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Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes

A Meta-Analysis of Randomized Clinical Trials

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OBJECTIVES We sought to investigate the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in preventing the new onset of type 2 diabetes mellitus.

BACKGROUND Diabetes is a public health problem of epidemic proportions and its prevalence is on the rise. The typical American born today has a one in three chance of developing type 2 diabetes. This diagnosis is associated with an adverse cardiovascular prognosis and is considered the risk equivalent of established coronary disease. Even in high-risk individuals, diabetes is a preventable disease. Several studies have shown that ACE inhibitors and ARBs decrease the incidence of new-onset type 2 diabetes. However, the exact role of these agents in diabetes prevention has not yet been fully elucidated.

METHODS We conducted a meta-analysis of 12 randomized controlled clinical trials of ACE inhibitors or ARBs, identified through a MEDLINE search and a review of reports from scientific meetings, to study the efficacy of these medications in diabetes prevention.

RESULTS This showed that ACE inhibitors and ARBs were associated with reductions in the incidence of newly diagnosed diabetes by 27% and 23%, respectively, and by 25% in the pooled analysis.

CONCLUSIONS The use of an ACE inhibitor or ARB should be considered in patients with pre-diabetic conditions such as metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure, or coronary heart disease. (J Am Coll Cardiol 2005;46:821–6) © 2005 by the American College of Cardiology Foundation

More than 19 million adults in the U.S. and 150 million adults worldwide have diabetes; by the year 2025, the World Health Organization projects more than 300 million cases worldwide (1). The typical American born today has a one in three chance of developing type 2 diabetes; for Hispanic and African American people, the risk is almost one in two. For a man diagnosed with diabetes at age 40 years, the average life expectancy is reduced by approximately 11.6 years and quality of life years by 18.6 (2). A diagnosis of type 2 diabetes carries such adverse prognostic implications (about 70% of diabetic patients die of cardiovascular disease) that it is considered the risk equivalent of established coronary disease (3). Strategies to prevent type 2 diabetes are, therefore, of paramount importance in improving the health of the American population in the 21st century.

The recently characterized constellation of risk factors referred to as metabolic syndrome (due to underlying insulin resistance) is a well-recognized precursor of type 2 diabetes (4). These patients are also at a high risk for cardiovascular events caused by accelerated atherosclerosis, hypercoagulability, dyslipidemia, and endothelial dysfunction (4). Approximately 24% (47 million) of adult Americans have metabolic syndrome. The prevalence of this disorder is increasing sharply and in parallel with the obesity epidemic (5,6).

Insulin resistance plays a causal role in hypertension and atherosclerosis, and thus is present to some degree in most patients with these diseases. About 50% of hypertensive individuals are hyperinsulinemic (7), and up to 75% of people with type 2 diabetes have hypertension (8). Abnormal glucose metabolism is seen in approximately two of three patients presenting with an acute coronary syndrome (with about equal numbers of patients having impaired fasting glucose and overt diabetes) (9).

In the milieu of insulin resistance, the cardiovascular system is sensitized to the adverse trophic effects of the renin angiotensin aldosterone system (RAAS) (10,11), as evidenced by the frequent occurrence of diffuse arterial disease and left ventricular hypertrophy in diabetic patients, even when the lipid and blood pressure levels are normal. High insulin levels stimulate the angiotensin I receptor, which activates the RAAS (12) and also increases cardiac sympathetic nervous system function (13). Diabetic patients, in particular, benefit from blockade of the RAAS, with reduction of cardiovascular mortality up to 40% in a major, randomized, controlled trial (14).

Multiple large prospective trials have reported an unexpected reduction in the development of new type 2 diabetes mellitus in patients treated with anti-hypertensive agents. These trials predominantly used angiotensin-converting

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
PPAR = peroxisome proliferator-activated receptor
RAAS = renin angiotensin aldosterone system

enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and have consistently shown reductions in the risk of new diabetes ranging from 4% to 87% (Table 1).

To elucidate the role of ACE inhibitors and ARBs in diabetes prevention, we conducted a meta-analysis of all sizable randomized clinical trials of ACE inhibitors or ARBs that reported data on the incidence of diabetes at baseline and study end.

METHODS

Data identification. We identified all randomized trials of ACE inhibitors or ARBs in which the incidence of new-onset diabetes was reported. Candidate trials were sought through a computerized bibliographic search of the MEDLINE database (National Library of Medicine, Bethesda, Maryland) for the period January 1990 to December 2004, and were required to include randomization in their design. The ACE inhibitor and angiotensin blocker/antagonist classes were searched in subject headings, and individual drug names were used as keywords. "(Diabetes or mellitus or glucose or insulin)" within three words of "(new$ or emerg$ or prevent$ or develop$ or risk$)" were searched in the title/abstract/subject heading. One hundred ninety-one articles were identified. The same search strategy was used to find citations in the Cochrane Database of Systematic Reviews, ACP Journal Club, The Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials (Ovid Technologies Inc., New York, New York). One hundred two articles were identified with this search. The reference lists of all articles obtained were examined to identify additional trials. Abstracted studies from presentations at national meetings were included if they met the design criteria.

Research selection. All titles and abstracts from the search process were examined. Studies were retrieved if they met the following criteria: 1) randomized comparison of an ACE inhibitor or an ARB to placebo or another antihypertensive medication, 2) study duration of at least one year, 3) all study patients had a history of hypertension or at least one cardiovascular risk factor, and 4) the incidence of new-onset diabetes during the study was reported in both the treatment and the control groups (for those patients without diabetes at baseline). We identified 13 published

Table 1. Prevention of Type 2 Diabetes by ACE Inhibitors or ARBs

Trial (Ref. No.)	No. of Patients	Years of Follow-Up*	Percent of New Diabetics	Risk Ratio (95% Confidence Interval)†
CAPPP (15)	10,985	6.1	Captopril 337/5,183 (6.5%) Diuretic/beta-blocker 380/5,230 (7.3%)	0.79 (0.67–0.94)
STOP-2 (16)	6,614	5	Conventional drugs 97/1,961 (4.9%) ACE inhibitors 93/1,969 (4.7%)	0.96 (0.72–1.27)
HOPE (17)	9,297	5	Ramipril 102/2,837 (3.6%) Placebo 155/2,883 (5.4%)	0.66 (0.51–0.85)
LIFE (18)	9,193	4.8	Losartan 241/4,019 (6%) Atenolol 319/3,979 (8%)	0.75 (0.63–0.88)
ALLHAT (19)	33,357	4.9	Lisinopril 119/4,096 (8.1%) Chlorthalidone 302/6,766 (11.6%)	0.70 (0.56–0.86)
ANBP2 (20)	6,083	Median 4.1	Enalapril 138/2,800 (4.9%) HCTZ 200/2,826 (7.1%)	0.66 (0.54–0.85)
SCOPE (21)	4,937	3.7 Maximum 5	Candesartan 93/2,167 (4.3%) Placebo 115/2,175 (5.3%)	0.81 (0.61–1.02)
ALPINE (22)	392	1	Candesartan ± felodipine 1/196 (0.5%) Atenolol ± HCTZ 8/196 (4%)	0.13 (0.03–0.99)
CHARM (23)	7,599	3.2	Candesartan 163/2,715 (6%) Placebo 202/2,721 (7%)	0.78 (0.64–0.96)
SOLVD (24)	4,228	3.4	Enalapril 9/153 (5.9%) Placebo 31/138 (22.4%)	0.26 (0.13–0.53)
VALUE (25)	15,245	4.2	Valsartan 690/5,267 (13.1%) Amlodipine 845/5,152 (16.4%)	0.77 (0.69–0.86)
PEACE (26)	8,290	Maximum 7 Median 4.8	Trandolapril 335/3,432 (9.8%) Placebo 399/3,472 (11.5%)	0.83 (0.72–0.96)

*Mean years of follow-up or as indicated; †published risk ratios may have been derived from subgroup analyses and/or statistical models and do not necessarily equal crude incidence ratios.

ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALPINE = Anti-hypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; ANBP2 = The second Australian National Blood Pressure study; ARB = angiotensin receptor blocker; CAPPP = Captopril Prevention Project; CHARM = Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity; HCTZ = hydrocholorothiazide; HOPE = Heart Outcomes Prevention Evaluation; LIFE = Losartan Intervention For Endpoint Reduction in hypertension study; PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial; SCOPE = The Study on Cognition and Prognosis in the Elderly; SOLVD = Studies Of Left Ventricular Dysfunction; STOP-2 = The second Swedish Trial in Old Patients with hypertension; VALUE = Valsartan Antihypertensive Long-term Use Evaluation.

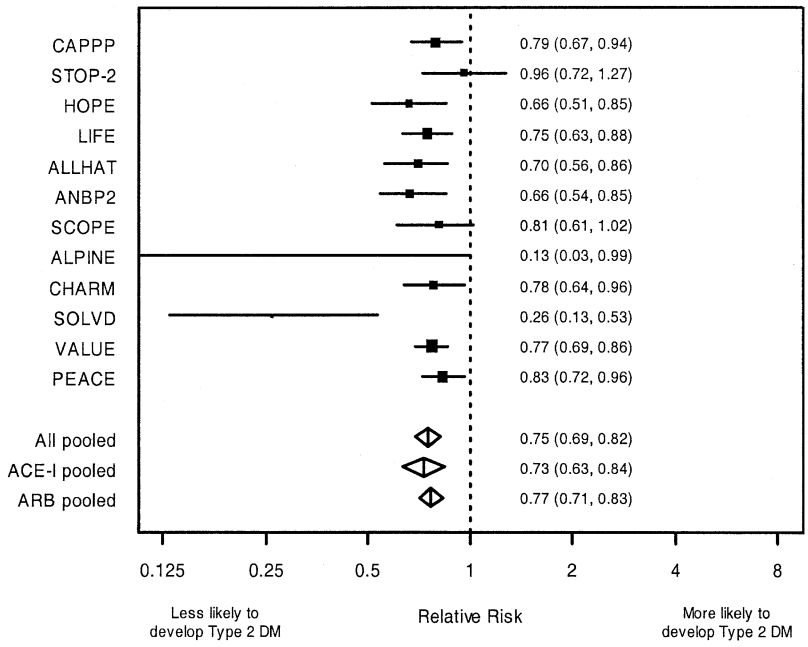

Figure 1. Pooled risk estimates of the different angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) trials shown in Table 1. DM = diabetes mellitus; other abbreviations as in Table 1.

studies of ACE inhibitors and ARBs (15–27). One study (27), however, was excluded because patients were not randomized to receive an ACE inhibitor, which was only used as an add-on therapy for blood pressure control. Therefore, a total of 12 studies were used in our analysis.

Data analysis. Pooled risk ratios were calculated using random effects meta-analysis described by DerSimonian and Laird (28,29). Risk ratios and confidence intervals for a new diagnosis of type 2 diabetes were obtained from published sources for each of the 12 studies. Seven studies (15–17,19,21,22,24) reported relative risks, four studies (18,20,23,26) reported hazard ratios, and one study (25) reported an odds ratio. It was assumed that the hazard ratios and odds ratio were reasonable approximations of relative risk. The 12 estimates and confidence intervals were log-transformed, and variances were calculated assuming Wald-type confidence intervals. A pooled estimate was then calculated as a weighted average of the log-risk ratios, with weights inversely related to the variances (i.e., estimates from studies with wide confidence intervals received less weight than those with narrow intervals). Because of differences in the types of drugs used, study designs, and methods, a random effects model was chosen, which incorporates an additional factor in the weights to account for between-study variability. Heterogeneity of effects was confirmed by the Cochran test, $p = 0.008$. The variance of the pooled estimate was calculated as the inverse of the sum of the weights, and a 95% confidence interval was derived assuming normality. Finally, the pooled estimate and confidence limits were back-transformed to the original ratio scale. Pooled risk ratios were calculated over all studies as well as separately for ACE inhibitors and ARB studies. Analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Of the 12 studies that met the criteria for entering the meta-analysis, 7 used ACE inhibitors (15–17,19,20,24,26) and 5 used ARBs (18,21–23,25). These trials involved 116,220 patients, of whom 72,333 did not have diabetes at baseline. Patients included in these studies had hypertension or at least one other cardiovascular risk factor. Two of the trials, namely Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) (23) and Studies Of Left Ventricular Dysfunction (SOLVD) (24), involved chronic heart failure patients, which is an insulin-resistant state in which the development of diabetes is particularly associated with increased morbidity and mortality (30).

The ACE inhibitors and ARBs were compared with placebo, diuretics, beta-blockers, or calcium-channel antagonists. Although the incidence of new-onset diabetes was defined differently among the trials, most used the American Diabetes Association criteria (31) of a fasting plasma glucose of ≥126 mg/dl at two different visits in patients with no diabetes at the time of enrollment.

The mean duration of follow-up ranged from 1 to 6.1 years. Reduction in the incidence of new-onset diabetes ranged from 4% to 87%. In two of the studies, namely the second Swedish Trial in Old Patients with hypertension (STOP-2) (16), and the Study on Cognition and Prognosis in the Elderly (SCOPE) (21), this did not reach statistical significance. Figure 1 shows pooled risk ratios of the different ACE inhibitor and ARB trials shown in Table 1. The reductions in risk of new-onset diabetes were 27% for ACE inhibitors, 23% for ARBs, and 25% for either ACE inhibitor or ARB (i.e., pooled over all studies).

DISCUSSION

Recent studies have suggested that ACE inhibitors and ARBs may play an important role in the prevention of type 2 diabetes; the current meta-analysis confirms such findings. This meta-analysis, involving 72,333 non-diabetic patients (approximately 338,000 patient-years of follow-up), showed that ACE inhibitors or ARBs produced a highly significant 25% reduction (or a decrease from 17.4 to 14.3 cases per 1,000 patient-years) in the incidence of new-onset diabetes. This is especially important because many common cardiovascular conditions such as coronary disease, congestive heart failure, and hypertension are associated with insulin resistance and increased risk for the development of diabetes (7,8,32). Type 2 diabetes markedly worsens long-term cardiovascular prognosis, and thus therapies to prevent this disease are of great interest (33).

However, there are some limitations to these trials. Important among these is the fact that only 9 (17–19,21–26) of the 12 trials were double-blind, whereas the other 3 (15,16,20) used the prospective randomized open-blinded end point design. The definition of diabetes differed among the trials. Only two trials, the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) (22) and the Antihypertensive Long-term Use Evaluation (VALUE) (25), included the development of diabetes as a pre-specified end point, whereas in the others, this end point was a post-hoc analysis. The ALPINE study showed a remarkable 87% reduction in the incidence of new-onset diabetes in the candesartan group as compared with the atenolol group. However, this study only included 392 patients and was of a short duration. On the other hand, the VALUE trial randomized a larger number of patients, and follow-up was a mean of 4.2 years.

A similar proportion of patients in the both the valsartan and the amlodipine arms of the VALUE trial needed adjunctive diuretic and/or beta-blocker therapy for blood pressure control, thus the highly significant 23% reduction in new diabetes cases was not attributable to increased insulin resistance caused by other medications in the amlodipine arm. The use of these adjunctive medications in some patients assigned to ACE inhibitors or ARBs in the other trials, however, may have affected the differences observed in the emergence of new-onset diabetes between the treatment groups, although the reduction of 23% in the VALUE trial was identical to that achieved by ARBs in our meta-analysis.

The International Verapamil-Trandolapril Study (INVEST) investigators (27) reported that in 16,176 non-diabetic, hypertensive patients with coronary artery disease, the incidence of new diabetes cases was significantly lower in the verapamil sustained-release/trandolapril strategy (7%) compared with the atenolol/hydrochlorothiazide strategy (8.2%) (relative risk, 0.85 [95% confidence interval, 0.77 to 0.95]). Further analysis (34) of the results of this study showed that the addition of 4 mg trandolapril to the 240-mg dose of verapamil significantly reduced the incidence of new-onset diabetes as compared with atenolol 50 mg (hazard ratio, 0.58 [95% confidence interval, 0.44 to 0.78]). However, trandolapril was an add-on therapy and patients were not randomized to receive it, therefore, this study was excluded from our meta-analysis.

The mechanisms of action whereby these medications prevent type 2 diabetes are speculative (24). The ACE inhibitors not only block the conversion of angiotensin I to angiotensin II, but also increase bradykinin levels through inhibition of kininase II-mediated degradation (35,36). In hypertensive rats, Tomiyama et al. (37) have shown improved insulin sensitivity with enalapril through an increase in endogenous kinins. The higher kinin levels lead to an increased production of prostaglandins (prostaglandin E_1 and prostaglandin E_2) and nitric oxide, which improve exercise-induced glucose metabolism (38) and muscle sensitivity to insulin (39–41), resulting in enhanced insulin-mediated glucose uptake. Furthermore, the peripheral vasodilatory actions of ACE inhibitors and ARBs lead to an improvement in skeletal muscle blood flow, the primary target for insulin action and an important determinant of glucose uptake. This effectively increases the surface area for glucose exchange between the vascular bed and skeletal muscles. Clinical evidence supporting this effect has been provided by Morel et al. (42), who have demonstrated improved insulin sensitivity when enalapril was given for 12 weeks to 14 obese, hypertensive, and dyslipidemic patients. A similar effect has also been reported with captopril (43).

The protection against new-onset diabetes may in part be related to adipocyte function. Mature adipocytes are integrally involved with the RAAS. Investigators have theorized that increased levels of angiotensin II inhibit pre-adipocyte differentiation into mature adipocytes, and this impairs the fat cells' ability to store fat. This in turn results in shunting of fats to the liver, skeletal muscle, and pancreas, which worsens insulin resistance. Reducing angiotensin II levels with an ACE inhibitor or blocking the angiotensin II receptor with an ARB may promote differentiation of pre-adipocytes to mature adipocytes, which serve as a sump for fat. Additionally, redistribution of the lipids from the peripheral tissues would improve insulin sensitivity (44).

Another theory relates to a possible protective effect of ARBs and ACE inhibitors on the pancreatic beta cell through inhibiting the vasoconstrictive effect of angiotensin II in the pancreas and increasing islet blood flow (45), which could improve insulin release by beta cells. Telmisartan, an ARB, has been shown to act as a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, similar to the thiazolidinediones rosiglitazone and pioglitazone, which preserve pancreatic beta-cell function (46). These experimental and clinical studies suggest that blocking the effects of angiotensin II (through ACE inhibition or receptor blockade) increases insulin sensitivity, skeletal muscle glucose transport, and pancreatic blood flow, which may contribute to the prevention of diabetes mellitus.

Therefore, an ACE inhibitor or ARB is a logical first-line

anti-hypertensive agent in patients with impaired fasting glucose or metabolic syndrome for multiple reasons, including the reduction in risk of progression to overt type 2 diabetes. Even in patients without diabetes or metabolic syndrome, what was previously thought to be a "high-normal" blood pressure (120/80 to 139/89 mm Hg) is associated with an increased risk of adverse cardiovascular events (47). In fact, this blood pressure range is now considered "pre-hypertension" per new Joint National Committee 7 guidelines (48). Some of the most widely used anti-hypertensives, particularly the traditional beta-blockers such as metoprolol and atenolol and diuretics (in high doses) such as hydrochlorothiazide and chlorthalidone, worsen insulin sensitivity and increase risk of new-onset type 2 diabetes (19). However, carvedilol, an alpha-beta blocker with antioxidant properties, has been shown to have neutral effects or to slightly improve rather than worsen insulin sensitivity (49).

Angiotensin-converting enzyme inhibitors and ARBs not only lower blood pressure but also may possess unique cardioprotective properties (10). They improve endothelial function and regress both left ventricular hypertrophy and arterial mass better than other anti-hypertensive agents that lower blood pressure equally as well (10). They also reduce rates of death, myocardial infarction, stroke, cardiac arrest, and revascularization procedures (10). Angiotensin-converting enzyme inhibitors have been shown to protect against oxidative stress and prevent glycosylation of proteins, which may confer cardiovascular benefit (50). These agents are generally well tolerated, especially the ARBs, which have a side effect profile similar to placebo. Thus, in patients with conditions associated with insulin resistance, such as metabolic syndrome, hypertension, impaired fasting glucose, family history of diabetes, obesity, congestive heart failure, or other risks for the development of type 2 diabetes, the use of an ACE inhibitor or ARB should be considered.

Additional trials will be needed to confirm the role of ACE inhibitors and ARBs in diabetes prevention, and no pharmacologic agent is currently approved for this particular indication. Prospective trials that specifically address this issue are underway, including the Diabetes REduction Approaches with ramipril and rosiglitazone Medications (DREAM) trial with the ACE inhibitor ramipril and the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial with the ARB valsartan. Finally, the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) will also investigate as a secondary end point whether it is possible to prevent the development of type 2 diabetes by blocking the RAAS with either an ACE inhibitor or an ARB or a combination of both. Using the same outcomes, the Telmisartan Randomized AssessmeNt Study in aCE iNtolerant patients with cardiovascular Disease (TRANSCEND) compares telmisartan with placebo for individuals who are unable to take ACE inhibitors because of intolerable side effects.

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