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 communitydwelling elderly patients. Caution is advised when initiating antihypertensive drugs in the elderly.

Arch Intern Med. 2012:172(22):1739-1744. Published online November 19, 2012. doi:10.1001/2013.jamainternmed.469

Author Affiliations: Ellesmere Health Care Centre and The Scarborough Hospital, Scarborough, Ontario (Dr Butt), and Department of Family and Community Medicine (Drs Butt, Mamdani, Tu, and Glazier); Applied Health Research Centre, Li Ka Shing Knowledge Institute (Dr Mamdani); Institute for Clinical Evaluative Sciences (Drs Austin, Tu, and Glazier and Ms Gomes); Department of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health (Dr Austin); Faculty of Pharmacy (Ms Gomes); and Centre for Research on Inner City Health (Dr Glazier), St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.



ORE 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 elderly14,15 that may lead to disability with loss of independence16 and even death.17

Most studies18-21 on the association of antihypertensive drug use 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 antagonists/ blockers23 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 communitydwelling elderly persons.

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1739



Figure 1. Antihypertensive drug use and hip fracture risk: self-controlled case series design. Time division for each patient is included to assess incidence of first acute hip fracture in relation to antihypertensive prescription. All patients in the analysis had at least 1 prescription for an antihypertensive drug and a single incident hip fracture.

METHODS

STUDY POPULATION

The Ontario Drug Benefit Program (ODBP) 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 antagonist/blockers (ARBs), calcium channel blockers (CCBs), or β-adrenergic blockers (BBs) (eTable 1; http://www .archinternmed.com). The ODBP database records all drugs prescribed from a minimally restrictive formulary for individuals aged 65 years and older²⁴ and has an error rate of less than 1%, demonstrating good reliability.²⁵ Incident hypertensive elderly patients were identified using previously published methods^{24,26,27} 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 excluded²⁴ (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 ODBP 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 prespecified 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 820.1 to 820.9. 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-V99) 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 hypotension35 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 periods³⁶ (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.

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1740

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

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

STATISTICAL ANALYSIS

Descriptive statistics on age, sex, antihypertensive drug classes, and history of hip fracture were computed. Conditional Poisson regression^{32,34} was used to estimate incidence rate ratios (IRRs) with 95% CIs for any antihypertensive drug and the 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 highrisk 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 (eTable 3) that are known to cause falls^{37,38} 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.³⁹ 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 charac-



Figure 2. Forest plot of antihypertensive drugs and hip fracture risk using incidence rate ratios with 95% Cls. Each data point and 95% Cl (error bars) represent results from the conditional Poisson regression analysis. The line at 1.0 represents no association; estimates to the right of the line represent an increased risk of hip fracture. ACE indicates angiotensin II converting–enzyme; ARB, angiotensin II receptor antagonist/blocker; BB, β-adrenergic blocker; and CCB, calcium channel blocker.

Table 2. Self-Controlled Case Series Analysis for the Association of Antihypertensive Drug Use and Hip Fracture

| Exposure Period | No. of Hip Fractures | Incidence Rate Ratio (95% CI) |
|---------------------------|-------------------------|----------------------------------|
| Any antihypertensive drug | | |
| Risk period | 143 | 1.43 (1.19-1.72) |
| Washout period | 104 | 1.04 (0.84-1.28) |
| Control period | 600 | 1 [Reference] |
| Thiazide diuretics | | |
| Risk period | 39 | 1.33 (0.94-1.88) |
| Washout period | 34 | 1.16 (0.80-1.67) |
| Control period | 176 | 1 [Reference] |
| ACE inhibitors | | |
| Risk period | 48 | 1.53 (1.12-2.10) |
| Washout period | 26 | 0.83 (0.55-1.25) |
| Control period | 188 | 1 [Reference] |
| ARBs | | |
| Risk period | 8 | 1.41 (0.65-3.05) |
| Washout period | 7 | 1.24 (0.55-2.79) |
| Control period | 34 | 1 [Reference] |
| CCBs | | |
| Risk period | 24 | 1.30 (0.83-2.02) |
| Washout period | 22 | 1.19 (0.75-1.88) |
| Control period | 111 | 1 [Reference] |
| BBs | | |
| Risk period | 24 | 1.58 (1.01-2.48) |
| Washout period | 15 | 0.99 (0.57-1.71) |
| Control period | 91 | 1 [Reference] |

Abbreviations: See Table 1.

teristics 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) demon-

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1741

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.¹⁸ 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.²¹ That study involved lowincome 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.18,19,40

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.¹⁵ Other designs involving a case-crossover study of inpatients²³ and an SCCS study involving elderly patients²² 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^{22,23} 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.²² 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.^{22,35,41} Our analysis of thiazide diuretics did not have enough power to detect a statistical difference (n = 337). 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.42

In contrast to the study on falls by Gribbin et al.²² 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,^{9,10,43} which produces marked venous pooling with a consequent fall in cardiac output and profound hypotension.9 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.²² β-Adrenergic blockers are less effective in controlling hypertension in older patients because the number of B-adrenergic receptors is decreased and the affinity for both agonist and antagonist is reduced.44 Adverse effects of bradycardia, decreased cardiac output, induction of peripheral vasoconstriction, and depression or confusion⁴⁵ 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/ fractures, 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.4 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.⁴⁶ 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.46-48 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%.49,50

Our study has important strengths. This was a large population-based study that used data from all commu-

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1742

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 washout 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 OBDP, 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.^{24,26,27} 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 fallcausing 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.

Accepted for Publication: July 16, 2012.

Published Online: November 19, 2012. doi:10.1001/2013.jamainternmed.469

Correspondence: Debra Butt, MD, MSc, CCFP, FCFP, Ellesmere Health Care Centre, 2060 Ellesmere Rd, Units 1-4, Scarborough, ON M1H-2V6, Canada (debra.butt @utoronto.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 Glazie: Stutt and Mamdani. *Obtained funding*: Butt. *Administrative, technical, and material support*: Butt, Mamdani, Tu, Gomes, and Glazier. *Study supervision*: Glazier.

Conflict of Interest Disclosures: Dr Mamdani reports that he is a consultant for Hoffman-La Roche, GlaxoSmithKline, Pfizer, Novartis, and Lilly and has received honoraria as a member of the advisory boards of AstraZeneca, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Hoffman-La Roche, Novartis, Novo Nordisk, and Pfizer.

Funding/Support: This work was funded by the Ontario Ministry of Health and Long-Term Care, a Career Investigator Award from the Heart and Stroke Foundation of Ontario (Dr Austin), and a Canadian Institutes of Health Research Fellowship Award in Primary Care (Dr Tu).

Role of the Sponsor: The sponsor did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Disclaimer: The opinions, results, and conclusions are those of the authors and no endorsement by the Ministry of Health and Long-Term Care or by the Institute for Clinical Evaluative Sciences is intended or should be inferred.

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

Additional Contributions: We thank Paddy Farrington, PhD (Division of Statistics, Open University, Milton Keynes, England), for his contribution to the study design and analytical assistance, and Alex Kopp, BSc, and Zhongliang Chen, MD, MSc (both of the Institute for Clinical Evaluative Sciences), for their help with the data preparation.

REFERENCES

- Hemmelgarn BR, Chen G, Walker R, et al. Trends in antihypertensive drug prescriptions and physician visits in Canada between 1996 and 2006. *Can J Cardiol.* 2008;24(6):507-512.
- Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003;289(18):2363-2369.

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1743

- Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA. 2002;287(8):1003-1010.
- 4. Mulrow C, Lau J, Cornell J, Brand M. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev.* 2000;(2):CD000028.
- Leenen FH, Dumais J, McInnis NH, et al. Results of the Ontario survey on the prevalence and control of hypertension. *CMAJ*. 2008;178(11):1441-1449.
- Neutel CI, Campbell NR. Antihypertensive medication use by recently diagnosed hypertensive Canadians. *Can J Cardiol.* 2007;23(7):561-565.
- Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. J Am Geriatr Soc. 2011;59(3):383-389.
- Shannon RP, Wei JY, Rosa RM, Epstein FH, Rowe JW. The effect of age and sodium depletion on cardiovascular response to orthostasis. *Hypertension*. 1986; 8(5):438-443.
- Capewell S, Capewell A. "First dose" hypotension and venodilatation. Br J Clin Pharmacol. 1991;31(2):213-215.
- Slavachevsky I, Rachmani R, Levi Z, Brosh D, Lidar M, Ravid M. Effect of enalapril and nifedipine on orthostatic hypotension in older hypertensive patients. J Am Geriatr Soc. 2000;48(7):807-810.
- Pool JL, Glazer R, Chiang YT, Gatlin M. Dose-response efficacy of valsartan, a new angiotensin II receptor blocker. J Hum Hypertens. 1999;13(4):275-281.
- Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS; CHS Collaborative Research Group. Orthostatic hypotension in older adults: the Cardiovascular Health Study. *Hypertension*. 1992;19(6, pt 1):508-519.
- Tinetti ME, Kumar C. The patient who falls: "it's always a trade-off." JAMA. 2010; 303(3):258-266.
- Speechley M, Tinetti M. Falls and injuries in frail and vigorous community elderly persons. J Am Geriatr Soc. 1991;39(1):46-52.
- Järvinen TL, Sievänen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ*. 2008;336(7636):124-126.
- Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. Am J Public Health. 1992;82(7):1020-1023.
- Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture: national analysis of comedications, comorbidity, and survival. *Age Ageing*. 2010;39(2):203-209.
- Wiens M, Etminan M, Gill SS, Takkouche B. Effects of antihypertensive drug treatments on fracture outcomes: a meta-analysis of observational studies. *J Intern Med.* 2006;260(4):350-362.
- Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. J Hypertens. 2006;24(3):581-589.
- Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between beta-blocker use and fracture risk: the Dubbo Osteoporosis Epidemiology Study. *Bone.* 2011;48(3):451-455.
- Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res. 2011;26(7):1561-1567.
- Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: self-controlled case series. *Pharmacoepidemiol Drug Saf.* 2011;20(8):879-884.
- Shuto H, Imakyure O, Matsumoto J, et al. Medication use as a risk factor for inpatient falls in an acute care hospital: a case-crossover study. *Br J Clin Pharmacol.* 2010;69(5):535-542.
- Tu K, Campbell NR, Duong-Hua M, McAlister FA. Hypertension management in the elderly has improved: Ontario prescribing trends, 1994 to 2002. *Hypertension*. 2005;45(6):1113-1118.
- Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol.* 2003;10(2):67-71.
- Friedman O, McAlister FA, Yun L, Campbell NR, Tu K; Canadian Hypertension Education Program Outcomes Research Taskforce. Antihypertensive drug persistence and compliance among newly treated elderly hypertensives in Ontario. *Am J Med.* 2010;123(2):173-181.

- Campbell NR, McAlister FA, Duong-Hua M, Tu K. Polytherapy with two or more antihypertensive drugs to lower blood pressure in elderly Ontarians: room for improvement. *Can J Cardiol.* 2007;23(10):783-787.
- Williams J, Young W. A summary of studies on the quality of healthcare administrative databases in Canada. In: Goel V, Williams JI, Young W, et al, eds. *Patterns of Health Care in Ontario: The ICES Practice Atlas.* 2nd ed. Ottawa, Ontario: Canadian Medical Association; 1996:339-346.
- Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516.
- Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. J Clin Epidemiol. 2000;53(2):183-194.
- Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized Medicare files. J Clin Epidemiol. 1992;45(7):703-714.
- Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med.* 2006;25(10):1768-1797.
- Tata LJ, West J, Smith C, et al. General population-based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. *Heart.* 2005;91(4):465-471.
- Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res.* 2009;18(1):7-26.
- Schoofs MW, van der Klift M, Hofman A, et al. Thiazide diuretics and the risk for hip fracture. Ann Intern Med. 2003;139(6):476-482.
- Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of selfcontrolled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol.* 2009;169(6):761-768.
- Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009;169(21): 1952-1960.
- Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis, I: psychotrophic drugs. J Am Geriatr Soc. 1999; 47(1):30-39.
- Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. *Stat Med.* 2006;25(15):2618-2631.
- Coutinho Ed Eda S, Silva SD. Medication as a risk factor for falls resulting in severe fractures in the elderly [in Portuguese]. *Cad Saude Publica*. 2002;18(5): 1359-1366.
- Gribbin J, Hubbard R, Gladman JR, Smith C, Lewis S. Risk of falls associated with antihypertensive medication: population-based case-control study. *Age Ageing.* 2010;39(5):592-597.
- Hajjar I. Postural blood pressure changes and orthostatic hypotension in the elderly patient: impact of antihypertensive medications. *Drugs Aging*. 2005;22 (1):55-68.
- Burton L, Norton M, Newton JL. Are some antihypertensives more prone to induce hypotensive side effects than others? *Age Ageing*. 2004;33(6):626-628.
- Hamdy RC, Hudgins LB, Compton R. Management of hypertension in older patients. South Med J. 1993;86(10):2S1-2S6.
- Aronow WS. Treating hypertension in older adults: safety considerations. *Drug* Saf. 2009;32(2):111-118.
- Tinetti ME, McAvay GJ, Fried TR, et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. *J Am Geriatr Soc.* 2008;56(8):1409-1416.
- Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997;337(18):1279-1284.
- Gill TM, Desai MM, Gahbauer EA, Holford TR, Williams CS. Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. *Ann Intern Med.* 2001;135(5):313-321.
- Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. *J Am Geriatr Soc.* 1995;43(11): 1214-1221.
- Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000; 355(9207):865-872.

ARCH INTERN MED/VOL 172 (NO. 22), DEC 10/24, 2012 WWW.ARCHINTERNMED.COM 1744

1744