

Antihypertensive Therapy and Incidence of Type 2 Diabetes in an Elderly Cohort

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OBJECTIVE — The aim of this study was to determine whether the incidence of type 2 diabetes differed among elderly users of four major antihypertensive drug classes.

RESEARCH DESIGN AND METHODS — This was a retrospective, observational cohort study of previously untreated elderly patients (aged ≥ 66 years) identified as new users of an antihypertensive drug class between April 1995 and March 2000. Using a Cox proportional hazards model, the primary analysis compared diabetes incidence in users of ACE inhibitors, β -blockers, and calcium channel blockers (CCBs), with thiazide diuretics allowed as second-line therapy. In the secondary analysis, thiazide diuretics were added as a fourth study group.

RESULTS — In the multivariable-adjusted primary analysis ($n = 76,176$), neither ACE inhibitor use (hazard ratio 0.96 [95% CI 0.84–1.1]) nor β -blocker use (0.86 [0.74–1.0]) was associated with a statistically significant difference in type 2 diabetes incidence compared with the CCB control group. In the secondary analysis ($n = 100,653$), compared with CCB users, type 2 diabetes incidence was not significantly different between users of ACE inhibitors (0.97 [0.83–1.1]), β -blockers (0.84 [0.7–1.0]), or thiazide diuretics (1.0 [0.89–1.2]).

CONCLUSIONS — Type 2 diabetes incidence did not significantly differ among users of the major antihypertensive drug classes in this elderly, population-based administrative cohort. These results do not support the theory that different antihypertensive drug classes are relatively more or less likely to cause diabetes.

Diabetes Care 27:2458–2463, 2004

In the past half-century, the importance of aggressively treating hypertension, particularly in patients with concomitant cardiovascular risk factors, has been increasingly recognized. There is now evidence that several major antihypertensive drug classes decrease cardiovascular morbidity and mortality (1). Therefore, the choice of antihypertensive therapy is

largely dependent upon additional factors such as age, the presence of comorbid medical conditions, and drug cost.

One additional factor that may potentially influence the choice of antihypertensive therapy is the possibility that certain antihypertensive drug classes may accelerate or delay development of type 2 diabetes. However, the results of previous

studies have been inconsistent, with some showing no difference between major antihypertensive drug classes and others suggesting a potentially protective effect of ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers (CCB) and a potentially harmful effect of β -blockers or thiazide diuretics (2,3).

There are several limitations to previous studies, including the fact that type 2 diabetes incidence has never been studied as a predefined primary end point and a lack of power to simultaneously compare the incidence of type 2 diabetes among several antihypertensive drug classes (2). Randomized controlled trials designed to address the benefit of renin-angiotensin inhibitors in diabetes prevention are ongoing but will not be completed until 2006–2008 and will not simultaneously compare all major drug classes (4–6). We used large, population-based administrative databases to determine whether the incidence of type 2 diabetes differed among users of the major antihypertensive drug classes in residents of Ontario, Canada.

RESEARCH DESIGN AND METHODS

Data sources

The five databases used in this study were the Registered Persons Database, the Ontario Drug Benefit Database (ODB), the Canadian Institute for Health Information Hospital Discharge Abstract Database (CIHI-DAD), the Ontario Health Insurance Plan (OHIP) database, and the Ontario Diabetes Database (ODD). Anonymous linkage of data was facilitated through the use of a patient-specific scrambled health care identifier, which was common to all databases. Ethics approval was obtained through the University of Toronto.

The OHIP database contains information on outpatient physician visits and diagnostic codes for all legal residents of Ontario. The Registered Persons Database contains demographic data on all residents of Ontario covered by OHIP and includes date of birth, sex, postal code,

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Received for publication 29 April 2004 and accepted in revised form 9 July 2004.

Abbreviations: CCB, calcium channel blocker; CIHI-DAD, Canadian Institute for Health Information Hospital Discharge Abstract Database; ODB, Ontario Drug Benefit Database; ODD, Ontario Diabetes Database; OHIP, Ontario Health Insurance Plan.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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and date of death (if applicable). Using a Statistics Canada Postal Code Conversion File, the postal code was linked to federal census data on income quintiles. The income quintile of the neighborhood in which an individual resides was imputed to all residents of the neighborhood and subsequently used as a proxy measure for individual socioeconomic status (7,8). The ODB database is comprised of individuals covered under the provincial drug benefit program, the vast majority being seniors >65 years of age. Prescription claims submitted electronically to the ODB have an overall discrepancy rate of 0.7% (95% CI 0.5–0.9) compared with the original written prescription (9). The CIHI-DAD contains data on hospital discharges across Canada, with up to 16 diagnoses and 10 procedures coded per individual admission. The frequency of missing demographic data within the CIHI-DAD has been found to be ~1% when validated against chart review (10).

The ODD identifies all incident and prevalent cases of diabetes within Ontario using hospital discharge abstracts from CIHI and physician service claims from OHIP. Individuals are diagnosed with diabetes and included in the ODD if they have diabetes listed as a diagnosis on one CIHI hospital discharge abstract or two OHIP claims within a 2-year period. The date of diagnosis reverts back to the date of the first claim. The ODD has been validated against primary data collection and has a sensitivity of 86%, specificity of 97%, and positive predictive value of 80% (11).

Cohort definition and outcomes ascertainment

Using these databases, we assembled a cohort of patients ≥ 66 years who were free from diabetes at baseline and who were newly prescribed monotherapy with ACE inhibitors, CCBs, or β -blockers between April 1995 and March 2000. We could not study angiotensin receptor blockers because of the small number of patients receiving them.

New users were defined as those patients who had not received a prescription for an antihypertensive study medication in the year before the date of study drug initiation. Patients who were 65 years of age upon entering the ODB would have had no prior records within this database and were excluded because it could not be determined if they were new or previous

users of antihypertensive medication. We also excluded patients who were on short-term therapy (<30 days), individuals with no recorded socioeconomic data, individuals with preexisting diabetes, or those who received a diagnosis of diabetes within 1 month of initiation of antihypertensive therapy (presumed to be existing cases of diabetes).

Because hypertension itself is associated with an increase in diabetes incidence independent of drug therapy, the cohort was limited to hypertensive patients only, using a previously defined algorithm (12). This was done by excluding all patients with nonhypertensive indications for antihypertensive agents. By linking to the CIHI-DAD and OHIP databases, any patient with one of the following diagnoses 5 years before the date of initial study drug prescription was excluded: myocardial infarction/angina, congestive heart failure, cardiac arrhythmia, renal disease, liver disease including esophageal varices, stroke, peripheral vascular disease, migraine, and transplants. Also excluded were patients receiving a prescription for one of the following medications during the 5 years before receiving their first study drug: arrhythmias (amiodarone, quinidine, disopyramide, digoxin, flecainide ACETate, mexiletine, procainamide, propafenone, sotalol), congestive heart failure (carvedilol, furosemide, metolazone, ethacrynic acid, sodium ethacrylate, spironolactone), angina (any nitrate including nitroglycerin), or glaucoma (timolol).

The primary outcome was time to diagnosis of diabetes. Cases of diabetes were identified by either new entry into the ODD or receipt of a new prescription for an antihyperglycemic agent (either insulin or an oral medication). Patients were censored if they developed diabetes, reached the end of the study (March 2000), discontinued therapy, or if they were prescribed another study drug. Drug discontinuation was defined as failure to refill the study drug within 120 days of the last prescription date. This was calculated by adding a 20% grace period to the 100-day maximum prescription length of the ODB, and all patients who discontinued the study drug were censored at this 120-day time point.

Our primary analysis compared ACE inhibitors, β -blockers, and CCBs, with CCBs chosen as the referent study group. In this analysis, thiazide diuretics were al-

lowed as add-on therapy, and the use of thiazides was controlled for in the analysis. This was done to try to maximize the duration of follow-up and limit the greater degree of censoring that would be expected if thiazides were added as a separate study group. A secondary analysis was also performed in an identical fashion to the primary analysis except that thiazide diuretics were added as a fourth study group.

Statistical analysis

All statistical analyses were carried out using SAS for UNIX, version 8.2 (SAS Institute, Cary, NC). At baseline, even minor differences between study groups were expected to be highly statistically significant, given the large sample size of the cohort. Therefore, statistical tests of significance were not applied when comparing demographic characteristics between groups.

A Cox proportional hazards model was developed to model time to diabetes as a function of antihypertensive drug treatment with inclusion of all covariates. The linearity assumption was tested using Martingale (13) residuals, and the validity of the proportional hazards assumption was verified using Schoenfeld residuals (14) and log-negative-log survival curves.

The model included the following covariates: age, sex, socioeconomic status, community size (rural versus nonrural), and medications affecting glycemic control (fibrin acid derivatives, niacin, lithium, atypical antipsychotics, phenytoin, and oral corticosteroids, statins, and α -blockers). Thiazide diuretics were also included as a covariate in the primary analyses.

We performed comorbidity adjustment by entering the total number of prescription drugs used by the patient in the year before the date of initial drug prescription as a covariate in the model. This method is similar to a previously used process where the number of chemically distinct prescription medications was used as a comorbidity measure (15). We also controlled for potential detection bias by incorporating the number of primary care physician visits and hospitalizations during the follow-up period (adjusted for duration of follow-up) as covariates in the model.

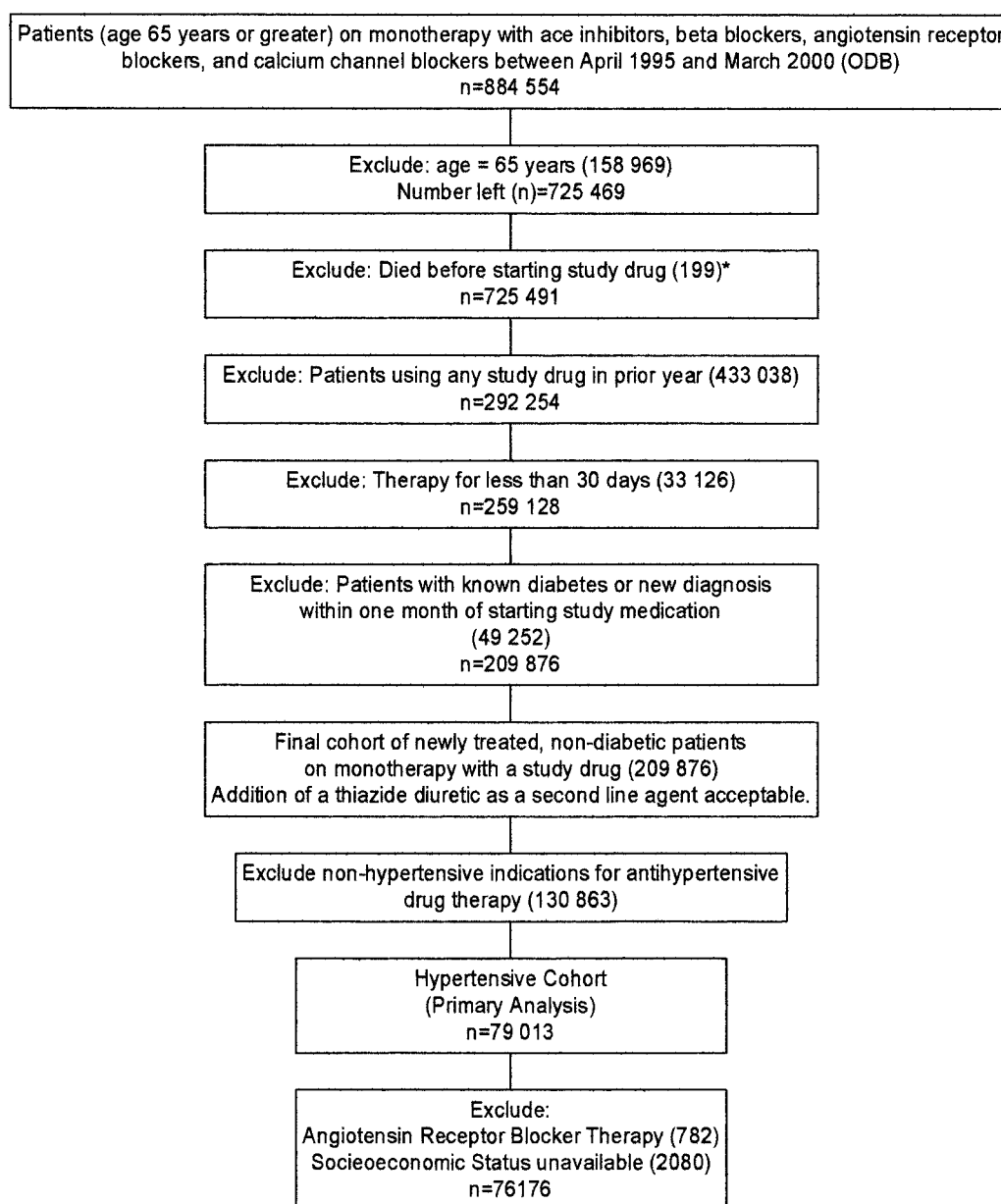


Figure 1—Creation of dataset for primary analysis. *Due to discrepancies between the ODB and the Registered Persons Database, individuals listed as deceased in the Registered Persons Database before receiving study drug were excluded.

RESULTS

Primary analysis in the hypertensive cohort

The hypertensive cohort consisted of 76,176 patients after exclusion of 2,080 individuals in whom socioeconomic status was unavailable (Fig. 1), including 19,598 patients on CCBs, 35,993 patients receiving ACE inhibitors, and 20,585 patients on β -blockers. Baseline levels of all covariates were very similar between study groups (Table 1).

Over one-half (53%) of the cohort was censored due to medication discontinuation, and a further 17% were censored because another study drug was added to their therapeutic regimen. This occurred in 18% of individuals taking ACE inhibitors, 17% of those on β -blockers, and 15% of those taking CCBs. The number of patients who were censored because of study end was 27%, and 1.9% of patients died. The total number of patients who were diagnosed with diabetes was 1,254, or 1.7% of the cohort, with

1,138 identified from the ODD, 136 from the ODB, and 363 by both methods.

Analysis of data from private, non-hospital laboratories in Ontario showed that the frequency of glucose testing, corrected for the duration of follow-up, was similar among study groups (Table 1). These data were available for 43% of the cohort or 32,971 individuals.

The proportional hazards assumption was verified, as was the linearity assumption for all variables except outpatient visits. This variable was binned into quintiles

Table 1—Baseline and follow-up characteristics of the hypertensive cohort

	CCB	ACE inhibitors	β -Blockers
<i>n</i>	19,598	35,993	20,585
Baseline			
Age (years)	73.2 \pm 5.9	73.3 \pm 6.1	72.8 \pm 5.7
Sex, female	62%	62%	64%
Socioeconomic status (income quintile)*	2.9 \pm 1.4	3.0 \pm 1.4	3.0 \pm 1.4
Drug comorbidity index†	4.54 \pm 4.74	4.36 \pm 4.40	4.34 \pm 4.47
Rural residence	14%	15%	16%
α -Blockers	4%	3%	3%
Atypical antipsychotics	0.6%	0.6%	0.7%
Corticosteroids	7%	6%	4%
Fibrates	1%	1%	1%
Lithium	0.3%	0.2%	0.6%
Niacin	0.1%	0.1%	0.1%
Phenytoin	0.6%	0.6%	0.7%
Resins	0.6%	0.5%	0.6%
Statins	13%	13%	12%
Thiazides	24%	29%	28%
During follow-up			
Mean length of follow-up (months)	11.6 \pm 11.7	11.2 \pm 11.4	9.8 \pm 10
Outpatient encounter index‡	13.7 \pm 18.9	13.7 \pm 19.3	13.1 \pm 15.7
Hospitalizations index§	0.63 \pm 1.9	0.56 \pm 1.7	0.58 \pm 2.0
Glucose testing index	1.1 \pm 2.9	1.1 \pm 2.9	1.0 \pm 2.3

Data are means \pm SD or percentage. *Income quintile: 1 (poorest) to 5 (richest). †Drug comorbidity index is the number of concomitant medications (index of comorbidity). ‡Outpatient encounter index = (number of outpatient primary care visits/length of follow-up) \times 365. §Hospital index = (number of hospitalizations/length of follow-up) \times 365. ||Glucose testing index = (frequency of glucose measurements/length of follow-up) \times 365. This variable was available in 43% of the entire cohort and 45, 44, and 40% of the CCB, ACE inhibitor, and β -blocker groups, respectively.

that subsequently met the linearity assumption. After adjustment for all covariates, neither ACE inhibitor use (HR 0.96 [95% CI 0.84–1.1], $P = 0.53$) nor β -blocker use (0.86 [0.74–1.0], $P = 0.06$) was associated with a statistically significant difference in time to diabetes

development compared with CCB therapy (Table 2).

Secondary analysis using thiazide diuretics as a fourth study group

This cohort was comprised of 100,653 patients, including 27,209 patients in the

ACE inhibitor group, 15,575 patients in the β -blocker group, 15,534 patient in the CCB group, and 42,335 patients in the thiazide diuretic group. Baseline levels of all covariates were again very similar (data available upon request).

A total of 1,367 events occurred in this secondary analysis, with a diabetes incidence rate of 1.2% over a mean follow-up period of 9.5 months. Compared with CCB users and after adjustment for covariates, the time to development of diabetes was not significantly different in users of ACE inhibitors (HR 0.97 [95% CI 0.83–1.1], $P = 0.68$), β -blockers (0.84 [0.7–1.0], $P = 0.07$), or thiazide diuretics (1.0 [0.89–1.2], $P = 0.62$) (Table 2).

CONCLUSIONS— In summary, in an elderly cohort of hypertensive individuals derived from large, population-based administrative databases, we found no significant difference in time to diabetes incidence between users of four major antihypertensive drug classes. Although there have been several previous cohort studies in this area (2), only one has simultaneously compared these four drug classes in a methodologically rigorous fashion (16). This study, based on data from 3,804 individuals in the Atherosclerosis Risk in Communities cohort, found that users of β -blockers had an increased risk of developing diabetes compared with nontreated, hypertensive patients (relative risk 1.28 [95% CI 1.04–1.57]). In contrast, users of ACE inhibitors, thiazide diuretics, and CCBs had no increased or reduced risk. Although previous randomized controlled trials have inconsistently demonstrated that the incidence of type 2 diabetes may be potentially low-

Table 2—Hazard ratios of developing diabetes compared with CCB arm

Model	ACE inhibitors	β -Blockers	Thiazide diuretics
Primary analysis in the hypertensive cohort			
Unadjusted	0.92 (0.81–1.0)	0.82 (0.70–0.95)	—
Adjusted for age, sex	0.92 (0.81–1.0)	0.81 (0.70–0.95)	—
Adjusted for age, sex, socioeconomic status, drug index, hospital index, outpatient index, and use of thiazides	0.96 (0.84–1.1)	0.85 (0.73–1.0)	—
Adjusted for all covariates*	0.96 (0.84–1.1)	0.86 (0.74–1.0)	—
Secondary analysis: thiazide diuretics as a fourth study arm			
Adjusted analysis*	0.97 (0.83–1.1)	0.84 (0.7–1.0)	1.0 (0.89–1.2)

Data are hazard ratios (95% CI). *Adjusted for age, sex, socioeconomic status, hospitalization index, outpatient index, drug index, rural residence, and use of niacin, phenytoin, resins, statins, α -blockers, atypical antipsychotics, corticosteroids, fibrates, and lithium. The primary analysis is also adjusted for thiazide diuretic use.

ered with ACE inhibitor or CCB therapy, and raised with β -blocker or thiazide diuretic therapy, current evidence is far from definitive (2). The results of our analyses, involving >100,000 patients, provides no convincing evidence that any of these classes of antihypertensive agents are associated with an increase or decrease in diabetes incidence.

The major strengths of our study include the use of a large, population-based sample of hypertensive patients that is not as highly selected as that seen in randomized controlled trials, a validated end point (the ODD), and the ability to adjust for a large number of potentially important covariates affecting diabetes incidence. The large sample size and large number of diabetes cases makes inadequate power an unlikely explanation for the observed null result. Given the results of our study, we estimate at least 90% power to detect a clinically meaningful relative risk reduction of 20% in the primary outcome between groups (17).

β -Blocker therapy was associated with a nonstatistically significant reduction in the incidence of diabetes in our analysis. If true, this apparent protective effect of β -blockers is most likely due to confounding by indication. Physicians may avoid prescribing β -blockers in patients at high risk of developing diabetes because of previous evidence to linking these agents to weight gain and deterioration in metabolic control (18–22). Preferential prescribing of other antihypertensive drug classes in such high-risk patients may increase the diabetes incidence rates in these study groups. It is notable that no previous study to date has demonstrated a protective effect of β -blocker therapy in lowering diabetes incidence (2).

If thiazide diuretics are indeed diabetogenic, or if ACE inhibitors and CCBs truly prevent type 2 diabetes, one might expect to see differences among these drug classes in reducing cardiovascular end points. Studies to date have not confirmed that such differences exist. Although no specific comparison of such agents has been performed in patients with pre-diabetes, the recent Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) did not find any significant differences in the incidence of nonfatal myocardial infarction or fatal coronary heart disease among chlorthalidone-, lisinopril-, and amlodipine-based therapy. Recent meta-analyses

have also failed to demonstrate major differences between ACE inhibitor or CCB-based therapy and thiazide/ β -blocker-based therapy in preventing coronary disease, cardiovascular mortality, or overall mortality (1,23).

Randomized controlled trials involving large numbers of patients at high risk for developing diabetes would provide more definitive data and are currently underway. In the Diabetes Reduction Approaches with Medication Study, 5,269 patients with impaired glucose tolerance will be randomized to ramipril or rosiglitazone versus placebo in a 2×2 factorial design (6). New-onset diabetes is the primary end point. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is a double blind, parallel group trial with telmisartan, ramipril, and telmisartan plus ramipril study arms. This study of 23,000 patients will determine the effect of one or both agents on a composite end point of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure over a 5.5-year follow-up period (4). Patients unable to tolerate an ACE inhibitor will be enrolled in a parallel study of telmisartan versus placebo called TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Patients with Cardiovascular Disease) (4). Incidence of type 2 diabetes is a secondary end point in both of these studies. In the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) trial, 7,500 patients with impaired glucose tolerance will be randomized to nateglinide, valsartan, dual therapy, or placebo for at least 3 years. Incidence of type 2 diabetes and cardiovascular disease are the primary end points in this study (5). All of these trials are scheduled for completion between 2006 and 2008.

Although we did not have information on BMI, race, physical activity, and sedentary lifestyle, we feel that the risk of bias due to inability to control for these variables is likely quite small. The known baseline characteristics of the study groups were nearly identical, and it is unlikely that one or more of the above-unmeasured covariates systematically influenced the initial choice of antihypertensive therapy and resulted in widespread differences in prescribing patterns.

In addition to the nonrandomized de-

sign, there are other potential limitations to our study. Exposure status was defined on the basis of prescription drug claims, and it was assumed that individuals who filled a prescription were adherent with the medication. The incidence of diabetes within the cohort was <2%, which is lower than that seen in previous studies (2) and lower than that expected for a population of patients with hypertension (24). This can be at least partially explained by the fact that we excluded patients with preexisting diabetes and cases of diabetes diagnosed within 1 month of starting study drug (49,252 patients) (Fig. 1). In addition, the advanced age of the cohort likely resulted in most cases of type 2 diabetes already being diagnosed; increasing age beyond 65 years within the cohort was associated with a statistically significant decrease in the frequency of developing type 2 diabetes (HR 0.96 [95% CI 0.95–0.97], $P < 0.0001$). The high degree of censoring within the cohort, leading to a shortened duration of follow-up, also may have contributed to a lower incidence of type 2 diabetes within the study. The frequency of censoring was high because of the high rate of drug discontinuation, frequent addition of a study drug from another class, and an open cohort accrual period in which subjects entering the study during its latter stages were automatically censored at the end of the study. High rates of drug discontinuation were not unexpected, given previous administrative data showing 4-year discontinuation rates of 54% in newly diagnosed hypertensive patients (25). In the more highly selected population enrolled in the ALLHAT, 5-year discontinuation rates were 20–30%, and >40% of individuals required multiple drug therapy (26).

It has been previously estimated that up to one-third of cases of type 2 diabetes may be undiagnosed (27), and in many patients, type 2 diabetes is asymptomatic and detectable only on the basis of laboratory testing. Within our study, differences in type 2 diabetes incidence may also have been due to differences in the frequency of testing between study groups rather than an effect of different antihypertensive agents. This may have occurred if physicians were not checking for type 2 diabetes in cohort patients with regular frequency or if ascertainment was occurring in an unequal fashion between study groups. Because this was a retro-

spective, observational study, there was no method of ensuring that individuals received regular fasting glucose measurements through the follow-up period for the entire cohort. However, in ~40% of the cohort, fasting glucose measurements were equal across study groups.

In conclusion, in a large, population-based analysis of elderly hypertensive individuals, we found no evidence that any of the four major classes of antihypertensive agents were associated with an increase or decrease in type 2 diabetes incidence. Until this issue is clarified by ongoing randomized controlled trials and future research, we suggest that clinicians guide their choice of initial antihypertensive therapy on the basis of more established factors, such as the available evidence regarding efficacy, economic considerations, and the presence of comorbid medical conditions.

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