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Effect of Renin Angiotensin System [RAS] Blockade on Blood Glucose Levels in Prediabetic Hypertensive Patients

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Authors' contributions

This work was carried out in collaboration between all the authors. Author SB designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors VDR, DR and SRR managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Introduction: Patients with hypertension have an increased prevalence of type II diabetes mellitus and impaired glucose tolerance. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have pre-diabetes by 2030. A proportion of 5-10% of people per year with pre-diabetes will progress to diabetes, with the same proportion converting back to normoglycemia. Blockade of Renin Angiotensin System [RAS] either by an Angiotensin converting enzyme (ACE) inhibitor or an Angiotensin receptor blocker (ARB) would slow down the progression of prediabetic state to diabetes.
Methods: This was an open labeled, prospective, observational cohort study and a total of 71 prediabetic hypertensive patients who were prescribed either an ACE inhibitor or ARB monotherapy were enrolled into the study. An oral Glucose Tolerance Test (GTT) was done in all the patients at baseline, end of 6 months and end of 1 year of treatment with RAS blockade.
Results: At the end of 1 year, out of cohort of 59 prediabetic hypertensive patients who completed the study, 28.81% were in the Normal glucose tolerance (NGT) group, 23.72% developed diabetes whereas 47.45% remained prediabetic at the end of study.

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In the prediabetic group, significant negative correlation was observed between Initial Systolic Blood Pressure (SBP1), Age, their interaction (Age × SBP1) and fall in GTT. Significant regression of fall in GTT with SBP1 and interaction of age and initial SBP (Age × SBP1) implies that initiation of treatment at an early age, at lower initial systolic blood pressure levels have a beneficial effect on the glucose tolerance state.

Conclusion: In prediabetic hypertensive patients, the blockade of RAS with either ACE inhibitor or ARB has significant preventive effect on the progression of Type II DM. The beneficial effect is more marked if the RAS based pharmacotherapy is initiated at low initial systolic blood pressure, especially at a relatively younger age. The exact nature of beneficial role of RAS blockade in addition to their hypotensive effect should be investigated by further studies.

Keywords: Prediabetic; renin angiotensin system blockade; systolic BP; Age; glucose tolerance test.

1. INTRODUCTION

Hypertension is the leading cause of morbidity and mortality worldwide [1]. The concomitant manifestation of type II diabetes mellitus leads to a substantial further increase in risk [2]. It has been estimated that the prevalence of type II diabetes will double from 150 to 300 million in the next 25 years [3]. Insulin resistance often predates hypertension and has been found to predict the emergence of future hypertension in healthy, normotensive individuals [4]. Patients with hypertension have an increased prevalence of type II diabetes mellitus and impaired glucose tolerance [5]. Hypertension, obesity and diabetes or prediabetes cluster together in the pathogenesis of metabolic syndrome [6]. Prediabetes (intermediate hyperglycemia) is a high-risk state for diabetes that is defined by glycemic variables that are higher than normal, but lower than diabetes thresholds. About 5-10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycemia. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have prediabetes by 2030 [7]. Prediabetes is associated with the simultaneous presence of insulin resistance and β-cell dysfunction-abnormalities that start before glucose changes are detectable. Not only hypertensive patients with diabetes, but also hypertensive patients without diabetes tend to be resistant to insulin stimulated glucose uptake and are hyperinsulinemic compared with normotensive controls [8].

Prior studies suggest that treatment with different antihypertensive drug classes may have varying effects on glucose metabolism and changes in insulin sensitivity are associated with these adverse effects on glucose control [9]. Several trials involving hypertensive patients with prediabetes have suggested that agents that block or inhibit the renin angiotensin system [RAS] may also prevent development of type II diabetes. 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 [10]. 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. 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 which could improve insulin release by beta cells [11]. ARBs have been shown to act as a peroxisome proliferator activated receptor (PPAR)-gamma agonist, similar to the thiazolidonediones like rosiglitazone and pioglitazone, which

preserve pancreatic beta-cell function [12]. These experimental and clinical studies suggest that RAS blockade increases insulin sensitivity, skeletal muscle glucose transport, and pancreatic blood flow, which may contribute to the prevention of diabetes mellitus. Still the role of antihypertensive agents that inhibit the RAS in the acceleration or deceleration of diabetes manifestation remains controversial.

This study attempts to find the role of RAS blockade on the glucose tolerance in the hypertensive prediabetic patients. This study also attempts to find the contribution of other associated factors such as Age, Sex, BMI, and Blood pressure levels of patients on the blood glucose levels of patients on ACE inhibitors / ARBs.

2. MATERIALS AND METHODS

This was an open labeled, prospective, observational cohort study. The study was conducted at the Out Patient Department (OPD) of General Medicine, Mamata General Hospital, a tertiary care institute in the district of Khammam, Andhra Pradesh, India. Total duration of the study was one year i.e., from September 2011- August 2012.

The study protocol was approved by the Mamata Institutional Ethics Committee prior to the initiation of the study and written informed consent was taken from patients before enrolment into the study. Informed consent contains purpose of the study, plan of investigations, and the duration of follow up. The study purpose and plan was explained to patients and queries related to the study, if any were clarified.

2.1 Eligibility Criteria

2.1.1 Inclusion criteria

- Age ≥ 18 years and ≤75 years of either gender
- Systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg,
- Patients on monotherapy of ACE-inhibitors / Angiotensin II-receptor blockers for the control of their blood pressure.
- Impaired glucose tolerance with blood glucose levels between 140 – 200 mg/dl in oral Glucose Tolerance Test (Oral GTT)

2.1.2 Exclusion criteria

- Previous or current antidiabetic medications
- Patients with higher blood glucose levels > 200mg/dl, with overt diabetes
- "Brittle" pre-diabetic patients in whom the physician anticipates to initiate antidiabetic medications within next 6 months
- Hypertensive patients in whom the physician anticipates to start polytherapy within next 6 months
- Female patients who are pregnant or nursing or planning pregnancy within the duration of the study
- Suspected or known secondary cause of hypertension.

2.2 Visit Schedule

Patients presenting to OPD of General Medicine with the symptoms of hypertension and were prescribed ACE inhibitor/ARB monotherapy for the treatment of hypertension, were subjected to oral GTT after taking consent. Preparation for the oral GTT involves fasting overnight (from 8 to 16 hours) and participating normally in activities of daily living. The patient should eat and drink as they normally do prior to the test. The morning of the test, the person should not consume caffeine or smoke. These were the measures taken to control errors during interpretation of the test results. Seventy five grams of plain glucose was mixed in 100 ml of water and administered orally. The blood glucose levels were then measured after 2 hours of glucose intake by a standardized glucometer. Those patients with Impaired Glucose Tolerance (IGT i.e., oral GTT: 140-200mg/dl) were enrolled into the study. Second and third visit were scheduled at 6 and 12 months interval from the time of enrolment. SBP, DBP and blood glucose levels using oral GTT were measured during these visits.

2.3 Sample Size

A total of 72 prediabetic hypertensive patients were enrolled into the study, of whom 11 patients did not turn up for the second visit where as 2 patients did not turn up for the third visit and were treated as drop outs. A total of 59 patients who were on ACE inhibitors / ARBs completed one year of follow up and were subjected to analysis.

2.4 Statistical Analysis

Data is expressed as Mean ± SE. Statistical analyses was performed with Microsoft Excel program. One-way ANOVA was used to compare continuous variables among three groups i.e., NGT, IGT and Diabetic. The LSD method was used for multiple comparisons. Pearson correlations were used to evaluate the relation between blood glucose levels and different variables. Determination of nature of relationship was done by multiple regression analysis by overall and partial F test. The significance level was set as $P < 0.05$.

3. RESULTS

Out of 59 prediabetic hypertensive patients, 32 patients received ARBs (54.23%) and 27 patients received ACE inhibitors (45.76%). Losartan hydrochloride was the commonly prescribed ARB in a dose of 50 mg once or twice daily and Enalapril maleate was the commonly prescribed ACE Inhibitor in a dose of 5-10 mg once or twice daily. Mode of analysis was done based on sex distribution, age distribution and BMI distribution (as shown in Table No I, II and III).

Table No.I

Sex Distribution (N = 59)

Parameters	Female n = 24	Male n = 35
%	40.67%	59.32%
Age (Year)	49.38 ±11.54	49.23 ±10.64
BMI	26.52 ±5.14	27.51 ±5.21
BP (Systolic)	144.92 ±12.69	147.26 ±11.16
BP (Diastolic)	85.75 ±4.58	87.37 ±4.54
Blood Glucose (GTT) mg /dL	163.92 ±10.63	164.40 ±14.10

Table No. II

Age Distribution

Variables	Age (30-40)	Age (41-50)	Age (>50)
Number (%)	13 (22.03)	19 (32.20)	27 (45.76)
BMI	27.19 ± 4.34	28.58 ± 5.27	26.03 ± 5.36
Blood Glucose (mg/dL)	151.92 ±14.15	148 ± 23.02	177.15 ± 13.08
SBP (mmHg)	140 ± 10.39	142.11 ± 11.92	152.30 ± 6.49
DBP (mmHg)	83.38 ±3.5	85.38 ± 4.06	87.26 ± 3.04

Table No. III

BMI Distribution

BMI →	< 23.0 (Normal Wt)	23.0 - 27.5* (Overweight)	> 27.5* (Obese)
Number (%)	16 (27.11%)	20 (33.89%)	23 (38.98%)
Blood Glucose (mg/dL)	161.56 ±10.31	165 ±13.94	164.78 ±13.34
SBP (mmHg)	143.0 ±12.73	144.60 ±12.73	150.09±9.39
DBP (mmHg)	86.0 ±3.93	87.5 ±5.02	86.52 ±4.72

At the end of 12 months, patients were categorized into three groups depending on blood glucose in GTT, those with blood glucose levels less than 140mg/dl were termed as Normal Glucose Tolerance (NGT), between 140-200mg/dl as Impaired Glucose Tolerance (IGT) or prediabetic and more than 200mg/dl as diabetics (DM). At the end of study there were 17 (28.81%) patients with NGT, 28 (47.45%) with IGT and 14 (23.72%) with diabetes. The mean age of the diabetic group (54.0±11.8years) was higher than IGT (51.04±9.72years) and NGT (42.53±9.26 years). There was progressive increase in mean age as the glucose tolerance progresses from NGT to IGT and DM. Mean BMI of the prediabetic (27.84±5.27) and diabetic (27.52±4.96) were higher than normal glucose tolerant patients (25.56±5.10). The mean initial SBP and DBP was higher in diabetics (154.43±5.03; 90.0±4.44 mmHg) than prediabetics (146.0±12.37; 85.64±3.96 mmHg) and NGT (139.65±10.82;85.76±4.63 mmHg). The mean blood glucose levels in GTT was higher in the diabetic group (178.14±9.57mg/dl) than pre diabetic (163.36 ±9.92mg/dl) and NGT (154.12 ±8.10mg/dl) as shown in Table no IV.

One-Way ANOVA test was done for multiple comparison with LSD Test (as shown in Table no V) showed significant difference in age, initial SBP, initial DBP, fall in DBP and change in blood glucose in glucose tolerance test, among the three groups ($P < 0.05$). However BMI and fall in SBP did not show significant difference among the groups ($P > 0.05$). Patients of low age group (42.53 ± 9.26 yr) became euglycemic from pre-diabetic state, Patients of medium age group (51.04 ± 09.72 yr) remained as pre-diabetics and higher age groups (54.00 ± 11.82 yr) deteriorated from pre-diabetic state to diabetic state. After observing significant difference among groups in one way ANOVA test for multiple comparisons with LSD, parameters such as age, BMI, initial SBP, initial DBP, fall in SBP and fall in DBP were taken as independent variables and were correlated with the change in blood glucose levels in GTT (GTT Δ) as dependent variable by Pearson's correlation coefficient. Only initial systolic blood pressure (SBP1) had highly significant ($r = - 0.62$; $t = 4.06$; $P < 0.001$) correlation with change in GTT (GTT Δ). There was negative correlation (-0.62) between

SBP1 and GTT Δ indicating that if the initial systolic BP is low, there shall be significant decrease in GTT. The 'Age' of the patient also has shown significant negative correlation with GTT Δ ($r = -0.37$; $t = 2.04$; $P < 0.05$). As SBP1 and Age were showing significant correlation with fall in GTT, the interaction of age and SBP1 ['Age x SBP1'] was taken as an independent factor and correlated with the change in GTT Δ. Correlation and regression analysis were done in prediabetic, NGT and diabetic groups.

Table No. IV

Summarization at the End of Study

Criteria	NGT	Pre-diabetic/IGT	Diabetic(DM)
n (%)	17 (28.81)	28 (47.45)	14 (23.72)
Age (years)	42.53 ±9.26	51.04 ±9.72	54.0 ±11.82
BMI	25.56 ±5.10	27.84 ±5.27	27.52 ±4.96
NW / OW / OB %	7 /4 /6 41.18/23.53/35.29	8 /4 /16 28.57/14.29/57.14	2 /3 /9 14.29/21.43/64.28
+ve F/H (HTN &/or DM)	15 (41.17%)	17 (60.71%)	9 (64.29%)
SBP (mmHg)	139.65 ±10.82	146 ±12.37	154.43 ±5.03
DBP (mmHg)	85.76 ±4.63	85.64 ±3.96	90.0 ±4.44
Blood Glucose (GTT) mg/dL	154.12 ±8.10	163.36 ±9.92	178.14 ±9.57

NW = Normal Weight; OW = Overweight.; OB = Obese , HTN = Hypertension

Table no: V Comparison between the groups

Parameters	Prediabetics (n=28)	Diabetics (n=14)	Euglycemics (n=17)	P value
Age	51.04 ±9.72	54.00±11.82	42.53±9.26	** (p <0.05)
BMI	27.84±5.27	27.52±4.96	25.56±5.10	ns(p >0.05)
DBP1	85.64±3.96	90.00±4.44	85.76±4.63	**(p <0.05)
SBP1	146.29±12.37	154.43±5.03	139.65±10.82	**(p <0.05)
Δ DBP	3.57±4.40	9.00±4.82	5.29±4.36	**(p <0.05)
Δ SBP	4.57±6.57	8.29±5.01	4.47±8.23	ns(p >0.05)
Δ GTT	3.86±13.37	-29.21±29.57	24.00±7.50	**(p <0.05)
ONE WAY ANOVA TEST with multiple comparisons using LSD Test				

In prediabetic group, significant negative correlation between GTTΔ and 'Age' (r = 0.37, $P < 0.05$), 'SBP1' (r = 0.48, $P < 0.001$) and interaction of 'Age x SBP1' (r = 0.59, $P < 0.01$) was observed. There was no such correlation observed in NGT/euglycemic group (r = 0.48, $P > 0.05$). The diabetic group also showed no significant correlation between age, SBP1 and their interaction with GTT Δ. (r = 0.53, $P > 0.05$). As 'Diabetic' and 'Euglycemic' groups were not found to have significant correlation with GTT change, only the 'pre-diabetic' group was put under regression analysis. The factors 'Age', 'SBP1' and their interaction ('Age x SBP1') were subjected to 'Over all F test' and 'Partial F test'. In the overall F test, Age was not significantly ($P > 0.05$) responsible as an independent factor for change in GTT. But SBP1 and interaction of 'Age x SBP1' was significantly ($P < 0.05$) responsible for the change in GTT observed in prediabetic group. In partial F test, Age was again independently not found to be responsible for change in GTT, but the SBP1 and the interaction of 'Age x SBP1' were significantly ($P < 0.05$) responsible for the GTT Δ. From the regression analysis (overall and partial), the 'Age' factor by itself was not found to be responsible for fall in blood glucose level of GTT. The initial SBP (SBP1) was found to be highly responsible ($P < 0.01$) for the fall in GTT .The interaction of age and initial SBP (Age × SBP1) was found to be significantly ($P < 0.05$) responsible for fall in GTT.

4. DISCUSSION

The present study was undertaken to study the effect of ACE Inhibitors /ARBs on blood glucose level in hypertensive prediabetic patients by periodic oral Glucose Tolerance Test (GTT) and to evaluate the exclusive role of RAS blockade, if any, in relation to other contributing factors such as Age, Sex, BMI, Blood pressure which may have confounding effect on the outcome. In the clinical setting, several large-scale randomized controlled trials have shown that blockade of RAS with either ACE inhibitors or ARBs significantly reduces the incidence of new-onset diabetes. A number of trials have shown significant reductions in the incidence of type II diabetes with renin-angiotensin blocking treatment strategies in comparison to placebo, diuretics or beta blockers [13–19]. Most of these analyses were however post-hoc and endpoints are not predefined or the development of diabetes not the primary endpoint. Trials with a pre-defined new-onset diabetes endpoint were ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) [14], VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) [15], DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications) [13] and more recently, NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) [16]. While there was a significant reduction of new onset diabetes in ASCOT-BLPA, VALUE and NAVIGATOR, there was none in DREAM. The LIFE (Losartan Intervention For Endpoint reduction in hypertension) and VALUE studies have shown that Losartan and Valsartan reduce the incidence of new-onset diabetes compared with β-blocker–based and calcium channel blocker–based regimen respectively [15,17]. In the LIFE study, the incidence of new-onset diabetes was 25% lower in the Losartan group than in the atenolol group [17]. In the VALUE study, the incidence of new-onset diabetes was significantly lower in Valsartan-based regimen by 23% compared with an amlodipine-based regimen [15]. The Valsartan group had a greater proportion of patients taking concurrent thiazide diuretics. Despite the negative impact of thiazide diuretics on glucose metabolism, the Valsartan group had a lower incidence of new-onset diabetes than the amlodipine group [15]. In the SCOPE (Study on Cognition and Prognosis in the Elderly) trial, elderly patients (aged 70-89 years) with isolated systolic hypertension who were randomised to a candesartan treatment group were found to have a 28% reduction in the risk of developing new-onset diabetes over 3.6 years compared with those randomized to the placebo group [18]. In the recent PEACE (Prevention of Events with Angiotensin

Converting Enzyme inhibition) trial, patients with stable coronary artery disease had a significantly lower incidence of new-onset diabetes when randomised to trandalopril than the placebo over a median follow-up period of 4.8 years [19]. In the Ramipril-based versus Diuretic-based Antihypertensive Primary Treatment in Patients with Pre-diabetes (ADaPT) Study [20], both treatments were equally effective in reducing BP and new-onset diabetes was less frequent in the ramipril than in the diuretic group at the 4 year follow-up. However no significant differences were found for a change in HbA1c as well as for fasting blood glucose levels during follow-up [20]. Among the several meta-analyses [21–24] of which the one by Al-Mallah [21] is the most comprehensive and the one by Tocci [22] is the most recent one. The results of both meta-analyses were virtually identical although Al-Mallah also included results of trials with active comparators (diuretics, beta-blocker, and calcium channel blockers) while Tocci only considered placebo controlled trials. Al-Mallah reported a relative risk of 0.78 (95% CI 0.70–0.88) for the development of diabetes with ACE inhibitors and a relative risk of 0.8 (95% CI 0.75–0.86) for ARBs versus non-RAS based treatments [21]. In the analysis by Tocci both ACE inhibitors and ARBs reduced new-onset diabetes as compared to placebo [22]. Given that 50 to 100 patients have to be treated with RAS blocking agents to prevent one case of new onset diabetes [21]. For this purpose the oral glucose tolerance test (OGTT) is useful but it is not convenient under daily practice conditions and the determination of fasting glucose or the HbA1c alone yields low sensitivity (62 and 58% respectively) [25].

In our study, at the end of 1 year, out of cohort of 59 prediabetic hypertensive patients who completed the study, 28.81% were in NGT group, 23.72% developed diabetes whereas 47.45% remained prediabetic at the end of study. Our key finding is in line with the large prospective randomized studies such as ASCOT-BPLA, VALUE, DREAM and NAVIGATOR and meta-analyses, which reported a significantly reduced incidence of new-onset diabetes with RAS based pharmacotherapy in pre-diabetic, hypertensive patients. These findings in patients on ARBs can be attributed to their PPAR gamma agonist activity which is partly responsible for its euglycemic effect in addition to its hypotensive effect. On further analysis, our results have shown that in the prediabetic group, significant negative correlation was observed between initial SBP (SBP1), Age, their interaction (Age × SBP1) and fall in GTT. Significant regression of fall in GTT with SBP1 and interaction of age and initial SBP (Age × SBP1) implies that initiation of treatment at an early age, at lower initial systolic blood pressure levels have a beneficial effect on the glucose tolerance state.

5. CONCLUSION

In prediabetic hypertensive patients, the blockade of RAS with either ACE inhibitor or ARB has significant preventive effect on the progression of Type II DM. The beneficial effect is more marked if the RAS based pharmacotherapy is initiated at low initial systolic blood pressure, especially at a relatively younger age. The exact nature of beneficial role of RAS blockade in addition to their hypotensive effect should be investigated by further studies.

CONSENT

All authors declare that ‘written informed consent was obtained from the patients prior to their enrolment into the study.

ETHICAL APPROVAL

All authors hereby declare that the study was approved by the Mamata Institutional Ethics Committee prior to the initiation of the study and was therefore performed in accordance with the ethical standards laid down in the Declaration of Helsinki, 1964.

STUDY LIMITATIONS

1. Limitations of our study are mainly the observational, not randomized character, which doesn't prevent bias through unknown impacting parameter.
2. Follow-up period should have been more than a year as prediabetic hypertension is a long standing, chronic disorder.
3. Cardiovascular events should have been monitored as cardiovascular morbidity & mortality is quite high in prediabetic hypertensive patients.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. American Diabetes Association: Treatment of hypertension in adults with diabetes. Position statement. Diabetes Care. 2003;26:S80-82.
2. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003; 24(11):987-1003.
3. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21:1414 –31.
4. Pollare T, Lithell H, Berne C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. Metabolism. 1990;39(2):167-72.
5. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities-the role of insulin resistance and the sympatho adrenal system. N Engl J Med 1996;334:374–81.
6. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
7. Adam G Tabák, Christian Herder, Wolfgang Rathmann, Eric J Brunner, Mika Kivimaki. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;60:283-9
8. Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006;355(15):1551-62.
9. Lind L, Pollare T, Berne C, Lithell H. Long-term metabolic effects of antihypertensive drugs. Am Heart J. 1994;128:1177–83.
10. Uehara M, Kishikawa H, Isami S, et al. Effect on insulin sensitivity of angiotensin converting enzyme inhibitors with or without a sulphydryl group: bradykinin may improve insulin resistance in dogs and humans. Diabetologia. 1994;37:300–7.
11. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. Diabetologia. 1998;41:127–33.

12. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor gamma activity. Circulation. 2004;109:2054 –57.
13. Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, Diaz R, Avezum A, Lanas F, Probstfield J, Fodor G, Holman RR: Effect of ramipril on the incidence of diabetes. N Engl J Med 2006; 355(15):1551–62.
14. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: 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 controlled trial. Lancet. 2005;366(9489):895–906.
15. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022–31.
16. Califf RM, Boolell M, Haffner SM, Bethel MA, McMurray J, Duggal A, and Holman RR: 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(4):623–32.
17. Dahlof B, Devereux RB, Kjeldsen SE, et al. 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.
18. Papademetriou V, Farsang C, Elmfeldt D, et al. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol. 2004;44:1175-80.
19. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin converting- enzyme inhibition in stable coronary artery disease. N Engl J Med, 2004;351:2058-68.
20. Zidek W, Schrader J, Luders S, Matthaei S, Hasslacher C, et al. Ramipril-based versus diuretic-based antihypertensive primary treatment in patients with pre-diabetes (ADaPT) study. Cardiovasc Diabetol. 2012;11:1.
21. Al-Mallah M, Khawaja O, Sinno M, Alzohaili O, Samra AB: Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis. Cardiol J 2010;17(5):448–56.
22. Tocci G, Paneni F, Palano F, Sciarretta S, Ferrucci A, Kurtz T, Mancia G, Volpe M: Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers and Diabetes: A Meta-Analysis of Placebo-Controlled Clinical Trials. Am J Hypertens. 2011;24(5):582–90.
23. Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005;46(5):821–26.
24. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, Khunti K: Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334(7588):299.

25. Luders S, Hammersen F, Kulschewski A, Venneklaas U, Zuchner C, Gansz A, Schnieders M, Pfarr E, Sturm CD, Paar WD, Schrader J: Diagnosis of impaired glucose tolerance in hypertensive patients in daily clinical practice. Int J Clin Pract. 2005;59(6):632–8.

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