Antihypertensive Therapy and Incidence of Type 2 Diabetes

A systematic review

RAJ PADWAL, MD, FRCP[1]
ANDREAS LAUPACIS, MD, FRCP[2,3,4]

OBJECTIVE — To systematically review the available evidence examining the effects of the major antihypertensive drug classes on the incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Cochrane Controlled Trials Register, Medline, and Embase were searched for English-language case-control, cohort, and randomized controlled trials involving the major antihypertensive classes and reporting type 2 diabetes as an end point. Reference lists of original studies and narrative reviews were also hand searched. One reviewer (R.P.) performed the electronic searches. Both reviewers independently extracted data and assessed all potentially relevant studies for inclusion and methodological quality. Abstracts were not included, and unpublished studies were not sought.

RESULTS — One case-control study, 8 cohort studies, and 14 randomized controlled trials met inclusion criteria. No study examined diabetes incidence as a primary end point. Poor methodological quality limits the conclusions that can be drawn from most nonrandomized trials. Evidence from randomized studies is also potentially limited by several sources of bias, including treatment contamination and bias inherent in post hoc analyses. Data from the highest-quality studies suggest that diabetes incidence is unchanged or increased by thiazide diuretics and β-blockers and unchanged or decreased by ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers.

CONCLUSIONS — The major antihypertensive classes may exert differential effects on diabetes incidence, although current data are far from conclusive. Ongoing placebo-controlled randomized trials involving potentially beneficial drug classes and examining diabetes incidence as a primary end point should provide more definitive evidence.

Diabetes Care 27:247–255, 2004

Type 2 diabetes accounts for ~90% of the estimated 17 million people, or 6.2% of the U. S. population, who currently suffer from diabetes (1). The prevalence of type 2 diabetes is expected to increase dramatically in the coming decades, primarily due to the increasing prevalence of obesity (2–4). Furthermore, the burden of pre-diabetes is already substantial, with impaired glucose tolerance (IGT) affecting an estimated 16 million and impaired fasting glucose (IFG) affecting ~10 million U.S. adults aged 40–74 years (1).

Patients with type 2 diabetes, metabolic syndrome X, and pre-diabetes are often treated with antihypertensive medications because of concomitant hypertension or cardiovascular disease (5,6). The frequency of antihypertensive drug usage in such patients will undoubtedly grow as current guidelines recommending aggressive control of blood pressure and cardiovascular risk are implemented (6,7).

Previous studies have shown that antihypertensive agents may exert different effects on glycemic control (8–10). In general, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers seem to have neutral or beneficial effects, whereas β-blockers and thiazide diuretics tend to worsen insulin resistance or glycemic control. However, these are broad generalizations, and studies have shown conflicting results, even between agents within the same class (8–10). Differences in study design, study duration, sample size, comparison groups, laboratory techniques, patient populations, drug dosage, and agent used likely explain the discrepancies in results.

Rather than using surrogate end points, such as blood glucose levels or insulin sensitivity, it may be more clinically relevant to examine the effect of various antihypertensive agents on outcomes such as the incidence of type 2 diabetes. If other factors are equal, agents that delay or prevent the onset of diabetes may be preferred therapy, particularly in those individuals at high risk of developing type 2 diabetes. Given the large projected increase in the use of antihypertensive agents in this population, we conducted a systematic review in order to summarize the available evidence examining the effects of the major antihypertensive drug classes on type 2 diabetes incidence.

From the [1]Division of General Internal Medicine, University of Alberta, Edmonton, Alberta, Canada; [2]The Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; the [3]Faculty of Medicine and Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; and the [4]Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada.

Address correspondence and reprint requests to Raj Padwal, Division of General Internal Medicine, University of Alberta Hospital, 2E3 Walter C. Mackenzie Health Sciences Center, Edmonton, AB, Canada T6G 2B7. E-mail: rpadwal@ualberta.ca.

Received for publication 2 July 2003 and accepted in revised form 22 September 2003.

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; CAPPP, Captopril Prevention Project; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; EWPHE, European Working Party on High Blood Pressure in the Elderly; HAPPHY, Heart Attack Primary Prevention in Hypertension; HOPE, Heart Outcomes Prevention Evaluation Trial; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; INSIGHT, Intervention as a Goal in Hypertension; NORDIL, Nordic Diltiazem; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program.

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

Table 1—*Case-control and cohort studies*

Study	Population (age)*	Definition of type 2 diabetes	Risk of type 2 diabetes (95% CI)	Follow-up (years)/(rate†)	Major limitations
Case-control study					
Gurwitz et al. (11)	4,794 case and 3,211 control subjects (New Jersey Medicaid administrative database) (≥35 years)	New users of type 2 diabetes medication	Thiazides: 1.0 (referent); AB: 1.1 (0.75–2.0); ACE inhibitors: 1.2 (0.9–1.5); BB: 0.95 (0.8–1.1); CCB: 1.1 (0.9–1.3)	Not applicable	*1*) Missed untreated cases of type 2 diabetes; 2) no control for BMI, baseline glucose, FH, or exercise
Cohort studies					
Bengtsson et al. (12)	1,462 women from Sweden (38–60 years)	Two FPG levels ≥7.0 mmol/l or physician-reported diagnosis	RR compared with women not taking antihypertensive drugs: diuretics: 3.4 (1.5–7.9); BB: 5.7 (2.6–12.5); diuretics and BB: 11.4 (5.0–26.0)	12 (79%)	*1*) No adjustment for hypertension status, concomitant meds, exercise, FH, or SES
Gress et al. (13)	3,804 hypertensive subjects from the Atherosclerosis Risk in Communities (ARIC) cohort in the U.S. (45–64 years). Hypertensive subgroup of original cohort of 13,877 patients	FPG ≥7.0 mmol/l or RPG ≥11.1 mmol/l or use of antidiabetic agent or physician-reported diagnosis	HR of diabetes compared to no therapy: thiazides: 0.91 (0.73–1.13); BB: 1.28 (1.04–1.57); CCB: 1.17 (0.83–1.66); ACE inhibitors: 0.98 (0.72–1.34)	6 (not specified; follow-up rate in larger cohort was 90%)	*1*) No major limitations
Gurwitz et al. (14)	2,737 subjects from the East Boston Senior Health Project (≥65 years) (cohort divided into two 3-year follow-up intervals)	New use of an antidiabetic agent at the end of two 3-year intervals	RR compared to no antihypertensive therapy: thiazides: 0.99 (0.59–1.6); nonthiazides: 1.8 (1.1–3.0)	Two 3-year periods (91%)	*1*) Missed cases of untreated diabetes; 2) no adjustment for baseline glucose, race, FH, SES, or concomitant meds 3) nonthiazides analyzed as one group
Morales et al. (15) (San Antonio Heart Study)	146 hypertensive Mexican-American and Caucasian subjects (25–64 years)	FPG ≥7.8 mmol/l or RPG ≥11.1 mmol/l or use of antidiabetic agent	Users of thiazides and/or BB compared with users of other agents and untreated hypertensives: OR 1.2 (0.26–5.46)	8 (80%)	*1*) No adjustment for concomitant meds, exercise, FH, or SES; 2) diuretics and BB analyzed as one group and compared to other treated and untreated hypertensives; 3) small sample size
Mykkanen et al. (16)	480 hypertensive patients from Finland (65–74 years)	FPG ≥7.8 mmol/l or PG ≥11.1 mmol/l 2-h post-OGTT or physician reported	Diuretics plus BB versus untreated hypertensive patients: OR 2.1 (1.1–4.3)	3.5 (88%)	*1*) No adjustment for concomitant meds, exercise, FH, or SES; 2) diuretics and BB combined into one category; 3) small sample size

Continued

Table 1—*Continued*

Study	Population (age)*	Definition of type 2 diabetes	Risk of type 2 diabetes (95% CI)	Follow-up (years)/(rate†)	Major limitations
Rajala et al. (17)	207 subjects with IGT from Finland	One 2-h level ≥11.1 mmol/l on OGTT or 2 FPG levels ≥6.7 mmol/l	Compared with nonhypertensives: thiazides ± other antihypertensive agents: OR 7.7 (2.1–28.2); other agents (BB, CCB, ACE inhibitors, AB): OR 2.6 (1.0–6.7)	4.6 (84%)	*1*) Separate analysis not performed for each antihypertensive class because of very small sample size; *2*) no adjustment for age, sex, exercise, concomitant meds, SES, or FH; 3) control group was nonhypertensive patients
Samuelsson et al. (18)	659 hypertensive men from Sweden (47–54 years)	Annual urine dipstick for glucosuria, confirmed by a FPG ≥7.0 mmol/l	Users of BB compared with nonusers: RR 2.1 (1.2–3.9); users of thiazides compared with nonusers: RR 0.74 (0.5–1.2)	10 (not specified)	*1*) Number of patients on multi-drug therapy and combined BB/thiazide therapy (excluded) unclear; *2*) no adjustment for age, baseline glucose, concomitant meds, SES, exercise, or FH
Skarfors et al. (19)	1,834 Swedish men (47–53 years)	FPG ≥7.8 mmol/l or PG ≥11.1 mmol/l 2-h post-OGTT	Users of thiazides, BB or hydralazine compared with nonusers: OR 1.7 (1.1–2.6)	10.2 (not specified)	*1*) Separate analysis not performed for each antihypertensive class; *2*) no adjustment for age, exercise, SES, or concomitant meds

*Patients with diabetes at baseline are not included in the sample sizes reported. †Refers to the percentage of patients with complete follow-up rounded up. AB, α-blockers; BB, β-blockers; BP, blood pressure; CCB, calcium channel blockers; FPG, fasting plasma glucose; FH, family history; OGTT, oral glucose tolerance test; RPG, random plasma glucose; SES, socioeconomic status.

RESEARCH DESIGN AND METHODS

— The Cochrane Controlled Trials Register (Cochrane Library, Third Quarter, 2003), Medline (1966 to September, week 3, 2003), and Embase (1980 to week 39, 2003) were searched for English-language articles examining the effects of antihypertensive agents on the incidence of type 2 diabetes. Reference lists of original studies and narrative reviews were also hand searched. Studies were required to report type 2 diabetes incidence or provide sufficient data to calculate this end point. The search was limited to adult patients (aged >18 years) and included the following MeSH headings: diabetes mellitus, antihypertensive agents, glucose intolerance, metabolic syndrome X, insulin resistance, and impaired fasting glucose.

Case-control studies, cohort studies, and randomized controlled trials involving the following drug classes were included: diuretics, β-blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and α-blockers. Case series and reports were not included. Studies in which <10 patients developed type 2 diabetes were excluded if they were not adequately powered to provide any meaningful comparison between groups. Studies published only in abstract form were also excluded because of the difficulty in judging study quality from an abstract alone.

One reviewer (R.P.) performed the electronic searches and reviewed the results. Articles that clearly did not meet inclusion criteria were rejected on initial review. If uncertainty existed, the full text of the article was reviewed. Two reviewers (R.P. and A.L.) independently assessed all potentially relevant studies for inclusion and performed data extraction. Disagreements were resolved by consensus. Reviewers were not blinded to the journal, author, or institution of publication.

RESULTS

— Of 250 potentially appropriate studies, 227 were excluded because diabetes was not an end point (n = 218), the number of diabetes cases was too low for adequate power (n = 6), data were not extractable (n = 2), or the analysis was flawed (n = 1). The 23 studies that met the inclusion criteria included 1 case-control study, 8 cohort studies, and 14 randomized controlled trials. Quantitative meta-analysis was not attempted due to differences in study designs,

Table 2—*Randomized controlled trials*

Study	Population (age)*	Definition of type 2 diabetes	Mean follow-up (years)/(rate†)	Incidence of type 2 diabetes RR (95% CI)	Major limitations
ALLHAT (21)	14,816 hypertensive patients from North America at high cardiovascular risk (≥55 years) (reserpine, clonidine and/or hydralazine were add-on therapy)	FPG ≥7.0 mmol/l	4 (38%)	Amlodipine (9.8) vs. chlorthalidone (11.6%): 0.80 (0.64–0.99)‡; lisinopril (8.1) vs. chlorthalidone (11.6%): rr 0.70 (0.56–0.86)‡	*1*) Post hoc analysis; 2) of those that had a baseline FPG; measurement, only 38% had a repeat measurement at 4 years
ALPINE (22)	392 hypertensive patients from Sweden (mean age 55 years)	Physician-reported or prescription of diabetes medication or two FPG levels ≥7 mmol/l. Predefined end point	1 (100%)	Candesartan ± felodipine (0.5) vs. HCTZ ± atenolol (4.1%): 0.13 (0.02–0.99)‡	*1*) Low number of type 2 diabetes case subjects (nine total) resulting in wide CIs
CAPPP (23)	10,413 hypertensive patients from Sweden and Finland (25–66 years) (diuretics were second-line therapy in the ACE inhibitor arm and CCBs were add-on therapy in both arms)	Two FPG levels ≥6.7 mmol/l (predefined end point)	6.1 (100%)	Captopril (6.5) vs. BB/thiazides (7.2%): 0.86 (0.74–0.99) from intention-to-treat analysis; 0.79 (0.67–0.94) from on-treatment analysis	*1*) Open-label design; 2) add-on therapy in the ACE inhibitor group was a diuretic, which may have contaminated results; 3) relative proportions of patients on BB and thiazide therapy not given
CHARM (24)	5,439 patients with symptomatic heart failure (≥18 years)	Not specified (predefined end point)	3.1 (100%)	Candesartan (6) vs. placebo (7%): 0.78 (0.64–0.96)	
EWPHE (25)	840 patients enrolled in trial (≥60 years) (on-treatment analysis)	Physician reported	4.7 (85%)	Triamterene plus HCTZ ± methyldopa (7.0) vs. placebo (4.7%): 1.5 (0.85–2.6)	*1*) Post hoc analysis; 2) diagnosis depended on physician reporting; 3) small sample size
HAPPHY (26)	6,569 caucasian men enrolled in the trial (40–64 years) (hydralazine and spironolactone were second-line agents)	FPG >6.8 mmol/l and two positive urine dipsticks for glucosuria	3.8 (98%)	Thiazides (2.3) vs. BB (2.6%): 0.88 (0.65–1.19)	*1*) Open-label design; 2) 4% of patients were on both thiazides and BB; 3) post hoc analysis
HOPE (27)	5,720 patients from 19 countries at high cardiovascular risk (≥55 years)	Patient self reported	4.5 (99%)	Ramipril (3.6) vs. placebo (5.4%): 0.66 (0.51–0.85)	*1*) Diabetes not a predefined end point; 2) type 2 diabetes was self-reported
INSIGHT (28)	5,019 hypertensive patients from Europe and Israel with at least one additional cardiovascular risk factor (55–80 years) (atenolol or enalapril were second-line agents)	RPG >11.0 mmol/l or use of antidiabetic medication. Prespecified end point	3 (98%)	Nifedipine (4.3) vs. HCTZ/amiloride (5.6%): 0.77 (0.62–0.96)‡	*1*) Relative percentage of patients on BBs and ACE inhibitors as second-line therapy in both study arms not stated
LIFE (29)	7,998 hypertensive patients from the U.S. and Europe with left ventricular hypertrophy (55–80 years); (thiazides were the preferred second-line agent)	2 FPG levels ≥6.7 mmol/l. Prespecified end point	4.8 (99%)	Losartan (6) vs. atenolol (8%): 0.75 (0.63–0.88)	*1*) Results may represent a beneficial effect of losartan, a deleterious effect of atenolol, or both; 2) relative frequency of thiazide use in each study arm not given
NORDIL (30)	10,154 hypertensive patients from Norway and Sweden (50–69 years) (ACE inhibitors or angiotension receptor blockers were add-on therapy in 25% of each study arm)	Exact criteria not specified (predefined end point)	4.5 (99%)	Diltiazem (4) vs. diuretics/BB (5%): 0.87 (0.73–1.04)	*1*) Open-label design (possible detection bias); 2) second-line agents were drugs from other study arms (contamination)
SCOPE (31)	4,342 hypertensive patients with mild to moderate hypertension (70–89 years) (thiazides/BB were common second-line agents)	Not specified (predefined end points)	3.7 (100%)	Candesartan (4.3) vs. placebo (5.3%): 0.81 (0.62–1.06)	*1*) 84% of patients in the placebo group and 75% of patients in the candesartan group were on additional agents

Continued

Table 2—*Continued*

Study	Population (age)*	Definition of type 2 diabetes	Mean follow-up (years)/(rate†)	Incidence of type 2 diabetes RR (95% CI)	Major limitations
SHEP (33)	4,153 subjects from the U.S. with isolated systolic hypertension (≥60 years) (reserpine was an additional second-line agent)	Self-reported or FPG ≥7.8 mmol/l or on antidiabetic medication	3 (not reported)	Chorthalidone ± atenolol (8.6) vs. placebo (7.5%): 1.2 (0.9–1.5)‡	*1)* 33% of participants in the placebo arm were on active antihypertensive therapy at the end of the study; *2)* post hoc analysis
STOP-2 (32)	5,893 hypertensive patients from Sweden (70–84 years)	Two FPG levels ≥6.7 mmol/l (predefined end points)	4 (100%)	ACE inhibitors vs. diuretics/BB: 0.96 (0.72–1.27); CCB vs. diuretics/BB: 0.97 (0.73–1.29); ACE inhibitors vs. CCB: 0.96 (0.74–1.31)§	*1)* Open-label design; *2)* second-line agents were drugs from other study arms (contamination)
Vermes et al (34)	311 patients with left ventricular dysfunction from Canada (<80 years) (local center of SOLVD trial)	FPG ≥7 mmol/l on two occasions	2.9 (94%)	Enalapril (6) vs. placebo (22%): 0.26 (0.13–0.53)‡	*1)* Post hoc analysis of a single study center; *2)* small sample size

*Patients with diabetes at baseline are not included in the sample sizes reported. †Refers to the percentage of patients with complete follow-up. ‡RRs and CIs calculated from the data presented or obtained from study authors. §Incidence rates of type 2 diabetes not provided in STOP-2. BB, β-blockers; CCB, calcium channel blockers.

patient populations, and methodological quality.

Case-control and cohort studies

These studies are summarized in Table 1 (11–19). None were originally designed for the primary purpose of determining the effect of antihypertensive therapy on type 2 diabetes incidence. In general, studies were of suboptimal quality and enrolled prevalent, not incident, hypertensive patients, making it difficult to adjust for duration of therapy and severity of comorbid illness. One study used normotensive control patients (17), and another used control patients that were not using hypertensive medications (12) but failed to adjust for the presence of hypertension in the analysis. Hypertension is an important confounder in these studies because of the tendency for high blood pressure and type 2 diabetes to cluster together (20). Information on drug dosages was not available in any study, and many studies also failed to adjust for several of the following potentially important covariates: age, sex, race, baseline glucose level, BMI, family history of diabetes, concomitant medications impairing glycemic control, physical activity, and socioeconomic status. Many studies also suffered from limited power and tried to compensate by combining various antihypertensive agents into the same comparison group, which made it impossible to distinguish the effects of a particular drug class.

The most methodologically rigorous cohort study was an analysis of data from 13,877 adults enrolled in the Atherosclerosis Risk in Communities cohort, a prospective study from four communities in the U.S. (13). This study controlled for all potentially important covariates, including the presence of hypertension. In an analysis confined to 3,804 hypertensive adults, users of β-blockers were at increased risk of type 2 diabetes compared with untreated hypertensive patients (RR 1.28; 95% CI 1.04–1.57). Users of ACE inhibitors, calcium channel blockers, and thiazide diuretics were not at increased or decreased risk for type 2 diabetes, although the study may have been underpowered to exclude clinically important differences for these drug classes.

Randomized controlled trials

Fourteen randomized controlled trials met inclusion criteria, none of which examined diabetes incidence as a primary end point (Table 2) (21–31). In eight trials, incidence of type 2 diabetes was a predefined secondary end point: the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) (22), the Captopril Prevention Project (CAPPP) (23), the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) (24) study, the Intervention as a Goal in Hypertension (INSIGHT) trial (28), the Losartan Intervention for Endpoint (LIFE) trial (29), the Nordic Diltiazem (NORDIL) trial (30), the Study on Cognition and Prognosis in the Elderly (SCOPE) (31), and the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) (32), and in the remainder this outcome was examined in post hoc analysis (21,23–25,29,30). All studies were double blind except the Heart Attack Primary Prevention in Hypertension trial (HAPPHY) (26), CAPPP (23), NORDIL (30), and STOP-2 (32), which utilized an open-label design with blinded end point assessment. The European Working Party on High Blood Pressure in the Elderly (EWPHE) (25) study reported on-treatment analysis, and the CAPPP (23) trial reported both on-treatment and intention-to-treat analysis. The remaining trials reported intention-to-treat analysis. In this study, only the results and sample sizes of patients who were free of diabetes at baseline are reported.

Placebo-controlled trials

Six randomized controlled trials were placebo-controlled studies (24,25,27, 31,33,34). Thiazide diuretic-based treatment regimens were associated with nonstatistically significant increases in the incidence of type 2 diabetes in the Systolic Hypertension in the Elderly Program (SHEP) (33) (RR 1.2; 95% CI 0.9–1.5) and EWPHE (25) (1.5; 0.85–2.6) trials. ACE inhibitor therapy lowered the incidence of self-reported diabetes in the Heart Outcomes Prevention Evaluation Trial (HOPE) (27) trial (0.66; 0.51–0.85) and laboratory-confirmed diabetes in a group of patients with left ventricular dysfunction (0.26; 0.13–0.53) (34). Treatment with angiotensin receptor blockers resulted in a statistically significant decrease in the incidence of type 2 diabetes in the CHARM (24) study (0.78; 0.64–0.96) and a nonsignificant decrease in type 2 diabetes incidence in the SCOPE

(31) study (0.81; 0.62–1.06). In the SCOPE trial, 84% of placebo-treated patients were on active therapy and approximately two-thirds were on diuretics or β-blockers.

Trials comparing active therapies

Eight trials compared the incidence of diabetes between different antihypertensive drug classes (21–23,26,28–30,32). All studies except HAPPHY (26) used second-line agents capable of affecting glycemic control, but only the NORDIL (30) study specified the frequency of use of each second-line agent in each study arm. In the CAPPP (23), NORDIL (30), and STOP-2 (32) trials, drugs from opposing study arms were used as second-line agents, raising the possibility of treatment contamination.

Three studies compared thiazide diuretic-based therapy with other antihypertensive agents (21,26,28). In the INSIGHT trial, nifedipine-based therapy significantly lowered type 2 diabetes incidence compared with amiloride/hydrochlorothiazide-based therapy (RR 0.77; 95% CI 0.62–0.96) (28). No significant difference in the incidence of type 2 diabetes was found between thiazide diuretic-based and β-blocker–based treatment regimens in the HAPPHY trial (0.88; 0.65–1.19) (26). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (21), type 2 diabetes incidence was lower in the amlodipine (0.80; 0.64–0.99) and lisinopril (0.70; 0.56–0.86) study arms than in the chlorthalidone arm of the trial. The follow-up rate of this end point was suboptimal because only 38% of patients with a baseline fasting plasma glucose measurement had a repeat measurement at 4 years.

Four trials compared thiazide/β-blocker combination therapy to other antihypertensive agents (23,30,32). In the CAPPP study, captopril-based therapy lowered the incidence of type 2 diabetes in both the intention-to-treat analysis (RR 0.86; 95% CI 0.74–0.99) and the on-treatment analysis (0.79; 0.67–0.94) (23). In the NORDIL study, diltiazem-based treatment was associated with a nonstatistically significant reduction in type 2 diabetes incidence (0.87; 0.73–1.04) compared with thiazide/β-blocker combination therapy (30). In the ALPINE study, a candesartan-based treatment regimen lowered the incidence of type 2 diabetes compared with a hydrochlorothiazide-based treatment regimen (0.13; 0.02–0.99) (22). Approximately 71% of patients received felodipine in the candesartan arm, and 84% of patients received atenolol in the hydrochlorothiazide arm. The wide CIs reflect the fact that only nine cases of type 2 diabetes occurred in this study. In the STOP-2 trial, neither ACE inhibitor nor calcium channel blocker–based therapy significantly reduced the incidence of type 2 diabetes compared with thiazide/β-blocker combination therapy (0.96; 0.72–1.27 for ACE inhibitors and 0.97; 0.73–1.29 for calcium antagonists) (32).

The LIFE trial demonstrated a reduction in type 2 diabetes incidence with losartan-based therapy compared with atenolol-based therapy in patients with left ventricular hypertrophy (RR 0.75; 95% CI 0.63–0.88) (29).

CONCLUSIONS — In summary, poor methodological quality limits the conclusions that can be drawn from most nonrandomized studies examining the relationship between antihypertensive agents and the incidence of type 2 diabetes. Data from the highest quality cohort study and randomized trials suggest that type 2 diabetes incidence is unchanged or increased by thiazide diuretics and β-blockers. The incidence of type 2 diabetes appears unchanged or decreased by ACE inhibitors, calcium channel blockers, or angiotensin receptor blockers. We were unable to find any previous systematic reviews on this topic, but our results are consistent with earlier narrative reviews (8–10,35).

It is important to note that no antihypertensive drug class has been evaluated in a placebo-controlled trial with diabetes incidence as a blinded, predefined end point. This is an important next step to address the limitations of current studies. It is also difficult to draw firm conclusions from the results of studies comparing two or more antihypertensive agents because the observed effects may represent a detrimental effect of one agent versus a beneficial effect of the other. For example, the results of LIFE and INSIGHT may reflect adverse effects of β-blockers or thiazide diuretics on metabolic control instead of any beneficial effect of angiotensin receptor blockers or calcium channel blocker therapy.

Many randomized controlled trials used second-line agents that could influence glycemic control. This would not be expected to bias results if the relative number of patients in each study arm on second-line therapy was equal, but such information was usually not reported. Randomized controlled trials that performed post hoc analyses may have several potential sources of bias. First, only positive results from post hoc analyses are likely to be reported, which may predispose to publication bias. Second, studies may not be adequately powered to detect differences between study arms for a post hoc end point. Third, because the end point is not preplanned, detection bias may occur if type 2 diabetes incidence is ascertained with different intensities in each study arm. This may also occur in open-label studies, where diabetes may be more avidly sought in thiazide or β-blocker arms because of previous evidence linking these drug classes to deteriorations in glycemic control.

One additional limitation to this review is the fact that our search was limited to English-language articles. We may have missed important articles published solely in other languages.

Nearly all randomized controlled trials reported intention-to-treat rather than on-treatment analyses when calculating diabetes risk. On-treatment analysis may be the more accurate method if large differences in treatment adherence between study arms were observed. In the ALLHAT trial, the rates of treatment adherence at the end of 5 years were 81% in the amlodipine arm, 80% in the chlorthalidone arm, and 73% in the lisinopril arm (21). In the HOPE trial, 90% of patients randomized to ramipril remained on the study drug and 27% of placebo-treated patients were taking open-label ACE inhibitors (27). The CAPPP trial reported both intention-to-treat and on-treatment analyses and found a greater difference between drug classes with the second analytic approach (23). However, as mentioned above, treatment contamination limits the conclusions that can be drawn from this trial. Ideally, trials should report both types of analyses, particularly when large discrepancies in treatment adherence between study arms are observed.

The major antihypertensive drug classes may affect glycemic control through a number of potential mechanisms. Thiazide diuretics may worsen glycemic control in a dose-dependent

fashion by impairing insulin secretion and decreasing peripheral insulin sensitivity (36–39). Development of hypokalemia appears to be an important precipitating factor, and prevention of hypokalemia using potassium supplementation attenuates thiazide-induced glucose intolerance (40–42). β-Blockade has been shown to inhibit both pancreatic insulin secretion (via β_2-receptors) and peripheral glucose utilization (43–46). Weight gain, diminished peripheral blood flow, and unopposed stimulation of α_2-receptor–mediated glycogenolysis have been proposed as additional potential diabetogenic mechanisms (43,47,48). β-Blockers with intrinsic sympathomimetic effects and β_1-selective blockers with β_2-agonist properties appear to have minimal detrimental (and possibly beneficial) effects on glycemic control (9,47).

ACE inhibitors may improve glycemic control preventing hypokalemia, promoting adipocyte differentiation, and improving insulin sensitivity by enhancing blood flow to skeletal muscle and other tissues (37,49–53). Inhibition of adrenergic activity, which impairs insulin secretion (via α_2-receptors) and glucose uptake, is another potential mechanism (51,54,55). Less data are available for angiotensin receptor blockers, which may act via similar mechanisms. Vasodilation and improved peripheral blood flow may explain the improvement in insulin sensitivity seen with calcium channel blockade (56).

Despite the potentially detrimental effects of β-blocker and thiazide therapy on glycemic control, it is important to recognize that both drug classes have been shown to reduce mortality and cardiovascular morbidity in hypertensive patients (57,58). β-Blockers are also of established benefit in reducing mortality postmyocardial infarction and in patients with heart failure (59,60). Therapy with β-blockers or thiazide diuretics should not be withheld in appropriate populations based on the results of this review and the potential for deterioration in glycemic control. Any potentially detrimental metabolic effects of these medications may be offset by improvements in other cardiovascular end points and overall mortality, and rational evidence-based prescription of these agents is recommended (61–63).

Ongoing randomized controlled trials should help to clarify the role of antihypertensive agents in diabetes prevention. In the Diabetes Reduction Approaches with Medication (DREAM) study, 5,269 patients with IGT will be randomized to ramipril or rosiglitazone versus placebo in a 2 × 2 factorial design (64). New-onset diabetes is the primary end point. The Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point 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 (65). Patients unable to tolerate an ACE inhibitor will be enrolled in a parallel study of telmisartan versus placebo called Telmisartan Randomized Assessment Study in ACE Inhibitor Intolerant Patients with Cardiovascular Disease (TRANSCEND) (65). Incidence of type 2 diabetes is a secondary end point in both of these studies. In the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, 7,500 patients with IGT 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 (66).

A number of additional unresolved issues remain. Are antihypertensive agents simply unmasking or masking latent diabetes by raising or lowering glucose levels in pre-diabetic patients, or does therapy result in a permanent detrimental or beneficial effect? If true, are the observed effects specific to certain agents or generalizable to the entire drug class? Because the majority of hypertensive patients require multiple drugs, it will also be important to determine whether the beneficial effects of one drug class offset the detrimental effects of another.

In summary, the major antihypertensive classes may exert differential effects on diabetes incidence, although current evidence is of suboptimal quality. Therefore, definitive conclusions cannot be made at this time and should await the results of ongoing randomized trials.

References

1. Centers for Disease Control and Prevention: *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2000*. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2002
2. Flegal KM, Carroll MD, Ogden CL, Johnson CL: Prevalence and trends in obesity among U. S. adults, 1999–2000. *JAMA* 288:1723–1727, 2002
3. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: The continuing increase of diabetes in the U.S. (Letter). *Diabetes Care* 24:412, 2001
4. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ: Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 24:1936–1940, 2001
5. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology and management. *JAMA* 287:2570–2581, 2002
6. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The sixth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 157:2413–2446, 1997
7. American Diabetes Association: Treatment of hypertension in adults with diabetes. *Diabetes Care* 26:S80–S82, 2003
8. Lithell HOL: Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care* 14:203–209, 1991
9. Houston MC: The effects of antihypertensive drugs on glucose intolerance in hypertensive non-diabetics and diabetics. *Am Heart J* 115:640–656, 1988
10. Perez-Stable K, Caralis PV: Thiazide-induced disturbances in carbohydrate, lipid, and potassium metabolism. *Am Heart J* 106:245–251, 1983
11. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J: Antihypertensive drug therapy and the initiation of treatment for diabetes mellitus. *Ann Intern Med* 118:273–278, 1992
12. Bengtsson C, Blohme G, Lapidus L, Lindquist O, Lundgren H, Nystrom E, Peterson K, Sigurdsson JA: Do antihypertensive drugs precipitate diabetes? *BMJ* 289:1495–1497, 1984
13. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 342:905–912, 2000
14. Gurwitz JH, Field TS, Glynn RJ, Manson JE, Avorn J, Taylor JO, Hennekens CH: Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. *J Am Geriatr Soc* 42:1235–

1240, 1994
15. Morales PA, Mitchell BD, Valdez RA, Hazuda HP, Stern MP, Haffner SM: Incidence of NIDDM and impaired glucose tolerance in hypertensive subjects. *Diabetes* 42:154–161, 1993
16. Mykkanen L, Kuusisto J, Pyorala K, Laakso M, Haffner SM: Increased risk of non-insulin-dependent diabetes mellitus in elderly hypertensive subjects. *J Hypertens* 12:1425–1432, 1994
17. Rajala U, Qiao Q, Laakso M, Keinanen-Kiukaanniemi S: Antihypertensive drugs as predictors of type 2 diabetes among subjects with impaired glucose tolerance. *Diabetes Res Clin Pract* 50:231–239, 2000
18. Samuelsson O, Hedner T, Berglund G, Persson B, Andersson OK, Wilhelmsen L: Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Goteborg, Sweden. *J Hum Hypertens* 8:257–263, 1994
19. Skarfors ET, Selinus KI, Lithell HO: Risk factors for developing non-insulin dependent diabetes: a 10 year follow-up of men in Uppsala. *BMJ* 303:755–760, 1991
20. Jarrett RJ, Fitzgerald AP: Non-insulin-dependent diabetes mellitus, glucose intolerance, blood pressure, hypertension, and anti-hypertensive drugs. *Diabet Med* 11:646–649, 1994
21. The ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. *JAMA* 288:2981–2997, 2002
22. Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svenson A, Samuelsson O: Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens* 21:1563–1574, 2003
23. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. *Lancet* 353:611–616, 1999
24. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, Yusuf S: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 362:759–766, 2003
25. Fletcher A, Amery A, Birkenhager W, Bulpitt C, Clement D, de Leeuw P, Deruyterre ML, de Schaepdryver A, Dollery C, Fagard R, Forette F, Forte J, Henry JF, Koistinen A, Leonetti G, Lund-Johansen P, Nissinen A, O'Brien E, O'Malley K, Pelemans W, Petrie J, Staessen J, Terzoli L, Thijs L, Tuomilehto J, Webster J, Williams B: Risks and benefits in the trial of the European Working Party on High Blood Pressure in the Elderly. *J Hypertens* 9:225–230, 1991
26. Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, Hornkvist P, Pennert K, Tuomilehto J, Wedel H: Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 5:560–572, 1987
27. Yusuf S, Gerstein H, Hoogwerf B, Pogue J, Bosch J, Wolffenbuttel BHR, Zinman B: Ramipril and the development of diabetes. *JAMA* 286:1882–1885, 2001
28. Mancia G, Broun M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G, Ruilope LM: Outcomes with nifedipine GITS or co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 41:431–436, 2003
29. Dahlof B, Devereux RB, Kjeidsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 359:995–1003, 2002
30. Hansson L, Hedner T, Jund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlof B, Karlberg BE: Randomized trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 356:359–365, 2000
31. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A: The Study on Cognition and Prognosis in the Elderly (SCOPE): principle results of a randomized double-blind intervention trial. *J Hypertens* 21:875–886, 2003
32. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, Wester PO, Hedner T, de Faire U: Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 354:1751–1756, 1999
33. Savage PH, Pressel SL, Curb D, Schron EB, Applegate WB, Black HR, Cohen J, Davis BR, Frost P, Smith W, Gonzalez N, Guthrie GP, Oberman A, Rutan G, Probstfield JL, Stamler J: Influence of long-term, low-dose, diuretic-based antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension. *Arch Intern Med* 158:741–751, 1998
34. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC: Enalapril reduces the incidence of diabetes in patients with chronic heart failure. *Circulation* 107:1291–1296, 2003
35. Gambardella S, Frontoni S, Pellegrinotti M, Testa G, Spallone V, Menzinger G: Carbohydrate metabolism in hypertension: influence of treatment. *J Cardiovasc Pharmacol* 22 (Suppl. 6):S87–S97, 1993
36. Fajans SS, Floyd JC, Knopf RF, Bull J, Guntsche EM, Conn JW: Benzothiadiazine suppression of insulin release from normal and abnormal islet cell tissue in man. *J Clin Invest* 45:481–493, 1966
37. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 321:868–873, 1989
38. Harper R, Ennis CN, Heaney AP Sheridan B, Gormley M, Atkinson AB, Johnston GD, Bell PM: A comparison of the effects of low and conventional dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. *Diabetologia* 38:853–859, 1995
39. Harper R, Ennis CN, Sheridan B, Atkinson AB, Johnston GD, Bell PM: Effects of low dose versus conventional dose thiazide diuretic on insulin action in essential hypertension. *BMJ* 309:226–230, 1994
40. Rowe JW, Tobin JD, Rosa RM, Andres R: Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism* 29:498–502, 1980
41. Gorden P, Sherman BM, Simopoulos AP: Glucose intolerance with hypokalemia: an increased proportion of circulating preinsulin-like component. *J Endocrinol Metab* 34:235–240, 1972
42. Helderman JH, Elahi D, Andersen DK, Raizes GS, Tobin JD, Shocken D, Andres R: Prevention of glucose intolerance of thiazide diuretics by maintenance of body potassium. *Diabetes* 32:106–111, 1983
43. Pollare T, Lithell H, Selinus I, Berne C: Sensitivity to insulin during treatment with atenolol and metoprolol: a randomized, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 298:1152–1157, 1989
44. Cerasi E, Luft R, Efendic S: Effect of adrenergic blocking agents on insulin response to glucose infusion in man. *Acta Endocrinol* 69:335–346, 1972

45. Lithell H, Pollare T, Vessby B: Metabolic effects of pindolol and propranolol in a double-blind cross-over study in hypertensive patients. *Blood Press* 1:92–101, 1992
46. Kaneto A, Miki E, Kosaka K: Effect of beta and $beta_2$ adrenoreceptor stimulants infused intrapancreatically on glucagons and insulin secretion. *Endocrinology* 97: 1166–1173, 1975
47. Jacob S, Rett K, Henriksen EJ: Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of beta-blocking agents? *Am J Hypertens* 11:1258–1265, 1998
48. Wright AD, Barber SG, Kendall MJ, Poole PH: Beta-adrenoceptor-blocking drugs and blood sugar control in diabetes mellitus. *BMJ* 1:159–161, 1979
49. Jauch KW, Hartl W, Guenther B, Wicklmayr M, Rett K, Dietze G: Captopril enhances insulin responsiveness of forearm muscle tissue in non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* 17:448–459, 1987
50. Torlone E, Rambotti AM, Perriello G, Botta G, Santeusanio F, Brunetti P, Bolli GB: ACE-inhibition increases hepatic and extrahepatic sensitivity to insulin in patients with type 2 diabetes mellitus and arterial hypertension. *Diabetologia* 34: 119–125, 1991
51. Lithell H: Metabolic effects of antihypertensive drugs interacting with the sympathetic nervous system. *Eur Heart J* 13 (Suppl. A):S53–S57, 1992
52. Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM: Mature adipocytes inhibit in vitro differentiation of human preadipocytes via angiotensin-type 1 receptors. *Diabetes* 51:1699–1707, 2002
53. Sharma AM, Janke J, Gorzelniak K, Engeli S, Luft F: Angiotensin blockade prevents type 2 diabetes by formation of fat cells. *Hypertension* 40:609–611, 2002
54. Holm G: Adrenergic regulation of insulin release. *Acta Med Scand Suppl* 672:21–25, 1983
55. Diebert DC, DeFronzo RA: Epinephrine-induced insulin resistance in man. *J Clin Invest* 65:717–721, 1980
56. Pitre M, Gaudreault N, Santure M, Nadeau A, Bachelard H: Isradipine and insulin sensitivity in hypertensive rats. *Am J Physiol* 276:E1038–E1048, 1999
57. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD: Health outcomes associated with antihypertensive therapies used as first-line agents. *JAMA* 277:739–745, 1997
58. The Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 356:1955–1964, 2000
59. Heidenreich PA, Lee TT, Massie BM: Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 30:27–34, 1997
60. Freemantle N, Cleland J, Young P, Mason J, Harrison J: Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 318:1730–1737, 1999
61. Frolich E: Treating hypertension: what are we to believe? *N Engl J Med* 348:639–641, 2003
62. Appel LJ: The verdict from ALLHAT: thiazide diuretics are the preferred initial therapy for hypertension. *Lancet* 288: 3039–3042, 2002
63. Cruickshank JM: Beta-blockers and diabetes: the bad guys come good. *Cardiovasc Drugs Ther* 16:457–470, 2002
64. The Oxford Center for Diabetes, Endocrinology and Metabolism: DREAM overview [article online]. Available from http://www.dtu.ox.ac.uk/index.html?maindoc=/dream. Accessed October 2003
65. Yusuf S: From the HOPE to the ONTARGET and the TRANSCEND studies: challenges in improving prognosis. *Am J Cardiol* 89 (Suppl.):18A–26A, 2002
66. Navigator press release: The NAVIGATOR study [article online], 2001. Available from http://www.bioportfolio.com/news/novartis_2.htm. Accessed October 2003