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Angiotensin converting enzyme inhibitors for prevention of new-onset type 2 diabetes mellitus: A meta-analysis of 72,128 patients

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ABSTRACT

Backgroud: Angiotensin converting enzyme inhibitors (ACEIs) have been linked to reduced risk of new-onset diabetes, but the evidence was insufficient.
Objective and methods: The aim of this study was to evaluate the effect of ACEIs on the development of new-onset type 2 diabetes. Randomized controlled trials (RCTs) about ACEIs and new-onset diabetes were identified by electronic and manual searches.
Results: Nine RCTs with 92,404 patients (72,128 non-diabetic patients at baseline) were included in this study. Compared with control group, incidence of new-onset diabetes was significantly reduced in the ACEIs group [OR 0.80, (0.71, 0.91)], irrespective of achieved blood pressure levels at the follow-up. ACEIs therapy was associated with significant reduction in the risk of new-onset diabetes compared with beta-blockers/diuretics [OR 0.78, (0.65, 0.93)], placebo [OR 0.79, (0.64, 0.96)], or calcium channel blockers [OR 0.85, (0.73, 0.99)]. ACEIs treatment was associated with significant reduction in the risk of new-onset diabetes in patients with hypertension [OR 0.80, (0.68, 0.93)], coronary artery disease (CAD) or cardiovascular disease [OR 0.83, (0.68, 1.00)], or heart failure [OR 0.22, (0.10, 0.47)]. Among patients with impaired glucose tolerance or impaired fasting glucose, ramipril did not significantly reduce the incidence of diabetes [OR 0.91, (0.79, 1.05)], but significantly increased regression to normoglycemia.
Conclusion: ACEIs have beneficial effects in preventing new-onset diabetes. ACEIs provide additional benefits of lowering the risk of new-onset diabetes in patients with hypertension, CAD or other cardiovascular disease.

1. Introduction

Diabetes and its complications are major causes of morbidity and mortality in the U.S. [1]. In 2005–2006, the crude prevalence of total diabetes in American population aged ≥20 years was 12.9%, and over 40% of individuals had diabetes or pre-diabetes [2]. Subjects with hypertension have propensity for development of diabetes. A prospective cohort study had found that type 2 diabetes was almost 2.5-fold more likely to develop in hypertensive than in individuals with normal blood pressure [3].

Although previous meta-analyses [4–7], which evaluated the efficacy of angiotensin converting enzyme inhibitors (ACEIs) on the development of new-onset diabetes, have found a benefit of ACEIs overall, some uncertainties still exist. In addition, 2 additional trials [8,9] with 17,487 participants were reported after these meta-analyses were published. Among the 2 trials, the DREAM trial [8] observed the effect of ramipril on the development of new-onset diabetes in patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). It is still unclear whether ACEIs have beneficial effects on new-onset diabetes in patients with high risk of developing diabetes except hypertension. It is still unknown whether there was an association between incidence of new-onset diabetes and a difference in achieved blood pressure level. The persisting uncertainties form the basis of our meta-analysis.

2. Methods

2.1. Search strategy

Electronic databases including PubMed (1966–2011), EMBase (1980–2011), BIOSIS Previews (1997–2011), and Cochrane central register of controlled trials (4th Quarter 2010) were searched to identify relevant studies. Reference lists of identified studies were scrutinized to reveal additional citations. Conference proceedings from American College of Cardiology (2003–2010), American Heart Association (2003–2010), European Society of Cardiology Congress (2003–2010), American Diabetes Association (2003–2010), and EASD annual meeting (2003–2010) were also searched.

2.2. Criteria for study selection

Studies were considered for inclusion if they met the following criteria: 1) type of study design was randomized controlled trials (RCTs); 2) compared an ACEI with placebo or non-ACEI drugs; 3) reporting the incidence of new-onset diabetes and 4) study duration ≥1 year. Since ACEIs and angiotensin receptor blockers (ARBs) have the

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similar inhibitory effects on the renin angiotensin system, RCTs that compared ACEIs with ARBs directly were not included in this study.

2.3. Data extraction and assessment of study quality

Data were extracted independently by 2 investigators. Discrepancies were resolved by consensus or a third author adjudication. The following data were abstracted from each study: details of participant characteristics [age, gender, body mass index (BMI), race and comorbidity], interventions in each group (categories of ACEIs, dose titration and coexisting drugs), the total number of patients, the number of non-diabetic individuals at baseline, the number of new-onset diabetes during follow-up, criteria for defining diabetes, prespecified endpoints and duration of follow-up. Methodological quality of included RCTs was assessed by several domains: randomization; allocation concealment; blinding of investigators, participants, and outcome assessors; completeness of follow-up; description of withdrawals; and application of intention-to-treat analysis.

2.4. Statistical analysis

We referred to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [10] in this meta-analysis. Results were expressed as odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes. Heterogeneity across trials was assessed via a standard Chi square test with significance being set at $P<0.10$ and also assessed by means of I^2 statistic with significance being set at $I^2>50\%$. Random effects model was used for statistical analysis due to wide clinical and methodological variability across the trials. Subgroup analyses were performed according to different categories of ACEIs, controls or primary diseases. Statistical analysis was performed using Review Manager 5.0 (The Cochrane Collaboration, Oxford, England). A value of $P<0.05$ was considered statistically significant.

3. Results

3.1. Study selection

A total of 9 RCTs [8,9,11–17] with 92,404 intention-to-treat (ITT) participants (72,128 non-diabetic participants at baseline) were identified for inclusion from 150 potentially relevant publications.

3.2. Baseline characteristics and study quality

Table 1 summarizes the baseline characteristics and study quality of 9 trials [8,9,11–17]. The confounding factors that affected new-onset diabetes were well balanced in each arm. Among these trials, 5 trials [8,9,11–13] with 28,900 non-diabetic patients compared ACEIs with placebo; 4 trials [14–17] with 35,538 non-diabetic patients compared ACEIs with diuretics/beta-blockers; and 2 trials [14,17] with 15,501 non-diabetic patients compared ACEIs with calcium channel blockers (CCBs). Four trials performed in 43,228 non-diabetic patients with hypertension [14–17], 1 trial in 291 patients with heart failure [13], 1 trial in 5269 patients with IGT or IFG [8], and 3 trials in 23,340 patients with coronary artery disease (CAD) or other cardiovascular disease [9,11,12].

3.3. Incidence of new-onset type 2 diabetes

The diagnosis criteria of type 2 diabetes mellitus (T2DM) were not described in four trials [9,12,15,17]. T2DM was defined differently among the remaining 5 trials. The WHO 1999 criteria for T2DM were adopted in 3 trials [8,13,14], while the WHO 1985 criteria were applied in 1 trial [16]. HbA1c > 110% upper limit of normal was taken as the diagnosis criteria of T2DM in 1 trial [11].

Overall, there were 2325 new cases of T2DM (2325/30,228, 7.7%) in the ACEIs group compared with 3933 new cases (3933/41,900, 9.4%) in the control group [OR 0.80, 95%CI 0.71–0.90, $P=0.0003$]. Compared with the control group, incidence of new-onset diabetes was significantly reduced in the ACEIs group, irrespective of achieved blood pressure (BP) levels [ACEIs with lower achieved BP, OR 0.82, (0.69, 0.97); ACEIs with higher achieved BP, OR 0.79, (0.64, 0.98)].

ACEIs therapy was associated with a significant reduction in the risk of new-onset diabetes compared with beta-blocker/diuretics [OR 0.78, (0.65, 0.93)], placebo [OR 0.79, (0.64, 0.96)], or CCBs [OR 0.85, (0.73, 0.99)] (Fig. 1).

ACEIs treatment was associated with a significant reduction in the risk of new-onset diabetes in patients with hypertension [OR 0.80, (0.68, 0.93)], CAD or cardiovascular disease [OR 0.83, (0.68, 1.00)], or heart failure [OR 0.22, (0.10, 0.47)] (Fig. 2). Among patients with IGT or IFG, ramipril did not significantly reduce the incidence of diabetes [OR 0.91, (0.79, 1.05)], but significantly increased regression to normoglycemia.

4. Discussion

This meta-analysis indicated that ACEIs overall have beneficial effects on the prevention of new-onset diabetes, irrespective of achieved BP levels. ACEIs appear superior to beta-blockers/diuretics, placebo or CCBs for prevention of new-onset diabetes. ACEIs treatment was associated with significant reduced risk of new-onset diabetes in patients with hypertension, CAD or cardiovascular disease, or heart failure. Among patients with IGT or IFG, ramipril did not significantly reduce the incidence of diabetes, but significantly increased regression to normoglycemia.

In this study, it has demonstrated that ACEIs treatment was associated with significant reduced risk of new-onset diabetes in patients with hypertension, CAD or cardiovascular disease, or heart failure. It suggests that ACEIs could provide additional benefits of lowering the risk of new-onset diabetes in patients with hypertension, CAD or other cardiovascular disease. To be noted, there are conflicting results in patients with CAD among the relevant three trials [9,11,12] though the participants recruited in these 3 trials had large similar characteristics. Differing from the HOPE trial [11] and the PEACE trial [12], the incidence of new-onset diabetes was comparable between the perindopril group and the placebo group [389/5389 (7.2%) vs 397/5327 (7.5%), $P>0.05$] in the EUROPA trial with the data provided by a combined analysis [18]. However, it is conflicting about the incidence of new-onset diabetes in the EUROPA trial in different manuscripts [18,19]. It is reported that among the 10,716 non-diabetic patients at baseline in the EUROPA trial, only 6895 patients (6895/10,716, 64.3%) had a fasting glucose taken as part of the study [19]. Moreover, the distribution of these 6895 patients in the two groups was unavailable. So it may be incorrect about the incidence of new-onset diabetes in the 2 groups provide by the combined analysis [18].

Patients with IFG or IGT have an increased risk of T2DM. The DREAM trial [8] has found that among patients with IGT or IFG, the use of ramipril 15 mg for median 3.0 years, along with healthy diet and lifestyle, had no significant influence on the risk of the development of T2DM (40.3% vs 43.3%, $P>0.05$), though the incidence of regression to normoglycemia was significantly increased in the ramipril group than in the placebo group (42.5% vs 38.2%, $P<0.05$). Moreover, the incidence of the development of T2DM was comparable between ramipril group and placebo group in subgroup patients with isolated IFG, isolated IGT, or IFG combined with IGT respectively. The NAVIGATOR trial [20] has demonstrated that among patients with IGT combined with CV disease or CV risk factors, the use of valsartan 160 mg for median 5 years, along with lifestyle modification, led to a relative reduction of 14% in the incidence of diabetes (33.1% vs 36.8%, $P<0.0001$). At present, it is unreasonable to conclude that ARBs are superior to ACEIs in preventing new-onset diabetes in patients with IGT. On one hand, there were great differences between the DREAM trial and the NAVIGATOR trial in sample size (5269 vs 9306), follow-up period (median 3 years vs median 5 years), abnormal glucometabolic state (IGT or IFG vs IGT), age (54.7 ± 10.9 vs 63.8 ± 6.8), concomitant disease (no CV disease vs CV disease or CV risk factors) and the proportion of hypertensive patients (43.5% vs 77.5%). On the other hand, it has revealed that plasma glucose levels 2 h after an oral glucose load was significantly lower in the ramipril group than in