The role of renin blockers in the prevention of diabetes

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ABSTRACT

Objectives: To evaluate the role of renin blockers angiotensin converting enzymes inhibitors (ACEI) or angiotensin receptor blockers (ARB) in the prevention of diabetes.

Methods: We did a meta-analysis using the Cochrane group methodology of all available randomized controlled trials (RCTs) that evaluated the role of renin blockers in which outcomes of new-onset diabetes was reported. This meta-analysis was conducted between April 2005-April 2006 at King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia.

Results: Thirteen trials including 91,388 individuals met the inclusion criteria. There was a statistically significant reduction in the incidence of new-onset diabetes in patients receiving renin blockers compared to other antihypertensive agents [relative risks=0.79; 95% confidence interval=0.75-0.84). There was a statistically significant reduction in the incidence of new-onset diabetes in patients receiving renin–blockers compared to diuretics, conventional antihypertensive therapy (diuretics or beta-blockers), and calcium channel blockers.

Conclusion: Renin blockers reduce the incidence of new-onset diabetes and should be considered as first line therapy, when indicated, in patients at high risk for diabetes.

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The prevalence of diabetes is increasing all over the world. From 2003 to 2025, the worldwide prevalence of diabetes in adults is expected to increase from 190 million to 328 million.[1]

Diabetes is associated with 5.2% of global mortality and accounts for at least 10% of the total health care expenditure in many countries.[1,2] Hypertension (HTN) is associated with increased incidence of diabetes. Diabetes is also associated with left ventricular hypertrophy and congestive heart failure (CHF).[3] Renin blockers are well established therapeutic interventions in the management of HTN and CHF.[4,5] Renin blockers are shown to increase insulin sensitivity and therefore, are suggested as an effective intervention in preventing diabetes.[6] Interventions that can be utilized in the treatment of HTN, CHF and prevents diabetes are expected to have a significant impact on patients with these conditions.

The primary objective of this meta-analysis is to evaluate the role of renin blockers [angiotensin converting enzymes inhibitors (ACEI) or angiotensin receptor blockers (ARB)] in the prevention of diabetes.

Methods. We included randomized controlled trials (RCTs) of angiotensin converting enzyme inhibitors or ARBs in which the incidence of new onset diabetes was reported. Studies of adults of either gender (18 years or older) were accepted. We included studies that compared ACE inhibitors or ARBs to placebo or other antihypertensive medications.

The primary outcome was the reduction in the incidence of new onset diabetes. The following bibliographic databases were searched to identify the relevant primary studies: The Cochrane Controlled Trials Register (CCTR), MEDLINE, and EMBASE. A computerized search of MEDLINE was performed using the OVID platform, to search the MEDLINE database for articles published between January 1966 and June 2005, and the EMBASE database from 1980 to June 2005. The search strategy was conducted using the MeSH terms: "Angiotensin blockers" "Angiotensin Converting Enzymes Inhibitors", "Angiotensin Receptor Blockers", "Diabetes Mellitus", "Prevention", "Incidence", and "Randomized Controlled Trials". These terms were used in various combinations. The Cochrane library was searched for relevant articles using the same search strategy. Relevant articles were retrieved through a manual review of references. No language restrictions were applied.

All identified trials were reviewed independently by 2 reviewers to determine whether trials should be included or excluded. Disagreement was resolved by discussion. Both reviewers determined the methodological quality of each trial independently and any disagreement was resolved by discussion. The same 2 reviewers assessed the methodological quality of each trial according to Jadad score.[7] After independent evaluation, the 2 reviewers discussed the results for each study and any discrepancy was resolved by discussion. Data were independently extracted by the same reviewers and cross-checked, discrepancies were resolved by discussion.

The Cochrane Statistics package RevMan, version 4.2 was used in the analysis. Relative risk (RR) and risk difference (RD) with 95% CI's were reported. If there was a statistically significant RD the numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated. Heterogeneity was tested using the Cochrane Q statistic with significance at $p < 0.10$, in addition, we tested heterogeneity using the I^2 method with a value greater than 50% was considered to indicate substantial heterogeneity.[8] Potential sources of heterogeneity of treatment effect were explored using pre-specified subgroup analysis where there were sufficient studies to analyze including: dose of ACE inhibitor or the ARBs, and study quality variability. Whenever there is statistically significant between-study heterogeneity the weighted estimate of the typical treatment effect across trials (RR) was calculated using the random effects model to test robustness of the results.

Details of the included studies are provided in (**Table 1**). Thirteen trials including 91,388 individuals met the inclusion criteria. More than 45% of the participants were females. Studies duration ranged between 1 to 8 years (**Table 1**). The assessment of the quality of individual studies is presented in **Table 1**. All studies were analyzed using the intention to treat principle.

Results. There was a statistically significant reduction in the incidence of diabetes in trials that compared renin

Table 1 - Characteristics of included trials.

Study	Duration	Participants	Interventions	Jadad score
LIFE[9]	4 years	9193 patients, 55-80 years, with essential HTN and ECG signs of LVH	Losartan based compared with atenolol based regimens	5
ALLHAT[10]	8 years	33357 participants, aged ≥55 years with HTN and at least one other CHD risk factor	chlorthalidone 12.5-2.5 mg/d amlodipine 2.5-10 mg/d or lisinopril 10-40 mg/d	5
HOPE [11]	4.5 years	9,541 patients at high risk for cardiovascular disease.	Ramipril 10 mg compared with placebo	5
ANBP[12]	4.1 years	6083 patients with HTN, aged 65-84 years	Compared ACE I with diuretics	3
CAPPP[13]	6.1 years	10985 patients, men and women, aged 25-66 years with HTN	Captopril or conventional therapy with diuretics, ß-blocker or both	3
CHARM[14]	37.7 mos	7601 patients, aged mean age 66 years with symptomatic CHF	Compared candesartan with placebo	5
SCOPE[15]	3-7 years	4964 patients, aged 70-89 years with HTN	Compared candesartan with placebo.	5
AIPINE[16]	1 year	392 patients, mean age 55 years, with HTN	Compared candesartan with HCTZ alone or with ß blockers	5
VALUE[17]	4.2 years	15245 patients, with HTN treated and non-treated, aged ≥50 years	Compared valsartan-based therapy with amlodipine-based therapy.	5
STOP-2[18]	26 mos	6614 patients, aged 70-84 years with HTN	Compared conventional therapy with ACE I and calcium antagonist	3
PEACE[19]	4.8 years	patients with stable coronary artery disease, 46% had HTN, mean age 64 years	Compared trandolapril with placebo.	5
SOLVD[20]	2.9 years	Subgroup analysis of 391 patients Enrolled in SOLVD trial, mean age 56 years, 18% of patients with HTN	Compared enalapril with placebo.	5
DREAM[21]	3 years	5269 participants without cardiovascular disease but with impaired fasting glucose levels or impaired glucose tolerance	Compared ramipril (up to 15 mg per day) with placebo	5

LIFE - Losartan Intervention for Endpoint Reduction in Hypertension Study, ALLHAT - Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trail, HOPE - Heart Outcomes Prevention Evaluation Study, ANBP - Australian National Blood Pressure Study, CAPPP - Captopril Prevention Project, CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity, SCOPE - Study on Cognition and Prognosis in the Elderly Trial, AIPINE - Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation Trial, VALUE - Valsartan Antihypertensive Long-term Use Evaluation Trial, STOP 2 - Swedish Trial in Old Patients with Hypertension-2 Study, PEACE - Prevention Of Events with Angiotensin Converting Enzyme Inhibition Trial, SOLVD - Studies of Left Ventricular Dysfunction Trial, DREAM - Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Trial, HTN - hypertension, CHD - coronary heart disease, ACE - angiotensin converting enzyme, ECG - electrocardiography, LVH - left ventricular hypertrophy, HCTZ - hydrochlorothiazide.

blockers to placebo, (RR=0.83; 95% CI=0.77-0.90, NNT=568, test for heterogeneity: *p*=0.002, I²=76%). This effect remained statistically significant using the random effect model (RR=0.77; 95% CI=0.64-0.92).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 8 trials that compared renin blockers to other agents, (RR=0.79; 95% CI=0.75-0.84, NNT=436), **Figure 1**.

There was a statistically significant reduction in the incidence of diabetes in trials that compared renin blockers to calcium channel blockers, (RR =0.81; 95% CI=0.74-0.88, NNT=62).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 3 trials that compared renin blockers to diuretics, (RR=0.66; 95% CI=0.57-0.77, NNT=62).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 3 trials that compared renin blockers to conventional antihypertensive, (RR=0.79; 95% CI=0.72, 0.87, NNT=153).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 4 trials that compared renin blockers to placebo, (RR=0.83; 95% CI=0.77-0.91, NNT=56, test for heterogeneity: *p*=0.001, I²=81.9%). This effect remained statistically significant using the random effect model (RR=0.74; 95% CI=0.58-0.94)

There was a statistically significant reduction in the incidence of diabetes in the analysis of 5 trials that compared ACEI to other agents, (RR=0.79; 95% CI=0.72-0.86, NNT=290), Test for heterogeneity: *p*=0.03, I²=63.1%). This effect remained statistically significant using the random effect model (RR=0.78; 95% CI=0.67-0.90).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 2 trials that compared ACEI to diuretics, (RR=0.66; 95% CI=0.57-0.78, NNT=95).
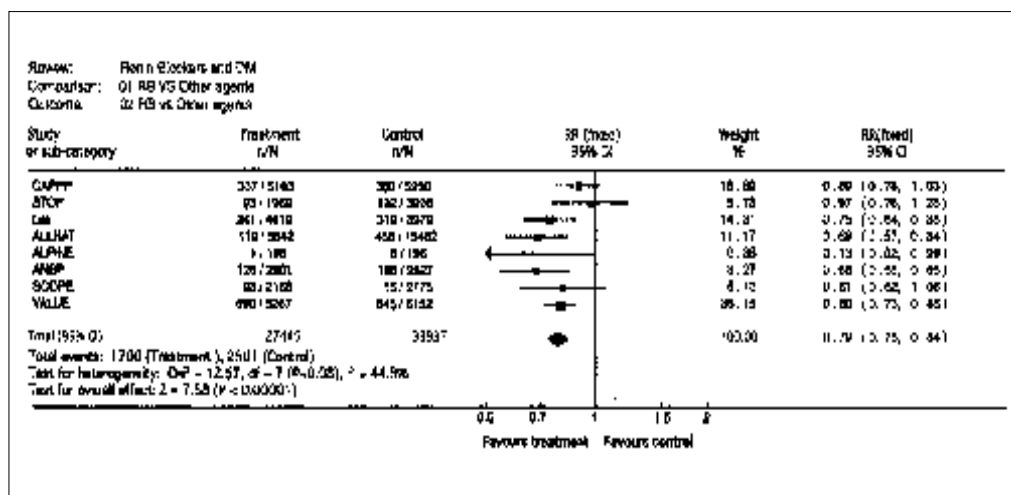

Figure 1 - Pooled analysis of eight RCTs evaluating the role of renin blockers in the prevention of diabetes.

Table 2 - Characteristics of ongoing studies.

Study	Participants	Interventions	Outcomes
ONTARGET[22]	25620 patients at high-risk for coronary, peripheral, or cerebrovascular disease	Telmisartan 80 mg, ramipril 10 mg, and telmisartan 80 mg plus ramipril 10 mg	Cardiovascular death, myocardial infarction, stroke, New onset diabetes, or hospitalization for heart failure
NAVIGATOR[23]	7,500 patients with impaired glucose tolerance and increased risk for a cardiovascular disease	Nateglinide 30–60 mg 3 times daily and Valsartan 80–160 mg once daily using a 2x2 factorial design	New onset diabetes mellitus and Cardiovascular morbidity and mortality

ONTARGET - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, NAVIGATOR - Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial

There was no statistically significant reduction in the incidence of diabetes in the analysis of 2 trials that compared ACEI to calcium channel blockers, (RR=0.84; 95% CI=0.70-1.01).

There was a statistically significant reduction in the incidence of diabetes in the analysis of 4 trials that compared ARB to other agents, (RR=0.78; 95% CI =0.73-0.85, NNT=42).

Discussion. Renin blockers are associated with significant reduction in the incidence of diabetes. This effect is associated with the use of ACEI or ARB, and is consistent when renin blockers are compared to placebo or the different classes of antihypertensive medications. The effect of renin blockers in the prevention of diabetes reported in this meta-analysis is an under-estimate of the real effect of renin blockers as most of the included trials reported significant use of renin blockers in the control group (**Table 1**). The beneficial effects of renin blockers in the prevention of cardiovascular morbidity and mortality in patients with hypertension, and congestive heart failure are well established.[4,5] The results of this meta-analysis support the use of renin blockers as the first line therapy, when indicated (namely, for the treatment of hypertension, and CHF), in patients at high risk for diabetes, such as patients with metabolic syndrome. We have to acknowledge that this analysis is based on the post hoc analysis of the included trials and most of the included trials were not designed to study the role of renin blockers in the prevention of diabetes. There are several ongoing trials designed to study the effects of renin blockers on the incidence of new-onset diabetes (**Table 2**).

Renin blockers reduced the incidence of new-onset diabetes and should be used as the first line therapy, when indicated, in patients at high risk for diabetes.

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Related topics

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