The Impact of ACE Inhibitors or Angiotensin II Type 1 Receptor Blockers on the Development of New-Onset Type 2 Diabetes

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OBJECTIVE — Angiotensin II has been shown to increase hepatic glucose production and decrease insulin sensitivity. Patients who utilize either an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) may experience a decreased incidence of new-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS — Three reviewers conducted a systematic literature search of Medline, EMBASE, CINAHL, and the Cochrane Library (1966 to present) to extract a consensus of trial data involving an ACEI or ARB with an end point of new-onset type 2 diabetes. Studies were included if they were randomized controlled trials verses placebo/routine therapy. A random-effects model was utilized. Subgroup and sensitivity analyses were conducted.

RESULTS — Eleven trials were identified, including 66,608 patients. An ACEI or ARB prevented new-onset type 2 diabetes (odds ratio 0.78 [95% CI 0.73–0.83]). The influence of either an ACEI (six trials) or an ARB (five trials) alone on new-onset type 2 diabetes was similar (0.79 [0.71–0.89] and 0.76 [0.70–0.82], respectively). Regardless of indication for use, hypertension (seven trials), coronary artery disease (two trials), or heart failure (two trials), reductions in new-onset type 2 diabetes were maintained (0.79 [0.72–0.85], 0.76 [0.60–0.95], and 0.70 [0.50–0.96], respectively). No statistical heterogeneity was observed for any evaluation ($P > 0.1$ for all comparisons). ACEIs and ARBs did not reduce the odds of mortality, cardiovascular, or cerebrovascular events versus control therapy among all of these studies combined or the hypertension trials. ACEIs and ARBs did reduce the odds of these outcomes among the coronary artery disease studies versus control therapy.

CONCLUSIONS — ACEIs or ARBs may decrease patients' odds of developing new-onset type 2 diabetes but does not reduce the odds of mortality, cardiovascular, or cerebrovascular outcomes over the study follow-up periods among patients with hypertension.

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Given the elevated risk of morbidity and mortality among patients with type 2 diabetes, prevention of type 2 diabetes is a worthwhile goal. Substantive weight loss eliminates insulin-resistant fatty tissue and reduces the risk of progressing from impaired glucose tolerance to full-blown type 2 diabetes by 37–58% (1). Metformin and thiazolidinedione therapy also reduces the rate of type 2 diabetes onset among patients with impaired glucose tolerance or gestational diabetes history by 31–55% (1).

ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been used for years to reduce the rate of diabetic nephropathy progression in patients with type 2 diabetes (2). In addition, ACEIs and ARBs enhance insulin sensitivity and therefore benefit patients at high risk of developing type 2 diabetes. ACEIs improved the insulin sensitivity index by 12.1 ± 15.8% in a compilation of 20 pharmacologic trials, while ARBs raised the insulin sensitivity index by 18.7 ± 17.9% in a compilation of 9 pharmacologic trials (1).

ACEIs and ARBs have been studied versus placebo or control therapy in numerous clinical trials of patients who had hypertension, coronary artery disease, or chronic heart failure. In secondary subgroup analyses, the impact of ACEI or ARB usage on the development of new-onset type 2 diabetes has been evaluated. While many trials showed significant benefits in preventing new-onset type 2 diabetes, several other trials did not (3–17). One way to reconcile these clinical trial differences is through the use of meta-analysis. Meta-analysis allows incorporation of data from several studies into a single analysis with increased power to detect previously unidentified differences. Through meta-analysis, we seek to determine the impact of ACEI or ARB usage on the development of new-onset type 2 diabetes.

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Abbreviations: ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

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

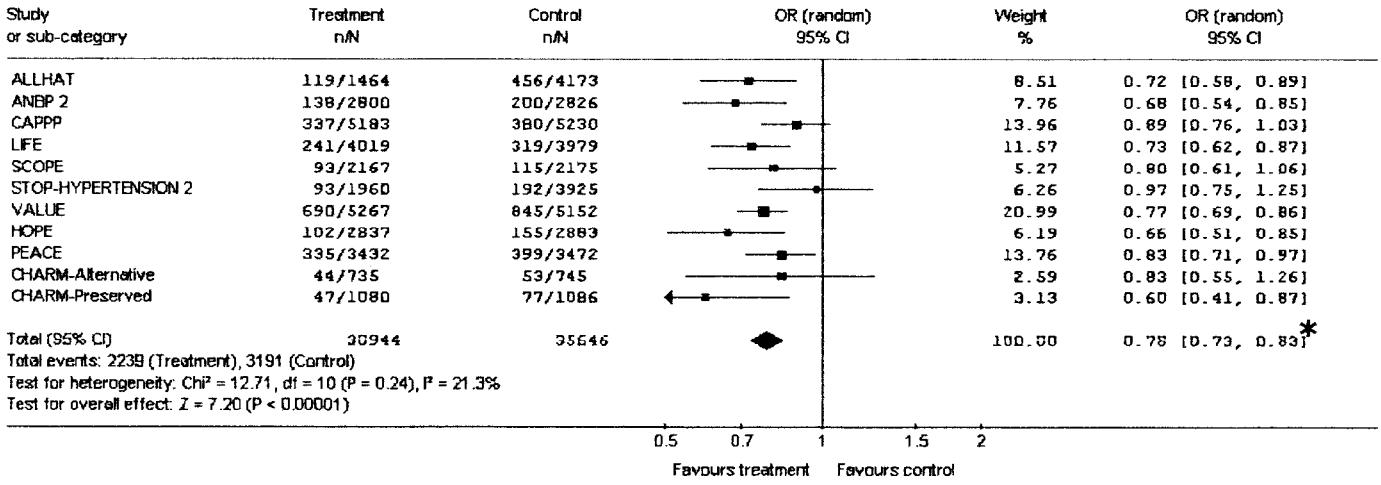

Figure 1—*Studies (11 studies) evaluating new-onset type 2 diabetes. *Absolute risk reduction = 1.7% (95% CI 1.3–2.1); number needed to treat = 58.*

RESEARCH DESIGN AND METHODS

— Randomized clinical trials of ACEI or ARB use with a primary or secondary end point of new-onset type 2 diabetes were identified by three reviewers (E.L.G., M.K., and C.I.C.) through a systematic literature search of Medline, EMBASE, CINAHL, and the Cochrane Library (1966 to September 2004). A search strategy using the MeSH and text keywords "type 2 diabetes," "diabetes mellitus," "benazepril," "captopril," "enalapril," "fosinopril," "lisinopril," "moexipril," "quinapril," "ramipril," "trandolapril," "candesartan," "eposartan mesylate," "irbesartan," "losartan," "telmisartan," and "valsartan" was conducted. In addition, a manual review of the bibliographies of primary and review articles was performed to identify any additional relevant studies. The results were further limited to human studies and the English language.

Studies were included in this meta-analysis if they were randomized controlled trials versus placebo or routine treatment and reported the incidence of new-onset type 2 diabetes. New-onset type 2 diabetes was treated as a dichotomous variable and reported as odds ratios (ORs) with 95% CIs. Pooled ORs were calculated utilizing Review Manager 4.2.7 software using a random-effects model (DerSimonian and Laird methodology). Statistical heterogeneity scores were assessed with a χ^2 test.

To assess the potential for publication bias, a funnel plot of included studies was reviewed. The funnel plot pictorially represents each study included in the meta-analysis plotted by its effect size (ORs) on the horizontal axis and variance (SE of the log OR) on the vertical axis. In the absence of publication bias, it would be expected that the plot would resemble an inverted funnel with less-precise studies having greater variance scattered at the bottom to either side of the more precise studies. If publication bias is present in a meta-analysis, the plot would likely not resemble an inverted symmetrical funnel.

To establish the effect of any clinical heterogeneity between studies on the meta-analysis' conclusions, subgroup analysis was conducted. The effect of either an ACEI or ARB and indication for use (e.g., hypertension, coronary artery disease, and chronic heart failure) were examined. To determine the effect of including unblinded studies on the meta-analysis' conclusions, sensitivity analysis was conducted. The meta-analysis was reanalyzed excluding unblinded studies. The impact of ACEI or ARB therapy on mortality, cardiovascular, and cerebrovascular end points versus control therapy was also determined for all included studies, such as studies of ACEIs or ARBs alone, hypertention studies, coronary artery disease studies, and heart failure studies.

RESULTS

— Fourteen studies (3–17) were initially identified, with three studies (3–5) being excluded due to failure to meet inclusion criteria. Two trials (4,5) were excluded because they were not randomized controlled trials. One trial (3) was excluded because it only evaluated the combination of candesartan plus felodipine; therefore, the effects of candesartan alone on the development of type 2 diabetes could not be determined.

Of the remaining 11 trials (6–17), 7 trials (6–10,14,16–17) evaluated patients being treated for hypertension, 2 trials (13,15) evaluated patients being treated for coronary artery disease, and 2 trials (11,12) evaluated patients for heart failure. Patient enrollment ranged between 2,028 and 33,357 patients. The mean patient age ranged between 53 and 76 years, with greater than half of the participants being men. In three trials (6,7,14), patients in the control group received placebo; the remaining eight trials (8–13,15) permitted use of ACEIs or ARBs in the control group, with use ranging from 2 to 23%. The mean length of study ranged from 34 months to 6 years. Four studies (7–9,14) defined new-onset type 2 diabetes according to the World Health Organization standards (7,9,14,18) or as a fasting plasma glucose level >126 mg/dl (8). Five studies (6,10–13) did not define new-onset type 2 diabetes, and the two remaining studies (15–17) allowed self-reporting to define new-onset type 2 diabetes diagnosis.

An ACEI or ARB prevented new-onset of type 2 diabetes (OR 0.78 [95% CI 0.73–0.83], test for statistical heterogeneity $P = 0.24$) (Fig. 1). The influence of either an ACEI (six studies) (6–8,13,15–17) or an ARB (five studies) (9–12,14) alone on new-onset type 2 diabetes was similar (0.79 [0.71–0.89] and 0.76

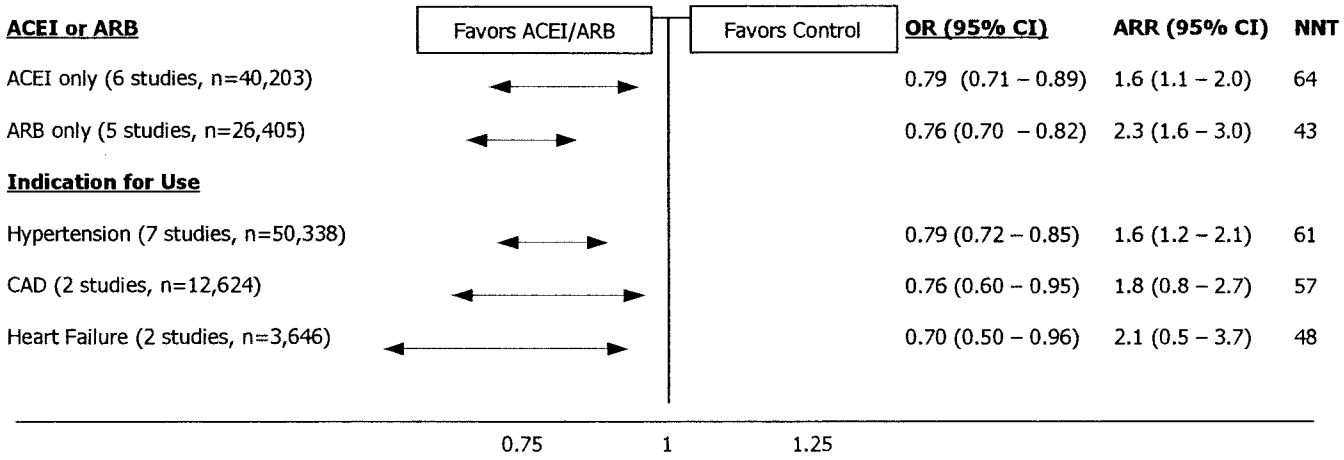

Figure 2—*Subgroup analyses of ACEI and ARB studies evaluating new-onset type 2 diabetes. ARR, percent absolute risk reduction; CAD, coronary artery disease; NNT, number needed to treat.*

[0.70–0.82], respectively, test for statistical heterogeneity $P = 0.10$ and $P = 0.71$, respectively) (Fig. 2).

Regardless of indication for use, e.g., hypertension (6–10,14,16,17) ($n = 7$ studies), coronary artery disease (two studies) (13,15), or heart failure (two studies) (11,12), reductions in new-onset type 2 diabetes were maintained (OR 0.79 [95% CI 0.72–0.85], 0.76 [0.60–0.95], and 0.70 [0.50–0.96], respectively, test for statistical heterogeneity $P = 0.23$, $P = 0.12$, and $P = 0.24$, respectively).

Sensitivity analyses were conducted to evaluate the effect of including unblinded studies in this meta-analysis. The exclusion of unblinded trials (two studies) (6,7) had little effect on the meta-analysis' conclusions: (OR 0.75 [95% CI 0.71–0.80], test for statistical heterogeneity $P = 0.66$). This meta-analysis' funnel plot appears relatively symmetrical; however, publication bias cannot be ruled out (Fig. 3). In evaluating our funnel plot, we can only report that there may be nonovert publication bias, which is difficult to quantify.

Among all included trials (6–17), ACEIs and ARBs did not reduce the risk of mortality, stroke, myocardial infarction, or fatal myocardial infarction versus control therapy, but the risk of cardiovascular mortality trended lower (OR 0.93 [95% CI 0.86–1.01]) (Table 1). Among hypertension trials (6–10,14,16,17), the OR was very close to one for all aforementioned outcome analyses, except for fatal myocardial infarction, where a trend toward a reduction with ACEI or ARB therapy was noted (0.88 [0.76–1.02]). Among patients with coronary artery disease (13,15), reductions in mortality (0.85 [0.77–0.94]), stroke (0.70 [0.59–0.84]), and myocardial infarction (0.79 [0.69–0.89]) occurred. A trend toward lower cardiovascular mortality occurred (0.82 [0.64–1.06]), but no difference in fatal myocardial infarction occurred. Among heart failure trials (11,12), no significant reductions occurred in the aforementioned end points evaluated.

CONCLUSIONS — In our meta-analysis, 66,608 patients were evaluated for development of new-onset type 2 diabetes (6–17). Given our study results, it is clear that blocking the renin-angiotensin system with an ACEI or ARB significantly reduced the odds of developing type 2 diabetes. It is also clear that the beneficial results will occur regardless of whether ACEIs or ARBs are used. Although there are pharmacologic differences between ACEIs and ARBs, such as the ability of ACEIs to preserve bradykinin or the ability of ARBs to block angiotensin II generated by tonin and cardiac chymase, these differences do not seem to translate into differences in the development of new-onset type 2 diabetes (19,20). This is consistent with ACEIs or ARBs abilities to reduce mortality in chronic heart failure and is reflective of their ability to raise insulin sensitivity in pharmacologic trials (1,3,19).

Blockade of the renin-angiotensin system with an ACEI or ARB prevents new-onset type 2 diabetes in studies of hypertension, coronary artery disease, and chronic heart failure. However, in the

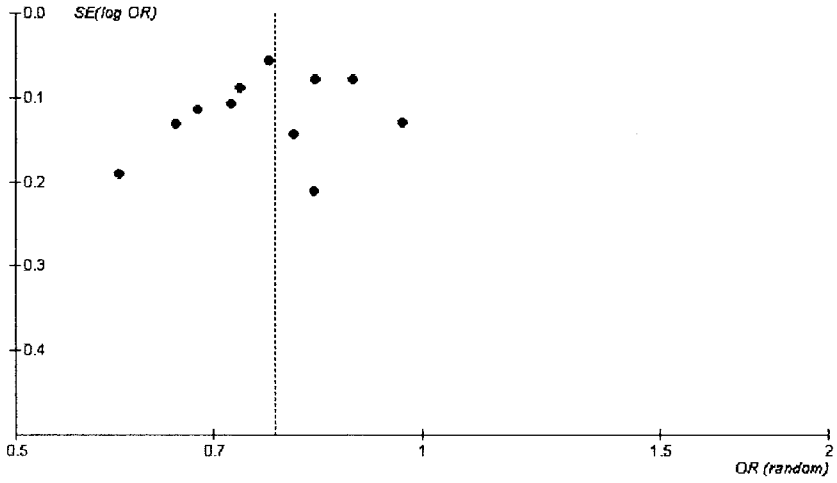

Figure 3—*Funnel plot of all included studies (11 studies) evaluating new-onset type 2 diabetes.*

Table 1—*Effect of ACEIs and ARBs on cardiovascular end points*

End point	*n* (studies)	*n* (patients)	OR (95% CI)
Mortality			
All studies	11	109,052	0.96 (0.91–1.01)
ACEI only	6	74,626	0.95 (0.88–1.03)
ARB only	5	34,426	0.96 (0.89–1.03)
HTN studies	7	86,414	1.00 (0.95–1.04)
CAD studies	2	17,587	0.85 (0.77–0.94)
HF studies	2	5,051	0.94 (0.79–1.12)
Cardiovascular mortality			
All studies	11	109,052	0.93 (0.86–1.01)
ACEI only	6	74,626	0.93 (0.81–1.06)
ARB only	5	34,426	0.93 (0.85–1.01)
HTN studies	7	86,414	0.99 (0.93–1.06)
CAD studies	2	17,587	0.82 (0.64–1.06)
HF studies	2	5,051	0.91 (0.76–1.08)
Stroke			
All studies	11	109,052	0.95 (0.81–1.12)
ACEI only	6	74,626	0.97 (0.80–1.18)
ARB only	5	54,141	1.04 (0.82–1.32)
HTN studies	7	86,414	1.04 (0.86–1.26)
CAD studies	2	17,587	0.70 (0.59–0.84)
HF studies	2	5,051	0.89 (0.67–1.18)
MI			
All studies	9	67,405	0.96 (0.83–1.12)
ACEI only	4	32,979	0.83 (0.73–0.94)
ARB only	5	34,426	1.11 (0.93–1.32)
HTN studies	6	53,057	0.98 (0.85–1.14)
CAD studies	1	9,297	0.79 (0.69–0.89)
HF studies	2	5,051	1.11 (0.54–2.29)
Fatal MI			
All studies	6	70,266	0.92 (0.82–1.04)
ACEI only	5	65,329	0.92 (0.82–1.04)
ARB only	1	4,937	0.99 (0.52–1.91)
HTN studies	5	61,976	0.88 (0.76–1.02)
CAD studies	1	8,290	1.00 (0.83–1.21)
HF studies	0		Not estimable
Nonfatal MI			
All studies	4	28,619	0.92 (0.75–1.13)
ACEI only	3	23,682	0.87 (0.69–1.11)
ARB only	1	4,937	1.14 (0.77–1.70)
HTN studies	4	28,619	0.92 (0.75–1.13)
CAD studies	0		Not estimable
HF studies	0		Not estimable

CAD, coronary artery disease; HF, heart failure; HTN, hypertension; MI, myocardial infarction.

included clinical trials, patients did not exclusively have only one disorder. In the CA PPP(7) and VALUE (9) hypertension trials, 25–46% of subjects had preexisting coronary heart disease. A lower percentage had coronary heart disease in the ALLHAT (1%) (9), STOP-Hypertension 2 (8%) (6), ANBP2 (8%) (16,17), and LIFE (16%) (14) hypertension trials. In the HOPE (15) and PEACE (13) trials, 43–46% of patients who had coronary artery disease with normal or near-normal left ventricular function had hypertension as well. In the CHARM-Alternative (12) and CHARM-Preserved (11) heart failure trials, 61 and 44% of patients had a previous myocardial infarction and 50 and 64% of patients had hypertension, respectively. Since the development of new-onset type 2 diabetes was not broken out in these various subgroups (hypertension without coronary heart disease or heart failure, coronary artery disease without hypertension or heart failure, etc.), we cannot fully describe the interplay between these various factors and new-onset type 2 diabetes.

The beneficial effect of ACEIs and ARBs on the incidence of diabetes is likely to be more important in higher-risk subjects for type 2 diabetes. While subgroup analysis stratifying the population for impaired fasting glucose versus normal would provide useful information, unfortunately, the original studies do not provide sufficient data for such an analysis.

The benefits of using an ACEI or ARB to delay the onset of type 2 diabetes may be markedly greater than represented in this meta-analysis. In most of the trials, there was open-label use of ACEIs or ARBs in the control groups and <100% use of these drugs in the ACEI or ARB treatment groups. In the PEACE trial (13), 1.5, 4.6, and 8.3% of subjects in the control group and 81.9, 78.5, and 74.5% of subjects in the ACEI group were using ACEIs at 1, 2, and 3 years, respectively. In the HOPE trial (21), 11.6 and 27.4% of control subjects and 98.3 and 89.7% of ACEI subjects were receiving ACEIs at 2 and 4 years, respectively. In the SCOPE (10), VALUE (9), CHARM-Preserved (11) and CHARM-Alternative (12), and ANBP2 (16,17) trials, 15.0, 19.3, 26.0, 15.0, and 12.4% of subjects in the control groups received either an ACEI or ARB, respectively. The use of ACEIs or ARBs in the control groups of the LIFE (14), STOP-Hypertension 2 (6), and CAPPP (7) trials was not apparent from the articles, but only 61.3% of subjects were still receiving their ACEI in the STOP-Hypertension 2 (6) treatment group. A reanalysis of the original trials based on the on-treatment analysis for this end point would help to identify the odds reductions that could be expected with ACEI or ARB therapy versus lack of these therapies.

Since type 2 diabetes increases the risk of cardiovascular and cerebrovascular end points while negatively impacting mortality, reducing the incidence of new-onset diabetes may be assumed to reduce the risk of these events as well. However, among ACEI and ARB trials evaluating new-onset diabetes, there were no significant differences in mortality, cardiovascular, or cerebrovascular end points versus control therapy (6–17). This was evident among hypertension trials where

the ORs hovered close to one for all outcomes except for fatal myocardial infarction, where a trend toward benefit was noted. This suggests that hypertension control and not the development of new-onset diabetes drives these end points over the study time period. It may be that longer-term follow-up is needed to reap the benefits of diabetes prevention or that this factor is not an important determinant of risk in this population.

The use of ACEI or ARB was associated with reduced mortality, cardiovascular, and cerebrovascular end points versus control therapy in studies of patients with pre-existing coronary disease (13,15). Given the time frame from onset of diabetes to diabetes-related mortality, cardiovascular, or cerebrovascular outcomes, it is difficult to attribute the additional benefits of ACEI or ARB therapy to the development of diabetes alone. ACEI and ARB therapy prevent pathogenic left ventricular and vascular remodeling, which could provide additional benefits versus control and is a confounder (22). However, with the increased risk of mortality, cardiovascular, and cerebrovascular events among patients with pre-existent coronary disease, the basal risk of these events occurring is accentuated, and the benefits of therapy might be more likely in the shorter term. Although the use of an ACEI or ARB was not beneficial in our heart failure analysis, the studies included in our meta-analysis (11,12) only made up a small fraction of the heart failure trials that have been conducted. We limited our meta-analysis to studies that also evaluated new-onset diabetes. When evaluating the totality of data in heart failure, ACEI and ARBs provide clear mortality benefit in patients with heart failure (22).

ACEIs and ARBs have a similar and significant ability to reduce the occurrence of new-onset type 2 diabetes among patients with hypertension, coronary artery disease, and heart failure. Although this does not seem to impact the occurrence of cardiovascular, cerebrovascular, or mortality outcomes in the short term, long-term benefits from preventing new-onset diabetes is possible.

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