Antihypertensive Medications and the Risk of Incident Type 2 Diabetes

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OBJECTIVE — The purpose of this study was to examine the association between the use of different classes of antihypertensive medications and the risk of incident type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a prospective study of three cohorts: the Nurses' Health Study (NHS) I and II and the Health Professionals Follow-up Study (HPFS). Antihypertensive medication use was ascertained by biennial questionnaires. After excluding participants who reported a history of diabetes at baseline, 41,193 older women (NHS I), 14,151 younger women (NHS II), and 19,472 men (HPFS), all with hypertension, were followed for 8, 10, and 16 years, respectively.

RESULTS — We documented 3,589 incident cases of diabetes. After adjustment for age, BMI, physical activity, the use of other antihypertensive medications, and other risk factors, the multivariate relative risk (RR) of incident diabetes in participants taking a thiazide diuretic compared with those not taking a thiazide was 1.20 (95% CI 1.08–1.33) in older women, 1.45 (1.17–1.79) in younger women, and 1.36 (1.17–1.58) in men. The multivariate RR in participants taking a β-blocker compared with those not taking a β-blocker was 1.32 (1.20–1.46) in older women and 1.20 (1.05–1.38) in men. ACE inhibitors and calcium channel blockers were not associated with risk.

CONCLUSIONS — Thiazide diuretic and β-blocker use were independently associated with a higher risk of incident diabetes. Increased surveillance for diabetes in patients treated with these medications may be warranted.

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The relation between the use of different classes of antihypertensive medications and the risk of incident type 2 diabetes is unclear (1). Although thiazide diuretic or β-blocker use may increase the incidence of diabetes, prior studies have reported conflicting results (1).

Many observational studies examining the relation between antihypertensive medications and diabetes risk have been limited by small sample size (2–5), inadequate adjustment for potential confounding (6–8), or referent groups comprised of individuals without hypertension (9). Data from post hoc analyses of randomized trials are also limited. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported that participants taking chlorthalidone were 1.4 times more likely to develop incident type 2 diabetes compared with those taking lisinopril (10). However, ACE inhibitors may lower the risk of diabetes (11). Thus, the ALLHAT data could represent a protective effect of lisinopril rather than an adverse effect of chlorthalidone. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) reported that participants treated with amlodipine were less likely to develop incident diabetes than participants treated with atenolol, but by the end of the trial most patients in the amlodipine arm were taking perindopril and most patients in the atenolol arm were taking bendroflumethiazide (12). Thus, the independent effects of thiazide diuretic, β-blocker, and ACE inhibitor use on the incidence of diabetes could not be assessed.

To determine whether thiazide diuretics, β-blockers, calcium channel blockers, and ACE inhibitors were independently associated with incident type 2 diabetes, we conducted a prospective study of three large cohorts: the Nurses' Health Study (NHS) I and II and the Health Professionals Follow-up Study (HPFS).

RESEARCH DESIGN AND METHODS

NHS I

In 1976, 121,700 female nurses between the ages of 30 and 55 years completed an initial questionnaire that provided detailed information on medical history, medications, and lifestyle. This cohort, like the cohorts for NHS II and HPFS, is followed by biennial mailed questionnaires that include inquiries about newly diagnosed diseases, including diabetes and hypertension. In the NHS I, thiazide use was determined in 1980, in 1982, and then every 6 years until 1994, when biennial updates queried the use of thiazide diuretics, β-blockers, calcium channel blockers, and "other" antihypertensive medications. ACE inhibitor use was first determined in 1996. In this study, NHS I participants were followed from 1994 to 2002.

NHS II

In 1989, 116,671 female nurses between the age of 25 and 42 years enrolled in NHS II by completing an initial questionnaire. Biennial questionnaires ascertained

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Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARIC, Atherosclerosis Risk in Communities; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; FFQ, food frequency questionnaire; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

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

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the use of thiazide diuretics and the use of "other" antihypertensive medications. The use of ACE inhibitors, calcium channel blockers, and β-blockers was first determined in 2001. In this study, NHS II participants were followed from 1991 (because before that date we lacked information on diet) to 2001.

HPFS

In 1986, 51,529 male health professionals between the ages of 40 and 75 years enrolled in HPFS by completing an initial questionnaire. Biennial questionnaires ascertained the use of thiazide diuretics, β-blockers, calcium channel blockers, and "other" antihypertensive medications. ACE inhibitor use was first determined in 2004. In this study, HPFS participants were followed from 1986 to 2002.

Ascertainment of incident diabetes

Participants who reported a diagnosis of diabetes on a biennial questionnaire were sent a supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy. Before 1996, a reported case of diabetes was considered confirmed if at least one of the following was reported: *1*) at least one typical symptom and a fasting plasma glucose of at least 140 mg/dl or a random plasma glucose of at least 200 mg/dl; *2*) at least two elevated plasma glucose levels (fasting ≥140 mg/dl, random ≥200 mg/dl, and/or a concentration ≥200 mg/dl after ≥2 h on glucose tolerance testing) on different occasions without symptoms; or *3*) treatment with a hypoglycemic medication (insulin or oral agents). Subjects with confirmed diabetes who began taking insulin within 1 year of diagnosis and who reported a history of ketoacidosis or ketonuria on at least two occasions were considered to have type 1 diabetes. The fasting glucose level for diagnosis was changed to 126 mg/dl in June 1996, and this lower threshold was used to define cases after 1996. The criteria for the classification of diabetes in the NHS have been published in detail previously (13). In a sample of NHS I and HPFS participants, 98 and 97% of the self-reported diabetes cases documented by the supplementary questionnaire, respectively, were confirmed by medical record review (13,14).

Ascertainment of hypertension

The baseline and biennial questionnaires were used to determine a history of hypertension. In a subset of NHS I participants who reported hypertension, medical record review confirmed documented systolic and diastolic blood pressures higher than 140 and 90 mmHg, respectively, in 100% (15). Self-reported hypertension has also been validated in the HPFS (16). In both cohorts, self-reported hypertension predicted subsequent cardiovascular events (15,16).

Ascertainment of other covariates

The semiquantitative food frequency questionnaire (FFQ) (first mailed to the HPFS in 1986, to the NHS I in 1980, and to the NHS II in 1991) asked about the average intake of >130 foods and beverages during the previous year. Respondents also provided information on the use of supplemental vitamins and minerals. Subsequently, a version of this FFQ has been mailed to study participants every 4 years. The reproducibility and validity of the FFQs in the HPFS and NHS I have been documented (17,18).

Information on age, weight, and height was obtained on the initial questionnaire. Self-reported weight was updated every 2 years. BMI was calculated as weight in kilograms divided by the square of height in meters. Self-reported weight has been validated in the HPFS and NHS I by direct weight measurement (19). Self-reported physical activity was updated every 4 years and was validated by activity diaries in the NHS II (20).

Statistical analysis

For each cohort, person-months of follow-up were counted from the date of the return of the baseline questionnaire to the diagnosis of type 2 diabetes, death, or the end of follow-up, whichever occurred first. We allocated person-months of follow-up according to antihypertensive drug exposure status at the start of each 2-year follow-up period.

Because we found that hypertension was a strong, independent predictor of type 2 diabetes in these cohorts, we restricted our study to participants who reported a history of hypertension. To address the possibility that surveillance for diabetes varied according to type of antihypertensive drug, we performed analyses restricted to patients reporting at least one symptom of diabetes at diagnosis (additional analyses including both symptomatic and asymptomatic patients also were performed).

We used Cox proportional hazards regression to simultaneously adjust for the use of each class of antihypertensive drug (yes or no), age, BMI, physical activity (quintiles of metabolic equivalents), family history of diabetes, postmenopausal hormone use, menopausal status, oral contraceptive use, smoking status (never, past, or current), alcohol consumption (seven categories), and dietary *trans* fat, polyunsaturated fat, cereal fiber, calcium, magnesium, and glycemic load (all in quintiles) (21–23). Because the use of furosemide, digoxin, and lipid-lowering medications and the presence of coronary artery disease, congestive heart failure, and atrial fibrillation might differentially affect diabetes surveillance, we also considered these factors as covariates in the NHS I and HPFS (data on these exposures were not obtained in the NHS II). The covariates included in the multivariate Cox models were updated throughout the study.

We calculated 95% CIs for all relative risks (RRs). All *P* values are two-tailed. All data were analyzed by using SAS software, version 8.2 (SAS Institute, Cary, NC).

RESULTS — After excluding participants who reported a history of diabetes at baseline, we prospectively studied 41,193 older women (NHS I), 14,151 younger women (NHS II), and 19,472 men (HPFS) with a history of hypertension. Over the course of the study, we documented a total of 3,589 cases of type 2 diabetes (2,069 in NHS I, 426 in NHS II, and 1,094 in HPFS). Of these patients, 1,829 reported at least one symptom at the time of diagnosis (966 in NHS I, 261 in NHS II, and 602 in HPFS).

At baseline, participants taking thiazide diuretics were slightly older, had a higher BMI, and were less physically active than participants not taking thiazide diuretics (Table 1). Dietary intake was similar between the two groups. Differences in other characteristics were not consistent across cohorts.

Thiazide use was independently associated with an increased risk of incident diabetes in older women, younger women, and men who reported at least one symptom at the time of diagnosis (Tables 2–4). After adjustment for age, BMI, use of each class of antihypertensive medication, physical activity, and other risk factors (Tables 2–4), the multivariate RRs of symptomatic diabetes in participants taking a thiazide diuretic compared with participants not taking a thiazide were 1.20 (95% CI 1.04–1.40) in older women, 1.51 (1.15–1.98) in younger women, and 1.31 (1.07–1.60) in men.

Table 1—*Baseline characteristics of older women (NHS I), younger women (NHS II), and men (HPFS) with a history of hypertension according to thiazide use*

	Thiazide use	
	Yes	No
Older women (NHS I)		
n	5,248	22,722
Age (years)	62.5	62.1
BMI (kg/m^2)	28.4	27.5
Physical activity (METs)	17.1	18.1
Currently smoking	542 (10.3)	2688 (11.8)
Family history of diabetes	1,324 (25.2)	5,542 (24.4)
Coronary heart disease	657 (12.5)	2,889 (12.7)
Current postmenopausal hormone use	2,124 (40.5)	8,483 (37.3)
Dietary intake		
Total energy (kcal/day)	1,746	1,726
Alcohol (g/day)	5.1	5.1
Total carbohydrates (g/day)	212	213
Saturated fat (g/day)	17	17
Polyunsaturated fat (g/day)	9.0	9.0
Trans fat (g/day)	2.3	2.3
Magnesium (mg/day)	329	328
Caffeine (mg/day)	210	215
Cereal fiber (g/day)	5.7	5.8
Glycemic index	52.7	52.8
Younger women (NHS II)		
n	740	5,158
Age (years)	39.8	37.7
BMI (kg/m^2)	30.9	29.1
Physical activity (METs)	17.9	18.9
Currently smoking	103 (13.9)	674 (13.1)
Family history of diabetes	228 (30.8)	1,638 (31.8)
Coronary heart disease	17 (2.3)	69 (1.3)
Currently using		
Oral contraceptive	21 (2.8)	313 (6.1)
Postmenopausal hormones	110 (14.9)	490 (9.5%
Dietary intake		
Total energy (kcal/day)	1,781	1,806
Alcohol (g/day)	2.6	3.2
Total carbohydrates (g/day)	219	220
Saturated fat (g/day)	23	23
Polyunsaturated fat (g/day)	12	12
Trans fat (g/day)	3.4	3.4
Magnesium (mg/day)	314	313
Caffeine (mg/day)	239	255
Cereal fiber (g/day)	5.4	5.6
Glycemic index	53.8	53.7
Men (HPFS)		
n	4,061	6,262
Age (years)	60.3	57.0
BMI (kg/m^2)	26.5	26.4
Physical activity (METs)	17.1	18.8
Currently smoking	383 (9.4)	600 (9.6)
Family history of diabetes	726 (17.9)	1,074 (17.2)
Coronary heart disease	416 (10.2)	863 (13.8)
Dietary intake		
Total energy (kcal/day)	1,927	1,964
Alcohol (g/day)	13.7	12.8
Total carbohydrates (g/day)	231	235
Saturated fat (g/day)	24	24
Polyunsaturated fat (g/day)	13	13
Trans fat (g/day)	2.8	2.8
Magnesium (mg/day)	353	356
Caffeine (mg/day)	219	216
Cereal fiber (g/day)	6.7	6.8
Glycemic index	52.9	53.1

Data are means or *n* (%). MET, metabolic equivalent.

The multivariate RRs of both symptomatic and asymptomatic cases of type 2 diabetes in participants taking a thiazide diuretic compared with participants not taking a thiazide diuretic were 1.20 (1.08–1.33) in older women, 1.45 (1.17–1.79) in younger women, and 1.36 (1.17–1.58) in men. Further adjustment for weight gain over the course of the study and waist circumference did not materially change the results.

β-Blocker use also was independently associated with an increased risk of incident diabetes in older women and men (Tables 2 and 4). After adjustment for age, BMI, use of each class of antihypertensive medication, physical activity, and other risk factors (Tables 2 and 4), the multivariate RR of symptomatic diabetes in participants taking a β-blocker compared with participants not taking a β-blocker was 1.25 (95% CI 1.08–1.43) in older women and 1.21 (1.01–1.45) in men. The multivariate RR of symptomatic and asymptomatic diabetes in participants taking a β-blocker compared with participants not taking a β-blocker was 1.32 (1.20–1.46) in older women and 1.20 (1.05–1.38) in men.

There was no relation between the use of calcium channel blockers or other antihypertensive medications and the risk of symptomatic diabetes in men (Table 4). There was no relation between the use of calcium channel blockers or ACE inhibitors and the risk of symptomatic diabetes in older women (Table 2). Calcium channel blockers were weakly associated with risk in older women (multivariate RR of 1.10 [95% CI 0.99–1.23]) but not men when asymptomatic cases of diabetes were included in the analyses. In older women, the multivariate risk of symptomatic diabetes in participants taking other antihypertensive medications was 1.19 (1.00–1.42). In younger women, the multivariate risk of symptomatic diabetes in participants taking other antihypertensive medications (a category including β-blockers) was 1.37 (1.05–1.77) (Table 3), and the multivariate risk of both symptomatic and asymptomatic diabetes in this group was 1.46 (1.19–1.80).

To address the possibility that differences in surveillance accounted for our results, we performed analyses restricted to participants who reported regular screening physical examinations in the 2 years before diagnosis. We also performed analyses excluding participants who reported no medical therapy for their

Table 2—*Antihypertensive medication use and the age-adjusted and multivariate relative risk of incident, symptomatic type 2 diabetes in hypertensive older women (NHS I), 1994–2002*

Medication	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR (95% CI)*
Thiazide diuretics				
No	723	193,271	1.0 (referent)	1.0 (referent)
Yes	243	51,389	1.30 (1.12–1.50)	1.20 (1.04–1.40)
β-Blockers				
No	668	183,053	1.0 (referent)	1.0 (referent)
Yes	298	61,608	1.34 (1.17–1.54)	1.25 (1.08–1.43)
Calcium channel blockers				
No	749	196,586	1.0 (referent)	1.0 (referent)
Yes	217	48,074	1.19 (1.02–1.39)	1.08 (0.92–1.26)
ACE inhibitors†				
No	578	149,970	1.0 (referent)	1.0 (referent)
Yes	133	38,016	0.89 (0.74–1.08)	0.91 (0.75–1.10)
Other				
No	811	212,345	1.0 (referent)	1.0 (referent)
Yes	155	32,315	1.27 (1.07–1.51)	1.19 (1.00–1.42)

*Adjusted for age (continuous), BMI (continuous), use of each class of antihypertensive medication (yes or no), physical activity (quintiles), smoking (current, past, or never), family history of diabetes, alcohol intake (seven categories), quintiles of dietary intake (glycemic load, calcium, magnesium, saturated fat, polyunsaturated fat, *trans* fat, and cereal fiber), medication use (furosemide, digoxin, and lipid-lowering medications), menopausal status, hormone replacement therapy (current, past, or never), and comorbid conditions (coronary heart disease, atrial fibrillation, and congestive heart failure). †Follow-up began in 1996.

hypertension. Finally, we analyzed the relation between monotherapy with each antihypertensive agent and risk. The RRs obtained from these restricted analyses were not materially different from those for the primary analyses.

CONCLUSIONS — We found that thiazide diuretic use was independently associated with an increased risk of type 2 diabetes in three distinct cohorts. The use of β-blockers also was independently associated with increased risk in older women and men. Although we did not ascertain the use of β-blockers in the cohort of younger women, the use of other antihypertensives, a category presumably including β-blockers, was associated with increased risk. The use of calcium channel blockers and ACE inhibitors was not associated with the development of type 2 diabetes.

A recent retrospective cohort study of 76,000 Canadians utilizing administrative data concluded that the use of thiazide diuretics and β-blockers was not associated with diabetes (24). However, the mean length of follow-up in that study was <1 year. An observational study of >3,500 hypertensive participants from the Atherosclerosis Risk in Communities (ARIC) cohort determined that individuals using β-blockers were 1.28 times more likely to develop diabetes than participants not taking β-blockers (95% CI 1.04–1.57) (25). Thiazide use was not associated with increased risk, but the ARIC study may have lacked statistical power to demonstrate such an association.

Post hoc analyses of randomized trials have also attempted to delineate the relation between thiazide diuretics, β-blockers, and the risk of diabetes. In an analysis of nearly 15,000 hypertensive patients in ALLHAT, the incidence of diabetes after 4 years in the chlorthalidone treatment arm was 11.6%, compared with 9.8 and 8.1% in the amlodipine and lisinopril arms, respectively (10). However, it is unclear whether the higher incidence of diabetes in the thiazide group represents an adverse side effect of chlorthalidone or a protective effect of lisinopril. Several other trials that appear to demonstrate an increased risk of diabetes with thiazide or β-blocker use also utilized referent groups treated with either ACE inhibitors or angiotensin receptor blockers (26–28).

If thiazide use increases the risk of diabetes, one might expect to see differences between thiazide diuretics and other drug classes in reducing cardiovascular end points. In fact, ALLHAT showed no evidence for the superiority of lisinopril or amlodipine versus chlorthalidone

Table 3—*Antihypertensive medication use and the age-adjusted and multivariate relative risk of incident, symptomatic type 2 diabetes in hypertensive younger women (NHS II), 1991–2001*

Medication	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariate R (95% CI)*
Thiazide diuretics				
No	184	68,158	1.0 (referent)	1.0 (referent)
Yes	77	13,485	1.87 (1.43–2.44)	1.51 (1.15–1.98)
Other				
No	93	44,765	1.0 (referent)	1.0 (referent)
Yes	168	36,877	1.69 (1.30–2.18)	1.37 (1.05–1.77)

*Adjusted for age (continuous), BMI (continuous), use of each class of hypertensive medication (yes or no), physical activity (quintiles), smoking (current, past, or never), family history of diabetes, alcohol intake (seven categories), quintiles of dietary intake (glycemic load, calcium, magnesium, saturated fat, polyunsaturated fat, *trans* fat, and cereal fiber), oral contraceptive use (past, current, or never), and coronary heart disease.

Table 4—*Antihypertensive medication use and the age-adjusted and multivariate relative risk of incident, symptomatic type 2 diabetes in hypertensive men (HPFS), 1986–2002*

Medication	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR (95% CI)*
Thiazide diuretics				
No	461	135,035	1.0 (referent)	1.0 (referent)
Yes	141	31,217	1.37 (1.12–1.67)	1.31 (1.07–1.60)
β-Blockers				
No	423	124,384	1.0 (referent)	1.0 (referent)
Yes	179	41,868	1.26 (1.06–1.50)	1.21 (1.01–1.45)
Calcium channel blockers				
No	491	138,955	1.0 (ref)	1.0 (ref)
Yes	111	27,297	1.13 (0.92–1.40)	1.03 (0.83–1.28)
Other				
No	487	134,744	1.0 (referent)	1.0 (referent)
Yes	115	31,508	0.97 (0.79–1.20)	0.94 (0.76–1.16)

*Adjusted for age (continuous), BMI (continuous), use of each class of antihypertensive medication (yes or no), physical activity (quintiles), smoking (current, past, or never), family history of diabetes, alcohol intake (seven categories), quintiles of dietary intake (glycemic load, calcium, magnesium, saturated fat, polyunsaturated fat, *trans* fat, and cereal fiber), medication use (furosemide, digoxin, and lipid-lowering medications), and comorbid conditions (coronary heart disease, atrial fibrillation, and congestive heart failure).

in the prevention of fatal coronary artery disease (10), even in those with impaired fasting glucose levels (29). In contrast to ALLHAT, ASCOT, a randomized trial including >19,000 hypertensive participants, was stopped early after a regimen of amlodipine and perindopril resulted in a lower incidence of nonfatal and fatal myocardial infarction than a regimen of atenolol and bendroflumethiazide (hazard ratio 0.90 [95% CI 0.79–1.02]) (12). Of interest, the amlodipine and perindopril treatment arm in ASCOT induced less diabetes than the atenolol and bendroflumethiazide arms (hazard ratio for incident diabetes 0.70 [0.63–0.78]) (12).

Despite emerging evidence that therapy with ACE inhibitors or angiotensin receptor blockers may decrease the risk of incident diabetes (1), our study did not demonstrate an association between ACE inhibitor use and risk. However, we ascertained ACE inhibitor use only in NHS I, and the frequency of use was less than that for other forms of antihypertensive treatment.

The limitations of our study deserve mention. In many patients, type 2 diabetes is asymptomatic. Therefore, differences in risk may have been due to differences in the frequency of testing associated with the use of individual antihypertensive agents. However, we performed analyses restricted to participants who reported at least one symptom at diagnosis. We also adjusted for the presence of diseases and other medications that could result in a higher frequency of laboratory testing. In addition, we performed analyses restricted to participants who reported regular screening physical examinations during the study. Finally, we performed analyses excluding untreated hypertensive participants.

Although the possibility of unknown confounding factors in any observational study cannot be eliminated, we were able to adjust for multiple known and suspected risk factors for diabetes, and we addressed the possibility of residual confounding by analyzing models with BMI as a continuous as well as a categorical variable. Another limitation is that our ascertainment of antihypertensive medication use relied on self-report. However, the resulting misclassification is likely to be random with respect to case status and therefore would bias the study results toward the null.

In summary, thiazide diuretic use was independently associated with an increased risk of incident type 2 diabetes in a large, prospective study of three distinct cohorts. β-Blocker use also was independently associated with risk. Our study suggests that individuals treated with these medications merit increased surveillance for diabetes.

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