Review Paper

Prevention of Type 2 Diabetes Mellitus to Reduce Cardiovascular Morbidity and Mortality: A Review of the Evidence

Thomas D. Giles, MD

Cardiovascular disease accounts for the majority of deaths in patients with type 2 diabetes mellitus. Lifestyle interventions aimed at weight loss and increased physical activity and therapy with antidiabetic drugs have proven effective in reducing the risk of new-onset diabetes in high-risk individuals. Substantial evidence also suggests that drugs that inhibit the renin-angiotensin system, namely angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, also prolong the time to onset of clinical diabetes. An open question is whether delay of new-onset diabetes with antidiabetic or antihypertensive agents reduces cardiovascular morbidity and mortality. A large ongoing study is investigating whether therapy with an oral antidiabetic drug or an angiotensin II receptor blocker reduces the incidence of new-onset diabetes and cardiovascular events in high-risk patients. J Clin Hypertens (Greenwich). 2009;11:512–519. ©2009 Wiley Periodicals, Inc.

Although type 2 diabetes mellitus is associated with a number of microvascular complications, including renal and retinal disease and neuropathy, the leading cause of death in people with diabetes is macrovascular or cardiovascular disease (CVD).[1] A number of randomized controlled clinical trials have demonstrated that reducing CVD risk factors in persons at high risk for type 2 diabetes reduces the risk of new-onset diabetes. Whether such intervention also reduces the risk of CVD is still to be determined.

CONCEPT OF PREDIABETES
According to current criteria for the diagnosis of diabetes, a fasting plasma glucose (FPG) level ≥126 mg/dL or 2-hour post-challenge glucose level ≥200 mg/dL constitutes diabetes, with FPG <100 mg/dL and post-challenge glucose level <140 mg/dL considered "normal." Impaired fasting glucose (IFG; FPG, 100–125 mg/dL) and impaired glucose tolerance (IGT; post-challenge glucose, 140–199 mg/dL), hyperglycemic states that do not meet the criteria for diabetes, are termed *prediabetes*,[2] and an estimated 57 million adults and children in the United States are prediabetic.[3] Neither IFG nor IGT are benign states, as they impart an increased risk of both progression to overt diabetes and CVD.[4] In a recently released consensus statement, the American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) recommended targeting hyperglycemia and comorbid risk factors, including hypertension and dyslipidemia, in patients with prediabetes.[5] Lifestyle intervention is recommended as first-line treatment, with the addition of pharmacologic therapies, including hypoglycemic and antihypertensive agents that inhibit the renin-angiotensin system (RAS), where appropriate.

INTERVENTIONS TO PREVENT OR DELAY THE ONSET OF DIABETES AND CVD
Lifestyle interventions aimed at weight loss and increased physical activity[6,7] and therapy with

From the Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA
Address for correspondence:
Thomas D. Giles, MD, 109 Holly Drive, Metairie, LA 70005
E-mail: tgiles1@tulane.edu

antidiabetic drugs[8–10] have proven effective in reducing the risk of new-onset diabetes in high-risk individuals, while the role of lipid-lowering agents is less clear[11–14] (Table I).

Lifestyle Interventions
Two different studies have convincingly demonstrated that lifestyle interventions that promote weight loss and increased physical activity can delay the onset of new diabetes in high-risk persons. In the first, the Finnish Diabetes Prevention Study, in obese adults with IGT, individualized counseling aimed at reducing weight and increasing physical activity for 3.2 years was associated with a 58% reduction in risk of new-onset diabetes.[6] Similar results were observed in the Diabetes Prevention Program (DPP), in which obese high-risk patients were randomized to lifestyle intervention, pharmacologic therapy (metformin), or placebo.[7] Compared with placebo, both interventions reduced the incidence of new-onset diabetes.

Both the Finnish Diabetes Prevention Study and the DPP demonstrated a reduction in cardiovascular risk factors. In the Finnish study, patients in the intervention group had significantly greater reductions in weight ($P<.001$), systolic ($P=.007$) and diastolic ($P=.02$) blood pressure, serum triglycerides ($P=.001$), and FPG levels ($P<.001$) at 1 year compared with the placebo group.[6] In the DPP, the incidence of metabolic syndrome was reduced by 41% in the lifestyle group ($P<.001$) and by 17% in the metformin group ($P<.03$) compared with placebo.[15]

Antidiabetic Agents
A number of studies assessing the use of different classes of antidiabetic drugs to prevent diabetes have shown delay or prevention of diabetes.[8–10] The Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) assessed the effect of the α-glucosidase inhibitor acarbose or placebo in patients with IGT. At 3.3-year follow-up, acarbose reduced the incidence of new-onset diabetes by 25%.[8] In a secondary analysis of STOP-NIDDM, the incidence of CVD events was reduced with active treatment from 4.7% to 2.1% (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.28–0.95; $P=.03$), mainly due to a reduction in myocardial infarction (MI) (HR, 0.09; 95% CI, 0.01–0.72; $P=.02$).[16] There was also a reduction in the incidence of new-onset hypertension (blood pressure >140/90 mm Hg [HR, 0.66; 95% CI, 0.49–0.89; $P=.006$]).

Similarly, in the glycemic arm of the 3-year Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone significantly reduced the incidence of the primary composite outcome of new-onset diabetes or death.[10] When the components of the primary outcome were analyzed separately, rosiglitazone was associated with a significant reduction in the incidence of new-onset diabetes, but not in all-cause mortality or in CVD event rates.

Lipid-Lowering Agents
Lipoprotein abnormalities are common in patients at high risk for diabetes.[17] As a result, the new ACE/AACE guidelines recommend that lipid goals in prediabetic patients be the same as those in patients with diabetes: low-density lipoprotein cholesterol <100 mg/dL, non–high-density lipoprotein cholesterol <130 mg/dL, and apolipoprotein B <90 mg/dL.[5] Post hoc analyses of placebo-controlled clinical trials of lipid-lowering agents, primarily statins, have reported conflicting results. In the West of Scotland Coronary Prevention Study (WOSCOPS), pravastatin reduced the incidence of new-onset diabetes by 30%.[11] By contrast, in the Heart Protection Study,[12] the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID),[13] and the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA),[14] statin therapy did not prevent the development of diabetes.

Antihypertensive Agents
Approximately 70% of patients with type 2 diabetes also have blood pressure values >140/90 mm Hg.[18] Type 2 diabetes is 2.5 to 5 times more likely to develop in patients with elevated blood pressure than in their normotensive counterparts.[19,20] A number of studies, including the Systolic Hypertension in Europe[21] and the Hypertension Optimal Treatment[22] trials, have clearly demonstrated that reductions in blood pressure significantly reduce the risk of major CVD events in diabetic patients. Current hypertension treatment guidelines suggest that blood pressure should be controlled to ≤130/80 mm Hg in both diabetic and prediabetic patients.[5,23,24] Data from the United Kingdom Prospective Diabetes Study (UKPDS) indicate that lowering systolic blood pressure to as low as 110 mm Hg may also provide benefit.[25] In general, antihypertensive agents that inhibit the RAS—angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—are recommended as first-line agents.[5]

The discussion of diabetes in the context of antihypertensive therapy has historically focused on the increased risk of new-onset diabetes associated with the use of diuretics and β-blockers; by contrast,

Table I. Randomized Controlled Clinical Trials Assessing the Effects of Lifestyle Modification and Pharmacologic Therapy With Antidiabetic and Lipid-Lowering Drugs on Risk of NOD

STUDY	PATIENT POPULATION	INTERVENTIONS[a]	PRESPECIFIED END POINT?	RESULTS
Lifestyle intervention				
Finnish Diabetes Prevention Study[6]	522 obese patients (mean BMI, 31 kg/m²) with IGT (2-hour post-challenge glucose, 140–200 mg/dL)	Individual counseling to reduce weight and increase physical activity or placebo for 3.2 years	Yes	NOD developed in 11% of patients in the intervention group and 23% in the placebo group (RR, 0.40; 95% CI, 0.30–0.70; P<.001)
DPP[7]	3234 nondiabetic obese patients (mean BMI, 34 kg/m²) with IFG (FPG, 95–125 mg/dL) and IGT (2-hour post-challenge glucose, 140–199 mg/dL)	Lifestyle intervention (goal of ≥7% weight loss and ≥150 min physical activity/wk); metformin (850 mg 2 times/d); or placebo for 2.8 years	Yes	58% reduction in risk of NOD with lifestyle intervention vs placebo (RR, 0.42; 95% CI, 0.34–0.52; P<.001); 31% reduction in risk of NOD with metformin vs placebo (RR, 0.69; 95% CI, 0.57–0.83; P<.001)
Antidiabetic drugs				
STOP-NIDDM[8]	1368 patients with IGT (140–199 mg/dL) and IFG (FPG, 100–140 mg/dL) with no history of CVD events within the previous 6 months	Acarbose (100 mg 3 times/d) or placebo for 3.3 years	Yes	25% reduction in risk of NOD with acarbose vs placebo (RR, 0.75; 95% CI, 0.63–0.90; P=.0015)
TRIPOD[9]	266 Hispanic women with previous gestational diabetes	Troglitazone (100 mg/d) or placebo for 2.5 years (median)	Yes	65% reduction in risk of NOD with troglitazone vs placebo (RR, 0.45; 95% CI, 0.25–0.83; P<.01)
DREAM[10]	5269 patients with IFG (FPG, 110–124 mg/dL) and/or IGT (2-hour post-challenge glucose, 140–199 mg/dL) but without CVD or renal disease	Rosiglitazone (8 mg/d) or placebo for 3.0 years (median)	Yes	62% reduction in risk of NOD with rosiglitazone vs placebo (RR, 0.38; 95% CI, 0.33–0.44; P<.0001); Reversion to normoglycemia in 50.5% of rosiglitazone group vs 30.3% of placebo group (RR, 1.71; 95% CI, 1.57–1.87; P<.001)
Lipid-lowering drugs				
WOSCOPS[11]	5974 nondiabetic men aged 45–64 years with dyslipidemia, normal renal function, and no history of MI, UA, or coronary revascularization	Pravastatin (40 mg/d) or placebo for 4.9 years	No	30% reduction in risk of NOD with pravastatin vs placebo (RR, 0.70; 95% CI, 0.50–0.99; P=.042)
Heart Protection Study[12]	14,573 patients with occlusive arterial disease without MI, stroke, or hospitalization for angina within 6 months, or substantially impaired renal function	Simvastatin (40 mg/d) or placebo for 5.0 years	Yes	15% increase in risk of NOD with simvastatin vs placebo (RR, 1.15; 95% CI, 0.99–1.34; P=NS)
LIPID[13]	6997 patients with dyslipidemia and MI or hospitalization for UA within 3 to 36 months	Pravastatin (40 mg/d) or placebo for 6 years	No	11% reduction in risk of NOD with pravastatin vs placebo (RR, 0.89; 95% CI, 0.70–1.13; P=NS)
ASCOT-LLA[14]	19,342 hypertensive patients with ≥3 other CVD risk factors	Atorvastatin (10 mg/d) or placebo for 3.3 years (median)	Yes	15% increase in risk of NOD with atorvastatin vs placebo (RR, 1.15; 95% CI, 0.91–1.44; P=NS)

Abbreviations: ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LIPID, Long-Term Intervention With Pravastatin in Ischemic Disease; MI, myocardial infarction; NS, not significant; NOD, new-onset diabetes; RR, relative risk; STOP-NIDDM, Study to Prevent Non-Insulin–Dependent Diabetes Mellitus; TRIPOD, Troglitazone in Prevention of Diabetes; UA, unstable angina; WOSCOPS, West of Scotland Coronary Prevention Study. [a]Mean years of follow-up unless indicated.

alpha-1 adrenoreceptor antagonists have been shown to improve insulin sensitivity. Newer clinical trials in patients with and without hypertension have demonstrated that calcium channel blockers have neutral metabolic effects, while ACE inhibitors and ARBs improve insulin sensitivity and reduce the risk of new-onset diabetes.[26]

Proposed Mechanisms for RAS Inhibitors and New-Onset Diabetes. The underlying mechanisms by which RAS inhibition reduces the development of diabetes are not clear. ACE inhibitors and ARBs have beneficial effects on insulin sensitivity that are likely attributable to a combination of factors. One possibility is that the vasodilatory effects of RAS inhibitors result in increased blood flow, thereby increasing insulin delivery to peripheral skeletal muscles.[27,28] Likewise, ACE inhibitors and ARBs may improve glucose metabolism via increased GLUT4-mediated transportation in skeletal muscle and fat cells.[29] RAS blockade is associated with potassium retention, which may lead to enhanced pancreatic secretion of insulin[28] and may protect pancreatic islets from glucotoxicity and oxidative stress by inhibiting NAD(P)H oxidase.[30] In addition, some ARBs activate peroxisome proliferator-activated receptor-γ, which is the same target as insulin-sensitizing drugs such as glitazone.[28] Moreover, ARBs increase levels of adiponectin, an adipocyte-derived protein thought to enhance insulin sensitivity.[30]

Clinical Trial Evidence. A recent meta-analysis of the results of 13 randomized clinical trials with a total of 93,451 patients with or without hypertension demonstrated that RAS blockade with an ACE inhibitor or ARB was associated with a 26% reduction in risk of new-onset diabetes (odds ratio [OR], 0.74; 95% CI, 0.66–0.81; $P<.001$).[31] A separate network meta-analysis of the results of 22 trials involving 143,153 patients with or without hypertension found that among the various classes of antihypertensive agents, ARBs and ACE inhibitors are associated with the lowest proportion of diabetes development during clinical trial follow-up (OR, 0.57; 95% CI, 0.46–0.72; $P<.0001$ for ARBs and OR, 0.67; 95% CI, 0.56–0.80; $P<.0001$ for ACE inhibitors), compared with initial diuretic therapy.[32] While useful, these meta-analyses are based on post hoc analyses of trials for which development of diabetes was not a primary end point. However, among recently completed clinical trials of RAS inhibitors and diabetes, a number included new-onset diabetes as a prespecified primary composite or secondary outcome measure (Table II).[33–43]

ACE Inhibitors. One of the first clinical studies to show a reduction in new-onset diabetes with an ACE inhibitor was the Heart Outcomes Prevention Evaluation (HOPE) study, in which ramipril reduced the risk of new-onset diabetes by 34% compared with placebo.[33] In the original Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) report, lisinopril was associated with a significant reduction in new-onset diabetes.[34] Among individuals who were nondiabetic at baseline, the incidence of diabetes at 4 years was 11.6% in the chlorthalidone group, 9.8% in the amlodipine group, and 8.1% in the lisinopril group.[34] A post hoc analysis in ALLHAT patients with the metabolic syndrome but not diabetes at baseline found that the incidence of new-onset diabetes was 17.1% in the chlorthalidone group, 16.0% in the amlodipine group, and 12.6% in the lisinopril group ($P<.05$ for lisinopril vs chlorthalidone). By contrast, the incidence of new-onset diabetes was less in the group without the metabolic syndrome: 7.7%, 4.2%, and 4.7% for chlorthalidone, amlodipine, and lisinopril, respectively ($P<.05$ for both comparisons). Moreover, the risk of combined CVD events was similar in those with and without the metabolic syndrome and in those in whom diabetes developed and those in whom it did not.[44] A separate subgroup analysis of ALLHAT compared outcomes by race in nondiabetic patients with and without the metabolic syndrome and found that, despite their more favorable metabolic effects (including lower fasting glucose levels), the ACE inhibitor and calcium channel blocker failed to show benefit in long-term cardiovascular risk reduction in hypertensive patients with the metabolic syndrome compared with the diuretic.[45] The lack of cardiovascular benefit with these agents was especially striking in black patients with the metabolic syndrome.

In a new subgroup analysis of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), the authors conclude that randomization of nondiabetic hypertensive patients to amlodipine with or without perindopril reduced the risk of new-onset diabetes by 34% compared with atenolol with or without bendroflumethiazide.[46] The authors postulated that the differential effects of the two antihypertensive regimens may be the result of the metabolically protective effects of perindopril combined with the neutral effects of amlodipine compared with the

adverse metabolic effects of both atenolol and thiazide diuretics.

In the hypertension arm of the DREAM trial, patients at high risk for diabetes were randomized to ramipril or placebo for 3 years. There was no significant difference in incidence of the primary composite outcome measure of new-onset diabetes or death in patients treated with ramipril vs placebo.[37] Likewise, ramipril did not significantly reduce the incidence of new-onset diabetes or CVD events. Ramipril-based therapy was, however, associated with a significant increase in regression to normoglycemia compared with placebo, confirming the blood glucose–lowering effect of the ACE inhibitor. Proposed explanations for the failure of the ACE inhibitor to delay the onset of diabetes in DREAM include the short duration of the study (median 3 years vs median ~4.5 years in previous ARB and ACE inhibitor trials) and the relatively low-risk profile of the study participants (mean age, 55 years; mean blood pressure, 136/83 mm Hg) such that the degree of RAS activation in DREAM participants was lower than in other studies. In addition, baseline glucose levels were far from the diagnostic threshold for diabetes, making diabetes less likely to develop.[37]

The ongoing ACE Inhibitor-Based vs Diuretic-Based Antihypertensive Primary Treatment in Patients with Prediabetes (ADaPT) trial may help to clarify the impact of ACE inhibitors on new-onset diabetes.[47] ADaPT is a 4-year open-label trial to determine the effect on incidence of new-onset diabetes of antihypertensive treatment based on ramipril vs treatment based on diuretics or β-blockers. The results of the trial, which includes 2015 patients with hypertension, IFG, and hemoglobin A_{1c} values of 6% to 6.5%, are expected in 2010.[47]

ARBs. Early evidence that ARBs reduce the risk of new-onset diabetes was provided by the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study, in which losartan was associated with a 25% reduction in new-onset diabetes compared with atenolol in hypertensive patients with left ventricular hypertrophy.[38] ARB-based therapy was associated with a similar reduction in new-onset diabetes (23%) in the Valsartan Long-Term Use Evaluation (VALUE), in which high-risk hypertensive patients were randomized to valsartan- or amlodipine-based therapy.[41] After a mean follow-up of 4.2 years, the incidence of new-onset diabetes was 23% lower in the valsartan group. A post hoc analysis of VALUE revealed that patients with new-onset diabetes during the 4.2-year follow-up period experienced significantly higher cardiac morbidity than those in whom diabetes did not develop; baseline diabetes was associated with doubling of risk of cardiac morbidity (HR, 2.20; 95% CI, 1.95–2.49; $P<.0001$), and new-onset diabetes during the study was associated with significantly higher cardiac morbidity compared with diabetes not developing (HR, 1.42; 95% CI, 1.16–1.77; $P=.0008$).[48] The post hoc analysis also revealed that the incidences of all-cause mortality (HR, 0.61; 95% CI, 0.49–0.77; $P=.0001$) and cardiac mortality (HR, 0.44; 95% CI, 0.28–0.70; $P=.0004$) were actually lower in patients in whom diabetes developed compared with those who remained normoglycemic during the trial, possibly due to increased use of aspirin, β-blockers, diuretics, and statins in these patients.[48,49]

ACE Inhibitor/ARB Combination. New-onset diabetes was a predefined secondary outcome in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), in which patients with vascular disease or high-risk diabetes received telmisartan, ramipril, or a combination of the 2 drugs.[43] Despite greater blood pressure lowering with combination therapy compared with either drug alone, rates of the primary composite outcome (CVD death, MI, stroke, or hospitalization for heart failure) and of new-onset diabetes were similar in the 3 treatment groups. Higher rates of adverse events with combination therapy, in addition to the lack of additional clinical benefit, suggest that full-dose combination therapy with an ACE inhibitor and an ARB may not be advisable.

ONGOING STUDY
Many of the unanswered questions related to new-onset diabetes and CVD risk are expected to be resolved in an ongoing clinical trial: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR).[50] NAVIGATOR is a large-scale, multinational, randomized, double-blind, placebo-controlled, 2×2 factorial study to determine whether treatment with the meglitinide drug nateglinide or valsartan will reduce progression to diabetes and new cardiovascular events in patients with IGT. A total of 9306 participants aged 50 years or older with IGT and known CVD or 55 years or older with IGT and ≥1 cardiovascular risk factor were randomized in a 1:1:1:1 ratio to treatment with nateglinide or matching placebo and to valsartan or matching placebo. The primary outcome measures are onset of diabetes and both a "hard" composite of major CVD events (death,

Table II. Randomized Double-Blind Clinical Trials Assessing the Effects of Inhibition of the Renin-Angiotensin System on Risk of NOD

STUDY	PATIENT POPULATION	INTERVENTION[A]	PRESPECIFIED END POINT?	RESULTS
ACE inhibitors				
HOPE[33]	9297 patients with history of CAD, stroke, PVD, or diabetes and ≥1 other CVD risk factor	Ramipril (up to 10 mg/d) or placebo for 5.0 years	Yes	34% reduction in risk of NOD with ramipril vs placebo (RR, 0.66; 95% CI, 0.51–0.85; P<.001)
ALLHAT[34]	33,357 hypertensive patients with ≥1 other CVD risk factor and no history of hospitalization or treatment for symptomatic HF or LVEF <35%	Chlorthalidone (12.5–25 mg/d), amlodipine (2.5–10 mg/d), or lisinopril (10–40 mg/d) for 4.9 years	No	Incidence of NOD at 4 years was 11.6% in the chlorthalidone group, 9.8% in the amlodipine group (P=0.4 vs chlorthalidone), and 8.1% in the lisinopril group (P<.001 vs chlorthalidone)
PEACE[35]	8290 with stable CAD and normal or slightly reduced left ventricular function	Trandolapril (2–4 mg/d) or placebo for 4.8 years (median)	No	17% reduction in risk of NOD with trandolapril vs placebo (RR, 0.83; 95% CI, 0.72–0.96; P=.001)
ASCOT-BPLA[36]	19,257 hypertensive patients with ≥3 other CVD risk factors and no history of MI, currently treated angina, cerebrovascular event within 3 months, or uncontrolled arrhythmias	Amlodipine (5–10 mg/d) (± perindopril [4–8 mg/d]) or atenolol (50–100 mg/d) (± bendroflumethiazide [1.25–2.5 mg/d]) for 5.5 years (median)	Yes	30% reduction in risk of NOD with amlodipine (± perindopril) vs atenolol (± diuretic) (RR, 0.70; 95% CI, 0.63–0.78; P<.0001)
DREAM[37]	5269 patients with IFG and/or IGT but without CVD or renal disease	Ramipril (up to 15 mg/d) or placebo for 3.0 years (median)	Yes	NOD developed 17.1% of patients in the ramipril group and 18.5% in the placebo group (RR, 0.91; 95% CI, 0.80–1.03; P=NS); reversion to normoglycemia in 42.5% of ramipril group vs 32.2% of placebo group (RR, 1.16; 95% CI, 1.07–1.27; P=.001)
ARBs				
LIFE[38]	9193 hypertensive patients with LVH without MI or stroke within 6 months, HF or LVEF ≤40%	Losartan (50–100 mg/d) (± HCTZ [12.5–25 mg/d]) or atenolol (50–100 mg/d) (± HCTZ [12.5–25 mg/d]) for 4.8 years	Yes	25% reduction in risk of NOD with losartan vs atenolol (RR, 0.75; 95% CI, 0.63–0.86; P=.001)
SCOPE[39]	4964 hypertensive patients aged 70–89 years without MI or stroke within 6 months or decompensated HF	Candesartan (8–16 mg/d) or placebo/other drugs for 3.7 years	No	19% reduction in risk of NOD with candesartan vs placebo (RR, 0.81; 95% CI, 0.61–1.02; P=.09)
CHARM[40]	7599 patients with HF (LVEF ≤40%)	Candesartan (4–32 mg/d) or placebo for 3.1 years	Yes	22% reduction in risk of NOD with candesartan vs placebo (RR, 0.78; 95% CI, 0.64–0.96; P=.02)
VALUE[41]	15,245 hypertensive patients with high risk of CVD events without history of MI or severe renal disease	Valsartan (80–160 mg/d) (± HCTZ [12.5–25 mg/d]) or amlodipine (5–10 mg/d) (± HCTZ [12.5–25 mg/d]) for 4.2 years	Yes	23% reduction in risk of NOD with valsartan vs amlodipine (RR, 0.77; 95% CI, 0.69–0.86; P<.0001)
TRANSCEND[41]	5926 patients intolerant to ACE inhibitors with CAD, PVD, CBVD, or diabetes with end organ damage	Telmisartan (80 mg/d) or placebo for 4.7 years (median)	Yes	15% reduction in risk of NOD with telmisartan vs placebo (RR, 0.85; 95% CI, 0.71–1.02; P=.081)
ACE inhibitor/ARB combination				
ONTARGET[43]	25,620 patients with CAD, PVD, CBVD, or diabetes with end organ damage	Ramipril (10 mg/d), telmisartan (80 mg/d), or ramipril (10 mg/d) + telmisartan (80 mg/d) for 4.7 years (median)	Yes	12% increase in risk of NOD with telmisartan vs ramipril (RR, 1.12; 95% CI, 0.97–1.29; P=NS); 9% reduction in risk of NOD with ramipril + telmisartan vs ramipril (RR, 0.91; 95% CI, 0.78–1.06; P=NS)

Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin II receptor blocker; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; CAD, coronary artery disease; CBVD, cerebrovascular disease; CHARM, Candesartan in Heart failure–Assessment of Reduction in Morbidity and Mortality; CI, confidence interval; CVD, cardiovascular disease; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; HCTZ, hydrochlorothiazide; HF, heart failure; HOPE, Heart Outcomes Prevention Evaluation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LIFE, Losartan Intervention for End Point Reduction in Hypertension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NOD, new-onset diabetes; NS, not significant; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PEACE, Prevention of Events With Angiotensin-Converting Enzyme Inhibition; PVD, peripheral vascular disease; RR, relative risk; SCOPE, Study on Cognition and Prognosis in the Elderly; TRANSCEND, Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease; VALUE, Valsartan Long-term Use Evaluation. [A]Mean years of follow-up unless indicated.

MI, stroke, or hospitalization for heart failure) and an "expanded" composite including the components of the "hard" composite plus coronary revascularizations and hospitalizations for unstable angina pectoris. The results of NAVIGATOR, which are anticipated this year, may provide clarification regarding whether reducing postprandial hyperglycemia and preventing diabetes can reduce cardiovascular complications (nateglinide treatment arm) and whether the link between metabolic dysfunction and CVD is mediated by angiotensin II and might be lessened by treatment with an agent that inhibits the RAS (valsartan treatment arm).[50]

CONCLUSIONS

Reducing the incidence of diabetes may lead to a reduction in CVD-related morbidity and mortality. Both lifestyle changes and antidiabetic pharmacologic interventions delay the onset of diabetes. Similarly, antihypertensive therapy with RAS blockade delays the onset of new diabetes. However, the potential association between new-onset diabetes and CVD outcomes has been identified only in post hoc analysis and not as a predetermined endpoint. The findings from NAVIGATOR are eagerly awaited to identify this association. Meanwhile, it is advisable to treat high-risk patients—those with prediabetes—with appropriate lifestyle measures to reduce weight and increase physical activity. The use of antidiabetic agents, RAS inhibitors, and statins to reduce cardiovascular risk factors, including hyperglycemia, hypertension, and dyslipidemia, should also be considered.

REFERENCES

1 Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114–126.

2 American Diabetes Association. Standards of medical care in diabetes: 2008. *Diabetes Care*. 2008;31(suppl 1):S12–S54.

3 American Diabetes Association. *Total Prevalence of Diabetes & Pre-Diabetes*. http://www.diabetes.org/diabetes-statistics/prevalence.jsp. Accessed August 7, 2008.

4 Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007;30:753–759.

5 American College of Endocrinology Task Force on Pre-Diabetes. *American College of Endocrinology Consensus Statement on the Diagnosis and Management of Pre-Diabetes in the Continuum of Hyperglycemia: When do the Risks of Diabetes Begin?* http://www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf. Accessed July 24, 2008.

6 Tuomilehto J, Lindström J, Eriksson JG, et al; for the Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired gluose tolerance. *N Engl J Med*. 2001;344:1343–1350.

7 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.

8 Chiasson J-L, Josse RG, Gomis R, et al; for the STOP-NIDDM Trial Research Group Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072–2077.

9 Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.

10 DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006; 368: 1096–1105.

11 Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation*. 2001;103:357–362.

12 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.

13 Keech A, Colquhoun D, Best J, et al; for the LIPID Study Group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care*. 2003;26:2713–2721.

14 Sever PS, Dahlöf B, Poulter NR, et al; for the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158.

15 Orchard TJ, Temprosa M, Goldberg R, et al; for the Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142: 611–619.

16 Chiasson J-L, Josse RG, Gomis R, et al; for the STOP-NIDDM Trial Research Group Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA*. 2003;290:486–494.

17 Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–1524.

18 Geiss L. Elevated blood pressure among U.S. adults with diabetes, 1988–1994. *Am J Prev Med*. 2002; 22: 42–48.

19 Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes

mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*. 2000;342:905–912.

20 Bays HE, Bazata DD, Clark NG, et al. Prevalence of self-reported diagnosis of diabetes mellitus and associated risk factors in a national survey in the US population: SHIELD (Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes). *BMC Public Health*. 2007;7:277.

21 Staessen JA, Fagard R, Thijs L, et al; for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350:757–764.

22 Hansson L, Zanchetti A, Carruthers SG, et al; for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755–1762.

23 Chobanian AV, Bakris GL, Black HR, et al; and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42:1206–1252.

24 The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. *J Hypertens*. 2007;25:1105–1187.

25 Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): a prospective observational study. *BMJ*. 2000;321:412–419.

26 Macfarlane DF, Paterson KR, Fisher M. Cardiovascular drugs as antidiabetic agents: evidence for the prevention of type 2 diabetes. *Diabetes Obes Metab*. 2008;10:533–544.

27 Jandeleit-Dahm KAM, Tikellis C, Reid CM, et al. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertens*. 2005;23:463–473.

28 Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. *J Hypertens*. 2006;24:3–10.

29 McGuire DK, Winterfield JR, Rytlewski JA, et al. Blocking the renin-angiotensin–aldosterone system to prevent diabetes mellitus. *Diabetes Vasc Dis Res*. 2008;5:59–66.

30 Östergren J. Renin-angiotensin-system blockade in the prevention of diabetes. *Diabetes Res Clin Pract*. 2007; 76S:S13–S21.

31 Andraws R, Brown DL. Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). *Am J Cardiol*. 2007;99:1006–1012.

32 Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.

33 Yusuf S, Sleight P, Pogue J, et al; for the Heart Outcomes Prevention Evaluation Study Investigators Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.

34 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.

35 PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058–2068.

36 Dahlöf B, Devereux RB, Kjeldsen SE, et al; for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359:995–1003.

37 DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355:1551–1562.

38 Dahlöf B, Sever PS, Poulter NR, et al; for the ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised trial. *Lancet*. 2005;366:895–906.

39 Lithell H, Hansson L, Skoog I, et al. The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875–886.

40 Pfeffer MA, Swedberg K, Granger CB, et al; for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759–766.

41 Julius S, Kjeldsen SE, Weber M, et al; for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.

42 The Telmisartan Randomised AssessmeNT Study in ACE iNTolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008; 372:1174–1183.

43 ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547–1559.

44 Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension. *Diabetes Care*. 2008;31:353–360.

45 Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2008;168:207–217.

46 Gupta AK, Dahlöf B, Dobson J, et al; on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. *Diabetes Care*. 2008;31:982–988.

47 Zidek W, Schrader J, Luders S, et al. First-line antihypertensive treatment in patients with pre-diabetes: rationale, design and baseline results of the ADaPT investigation. *Cardiovasc Diabetol*. 2008;7:22.

48 Aksnes TA, Kjeldsen SE, Rostrup M, et al. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial population. *Hypertension*. 2007;50:467–473.

49 Verdecchia P, Angeli F, Reboldi G. New-onset diabetes, antihypertensive treatment, and outcome. *Hypertension*. 2007;50:459–460.

50 Califf RM, Boolell M, Haffner SM, et al; for the NAVIGATOR Study Group Prevention of diabetes and cardiovascular disease in patients with impaired glucose tolerance: rationale and design of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial. *Am Heart J*. 2008; 156:623–632.