of hip fractures.

Methods: A population-based, self-controlled case series design using health care administrative databases identifying patients initiating an antihypertensive drug in Ontario, Canada. A cohort of newly treated hypertensive elderly patients was linked to the occurrence of hip fractures from April 1, 2000, to March 31, 2009, to create exposed cases. The risk period was the first 45 days following antihypertensive therapy initiation with control periods before and after treatment in a 450-day observation period. The outcome measure was the first occurrence for a proximal femoral fracture during the risk period. The analysis determined the relative incidence (incidence rate ratio), defined as the hip fracture rate in the risk period compared with control periods.

Results: Among the 301 591 newly treated hypertensive community-dwelling elderly patients, 1463 hip fractures were identified during the observation period. Hypertensive elderly persons who began receiving an antihypertensive drug had a 43% increased risk of having a hip fracture during the first 45 days following treatment initiation relative to the control periods (incidence rate ratio, 1.43; 95% CI, 1.19-1.72).

Conclusions: Antihypertensive drugs were associated with an immediate increased hip fracture risk during the initiation of treatment in hypertensive community-dwelling elderly patients. Caution is advised when initiating antihypertensive drugs in the elderly.


MORE THAN 50% OF ALL adults older than 65 years have hypertension,1 and the likelihood of developing hypertension during an average life span is more than 90%.2-4 The overall prevalence of hypertension is more than 50% among those aged 60 to 79 years.5 Furthermore, 72% of newly diagnosed hypertensive patients aged 60 years and older take antihypertensive medication.6

Hypertension, antihypertensive drugs, and fall injury form a complicated triad that may act to exacerbate fall risk in the elderly. Orthostatic hypotension with uncontrolled hypertension is a risk factor for falls.7 Initiating antihypertensive drugs in hypertensive elderly persons can potentially cause orthostatic hypotension with associated symptoms such as dizziness, fainting, or syncope.8-12 This effect is acute, occurs over a relatively short time,8-12 and may lead to falls.13 Some falls result in hip fractures in the elderly,14,15 that may lead to disability with loss of independence16 and even death.17

Most studies18-22 on the association of antihypertensive drugs and fracture risk have focused on long drug-exposure periods (at least several months) in which the underlying mechanism of action is thought to be related to bone metabolism. Studies indicate that initiation of antihypertensive drugs such as thiazide diuretics22 and angiotensin II receptor antagonists3 can increase fall risk in the elderly. However, there is little information to date about the immediate increased risk of hip fracture during the initiation of antihypertensive therapy in hypertensive elderly persons. Therefore, the purpose of this study was to examine the association between the initiation of antihypertensive drugs and the immediate risk of hip fracture in a large population of community-dwelling elderly persons.
Methods

The Ontario Drug Benefit Program (ODB) prescription drug database was used to identify all Ontario residents aged 66 years and older with a first prescription of one of the following antihypertensive drugs: thiazide diuretics, angiotensin II converting–enzyme (ACE) inhibitors, angiotensin II receptor antagonists/blockers (ARBs), calcium channel blockers (CCBs), or β-adrenergic blockers (BBs) (eTable 1; http://www.archinternmed.com). The ODB database records all drugs prescribed from a minimally restrictive formulary for individuals aged 65 years and older with a first antihypertensive drug prescription. All patients in the analysis had at least 1 prescription for an antihypertensive drug and a single incident hip fracture.

Study Population

The Ontario Drug Benefit Program (ODB) prescription drugs database was used to identify all Ontario residents aged 66 years and older with a first prescription of one of the following antihypertensive drugs: thiazide diuretics, angiotensin II converting–enzyme (ACE) inhibitors, angiotensin II receptor antagonists/blockers (ARBs), calcium channel blockers (CCBs), or β-adrenergic blockers (BBs) (eTable 1; http://www.archinternmed.com). The ODB database records all drugs prescribed from a minimally restrictive formulary for individuals aged 65 years and older and has an error rate of less than 1%, demonstrating good reliability.25 Incident hypertensive elderly patients were identified using previously published methods24,26,27 by excluding any patients with other conditions for which an antihypertensive drug may have been prescribed. This cohort was linked using encrypted health card numbers to the Ontario Health Insurance Plan physician claims database (containing physician billing information, diagnoses, and procedures), the Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD; providing detailed diagnostic and procedural information regarding hospital admissions),28 the Registered Persons Database (containing demographic information for all Ontario residents with a health card), and the Ontario Diabetes Database (containing information on all diabetic patients with high diagnostic accuracy)29 to identify exclusion criteria.24,26,27 Baseline characteristics, and outcome information. The International Classification of Diseases, Ninth Revision (ICD-9) codes were used for the Ontario Health Insurance Plan database and CIHI-DAD before 2002, and ICD-10 codes were used for CIHI-DAD beginning in 2002. Patients with diabetes mellitus, myocardial infarction or angina, heart failure or cardiomyopathy, tachyarrhythmias (if prescribed a BB or CCB), renal disease, transient ischemic attack or stroke, hyperthyroidism (if prescribed a BB), migraine headaches (if prescribed a BB or CCB), peripheral arterial disease, nephrolithiasis (if prescribed a diuretic), peripheral edema (if prescribed a diuretic), Raynaud phenomenon (if prescribed a CCB), esophageal spasm (if prescribed a CCB), or essential tremor (if prescribed a BB) before their initiation of antihypertensive treatment were excluded (eTable 2).

Such conditions were identified in the 4 previous years in the Ontario Health Insurance Plan database and CIHI-DAD and in the single previous year in the ODB database for marker medications specific to the just-mentioned conditions. Patients with diabetes mellitus were identified in the single previous year in the Ontario Diabetes Database. A 1-year washout period was specified to ensure that the cohort comprised all newly treated elderly patients and thus excluded patients with a first antihypertensive claim within 1 year before their entry into the cohort. Patients residing in long-term care homes (eg, nursing home residents) were excluded from this study.

Main Outcome

The cases were identified as the first occurrence of a hip fracture from April 1, 2000, through March 31, 2009. These hip fractures were linked to the cohort of newly treated hypertensive elderly patients to define the exposed cases. Before 2002, the main outcome of proximal femoral fracture was classified according to the ICD-9 and coded as S820.1 to S820.9. From 2002 onward, the ICD-10 classified these hip fracture codes as S72.0 to S72.2. The CIHI-DAD has been shown to reliably identify hip fractures with a 97% sensitivity and 98% positive predictive value.30,31 Patients who were hospital inpatients before the observation period, who resided in nursing homes, or who had trauma from transport accidents (ICD-9 codes: E800-E848 and V15.51; ICD-10: V01-V09) or pathological fracture (ICD-9: 733.1 and V13.51; ICD-10: M84.4, M90.7, and M8000/1) were excluded from this study.

Study Design

The self-controlled case series (SCCS) design (Figure 1) estimates the relative incidence of hip fracture for each person in the cohort during a high-risk period (shortly after initiation of exposure drug) compared with low-risk and unexposed periods (control periods) on the basis of data from cases only.32-34

A 45-day high-risk period immediately following antihypertensive initiation was selected to observe the effect of orthostatic hypotension because we were unclear on the precise period in which newly treated hypertensive elderly patients might be at risk for injurious falls. On the basis of this 45-day interval, control periods were defined as 3 consecutive 45-day periods in the preexposure (baseline, C1-C3) and postexposure periods (low risk, C4-C6). Two 45-day preexposure risk periods35 (P1 and P2) that preceded the start of the first antihypertensive prescription were identified. Periods prior to treatment, such as the immediate preexposure period, should generally not be used in the SCCS design because there may be a short-term reverse causation effect whereby the event (ie, hip fracture) affects the exposure, thereby violating an assumption of the design.32,34,36 Preexposure risk periods have been previously described36 for this design in which the event precipitated the need for an increase in exposure prescriptions; these periods were removed from the calculation of baseline incidence rate, preventing any spurious inflation of this quantity.36 The total duration of the preexposure periods (90 days) was selected for 2 reasons. The recovery period of a patient with a hip fracture from hospital admission to subsequent rehabilitative care in a hospitalized setting may last longer than 45 days. Also, prescriptions written in the hospital for antihypertensive drugs would not be captured in the ODBP and may account for a 90-day period. A 45-day washout period following the postexposure high-risk period accounted for transient changes in variations of drug class pharmacokinetics. The total observation period for each patient using the SCCS design was 450 days.
Table 1. Characteristics of 1463 Newly Treated Hypertensive Elderly Patients Who Experienced a Hip Fracture

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>80.8 (7.3)</td>
</tr>
<tr>
<td>Age groups, No. (%)</td>
<td></td>
</tr>
<tr>
<td>66-70</td>
<td>163 (11.1)</td>
</tr>
<tr>
<td>71-75</td>
<td>185 (12.6)</td>
</tr>
<tr>
<td>76-80</td>
<td>323 (22.1)</td>
</tr>
<tr>
<td>81-85</td>
<td>381 (26.0)</td>
</tr>
<tr>
<td>86-90</td>
<td>289 (19.8)</td>
</tr>
<tr>
<td>91-95</td>
<td>102 (7.0)</td>
</tr>
<tr>
<td>96-100</td>
<td>20 (1.4)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1180 (80.7)</td>
</tr>
<tr>
<td>Male</td>
<td>283 (19.3)</td>
</tr>
<tr>
<td>Antihypertensive drugs, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>337 (23.0)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>440 (30.1)</td>
</tr>
<tr>
<td>ARBs</td>
<td>65 (4.4)</td>
</tr>
<tr>
<td>CCBs</td>
<td>248 (17.0)</td>
</tr>
<tr>
<td>BBs</td>
<td>373 (25.5)</td>
</tr>
<tr>
<td>History of hip fracture, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (6.0)</td>
</tr>
<tr>
<td>No</td>
<td>1375 (94.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin II converting–enzyme; ARB, angiotensin II receptor antagonist/blocker; BB, β-adrenergic blocker; and CCB, calcium channel blocker.

STATISTICAL ANALYSIS

Descriptive statistics on age, sex, antihypertensive drug classes, and history of hip fracture were computed. Conditional Poisson regression was used to estimate incidence rate ratios (IRRs) with 95% CIs for any antihypertensive drug and individual drug classes. To control for confounding by age, age was included in the model and analyzed using 5-year age bands. We conducted a sensitivity analysis by splitting the 45-day high-risk period into 2 additional risk periods (0-14 days and 15-44 days) and determined their IRRs with 95% CIs. Also, a sensitivity analysis that involved the elimination of new users of psychotropic drugs (Table 3) that are known to cause falls during the observation period was conducted. New users of psychotropic drugs, defined as those who had not used these drugs in the 1 year prior to study entry, were prespecified to eliminate this group from the newly treated hypertensive elderly patients. The information on psychotropic drugs was obtained from the ODBP. The period of psychotropic drug elimination was from 180 days before the C3 period until the end of the C6 period. Data were analyzed using Stata SE, version 9.2 (StataCorp).

A sample size calculation for the SCCS study was conducted. With a 450-day observation period and 45-day risk period, a minimum of 605 exposed cases were required to have a power of 90% at the .05 significance level for an estimated relative incidence of 1.5.

This project was approved by the research ethics boards of the Sunnybrook Health Sciences Centre and the University of Toronto.

RESULTS

There were 301,591 newly treated Ontario hypertensive elderly patients who had 1463 hip fractures during a 10-year period. Table 1 provides the descriptive characteristics of the exposed cases. The mean (SD) age was 81 (7.3) years and most (80.7%) were women. Hypertensive elderly persons with hip fractures were most commonly exposed to ACE inhibitors (30.1%), whereas ARBs were used the least (4.4%). Only 6.0% of the exposed cases had a history of hip fracture.

Elderly people who started an antihypertensive drug for the treatment of hypertension had a 43% (IRR, 1.43; 95% CI, 1.19-1.72) increased risk of hip fracture during the first 45 days of treatment (Figure 2). Table 2 provides the IRRs for the different exposure windows of the antihypertensive drugs. The IRR estimates were generally consistent among the 5 different classes of antihypertensive drugs, but only the ACE inhibitors (IRR, 1.53; 95% CI, 1.12-2.10) and BBs (1.58; 1.01-2.48) demonstrated a statistically significant association with hip fracture risk.
strated statistical significance (Figure 2). Further subdivision of the postexposure risk period into 0 to 14 days and 15 to 44 days indicated that elderly people who initiated any antihypertensive drug for the treatment of hypertension had a 54% increased risk of hip fracture (IRR, 1.54; 95% CI, 1.25-1.90) during the 15- to 44-day period (eTable 4). This increased trend was observed for most antihypertensive drug classes except thiazide diuretics and was statistically significant for ACE inhibitors (IRR, 1.58; 95% CI, 1.09-2.29) and BBs (2.08; 1.29-3.34) (eTable 4). The washout periods consistently demonstrated a null effect for any antihypertensive drug with respect to hip fracture (Table 2).

Also, there was no change in the IRR estimates with the inclusion of age at 5-year age bands in the model, indicating that age was not an important confounder in this study. The main findings of the study were consistent in a sensitivity analysis that eliminated those with concurrent new use of other potential fall-causing drugs, such as psychotropic drugs, during the observation period (IRR, 1.42; 95% CI, 1.17-1.74).

**COMMENT**

To our knowledge, this is the first study to demonstrate an immediate increased risk of hip fracture on initiation of antihypertensive therapy in community-dwelling hypertensive elderly patients. The increased risk of hip fractures was significant during initiation of ACE inhibitors and BBs. This increased risk of hip fracture on antihypertensive therapy initiation persisted even with the elimination of new users of psychotropic drugs.

Much of the medical literature on the association of antihypertensive drug use and fractures has focused on long exposure periods. In a meta-analysis on the association of antihypertensive drugs and fractures, only 4 of the included 54 case-control and cohort studies assessed duration of thiazide drug exposure in which the shortest exposure period examined was less than 2 years. A recent cohort study of 376 061 hypertensive elderly patients aged 65 years and older involving monotherapy demonstrated low fracture rates with users of thiazide diuretics and ARBs compared with those using CCBs during different follow-up periods, including 1 to 90 days and greater than 365 days. That study involved low-income seniors; used longer follow-up periods; used covariate definitions based on health care data that did not include weight, height, and bone mineral density; and used CCBs as a standard for comparison in which evidence regarding its fracture risk has been inconsistent.

Our results on the association between antihypertensive drugs and immediate hip fracture risk are generally consistent with the results of previous observational studies using falls as an outcome. A fall is the main etiologic factor in more than 90% of hip fractures. Other designs involving a case-crossover study of inpatients and an SCCS study involving elderly patients have demonstrated an immediate increased risk of falls with an antihypertensive drug during the initiation of therapy. These findings support the underlying mechanism of orthostatic hypotension and suggest that residual confounding is unlikely to be a problem in this study.

In our study, use of any antihypertensive drug was associated with an immediate increased risk of hip fracture during the first 45 days of treatment (particularly at days 15-44). This was significant for ACE inhibitors and BBs. This is somewhat similar to the findings of a recent SCCS study that demonstrated an increased risk of the first occurrence of a fall with initiation of thiazides and BBs during the first 3 weeks of treatment but not with ACE inhibitors, ARBs, or CCBs. The aforementioned study used an elderly population receiving antihypertensive drugs for any indication, not just hypertension. We expected hypertensive elderly patients starting to receive thiazide diuretics to be at risk of hip fractures in comparison with other antihypertensive drug classes.

Our analysis of thiazide diuretics did not have enough power to detect a statistical difference. Thiazide diuretics inhibit sodium and chloride cotransport at the distal convoluted tubule, which increases urinary sodium excretion, leading to plasma and extracellular fluid volume decreases.

In contrast to the study on falls by Gribbin et al, we found that the initiation of ACE inhibitors was associated with an increased risk of hip fracture. The risk of first-dose hypotension has been described with the use of specific ACE inhibitors (eg, captopril, enalapril, lisinopril, and ramipril) and is related to venodilation, which produces marked venous pooling with a consequent fall in cardiac output and profound hypotension. However, our study found that initiation of BBs increased the risk of hip fracture, which is similar to the findings of the study on falls by Gribbin et al. β-Adrenergic blockers are less effective in controlling hypertension in older patients because the number of β-adrenergic receptors is decreased and the affinity for both agonist and antagonist is reduced. β-Adrenergic blockade decreases heart rate and blood pressure, and peripheral vasoconstriction, and depression or confusion also have been described with BBs and may result in fall injuries. By identifying and understanding the short period following antihypertensive drug initiation as a window when patients are particularly vulnerable to falls, physicians may help prevent injurious falls.

Antihypertensive drug use in the elderly for the treatment of hypertension is beneficial in preventing coronary heart disease and cerebrovascular disease. The potential for antihypertensive treatment to increase risk of hip fractures in the short term, while decreasing the risk of cardiovascular outcomes in the long term, merits further study. On the basis of this study, we are unable to determine an absolute risk reduction that would be helpful for determining the number needed to harm. However, epidemiologic studies in the elderly show that serious fall-related injuries such as fractures have functional, cognitive, and physical effects similar to myocardial infarction and stroke. Also, the incidence of nonfatal cardiovascular events in hypertensive elderly patients and of serious fall injury in the elderly at risk of falls is both 16% and 50. Our study has important strengths. This was a large population-based study that used data from all commu-
nity-dwelling elderly persons aged 66 years and older residing in Ontario, Canada, during a 10-year period. The population of newly treated hypertensive elderly persons consisted of 301,591 patients. The SCCS method was the best design to study this association owing to the short risk period of 45 days in comparison with the total observation period of 450 days, which is almost as efficient as the cohort method with the same number of cases.32,34 The SCCS method had several other advantages for this study: the influence of confounding by indication was minimized in comparison with other observational designs like case-control and cohort studies; selection bias was avoided because only cases were used; and fixed covariates that vary between individuals, such as genetic factors, socioeconomic status, location, frailty, bone mineral density, and underlying health status, were removed.32,34,36 Furthermore, this design works well for rare, nonrecurrent events, such as hip fractures.32,34 The sample size calculation for the SCCS method indicated that the result obtained for the main association of antihypertensive drug use and hip fracture outcome had sufficient power. In terms of risk periods, there was a high accuracy in our estimation of exposed and control periods given that the IRRs of hip fracture during the wash-out periods consistently demonstrated unity.

However, there are limitations to the study. Use of incident antihypertensive prescriptions may not reflect all true “newly” diagnosed hypertensive elderly patients. The ODBP database captures prescriptions only for seniors aged 65 years and older, and it is possible that these seniors were exposed to antihypertensive medications at a younger age or were not taking their prescribed medications. Also, physicians could have provided their hypertensive elderly patients with drug samples of antihypertensive medications during routine clinical appointments that would not have been captured by the ODBP, particularly for ACE inhibitors, ARBs, and CCBs, before actually prescribing them. The use of administrative databases to define newly treated hypertensive elderly patients was based on previously used algorithms that have not been validated but are accepted as a standard approach.39,20,27 This study provided information on the antihypertensive class effect, and no information was provided on specific subclasses within an antihypertensive drug class or drug doses.

There may also be unrecognized time-varying confounders that were not adjusted for using the SCCS method. Initiation of an antihypertensive drug may be associated with a change in exposure status for another independent risk factor for hip fracture, such as increased exercise. Such behavioral change would be difficult to measure. Despite this limitation, the effect estimates for the association of antihypertensive drugs and hip fracture risk during the initiation of therapy were consistent in a sensitivity analysis that removed other fall-causing drugs.

Therefore, this study suggests that initiating antihypertensive drugs may be a risk factor for hip fractures in community-dwelling elderly patients. In following practice guidelines for the treatment of hypertension as standardized approaches to disease management, physicians need to be aware of the effect of drug therapies on fracture risk because it may have important implications for the elderly population and the health care system.

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Correspondence: Debra Butt, MD, MSc, CCFP, FCFP, Ellesmere Health Care Centre, 2060 Ellesmere Rd, Units 1-4, Scarborough, ON M1H-2V6, Canada (debra.butttutoronto.ca).

Author Contributions: Dr Butt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Butt, Mamdani, Tu, Gomes, and Glazier. Acquisition of data: Butt and Glazier. Analysis and interpretation of data: Butt, Mamdani, Austin, and Gomes. Drafting of the manuscript: Butt. Critical revision of the manuscript for important intellectual content: Butt, Mamdani, Austin, Tu, Gomes, and Glazier. Statistical analysis: Butt and Mamdani. Obtained funding: Butt. Administrative, technical, and material support: Butt, Mamdani, Tu, Gomes, and Glazier. Study supervision: Glazier.

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Online-Only Material: eTables 1, 2, 3, and 4 are available at http://www.archinternmed.com.

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