

Review Article

ACEIs/ARBs for the prevention of type 2 diabetes in patients with cardiovascular diseases: a systematic review and meta-analysis

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Abstract: Purpose: Several studies have demonstrated that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce the incidence of type 2 diabetes in patients with cardiovascular diseases. Therefore, a systematic review and meta-analysis was performed to assess the clinical efficacy of ACEIs and ARBs in preventing type 2 diabetes. Methods: Randomized controlled trials (RCTs) were retrieved from PubMed, Embase, the Cochrane Library and Clinical Trials go through August 2015. Two reviewers independently assessed search results, extracted data, and appraised risk of bias. Results: A total of 21 studies met the inclusion criteria with a total of 111,768 subjects. Thereinto, 55962 patients randomly received ACEIs or ARBs, and 55824 received anti-hypertensive agents or a placebo. ACEIs and ARBs were associated with reductions in the incidence of newly diagnosed type 2 diabetes (ACEIs RR 0.76, 95% CI 0.67-0.87, $P < 0.001$; ARBs RR 0.79, 95% CI 0.74-0.85, $P < 0.001$; pooled analysis RR 0.78, 95% CI 0.73-0.84, $P < 0.001$). Conclusions: ACEIs or ARBs can reduce the incidence of type 2 diabetes, especially in patients with hypertension, metabolic syndrome, pre-diabetes phase, congestive heart failure, or coronary heart disease. ACEIs or ARBs is accordingly recommended as the first line antihypertensive agents in patients with cardiovascular diseases.

Keywords: Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), type 2 diabetes, cardiovascular diseases, meta-analysis

Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) have been demonstrated to have favorable effects on patients with cardiovascular diseases [1, 2]. As extensive studies have demonstrated that hyperglycaemia is associated with both insulin resistance and β -cell dysfunction, ACEIs or ARBs treatment reduces the incidence of type 2 diabetes in patients with cardiovascular diseases through blocking renin-angiotensin system, which probably involving insulin resistance and β -cell dysfunction [3-6]. Possible mechanisms contributing to the reduced incidence of diabetes include improvement in insulin-mediated glucose uptake and enhanced endothelial function [7, 8]. Recent guidelines from European Society of Hypertension and the European Society of Cardiology recommend patients with cardiovascular risks to receive ACEIs or ARBs therapy [9, 10].

Several large-scale clinical trials showed that ACEIs or ARBs could reduce the incidence of type 2 diabetes at study endpoint far more than the other antihypertensive agents or placebo. However, the efficacy of ACEIs or ARBs in different trials showed variable inhibition for the new-onset type 2 diabetes. In this study, we conducted a meta-analysis of random controlled trials (RCTs) to assess the effects of ACEIs or ARBs therapy in reducing the incidence of type 2 diabetes and their clinical perspectives.

Materials and methods

Information sources and search strategy

We identified eligible studies through electronic databases, including Medline, Embase, the Cochrane Library, and Clinical Trials gov from inception to August 2015 using pertinent terms (angiotensin-converting enzyme inhibitors (or

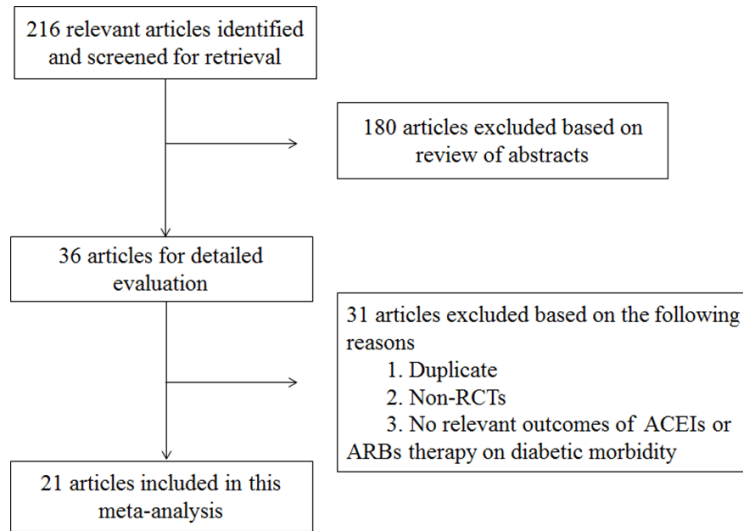


Figure 1. Flow diagram of citations.

ACEIs), angiotensin-receptor blockers (or ARBs), diabetes). In addition, we reviewed references from relevant original and review papers to identify eligible studies. There is no limit to the language in exploring literatures.

Study selection and data extraction

Studies meeting the following selection criteria were included in this meta-analysis: (i) The studies was RCTs comparing ACEIs or ARBs with placebo or other antihypertensive agents (such as calcium channel blocker (CCB), β -adrenoceptor blockers and diuretics); (ii) Follow-up duration was over at least one year; (iii) Treatment group and control group must report the morbidity of type 2 diabetes. Two reviewers independently screened and assessed the eligible trials to be included in this meta-analysis, and any discrepancy was resolved by consensus. To avoid duplication, the latest report was included in this study if the same group of patients were involved in multiple reports.

For each eligible trial included we extracted the following information: authors, year of publication, subject characteristics (age and sex), blood pressure (BP), body mass index (BMI), years of follow-up, sample size (treatment group and control group), the number of new-onset diabetes and morbidity, and so on.

Statistical analysis

We conducted this meta-analysis through Cochrane Collaboration's method. The random-effects model was used to consolidate data,

and calculate the relative risk (RR). Quantitative analysis was conducted based on the principle of intention to treat. The RR and 95% confidence intervals (CI) of new-onset diabetes were calculated for each outcome. The number of patients requiring treatment to reduce one new-onset diabetic subject was calculated utilizing the reciprocal of absolute risk reduction. Cochran's chi-squared test was used to examine heterogeneity among the included studies and I^2 , which is the proportion of the total variation due to heterogeneity between studies, was computed to determine the degree of inconsistency across studies. Heterogeneity was assessed by using I^2 statistics, with results ranging from 0 to 100% and values of 25, 50 and 75% representing low, moderate and high levels of heterogeneity, respectively [11]. Publication bias was assessed using visual inspection of funnel plots and Egger's weighted regression statistics, where asymmetrical funnel plot and Egger's p -value < 0.05 indicate potential publication bias [12]. All statistical analyses were performed by RevMan 5.0.

Results

A total of 21 trials (with data for 170483 subjects) fulfilling the inclusion criteria were included in this meta-analysis [13-33]. **Figure 1** presented the trial flow summary. The 21 trials were all published between 1999 and 2010 (**Table 1** with ACEIs and **Table 2** with ARBs). The follow-up time ranged from 1 year to 6.1 years. Subjects included mostly belonged to cardiovascular high-risk groups, and 111786 subjects were without diabetes at study entry. Characteristics of the studies included in the paper are presented in **Tables 1, 2**.

Heterogeneity test, sensitivity analysis and bias of publication

Heterogeneity test was performed in the all research results, and two subgroups (ACEIs and ARBs) were also conducted. The heterogeneity was detected in all studies and two sub-

ACEIs/ARBs for type 2 diabetes

Table 1. Characteristics of clinical trials included in the meta-analysis

Study	Year	ACEIs	Sample size	Follow-up (years)	Age (years)	BMI (kg/m ²)	BP (mmHg)	Risk factor	ACEI events (%)	ACEI overall number	Control events (%)	Control overall number	Risk ratio (95% CI)
Wright JT Jr [13]	2006	Ramipril	1094	3.8	55	31.00	150/95	HBP	45 (10.9)	410	70 (17.2)	204	0.53 (0.36-0.80)
Davis BR [14]	2002	Lisinopril	33357	4.9	66.9	29.76	146/84	HBP, CAD	119 (2.9)	4096	154 (3.8)	3954	0.74 (0.58-0.94)
Wing LM [15]	2005	Enalapril	6083	4.1	71.9	27.00	168/94	HBP	138 (4.92)	2800	200 (7.0)	2826	0.66 (0.53-0.83)
Hansson L [16]	1999	Captopril	10985	6.1	52.55	27.95	160/99	HBP	337 (6.5)	5183	380 (7.26)	5230	0.89 (0.76-1.03)
Bangalore S [17]	2006	Ramipril	5269	3	54.7	30.90	136/83	IFG/IGT	449 (17.1)	2623	489 (18.5)	2646	0.91 (0.79-1.05)
Yusuf S [18]	2001	Ramipril	9297	5	66	28.00	139/79	CAD	102 (3.6)	2837	155 (5.4)	2883	0.66 (0.51-0.85)
Rouleau JL [19]	2008	Quinapril	2553	2.95	61	Unclear	122/70	CAD	28 (2.4)	1159	35 (3.1)	1141	0.78 (0.47-1.29)
Braunwald E [20]	2004	Trandolapril	8290	4.8	64	Unclear	133/78	CAD, LVD	335 (9.8)	3432	399 (11.5)	3472	0.83 (0.71-0.97)
Vermes E [21]	2003	Enalapril	4228	3.4	56.45	Unclear	127/78	LVD	9 (5.9)	153	31 (22.4)	138	0.26 (0.12-0.57)
Hansson L [22]	1999	Enalapril/Lisinopril	6614	5	76	26.70	194/98	HBP	93 (4.7)	1969	97 (4.9)	1961	0.97 (0.73-1.31)

HBP-Hypertension; CVD-Cardiovascular disease; CAD-Coronary heart disease; LVH-Left ventricular hypertrophy.

Table 2. Characteristics of clinical trials included in the meta-analysis

Study	Year	ARBs	Sample size	Follow-up (years)	Age (years)	BMI (kg/m ²)	BP (mmHg)	Risk factor	ACEI events (%)	ACEI overall number	Control events (%)	Control overall number	Risk ratio (95% CI)
Lindholm LH [23]	2003	Candesartan	392	1	54.95	27.95	155/97	HBP	1 (1.5)	196	8 (4.1)	196	0.12 (0.01-0.97)
Ogihara T [24]	2008	Candesartan	4703	3.2	63.85	24.55	163/92	HBP, CVD	38 (2.8)	1343	58 (4.3)	1342	0.64 (0.43-0.98)
Yusuf S [25]	2003	Candesartan	7599	3.1	66	28	131/73	HF	163 (6.0)	2715	202 (7.4)	2721	0.80 (0.64-0.99)
Kasanuki H [26]	2008	Candesartan	2049	4.2	65	24.7	135/76	HBP, CAD	7 (1.1)	645	18 (2.9)	624	0.37 (0.15-0.89)
Sawada T [27]	2009	Valsartan	3031	3.27	66	Unclear	157/88	HBP, CVD	58 (5.2)	1116	86 (7.7)	1108	0.65 (0.46-0.92)
Lindholm LH [28]	2002	Losartan	9193	4.8	66.9	28.0	174/88	HBP, LVH	241 (6.0)	4019	319 (8.0)	3979	0.73 (0.62-0.87)
McMurray JJ [29]	2010	Valsartan	9306	5	63.7	30.4	139/82	IGT/IFG, CVD	1532 (33.1)	4631	1722 (36.8)	4675	0.85 (0.78-0.92)
Sloan MA [30]	2008	Telmisartan	20332	2.5	66.15	26.8	144/84	Stroke	125 (1.7)	7306	151 (2.1)	7283	0.82 (0.65-1.04)
Gayet JL [31]	2003	Candesartan	4937	3.7	76.4	26.95	166/90	HBP	93 (4.3)	2167	115 (5.3)	2175	0.80 (0.61-1.06)
Yusuf S [32]	2008	Telmisartan	5926	4.6	66.9	28.15	141/82	CVD	359 (20.1)	1895	393 (21.6)	1913	0.90 (0.77-1.06)
Julius S [33]	2004	Valsartan	15245	4.2	67.25	28.65	155/88	HBP, CVD	690 (13.1)	5267	845 (16.4)	5152	0.77 (0.69-0.86)

HBP-Hypertension; CVD-Cardiovascular disease; CAD-Coronary heart disease; LVH-Left ventricular hypertrophy.

Table 3. The results of stratified analysis

Variables	RR/95% CI	P	I ²	Q test model
Diabetes incidence as preset destination event	0.81 (0.73-0.90)	< 0.001	49%	Random
Diabetes incidence postmortem analysis	0.77 (0.70-0.84)	< 0.001	49%	Random
Follow-up time > 4	0.80 (0.75-0.86)	< 0.001	43%	Random
Follow-up time ≤ 4	0.72 (0.62-0.85)	< 0.001	56%	Random
Average age ≥ 65	0.78 (0.72-0.83)	< 0.001	28%	Random
Average age < 65	0.79 (0.70-0.90)	< 0.001	61%	Random
Hypertension	0.75 (0.68-0.83)	< 0.001	44%	Random
No hypertension	0.82 (0.76-0.90)	< 0.001	45%	Random
Placebo as control	0.82 (0.76-0.90)	< 0.001	45%	Random
Calcium ion antagonists as control	0.76 (0.69-0.83)	< 0.001	0%	Random
Other antihypertensive agents as control	0.73 (0.63-0.85)	< 0.001	55%	Random

Table 4. Heterogeneity test of ACEIs or ARBs for diabetes incidence

Study	RR	95% CI	I ²	Q test model
ACEIs and ARBs	0.78	0.73-0.84	48%	Random
ACEIs	0.76	0.67-0.87	63%	Random
ARBs	0.79	0.74-0.85	29%	Random

group, but I² was no more than 75%. Random-effects model accordingly was used for pooled data (**Table 4**). Sensitivity analysis showed that changes of RR and the upper and lower limits 95% CI were little after deleting certain data and eccentric points [21, 23, 26], which showed certain reliability. To recognize and control publication bias to further evaluate reliability of meta-analysis, we drew funnel plot through Review Manager 5 to observe its symmetry (**Figure 11**). Analysis results for funnel plots reminded unsymmetrical distribution in RR values and publication bias (ACEIs, P=0.012; ARBs, P=0.003). Trim and fill method was used to analyze publication bias, and there was no statistical difference in effect sizes (RR) before and after, which showed that publication bias was little and data were reliable.

ACEIs therapy and incidence of type 2 diabetes

In total of 10 studies investigated the therapeutic effects of ACEIs on new-onset type 2 diabetes [13-22]. A total of 87770 patients were included, and the average follow-up time was 4.3 years. In these ten studies, only one trial regarded incidence of type 2 diabetes as pre-set destination event [17], and the rest as retrospective analyses. The study performed by

Bangalore S et al. [17] compared ramipril with placebo to investigate the information about new morbidity and mortality in subjects with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) but no cardiovascular disease. Although trial data showed no significant difference between two groups (RR 0.91, 95% CI 0.79-1.05, P=

0.15), incidence rate in ramipril group was less than control group (17.1% versus 18.5%), and glucose levels of subjects with IFG or IGT were improved better at the study endpoint (HR 1.16, 95% CI 1.07-1.27, P=0.001). Four studies included [16, 17, 19, 22] showed no significant difference between ACEIs and control. However, the therapeutic effects of ACEIs were better than other antihypertensive agents or placebo in preventing new-onset diabetes through summarizing above clinical data. The total number of new-onset patients with diabetes was 3665, including 1655 in ACEIs group and 2010 in control group. ACEIs could significantly reduce the diabetic risk of 22% (RR 0.76, 95% CI 0.67-0.87, P < 0.001) (**Figure 2**). Data were pooled relative risks and 95% CI calculated by network meta-analysis of direct and indirect evidence from 10 studies [13-22]. Absolute risk reduction of ACEIs therapy in reducing new morbidity was 0.01 (1%).

ARBs therapy and incidence of type 2 diabetes

There were 11 reported studies to assess the therapeutic effects of ARBs on new-onset type 2 diabetes [23-33]. A total of 62468 patients were enrolled, and the average follow-up time was 3.6 years. In these studies, the new incidence of type 2 diabetes was set as pre-set

ACEIs/ARBs for type 2 diabetes

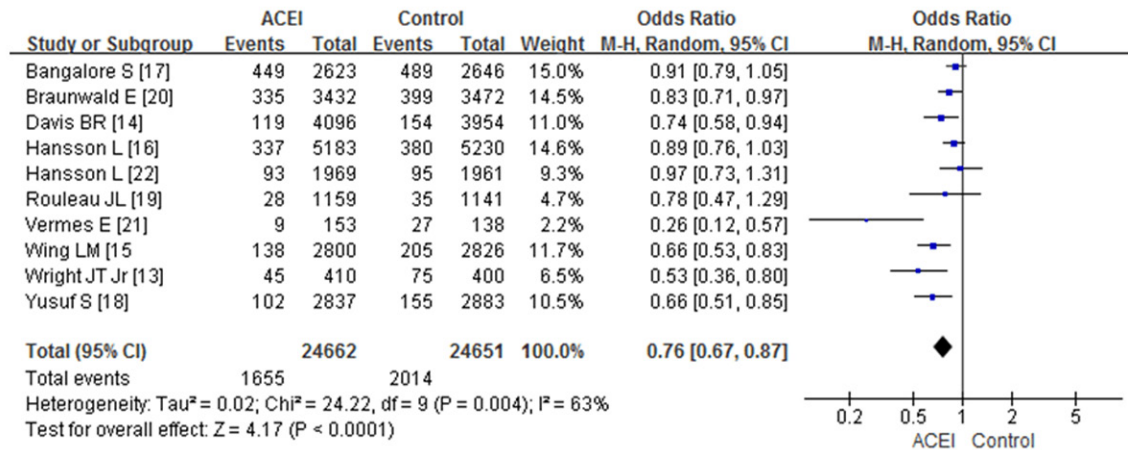


Figure 2. The meta-analysis for the ACEIs lowering new morbidity of diabetes.

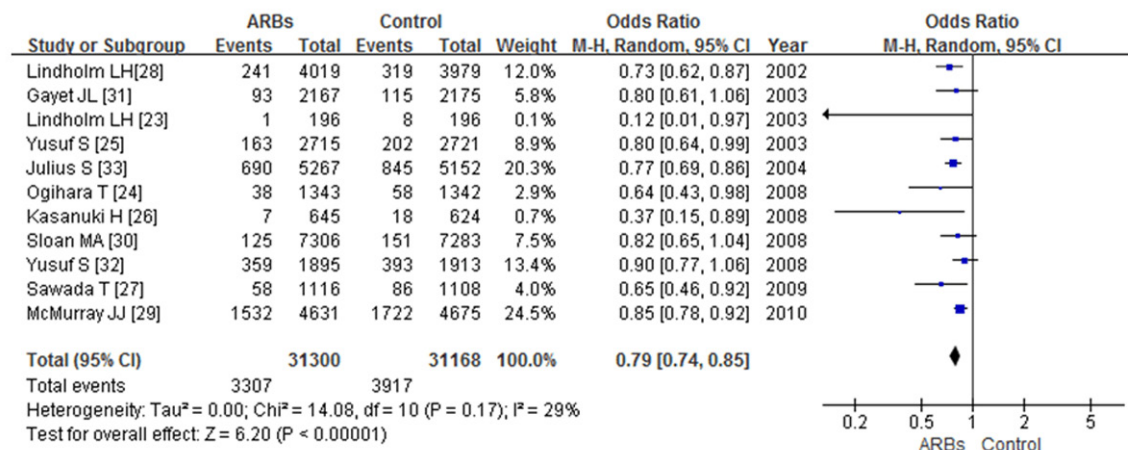


Figure 3. The meta-analysis for the ARBs lowering new morbidity of diabetes.

destination event in six trials [23-25, 29, 30, 33], and the rest as retrospective analyses. Lindholm LH et al. [23] compared candesartan with diuretics for the effects on glucolipid metabolism and BP. The results showed that diabetic morbidity in candesartan was significant less than control (0.5% versus 4.1%; RR 0.13, 95% CI 0.02-0.99, $P = 0.030$). But it was important to note that this study had some limitations, including short follow-up time and few subjects. McMurray JJ et al. [29] investigated whether valsartan could reduce the incidence of diabetes and cardiovascular diseases in subjects with IFG or IGT and meanwhile with cardiovascular diseases or cardiovascular risk factors. The trial data showed that diabetic morbidity in valsartan was significantly less than in placebo (33.1% versus 36.8%) (RR 0.86, 95% CI 0.80-0.92, $P < 0.001$). In all trials included, only three trials [30-32] showed no statistical

difference between ARBs and control. However, ARBs showed better efficacy than the other antihypertensive agents or placebo in preventing diabetes through clinical data analysis. The overall number of new-onset patients were 7224, including 3307 in ARBs group and 3917 in control group. ARBs could reduce the diabetic risk of 22%, which existed statistical significance (RR 0.79, 95% CI 0.74-0.85, $P < 0.001$) (Figure 3). Absolute risk reduction of ARBs therapy in reducing new diabetic morbidity was 0.02 (2%).

ACEIs and ARBs therapy and incidence of type 2 diabetes

Average follow-up time ranged from 1 year to 6.1 years in this meta-analysis. Control group contained CCB, β -receptor blocker, diuretics and placebo. After analyzing 111786 subjects

ACEIs/ARBs for type 2 diabetes

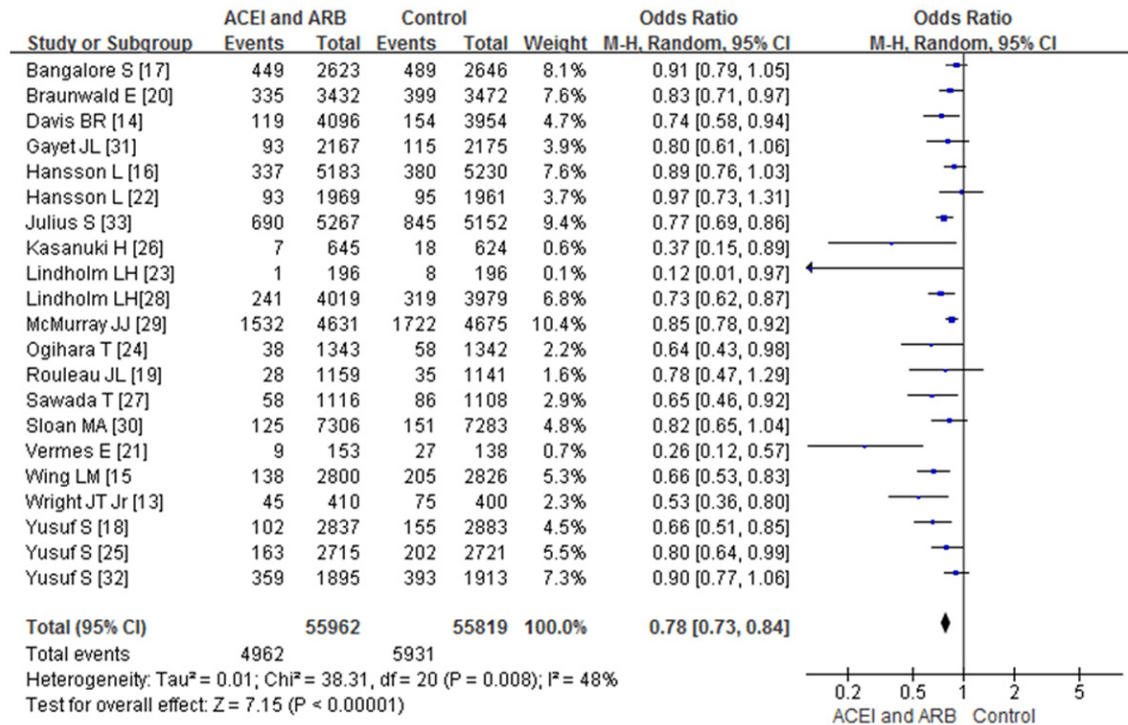


Figure 4. The meta-analysis of ACEIs and ARBs in lowering new morbidity of diabetes.

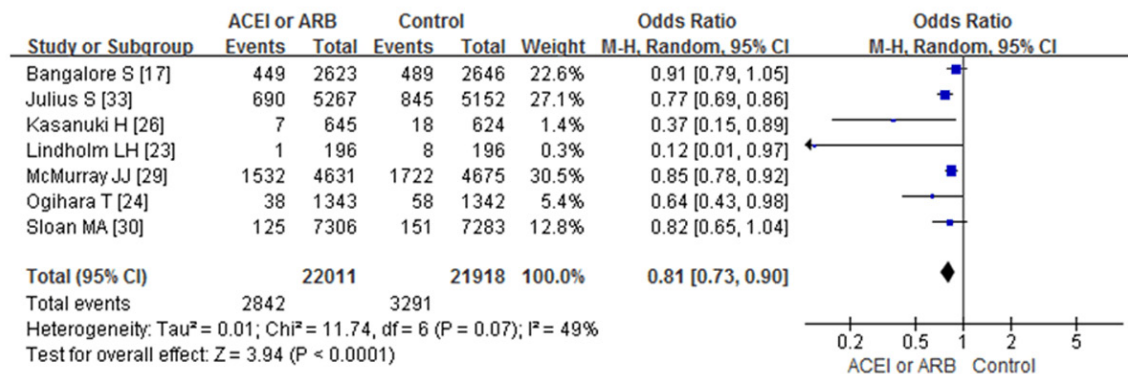


Figure 5. The new incidence of diabetes as pre-set endpoint event (ACEIs and ARBs).

without diabetes, it was found that 4962 new onset diabetic patients (8.87%) in group receiving ACEIs or ARBs, and 5972 patients (10.62%) in control group. Compared with control, ACEIs and ARBs could significantly reduce 20% onset risk of diabetes (RR 0.78, 95% CI 0.73-0.84, $P < 0.001$) (Figure 4), with statistical significance.

Stratified analysis

All the studies included in this meta-analysis were further performed to stratified analysis. Variables set included diabetic morbidity, fol-

low-up time, average age, hypertension and agents in control group. The results of stratified analysis were showed in Table 3.

The new incidence of diabetes as pre-set endpoint event or retrospective analysis

A total of 7 studies containing 43929 subjects regarded new incidence of diabetes as pre-set endpoint event. New diabetic patients were identified as 6133 subjects (13.96%) at end point. Compared with control (15.02%), diabetic morbidity in ACEIs or ARBs was reduced significantly (12.91%) (RR 0.81, 95% CI 0.73-0.90,

ACEIs/ARBs for type 2 diabetes

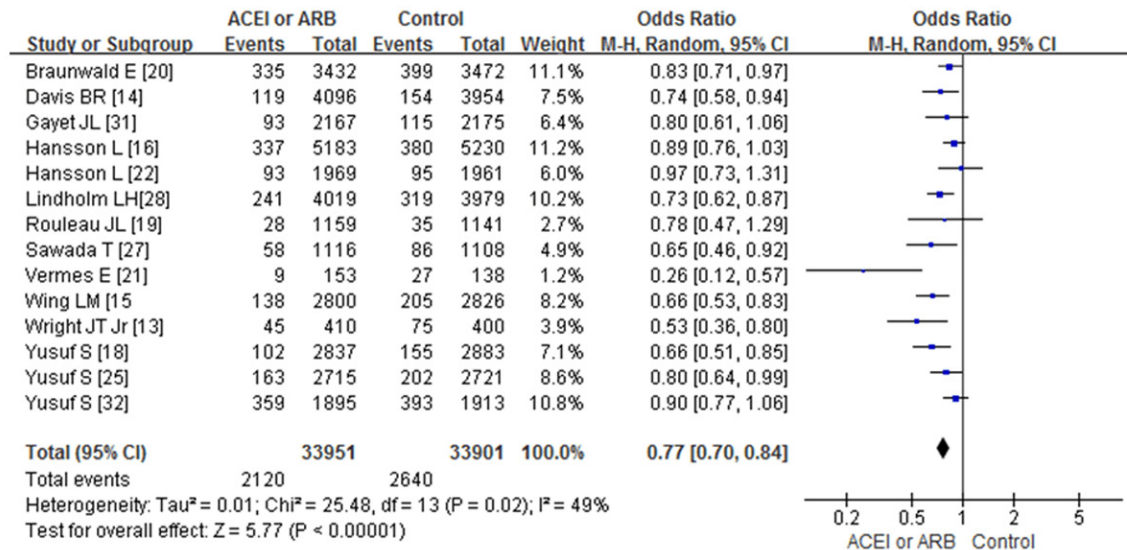


Figure 6. The new incidence of diabetes as retrospective analysis (ACEIs and ARBs).

$P < 0.001$) (**Figure 5**). New incidence of diabetes was set as retrospective analysis in 14 studies including 67857 subjects. New diagnosed diabetes were 4756 subjects (13.96%) at end point, 2120 in ACEIs or ARBs group (6.24%) and 2636 in control group (7.77%). Compared with control, risk of diabetes was reduced by 22% in ACEIs or ARBs (RR 0.77, 95% CI 0.70-0.84, $P < 0.001$) (**Figure 6**).

Average follow-up time

Average follow-up time > 4 years was identified in 11 studies containing 73442 subjects. New diagnosed patients were 8635 subjects (11.76%) at end point, 3953 in ACEIs or ARBs group and 4682 in control group. Compared with control (12.77%), new incidence of diabetes in ACEIs or ARBs was reduced significantly (10.75%) (RR 0.80, 95% CI 0.75-0.86, $P < 0.001$) (**Figure 7**). In addition, average follow-up time in 10 trials was less than 4 years. New diagnosed patients were 2254 subjects (5.88%) at end point. Compared with control (1245, 6.50%), new incidence of diabetes in ACEIs or ARBs was reduced significantly (1009, 5.26%) (RR 0.72, 95% CI 0.62-0.85, $P < 0.001$) (**Figure 7**).

Average age

Average age of patients ≥ 65 years was identified in 12 studies containing 73411 subjects, 2188 (5.94%) in ACEIs or ARBs group and 2735 (7.48%) in control group. Compared with control, new incidence of diabetes in ACEIs or ARBs

was reduced significantly (RR 0.78, 95% CI 0.72-0.83, $P < 0.001$) (**Figure 8**). Average age of subjects < 65 years was identified in 9 studies containing 38375 subjects, 2774 (14.50%) in ACEIs or ARBs group and 3192 (16.59%) in control group. New incidence of diabetes in ACEIs or ARBs group was less than in control group (RR 0.79, 95% CI 0.70-0.90, $P = 0.0002$) (**Figure 8**).

Whether or not suffering from hypertension

Subjects with primary hypertension in the baseline were observed in 12 trials. New-onset patients with diabetes were 4210 (7.24%), 1860 in ACEIs or ARBs group and 2350 in control group. Compared with control (8.12%), new incidence of diabetes in ACEIs or ARBs was reduced significantly (6.37%) (RR 0.75, 95% CI 0.68-0.83, $P < 0.001$) (**Figure 9**). A total of 9 studies contained subjects without diagnosed primary hypertension in the baseline. A total of 53623 subjects were included, and diagnosed diabetic patients were 3102 (11.60%) in ACEIs or ARBs group and 3577 (13.31%) in control group, respectively. incidence of diabetes in ACEIs or ARBs group was less than in control group (RR 0.82, 95% CI 0.76-0.90, $P < 0.001$) (**Figure 9**).

Agents in control group

According to the types of antihypertensive agents used, clinical trials were divided into

ACEIs/ARBs for type 2 diabetes

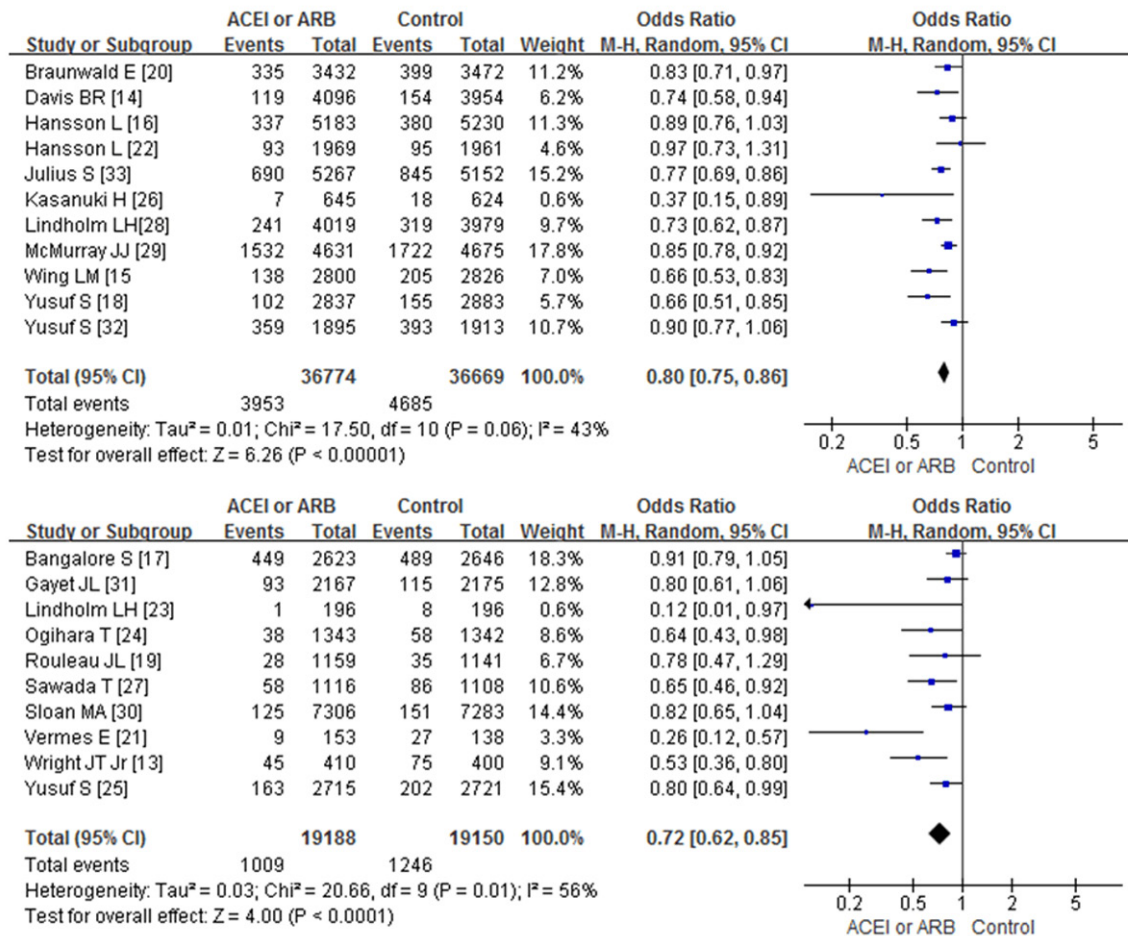


Figure 7. ACEIs or ARBs therapy affecting incidence of diabetes in different follow-up time.

placebo group, CCB group, and conventional antihypertensive drug group (including β -adrenoceptor blockers and diuretics). The enrolled studies were, in order, 9, 3 and 9. Compared with above three group, ACEIs or ARBs could reduce incidence of diabetes (RR 0.82, 95% CI 0.76-0.90, $P < 0.001$; RR 0.76, 95% CI 0.69-0.83, $P < 0.001$; RR 0.73, 95% CI 0.63-0.85, $P < 0.001$) (Figure 10).

Discussion

In this meta-analysis, we conducted statistical analysis for 21 studies included and systematically estimated ACEIs or ARBs prevention for diabetes from multiple levels. ACEIs and ARBs play function both involving ACE-Ang II-AT1R, and ACEIs can be replaced by ARBs during ACEIs intolerance. Some other studies demonstrated that the efficacies of ACEIs and ARBs in improving diabetic morbidity, glycometabolism and cardiovascular disease were no significant

difference [34, 35]. Hence, we merged ACEIs and ARBs to perform analysis. Our findings showed ACEIs and ARBs could reduce the onset risk of 22% and 18%, respectively. In addition, absolute risk reductions under the treatment of ACEIs and ARBs were 0.01 and 0.02, respectively.

Previous meta-analysis for ACEIs or ARBs lowering diabetic morbidity also proved that they were beneficial to reduce diabetic morbidity [36]. By contrast, this study incorporated more trials with large sample size, including the study performed by McMurray JJ et al. [29]. Whether valsartan could reduce diabetic morbidity was set as the first endpoint event, which made the results more representative and reliable. Whether ramipril could reduce diabetic morbidity in subjects with IFG/IGT was regarded as the first endpoint event in another trial [17]. Compared with control, ACEIs or ARBs could reduce the 10% morbidity.

ACEIs/ARBs for type 2 diabetes

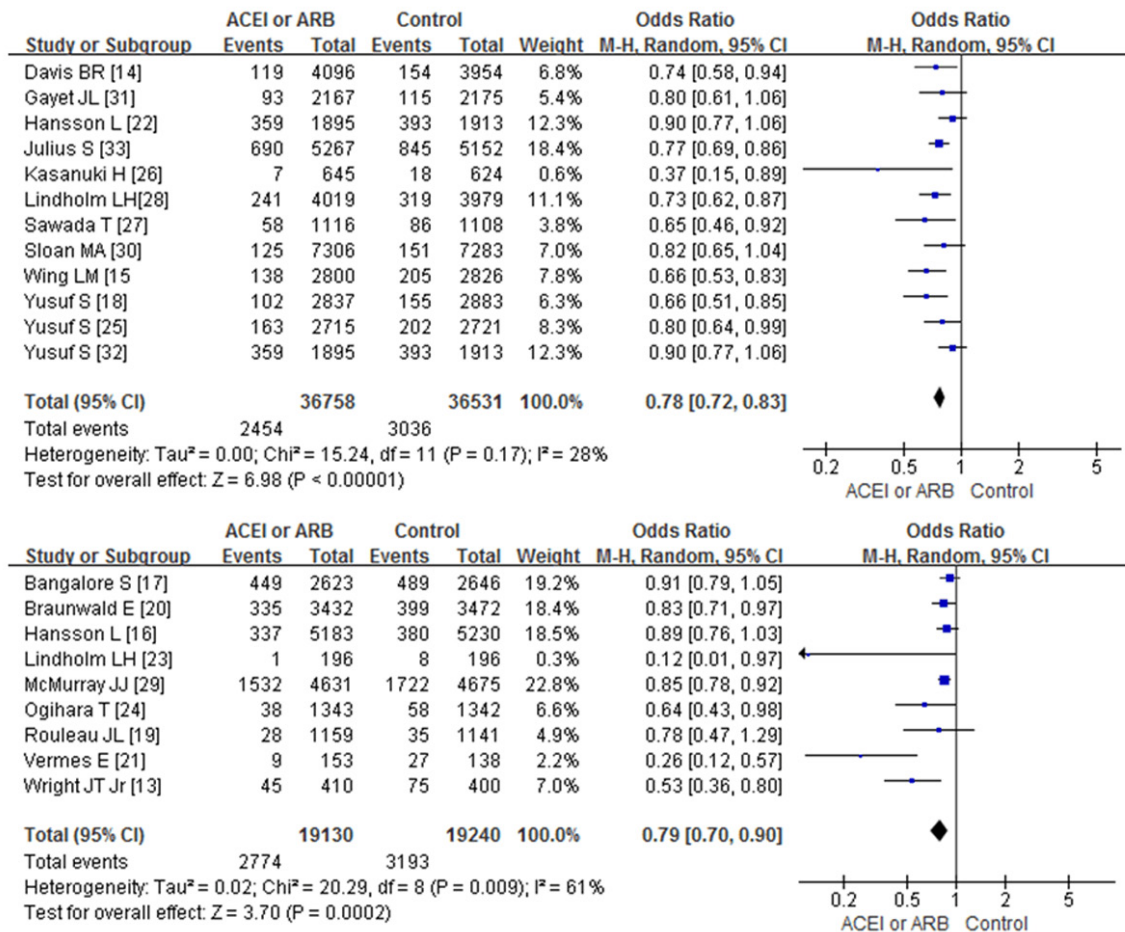


Figure 8. The meta-analysis for the relationship between average age and morbidity of diabetes.

The therapeutic efficacies of ACEIs or ARBs were not completely equivalent in all the studies. Some trials [18, 20, 29, 33] demonstrated the efficacy of ACEIs or ARBs in lowering diabetic morbidity, while some other trials [16, 17, 30, 32] could not prove it. As everyone knows that most of studies belonged to sampling research, which usually involved in representativeness of samples and statistical inference. Under the influences, such as race, region, life style, sample size, etc. one research conclusion does not always apply to the other situations. Meanwhile, we could notice that the different agents in control group had different effects on diabetic morbidity. The agents in control group, placebo had no effects on glycometabolism, CCB had neutral role and β -adrenoceptor blockers and diuretics probably increased diabetic morbidity, which indicated that one conclusion was not in step with the all.

Sub-group analyses for the incidence of type 2 diabetes were performed to reduce confound-

ing factors between different studies to further increase reliability of results. Whatever the incidence of diabetes was identified as the pre-set endpoint event or retrospective analysis, ACEIs and ARBs had better therapeutic effects compared with the control. The patients with and without hypertension, duration of follow-up and age all would not affect therapeutic effects with ACEIs and ARBs in reducing the incidence of type 2 diabetes. Although the decreased risks (RR 0.63~0.84) were different in the different sub-group analyses, this range was consistent with the merged RR (0.80), which indicated that ACEIs and ARBs have wide indications in clinical practice.

Most of subjects enrolled in the study were associated with cardiovascular risk factors, such as hypertension, coronary heart disease, congestive heart-failure, impaired glucose tolerance, etc. These risk factors have a close relationship with insulin resistance and poten-

ACEIs/ARBs for type 2 diabetes

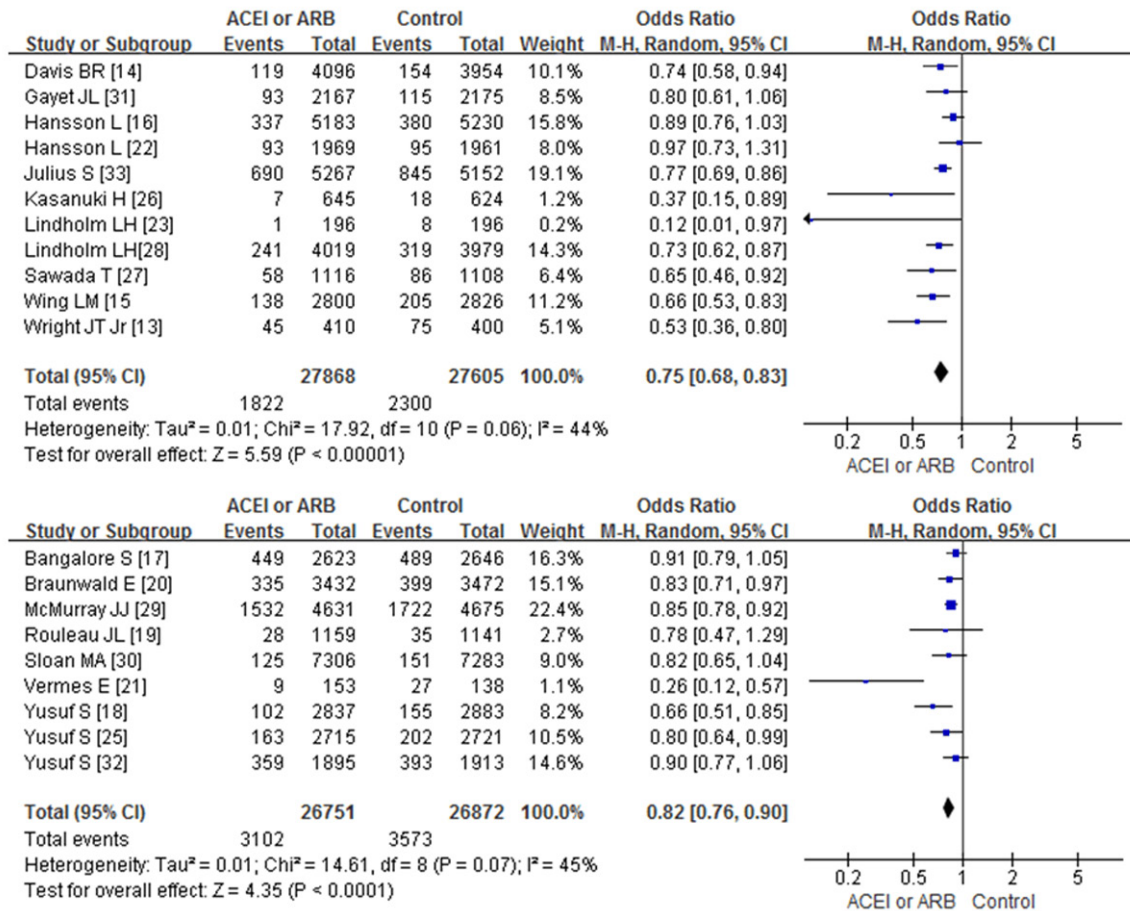


Figure 9. The meta-analysis for the relationship between subjects with or without hypertension and morbidity of diabetes.

tially increase the incidence of diabetes and in the meantime, type 2 diabetes probably deteriorates the long-term prognosis of patients with cardiovascular diseases. Therefore, diabetes prevention becomes particularly important [37]. Insulin resistance, regarded as prediction for type 2 diabetes, is considered as a key factor for the incidence of hypertension. One reported study indicated that 42% of diabetic patients have normal blood pressure levels, and 56% of hypertensive patients have normal blood glucose levels [38]. In essence, hypertension and type 2 diabetes have common disease pathways, such as obesity, inflammatory responses, oxidative stress, insulin resistance and mental stress [39]. This study demonstrated that ACEIs or ARBs could reduce the incidence of diabetes compared with placebo, calcium ion antagonist and conventional antihypertensive agents, which showed the advantage of ACEIs and ARBs in improving onset risk

of diabetes, as American Diabetes Association pointed out [40]. Therefore, ACEIs or ARBs should be proposed as the first antihypertensive agent for patients with high onset risk of type 2 diabetes, such as family history of type 2 diabetes, obesity, metabolic syndrome, IFG or IGT.

ACEIs and ARBs have benefits in the protection of heart in addition to decrease blood pressure [41]. ACEIs and ARBs have better pharmacological activity in improving endothelial cell functions and remodeling left ventricular hypertrophy [41]. In addition, they can reduce mortality of cardiovascular disease, myocardial infarction, stroke and sudden cardiac arrest [41]. In the treatment of hypertension guidelines, such as JNC7, ACEIs are the only one with all six powerful adaptations (cardiac failure, myocardial infarction, coronary artery disease risk factors, diabetes, chronic nephrosis and prevention of

ACEIs/ARBs for type 2 diabetes

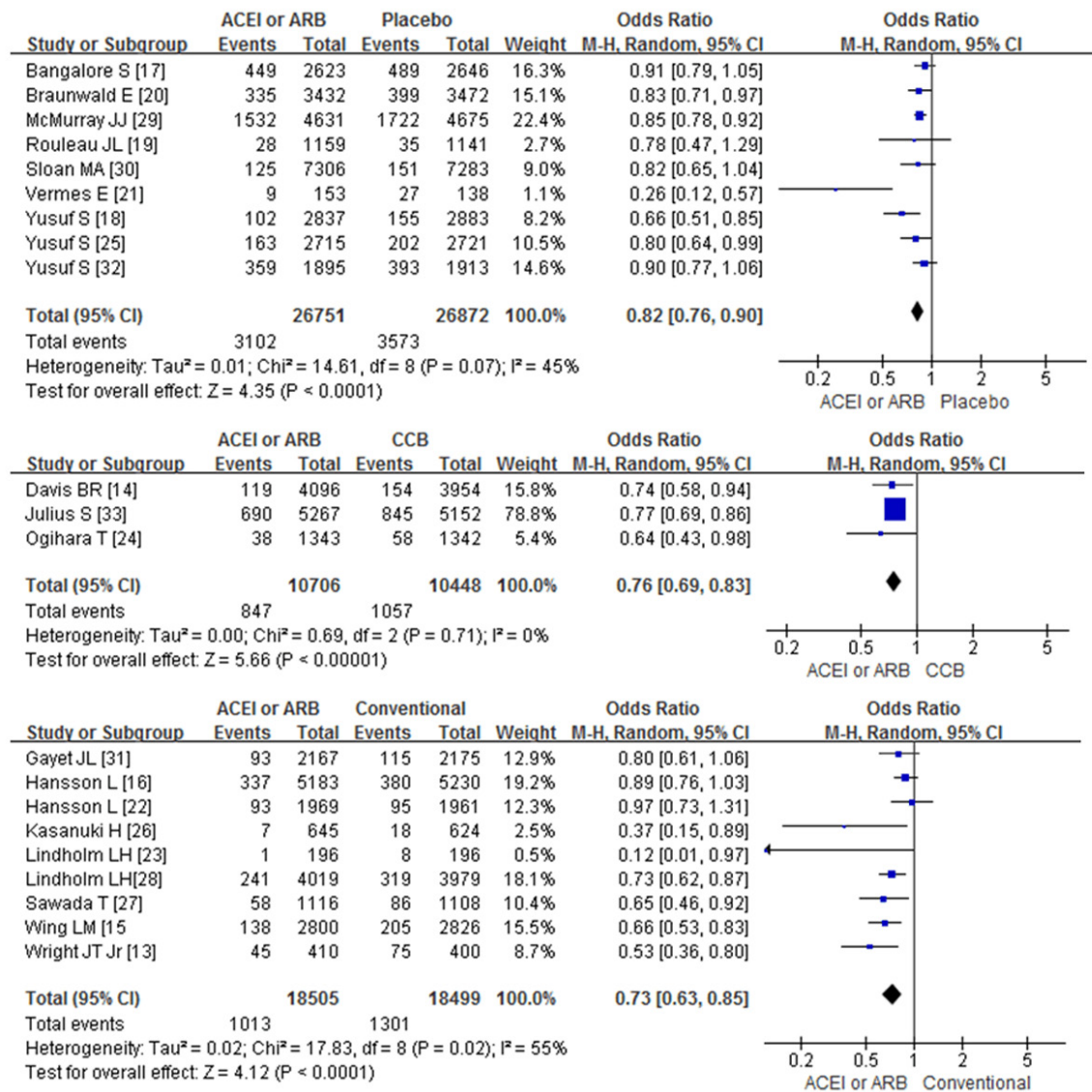


Figure 10. The meta-analysis for the relationship between different agents in control group and morbidity of diabetes.

recurrence of stroke). ARBs have three powerful adaptations (cardiac failure, diabetes and chronic nephrosis) [42]. Therefore, ACEIs and ARBs have more pharmacological benefits in patients with insulin resistance related diseases (metabolic syndrome, hypertension, IFG, family history of diabetes, obesity, congestive heart-failure) from two aspects: cardiovascular function and glucose metabolism function.

Like any other studies, the increased confounding factors, including sample size and quantity of RCTs, experimental design, characteristics of subjects, the definition for follow-up observation and endpoint event, will affect experimen-

tal results to some extent. Firstly, eight experiments were open-label in all enrolled studies [13, 15, 16, 22, 24, 26, 27, 30], and the rests were double-blind randomized controlled studies. Secondly, the diagnostic criteria of diabetes changed after 1999. The published studies before 1999 employed the earlier standard ($FBG \geq 7.8$ mmol/l), and later researches use the current standard ($FBG \geq 7.0$ mmol/l). Thirdly, the new incidence of type 2 diabetes was identified as the pre-set endpoint event in seven studies [17, 23, 24, 26, 29, 30, 33], and the rest as retrospective analysis. Fifth, this analytical investigation was grouped in the drug category, but it was worth noting that dif-

ACEIs/ARBs for type 2 diabetes

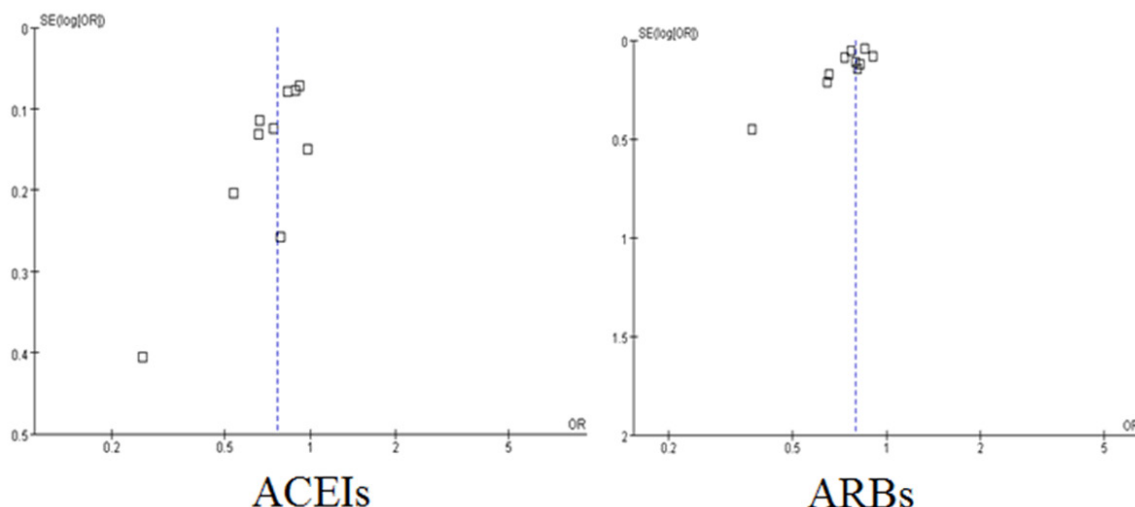


Figure 11. Funnel plot of ACEIs and ARBs.

ferent drugs in one sort had variable therapeutic effects, which was often ignored.

In conclusion, ACEIs and ARBs can decrease the incidence of new-onset type 2 diabetes, especially in patients with hypertension, metabolic syndrome, pre-diabetes phase, obesity, congestive heart failure, or coronary heart disease. This finding may be of special clinical benefit, so the use of an ACEI or ARB should be considered as the first line anti-hypertensive drug in these patients.

Disclosure of conflict of interest

None.

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References

- [1] LaMarr B, Valdez C, Driscoll K, Ryan M. Influence of pharmacist intervention on prescribing of angiotensin-converting-enzyme inhibitors, angiotensin II-receptor blockers, and aspirin for diabetic patients. *Am J Health Syst Pharm* 2010; 67: 290-294.
- [2] Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting enzyme inhibitors: the CHARM-alternative trial. *Lancet* 2003; 362: 772-776.
- [3] Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; 46: 3-19.
- [4] Aronow WS. Current role of beta-blockers in the treatment of hypertension. *Expert Opin Pharmacother* 2010; 11: 2599-2607.
- [5] Volpe M, Savoia C, Panina G, Cangianiello S. Therapeutic applications of angiotensin II receptor antagonists. *Ann Endocrinol (Paris)* 2000; 61: 47-51.
- [6] Wei Y, Sowers JR, Nistala R, Gong H, Uptergrove GM, Clark SE, Morris EM, Szary N, Manrique C, Stump CS. Angiotensin II-induced NADPH oxidase activation impairs insulin signaling in skeletal muscle cells. *J Biol Chem* 2006; 281: 35137-35146.
- [7] Liebson PR. Calcium channel blockers in the spectrum of antihypertensive agents. *Expert Opin Pharmacother* 2006; 7: 2385-2401.
- [8] Kristensen PL1, Høi-Hansen T, Boomsma F, Pedersen-Bjergaard U, Thorsteinsson B. Vascular endothelial growth factor during hypoglycemia in patients with type 1 diabetes mellitus: relation to cognitive function and renin-angiotensin system activity. *Metabolism* 2009; 58: 1430-8.
- [9] Taylor J. 2013 ESH/ESC guidelines for the management of arterial hypertension. *Eur Heart J* 2013; 34: 2108-2109.
- [10] Banach M, Rysz J. Current problems in hypertension and nephrology. *Expert Opin Pharmacother* 2010; 11: 2575-8.
- [11] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560.

- [12] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-634.
- [13] Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; 288: 2421-2431.
- [14] Davis BR, Cutler JA, Gordon DJ. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.
- [15] Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348: 583-592.
- [16] Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353: 611-616.
- [17] Mohan V. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; 355: 1551-1562.
- [18] Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342: 145-153.
- [19] Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, Myers MG, Calciu CD, Dalle-Ave S, Martineau P, Mormont C, van Gilst WH; IMAGINE (Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme) Investigators. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. *Circulation* 2008; 117: 24-31.
- [20] PEACE Trial Investigators. Angiotensin converting enzyme inhibition in stable coronary artery disease. *New Engl J Med* 2004; 351: 2058.
- [21] Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC; Studies Of Left Ventricular Dysfunction. Enalapril reduces the incidence of diabetes in patients with chronic heart failure insight from the studies of left ventricular dysfunction (SOLVD). *Circulation* 2003; 107: 1291-1296.
- [22] Hansson L, Lindholm L H, Ekblom T, Dahlöf B, Lanke J, Scherstén B, Wester PO, Hedner T, de Faire U. Randomised trial of old and new anti-hypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354: 1751-1756.
- [23] Lindholm LH, Persson M, Alaupovic P, Carlberg B, Svensson A, Samuelsson O. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens* 2003; 21: 1563-1574.
- [24] Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T; Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; 51: 393-398.
- [25] Yusuf S, Ostergren J B, Gerstein HC, Pfeffer MA, Swedberg K, Granger CB, Olofsson B, Probstfield J, McMurray JV; Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; 112: 48-53.
- [26] Kasanuki H, Hagiwara N, Hosoda S, Sumiyoshi T, Honda T, Haze K, Nagashima M, Yamaguchi J, Origasa H, Urashima M, Ogawa H; HIJ-CREATE Investigators. Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE). *Eur Heart J* 2009; 30: 1203-1212.
- [27] Sawada T, Yamada H, Dahlöf B, Matsubara H; KYOTO HEART Study Group. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study. *Eur Heart J* 2009; 30: 2461-9.
- [28] Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular

- morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995-1003.
- [29] NAVIGATOR Study Group, McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang FT, Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GE, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamás G, Tognoni G, Tuomilehto J, Villamil AS, Vozár J, Califf RM. Effect of valsartan on the incidence of diabetes and cardiovascular events. *New Engl J Med* 2010; 362: 1477-1490.
- [30] Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW; PROFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *New Engl J Med* 2008; 359: 1225-1237.
- [31] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; 21: 875-886.
- [32] Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008; 372: 1174-1183.
- [33] 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; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; 363: 2022-2031.
- [34] Vidt DG. Telmisartan, ramipril, or both in patients at high risk for vascular events. *Curr Hypertens Rep* 2008; 10: 343-344.
- [35] Kavgaci H, Sahin A, Ersoz HO, Erem C, Ozdemir F. The effects of losartan and fosinopril in hypertensive type 2 diabetic patients. *Diabetes Res Clin Pract* 2002; 58: 19-25.
- [36] Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201-207.
- [37] Fravel MA, McDanel DL, Ross MB, Moores KG, Starry MJ. Special considerations for treatment of type 2 diabetes mellitus in the elderly. *Am J Health Syst Pharm* 2011; 68: 500-509.
- [38] Cheung BM. The hypertension-diabetes continuum. *J Cardiovasc Pharmacol* 2010; 55: 333.
- [39] Solski LV, Longyhore DS. Prevention of type 2 diabetes mellitus with angiotensin-converting-enzyme inhibitors. *Am J Health Syst Pharm* 2008; 65: 935-40.
- [40] American Diabetes Association. Standards of medical care in diabetes-2010. *Diabetes Care* 2010; 33 Suppl 1: S11-61.
- [41] O'Keefe JH, Wetzel M, Moe RR, Bronsahan K, Lavie CJ. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? *J Am Coll Cardiol* 2001; 37: 1-8.
- [42] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206-52.