Antihypertensive Drug Therapies and the Risk of Ischemic Stroke

Olaf H. Klungel, PharmD, PhD; Susan R. Heckbert, MD, PhD; W. T. Longstreth, Jr, MD, MPH; Curt D. Furberg, MD, PhD; Robert C. Kaplan, MS, PhD; Nicholas L. Smith, MPH, PhD; Rozenn N. Lemaitre, MPH, PhD; Hubert G. M. Leufkens, PharmD, PhD; Anthonius de Boer, MD, PhD; Bruce M. Psaty, MD, PhD

Background: The relative effectiveness of various antihypertensive drugs with regard to the reduction of stroke incidence remains uncertain.

Objective: To assess the association between first ischemic stroke and use of antihypertensive drugs.

Methods: A population-based case-control study was performed among enrollees of the Group Health Cooperative of Puget Sound. Case patients included pharmacologically treated hypertensive patients who sustained a first ischemic stroke (fatal or nonfatal; n=380) between July 1, 1989, and December 31, 1996. Control subjects were a random sample of treated hypertensive enrollees without a history of a stroke (n=2790). Medical record review and a telephone interview of consenting survivors were used to collect information on risk factors for stroke. Computerized pharmacy records were used to assess antihypertensive drug use.

Results: Among 1237 single-drug users with no history of cardiovascular disease, the adjusted risk of ischemic stroke was higher among users of a β-blocker (risk ratio [RR], 2.03; 95% confidence interval [CI], 1.05-3.94), calcium channel blocker (RR, 2.30; 95% CI, 1.16-4.56), or angiotensin-converting enzyme inhibitor (RR, 2.79; 95% CI, 1.47-5.27) than among users of a thiazide diuretic alone. Among 673 single-drug users with a history of cardiovascular disease, the RRs were 1.22 (95% CI, 0.63-2.35), 1.18 (95% CI, 0.59-2.33), and 1.45 (95% CI, 0.70-3.02) among users of a β-blocker, calcium channel blocker, and angiotensin-converting enzyme inhibitor, respectively, compared with users of a thiazide diuretic alone.

Conclusions: In this study of pharmacologically treated hypertensive patients, antihypertensive drug regimens that did not include a thiazide diuretic were associated with an increased risk of ischemic stroke compared with regimens that did include a thiazide. These results support the use of thiazide diuretics as first-line antihypertensive agents.

Arch Intern Med. 2001;161:37-43

From the Cardiovascular Health Research Unit, Departments of Epidemiology (Drs Klungel, Heckbert, Longstreth, Kaplan, Smith, and Psaty), Medicine (Drs Longstreth, Lemaitre, and Psaty), Neurology (Dr Longstreth), and Health Services (Dr Psaty), University of Washington, Seattle; the Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences, Utrecht, the Netherlands (Drs Klungel, Leufkens, and de Boer); and the Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC (Dr Furberg).

THE PRIMARY purpose of the pharmacological treatment of hypertension is to prevent major cardiovascular complications such as stroke. The 4 most widely used antihypertensive drug classes include diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. Randomized clinical trials (RCTs) have not demonstrated major differences between these antihypertensive drug classes with regard to lowering of blood pressure,[1-4] quality of life,[3,5] or regression of left ventricular mass.[6-8] Results of recent meta-analyses of antihypertensive drug treatment compared with placebo suggest that low-dose diuretic therapy is effective in reducing the risk of stroke, coronary heart disease, congestive heart failure, and total mortality, whereas β-blockers prevent stroke and congestive heart failure but seem less effective in preventing coronary heart disease,[9] especially in the elderly.[10] The Systolic Hypertension in Europe Trial has demonstrated that compared with placebo, the calcium channel blocker nitrendipine reduces the incidence of stroke in older adults with isolated systolic hypertension.[11]

These findings from placebo-controlled trials suggest that β-blockers, diuretics, and calcium channel blockers are more effective than placebo in the primary prevention of stroke. Less consistent are the findings from individual RCTs with separate treatment arms for β-blockers and diuretics.[12-15] Although findings from the International Prospective Primary Prevention Study in Hypertension trial[14] suggested similar reductions in stroke incidence with β-blockers and diuretics, the Heart Attack Primary Prevention in Hypertension (HAPPHY)[15] and the Medical Research Council trials[12,13] observed a larger reduction of stroke incidence with

SUBJECTS AND METHODS

SETTING

The setting was the Group Health Cooperative of Puget Sound (GHC), a large staff-model health maintenance organization with more than 400 000 members in western Washington State.

SUBJECTS

Case patients included GHC enrollees, aged 30 to 79 years, who were treated pharmacologically for hypertension and who sustained an incident fatal or nonfatal ischemic stroke between July 1, 1989, and December 31, 1996. Potential ischemic stroke cases were identified from computerized GHC hospital discharge diagnoses, Washington State death files, and the billing records for GHC enrollees who received medical care or services from non-GHC providers. Diagnostic criteria for ischemic stroke were adopted from the Cardiovascular Health Study.[18] These criteria included (1) rapid onset of neurologic deficit or subarachnoid hemorrhage, (2) deficit persisting for longer than 24 hours unless computed tomography or magnetic resonance imaging show evidence of permanent damage, and (3) no underlying brain trauma, tumor, or infection to cause symptoms. Control subjects were obtained from a companion study of risk factors for myocardial infarction at GHC.[19] Controls were a randomly selected sample of these GHC enrollees who were treated pharmacologically for hypertension and were frequency matched to the myocardial infarction cases by sex, age (within decade), and calendar year.

Each subject was assigned an index date. For the cases, the index date was the date of the stroke; for controls, the index date was a randomly selected date within the calendar year for which they had been selected as controls. In most strata based on sex, 10-year age categories, and index year, the control-case ratio was larger than 3:1. We excluded cases and controls (1) who were enrollees for less than 1 year or who had fewer than 4 visits before their index dates, (2) who had had a previous stroke, (3) who had a diagnosis of congestive heart failure, (4) who did not have a diagnosis of hypertension in their medical record, and (5) whose stroke was a complication of a procedure or surgery. A history of stroke was assessed by medical record review. Subjects with a history of congestive heart failure were excluded because of concern about confounding by the indication of congestive heart failure for ACE inhibitors.

DATA COLLECTION AND DEFINITIONS

Information on demographics, health habits, cardiovascular risk factors, and comorbidities were abstracted from medical records or obtained from a telephone interview of consenting survivors. Abstraction of the information from the medical records was performed by trained research assistants who were aware of case-control status but unaware of the purpose of the study.

The GHC computerized pharmacy database was used to assess antihypertensive drug use. The pharmacy records contain information about the type, dose, and quantity of drug dispensed; the prescription fill date; and dosing instructions. When dosing instructions were missing from the pharmacy database, we used the instructions available in the medical record. The pharmacy data were searched for antihypertensive drug prescriptions immediately preceding the index date. When a subject who was assumed to be at least 80% compliant received enough pills to last until the index date, that person was classified as a potential current user on that date. This process was repeated to assess use at 30 and 60 days before the index date. A current user of antihypertensive drugs was defined as a user for at least 30 days before and on the index date. This definition excludes recent starters or switchers of antihypertensive drug therapies, whose drug course was first prescribed or changed within 30 days of the index date.

A subject was considered pharmacologically treated for hypertension when a recording of antihypertensive drug use for the indication of hypertension was present in the medical records and when the subject was classified as a current antihypertensive drug user at the index date according to data available in the computerized pharmacy database.

STATISTICAL ANALYSES

Complete data were uniformly available from the medical records for case-control status and medical conditions such as pharmacological treatment of hypertension, angina, and diabetes. In preliminary analysis of demographic and behavioral risk factor data, such as smoking, physical activity, race, marital status, and educational level, the agreement between medical record and self-reported measures (telephone interview) was good to excellent. Self-reported data, if available, were used for these variables; if not, then data from the medical record were used. Data were missing on smoking (1.1% of subjects), physical activity (8.0%), race (2.4%), educational level (27.0%), total cholesterol level (4.8%), duration of treatment for hypertension (10.5%), and pretreatment blood pressure (30.1%). We used an approximate Bayesian bootstrap method to impute missing values. This multiple imputation method is a modification of the hot-deck method and takes account of the imputation variability.[20] In sensitivity analysis, the results using multiple imputed data were similar to those in the analysis limited to subjects with complete data.

All statistical tests were 2-tailed. We used stratification and logistic regression to control for potential confounders of the association between antihypertensive drug therapy and ischemic stroke, and odds ratios to estimate the relative risk (RR). Data were analyzed using commercially available software (SAS, Version 6.12; SAS Institute, Cary, NC).

The association of ischemic stroke with antihypertensive drug therapies was assessed separately for subjects with and without clinical cardiovascular disease (CVD). We defined CVD as possible, probable, or definite diagnoses of angina, claudication, cardiac arrhythmias (including atrial or ventricular arrhythmia) or history of myocardial infarction, transient ischemic attack, coronary angioplasty, coronary bypass surgery, or carotid endarterectomy. First, we compared single-drug users of one of the major antihypertensive drug classes and users of major 2-drug combinations, with single-drug users of benzothiadiazide (thiazide) diuretics as the reference group. Second, we compared antihypertensive drug regimens that did not include a thiazide diuretic with regimens that included a thiazide diuretic, among single-drug users and users of 2 antihypertensive drugs from different drug classes.

diuretic therapy than β-blocker therapy. The Captopril Prevention Project trial[16] reported an increased risk of stroke in subjects receiving captopril compared with β-blockers or diuretics. However, the recently completed Swedish Trial in Old Patients with Hypertension-2 Study[17] demonstrated that in hypertensive patients older than 70 years, calcium antagonists and ACE inhibitors apparently did not differ from conventional therapy (β-blockers or diuretics) with regard to the reduction of the incidence of cardiovascular morbidity and mortality, including stroke. The Captopril Prevention Project and the Swedish Trial in Old Patients with Hypertension-2 trials were not designed to distinguish between β-blockers and diuretics.

To assess the association between antihypertensive drug therapy and incident ischemic stroke, we conducted a population-based case-control study among pharmacologically treated hypertensive patients.

RESULTS

During the study period, 611 treated hypertensive patients were hospitalized for or died out of the hospital of a first ischemic stroke. We also identified 3505 population-based controls who were eligible. We excluded 92 cases and 199 controls with congestive heart failure, 113 cases and 453 controls who were not sufficiently compliant with their antihypertensive drug regimens to be classified as current users, and 66 cases and 181 controls who recently started or switched any antihypertensive drug therapy. In total, 231 cases and 715 controls were excluded for 1 or more of these reasons. We included 380 ischemic stroke cases (21 fatal and 359 nonfatal) and 2790 controls who were treated pharmacologically for hypertension.

The clinical characteristics of cases and controls are summarized in **Table 1**. Compared with controls, cases were older and more likely to be men and had a higher systolic blood pressure at treatment and before treatment. A number of risk factors for ischemic stroke were more common among cases than controls.

Because of concern about confounding by indication, we compared characteristics of controls who were users of thiazide diuretics with controls who used other antihypertensive drugs separately for subjects with and without a history of CVD (**Table 2**). Among controls with no history of CVD, users of thiazide diuretics were slightly older and had a slightly longer history of treated hypertension, and fewer had diabetes than users of nonthiazides. Other risk factors for stroke were similar for users of thiazide diuretics compared with users of other antihypertensive drugs. Among control subjects with a history of CVD, users of thiazide diuretics were slightly younger, had a lower treated systolic blood pressure, and were less likely to have diabetes, angina, or a history of cardiovascular procedures than users of an antihypertensive drug regimen that did not include a thiazide diuretic.

STROKE RISK ASSOCIATED WITH INDIVIDUAL ANTIHYPERTENSIVE DRUG CLASSES VS THIAZIDE DIURETICS ALONE

Among 127 cases and 1566 controls free of CVD, the adjusted risk of ischemic stroke was 2.03- to 2.79-fold higher among users of single-drug therapy with β-blockers, calcium channel blockers, or ACE inhibitors than among users of a thiazide diuretic alone (**Table 3**). The use of β-blockers, calcium channel blockers, or ACE inhibitors in combination with a thiazide diuretic was not significantly associated with an increased risk of ischemic stroke compared with the use of a thiazide diuretic alone. The use of any 2 antihypertensive drugs not including a thiazide diuretic was associated with a 2.48-fold increase in the risk of ischemic stroke compared with the use of a thiazide diuretic alone. Among 186 cases and 912 controls with a history of CVD, the use of calcium channel blockers in combination with a thiazide diuretic or a nonthiazide 2-drug combination were each associated with an increased risk of ischemic stroke, compared with users of thiazide diuretics alone (Table 3). Use of other single antihypertensive drugs or 2-drug combinations, compared with

Table 1. Characteristics of Ischemic Stroke Cases and Controls*

	Controls		Cases	
Characteristic	No.*	Data†	No.*	Data†
Age, y	2790	65.6	380	70.3‡
Females, %	2790	33.3	380	53.7‡
Most recent blood pressure				
Systolic, mm Hg	2789	142.7	380	150.8‡
Diastolic, mm Hg	2789	83.5	380	83.5
Pretreatment blood pressure				
Systolic, mm Hg	1968	162.9	247	169.3‡
Diastolic, mm Hg	1968	99.7	247	100.1
Duration of treated hypertension, mo	2513	11.2	324	13.3‡
No. of antihypertensive drugs	2790	1.4	380	1.5‡
Cholesterol, mmol/L (mg/dL)	2653	6.03 (232.8)	364	6.28 (242.6)
Body mass index, kg/m^2	2726	28.6	365	28.6
Current smoking, %	2760	12.7	376	15.4
Sedentary, %	2582	20.2	333	28.8‡
Less than high school education, %	2095	13.4	218	16.1
Married, %	2790	75.4	380	61.8‡
White, %	2731	89.6	364	90.1
Diabetes, %	2790	11.1	380	30.5‡
Any cardiovascular disease, %	2790	37.5	380	60.3‡
History of myocardial infarction	2790	15.2	380	25.0‡
History of transient ischemic attack	2790	5.6	380	19.2‡
Atrial fibrillation	2790	5.0	380	14.5‡
Angina	2790	19.0	380	27.9‡
Cardiovascular procedure	2790	9.2	380	12.9‡

**Indicates numbers for whom data were available.*
†Data are given as means unless otherwise indicated.
‡P<.05, cases vs controls.

Table 2. Characteristics of Users of Thiazide Diuretics Compared With Users of Other Antihypertensive Drugs*

	CVD Absent		CVD Present	
	Thiazide (n = 840)	No Thiazide (n = 904)	Thiazide (n = 397)	No Thiazide (n = 649)
Most recent blood pressure				
Systolic, mm Hg	141.2	142.7	141.4	145.2†
Diastolic, mm Hg	84.2	84.7	81.3	81.2
Pretreatment blood pressure				
Systolic, mm Hg	162.2	163.0	164.8	163.4
Diastolic, mm Hg	100.4	99.6	98.8	96.8†
Duration of treated hypertension, y	11.1	9.8†	13.9	12.3†
Age, y‡	65.8	61.6†	69.2	70.2†
Total cholesterol, mmol/L (mg/dL)	5.95 (229.6)	6.05 (233.5)	6.12 (236.2)	6.24 (241.1)
Body mass index, kg/m^2	29.1	28.8	27.9	28.1
Current smoking, %	15.2	12.2	12.9	12.5
Diabetes,%	8.1	12.1†	8.1	16.8†
History of myocardial infarction, %	NA	NA	37.1	40.5
History of transient ischemic attack, %	NA	NA	13.3	14.9
Angina, %	NA	NA	41.8	54.8†
Claudication, %	NA	NA	14.6	13.9
Episode of congestive heart failure, %	NA	NA	8.0	8.2
Atrial fibrillation, %	NA	NA	12.2	14.2
Cardiovascular procedure, %	NA	NA	17.8	24.1†

*Comparisons are among control subjects treated for hypertension, adjusted for age, sex, and calender year. Thiazide indicates benzothiadiazide diuretics; CVD, cardiovascular disease; and NA, not applicable. Data are given as means unless otherwise indicated.

†P<.05.

‡Adjusted for sex and calender year.

Table 3. Adjusted Association Between Ischemic Stroke and Antihypertensive Drug Therapies*

	CVD Absent			CVD Present		
Drug	No. of Cases	No. of Controls	Adjusted OR (95% CI)	No. of Cases	No. of Controls	Adjusted OR (95% CI)
Thiazide	22	438	1.00 (Reference)	25	148	1.00 (Reference)
β-Blocker						
Alone	20	263	2.03 (1.05-3.94)	27	176	1.22 (0.63-2.35)
With thiazide	11	154	1.50 (0.70-3.25)	15	86	1.20 (0.57-2.53)
Calcium antagonist						
Alone	19	190	2.30 (1.16-4.56)	26	151	1.18 (0.59-2.33)
With thiazide	7	63	1.88 (0.75-4.75)	19	58	2.48 (1.17-5.29)
ACE inhibitor						
Alone	27	258	2.79 (1.47-5.27)	22	98	1.45 (0.70-3.02)
With thiazide	5	83	1.26 (0.44-3.60)	4	33	0.67 (0.20-2.29)
Nonthiazide combination	16	117	2.48 (1.20-5.11)	48	162	2.04 (1.09-3.83)

*CVD indicates cardiovascular disease; OR, odds ratio; CI, confidence interval; and ACE, angiotensin-converting enzymes. Among subjects without CVD, the RRs were adjusted for age, sex, calender year, diabetes, total cholesterol level, pretreatment systolic blood pressure, current smoking, and current use of aspirin. Among subjects with CVD, the RRs were also adjusted for history of myocardial infarction, transient ischemic attack, angina, atrial fibrillation, cardiovascular procedure, and current use of hepatic hydroxymethylglutaryl coenzyme reductase inhibitors. Nonthiazide combination includes 2 antihypertensive drugs, neither a thiazide diuretic.

the use of thiazide diuretics alone, was not significantly associated with an increased risk of ischemic stroke.

STROKE RISK ASSOCIATED WITH NONTHIAZIDE ANTIHYPERTENSIVE DRUGS VS THIAZIDE DIURETICS

The second analysis was conducted among 348 cases and 2608 controls who used 1 or 2 antihypertensive drugs (**Table 4**). Among 142 cases and 1652 controls free of CVD, subjects who did not use a thiazide diuretic had, after adjustment for potential confounding factors, an increased risk of ischemic stroke compared with subjects who used a thiazide diuretic (RR, 1.85; 95% confidence interval [CI], 1.26-2.71). Among subjects with a history of clinical CVD who did not use a thiazide diuretic, the increased adjusted risk of ischemic stroke compared with users of thiazide diuretics was not statistically significant (RR, 1.25; 95% CI, 0.87-1.80).

Additional adjustment for educational level, marital status, duration of treated hypertension, treated diastolic blood pressure, pretreatment diastolic blood pressure, body mass index (calculated as weight in kilograms divided by the square of height in meters, physical activity, glucose and potassium levels, and use of alcohol had trivial effects on the findings.

Table 4. Adjusted Association Between Ischemic Stroke and Thiazide Diuretic Therapy for Hypertension*

	CVD Absent		CVD Present	
	No. of Cases/Controls	Adjusted OR (95% CI)	No.of Cases/Controls	Adjusted OR (95% CI)
1 Drug				
Thiazide	22/438	1.00 (Reference)	25/148	1.00 (Reference)
No thiazide	75/760	2.42 (1.43-4.07)	91/460	1.40 (0.81-2.43)
2 Drugs				
Thiazide	29/337	1.00 (Reference)	42/186	1.00 (Reference)
No thiazide	16/117	1.40 (0.70-2.78)	48/162	1.33 (0.78-2.26)
1or 2 Drugs				
Thiazide	51/775	1.00 (Reference)	67/334	1.00 (Reference)
No thiazide	91/877	1.85 (1.26-2.71)	139/622	1.25 (0.87-1.80)

**Thiazide indicates benzothiadiazide diuretics; CVD, cardiovascular disease; OR, odds ratio; and CI, confidence interval. Among subjects without CVD, the RRs were adjusted for age, sex, calender year, diabetes, total cholesterol level, pretreatment systolic blood pressure, current smoking, and current use of aspirin. Among subjects with CVD, the RRs were also adjusted for history of myocardial infarction, transient ischemic attack, angina, atrial fibrillation, cardiovascular procedure, and current use of hepatic hydroxymethylglutaryl coenzyme reductase inhibitors.*

Stratified analysis revealed no effect modification of the association between ischemic stroke and use of thiazide diuretics in subgroups based on sex, median age (70 years), presence of diabetes, smoking status, median pretreatment blood pressure (diastolic, 100 mm Hg; systolic, 170 mm Hg), median treated blood pressure (diastolic, 84 mm Hg; systolic, 152 mm Hg), median total serum cholesterol level (6.16 mmol/L [238 mg/dL]), and median serum potassium level (4.1 mmol/L). The results were virtually the same for the use of thiazide diuretics below the daily modal dose and above or at the daily modal dose (25 mg for hydrochlorothiazide, 25 mg for chlorthalidone, and 5 mg for metolazone) and for the use of thiazide diuretics alone or in combination with potassium-sparing agents.

COMMENT

In this population-based case-control study among pharmacologically treated hypertensive patients without clinically recognized CVD, the use of antihypertensive drug regimens that did not include a thiazide diuretic was associated with an 85% increased risk of ischemic stroke compared with the use of an antihypertensive drug regimen that included a thiazide diuretic. Even among users of 2 antihypertensive drugs, the use of nonthiazide antihypertensive drug regimens was associated with a higher risk of ischemic stroke (40%). This association persisted after adjustment for many potential confounding factors, and was consistent across a variety of subgroups. Among subjects with clinically manifest CVD, this association was less pronounced.

The International Prospective Primary Prevention Study in Hypertension trial, in which β-blocker therapy was compared with non–β-blocker (mostly diuretic) therapy, showed no significant difference in stroke incidence between the treatment groups (RR, 0.97; 95% CI, 0.64-1.47). However, this trial may not allow a valid comparison of stroke risk because 67% of the patients allocated to β-blocker therapy also received a diuretic. The HAPPHY trial found a nonsignificantly higher risk of stroke for β-blockers compared with diuretics (RR, 1.29; 95% CI, 0.84-1.83). Findings from the Medical Research Council trials clearly suggest a higher risk of stroke with β-blocker therapy than with diuretic therapy in middle-aged subjects (RR, 2.28; 95% CI, 1.31-3.96),[12] and a nonsignificantly higher risk in older subjects (RR, 1.23; 95% CI, 0.86-1.79).[13] Results from the Captopril Prevention Project trial showed an increased risk of stroke with captopril therapy compared with β-blocker or diuretic therapy (RR, 1.25; 95% CI, 1.01-1.55). This increased risk of stroke may have been due to a failure of randomization.[21] In a clinical trial designed to assess the effects of antihypertensive therapy on carotid atherosclerosis,[22] subjects randomized to receive the calcium channel blocker isradipine had a higher rate of stroke events than those randomized to receive hydrochlorothiazide (RR, 2.00; 95% CI, 0.50-7.93). In the Swedish Trial in Old Patients with Hypertension-2 trial, subjects allocated to receive ACE inhibitors and calcium antagonists, respectively, had a similar risk of stroke compared with subjects allocated to receive β-blocker or diuretic therapy (respective RRs, 0.90 [95% CI, 0.74-1.08] and 0.88 [95% CI, 0.73-1.06]). These findings from RCTs tend to favor thiazide diuretics over other antihypertensive drug therapies for reduction of stroke risk and are consistent with the findings from our study. Additional support for a particular benefit of thiazide diuretics comes from the recent interim analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[23] Compared with patients who received chlorthalidone, patients treated with the α-blocker doxazosin mesylate had an increased risk of stroke (RR, 1.19; 95% CI, 1.01-1.40).

One possible explanation for these findings may lie in the fact that systolic blood pressure is more strongly associated with the occurrence of stroke than diastolic blood pressure,[24] and that thiazide diuretics may be more effective in lowering systolic blood pressure than other antihypertensive drugs, whereas the effect of thiazide diuretics on diastolic blood pressure is similar to that of other major antihypertensive drug classes.[3,4,12,13,16,22,23] Systolic blood pressure during treatment was also slightly

lower among users of thiazide diuretics in this study. Adjustment for systolic blood pressure during treatment had little effect on our results. For example, among those receiving monotherapy, the risk of ischemic stroke associated with not using compared with using a thiazide diuretic decreased from 2.42 to 2.30. However, we were not able to test this hypothesis adequately, because many of the current users of thiazide diuretics were not using a thiazide diuretic at the time when their blood pressure during treatment was recorded.

A biological mechanism independent of blood pressure cannot be excluded, as suggested by a post hoc analysis of the Swedish Trial in Old Patients with Hypertension trial in which two thirds of the actively treated patients received a β-blocker and a thiazide diuretic.[25] After matching on achieved blood pressure and controlling for initial blood pressure, the subjects receiving active treatment had a 42% decreased risk of stroke compared with those receiving placebo (RR, 0.58; 95% CI, 0.35-0.98), suggesting a non–blood pressure mediated benefit of antihypertensive therapy with β-blockers or diuretics beyond that achieved by merely lowering blood pressure. Moreover, recently it was demonstrated that diuretics may have an additional therapeutic advantage by restoring nocturnal blood pressure decline in patients with sodium-sensitive hypertension.[26]

The strengths of this observational study are the use of population-based case-control subjects, the completeness of case identification, the comparable ascertainment of potential confounding factors, and the use of pharmacy records to assess antihypertensive drug use in a comparable and unbiased fashion for cases and controls. We used restriction, stratification, and multivariate adjustment to minimize the influence of confounding.

An important limitation of this observational study is that antihypertensive drug treatment was not randomly assigned. Physicians and patients selected antihypertensive drug therapies, and this may have introduced bias. Despite adjustment for potential confounding factors, residual confounding due to incomplete or inaccurate measurement of covariates or unmeasured confounders cannot be excluded.

The preferred design to compare these antihypertensive drug therapies in terms of their risk or benefit with regard to cardiovascular outcomes is the controlled RCT. However, when clinical trial results are lacking or conflicting, well-designed observational studies can complement them. Furthermore, the highly selected nature of participants of RCTs and the strict, protocol-driven conditions under which trials are conducted may limit the generalizability of findings from RCTs to general practice. The common use of a large number of alternative antihypertensive drugs makes evaluation of these therapies in an observational setting feasible. The high degree of similarity in several important clinical characteristics between users of thiazide diuretics and users of other antihypertensive drugs among subjects without CVD suggests minimal confounding by those characteristics that were measurable.

CONCLUSIONS

This study suggests a particular benefit of thiazide diuretics in reducing the risk of ischemic stroke. Although the mechanism is not clear, the findings are consistent with those of previous RCTs. Ongoing large-scale clinical trials should help clarify this issue.[27] The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure currently recommends diuretics and β-blockers.[28] In the absence of additional clinical trial evidence, the results of our study support the use of thiazide diuretics as first-line antihypertensive agents.

Accepted for publication July 10, 2000.

The research reported in this article was supported in part by grants HL40628, HL43201, and HL60739 from the National Heart, Lung, and Blood Institute, Bethesda, Md. Dr Psaty is a Merck/SER Clinical Epidemiology Fellow, sponsored by the Merck Co Foundation, Rahway, NJ, and the Society for Epidemiologic Research, Baltimore, Md. Dr Kaplan was a Howard Hughes Medical Institute Predoctoral Fellow when this work was conducted.

Corresponding author and reprints: Olaf H. Klungel, PharmD, PhD, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute of Pharmaceutical Sciences, Sorbonnelann 16, 3584 CA Utrecht, the Netherlands (e-mail: o.h.klungel@pharm.uu.nl).

REFERENCES

1. Philipp T, Anlauf M, Distler A, Holzgreve H, Michaelis J, Wellek S. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study: HANE Trial Research Group. *BMJ.* 1997;315:154-159.
2. Applegate WB, Phillips HL, Schnaper H, et al. A randomized controlled trial of the effects of three antihypertensive agents on blood pressure control and quality of life in older women. *Arch Intern Med.* 1991;151:1817-1823.
3. Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713-724.
4. Materson BJ, Reda DJ, Cushman WC, et al, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. *N Engl J Med.* 1993;328:914-921.
5. Beto JA, Bansal VK. Quality of life in the treatment of hypertension: a meta-analysis of clinical trials. *Am J Hypertens.* 1992;5:125-133.
6. Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients: a metaanalysis of 109 treatment studies. *Am J Hypertens.* 1992;5:95-110.
7. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. *Circulation.* 1997;95:2007-2014.
8. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation.* 1995;91:698-706.
9. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA.* 1997;277:739-745.
10. Messerli FH, Grossman E, Goldbourt U. Are β-blockers efficacious as first-line therapy for hypertension in the elderly? a systematic review. *JAMA.* 1998;279:1903-1907.
11. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet.* 1997;350:757-764.
12. MRC Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ.* 1985;291:97-104.
13. MRC Working Party. MRC trial of treatment of hypertension in older adults: principal results. *BMJ.* 1992;304:405-412.
14. The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a ran-

domized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens.* 1985;3:379-392.
15. Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens.* 1987;5:561-572.
16. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet.* 1999;353:611-616.
17. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly hypertensive patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet.* 1999;354:1751-1756.
18. Price TR, Psaty BM, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. *Ann Epidemiol.* 1993;3:504-507.
19. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA.* 1995;274:620-625.
20. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991;10:585-598.
21. Cutler J. Which drug for treatment of hypertension? *Lancet.* 1999;353:604-605.
22. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. *JAMA.* 1996;276:785-791.
23. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2000;283:1967-1975.
24. Stamler J, Stamler S, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med.* 1993;153:598-615.
25. Ekbom T, Dahlof B, Hansson L, et al. The stroke preventive effect in elderly hypertensives cannot fully be explained by the reduction in office blood pressure: insights from the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Blood Press.* 1992;1:168-172.
26. Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation.* 1999;100:1635-1638.
27. Davis BR, Cutler JA, Gordon DJ, et al, for the ALLHAT Research Group. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens.* 1996;9:342-360.
28. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1997;157:2413-2446.