VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2010, Vol. 17, No. 5, pp. 448–456

ISSN 1897–5593

Do angiotensin converting enzyme inhibitors or angiotensin receptor blockers prevent diabetes mellitus? A meta-analysis

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Abstract

Background: *The prevalence of diabetes mellitus (DM) has increased exponentially in recent years, with 100 million people expected to develop diabetes in the coming 15 years. The impact of medical therapy on the incidence of new onset DM is not clear. We performed a systematic review and meta-analysis to study the impact of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the incidence of new onset DM.*

Methods: *MEDLINE, EMBASE, BIOSIS, Cochrane databases from inception until February 2009 for randomized controlled trials (RCT) that reported new incident DM with ACEI or ARB therapy. A total of 18 RCT are included in this meta-analysis. A random-effect model was used and between-studies heterogeneity was estimated with I^2.*

Results: *There were 50,451 patients randomized to ACEI or ARB and 50,397 patients randomized to other therapies. ACEI/ARB use was associated with a decrease in new onset DM (RR 0.78, 95% CI 0.70–0.88, $p = 0.003$ for ACEI and RR 0.8, 95% CI 0.75–0.86, $p < 0.0001$ for ARB). Treating 100 patients with ACEI or 50 patients with ARB prevents one case of new onset DM.*

Conclusions: *The cumulative evidence suggests that the use of ACEI/ARB prevents diabetes mellitus. This finding may be of special clinical benefit in patients with hypertension and pre-diabetes or metabolic syndrome.* (Cardiol J 2010; 17, 5: 448–456)

Key words: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diabetes mellitus

Editorial p. 435

Introduction

The prevalence of diabetes in the United States in 2007 was 23.6 million people, or 7.8% of the population (17.9 million with diagnosed, and 5.7 million people with undiagnosed, diabetes) [1]. Diabetes was the seventhcommonest cause of death listed on U.S. death certificates in 2006 [2]. Overall, the risk of death among people with diabetes is nearly twice that of people without diabetes of a similar age [1]. Even patients with pre-diabetes (impaired glucose tolerance and/or impaired fasting glucose) have an increased risk of heart disease and stroke [3].

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Received: 09.11.2009 Accepted: 12.01.2010

The Diabetes Prevention Program showed that lifestyle intervention in patients with pre-diabetes reduced the development of diabetes by 58% over a three-year period [4, 5].

Previous studies have shown a relationship between increased insulin resistance and renin angiotensin aldosterone system (RAAS) [6, 7]. Metabolic abnormalities linked to diabetes mellitus (DM) lead to activation of RAAS, and thereby increased angiotensin II and aldosterone levels [8]. Blocking angiotensin II decreases proinflammatory mediators and the oxidative stress. This in turn can prevent and delay the onset of DM, as well as prevents cardiac and renal events [9].

Multiple randomized controlled clinical trials have reported subgroup analysis in regards to the incidence of DM in patients receiving angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) in comparison to a placebo. However, most of these studies have been underpowered in terms of confirming the beneficial effects of ACEIs/ARBs in preventing new onset DM [10, 11]. We therefore conducted a systematic review and meta-analysis of all randomized controlled trials (RCT) using ACEIs or ARBs and reporting the incidence of new onset diabetes at the end of the study.

Methods

Search strategy

We conducted a search in MEDLINE (1948 to July Week 2, 2009), EMBASE (1988 to 2009 Week 29), COCHRANE databases (from inception until the second quarter of 2009) and BIOSIS for randomized controlled trials that involved the use of ACEIs or ARBs and onset of new onset DM. Various terms were used for search including new diabetes, prevent diabetes, diabetes mellitus, ACEIs or ARBs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and others. The search was performed without any language restrictions. The search was limited to human subjects. When an abstract from a meeting and a full article referred to the same trial, only the full article was included in the analysis. When there were multiple reports from the same trial, we used the most complete and/ /or most recently reported data.

Inclusion and exclusion criteria

All trials searched were assessed for: 1) randomization, 2) study duration of at least one year, 3) reported incidence of new onset diabetes as a pre-specified point or as a part of post-hoc analysis. Randomized controlled trial was defined according to the National Library of Medicine criteria (http:// //www.nlm.nih.gov/mesh/pubtypes2001.html). Diabetes was defined using the American Diabetes Association (ADA) criteria in most of the trials (fasting blood glucose levels ≥ 126 mg/dL on two different occasions) [12]. Data for each trial was abstracted by an investigator (MA) and was confirmed by a secondary investigator (AO). Trials which did not meet the above requirements were excluded from the meta-analysis.

Statistical analysis

The meta-analysis was performed by computing relative risks (RR) using a random-effects model. Quantitative analyses were performed on an intention-to-treat basis. RR for new onset diabetes was calculated along with the 95% confidence intervals (CIs). The number needed to treat to prevent one event was calculated by the inverse of the pooled absolute risk reduction. Between studies heterogeneity was analyzed by means of $I^2 = = [(Qdf)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Publication bias was assessed graphically using a funnel plot. All analyses were performed with RevMan Analyses Version 5.0.20 (© Nordic Cochrane Centre, Ringshopitalet 2008).

Results

Overall, we found 408 articles on the primary search, of which 173 were excluded as they were not randomized controlled trials (Fig. 1). From the

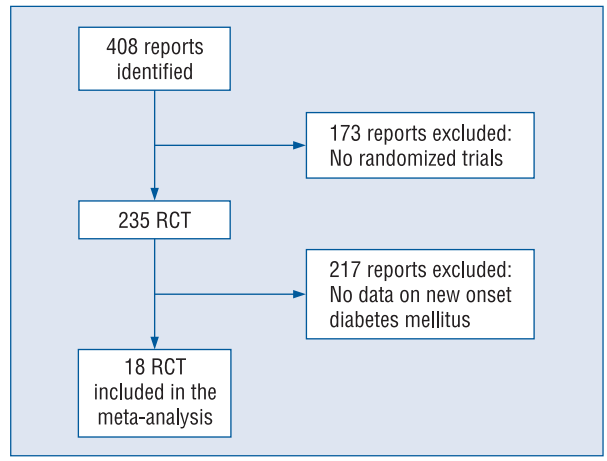

Figure 1. Summary of search strategy results; RCT — randomized controlled trials.

remaining 235 articles, we included 18 trials in total (Fig. 1), with ten using ACEIs (Table 1) and eight using ARBs (Table 2).

Trials involving ACEIs i.e. Studies of Left Ventricular Dysfunction (SOLVD) [13], The second Swedish Trial in Old Patients with hypertension (STOP-2) [14], African American Study of Kidney disease and hypertension (AASK) [15], The Heart Outcomes Prevention Evaluation Study (HOPE) [16], Ischemia Management with Accupril post-bypass graft via Inhibition of the converting Enzyme (IMAGINE) [17], Diabetes REduction Approaches with ramipril and rosiglitazone (DREAM) [18], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [19], Captopril Prevention Project (CAPP) [20], Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial (PEACE) [21] and The second Australian National Blood Pressure study (ANBP2) [22] had a total number of 49,318 patients. Only DREAM [18] trial in ACEIs group had incidence of new onset DM as the pre-specified end point, others were post-hoc analysis. ALLHAT [19] had the largest number of patients while AASK [15] had the smallest number of patients in this sub-group. Four trials i.e. STOP2 [14], DREAM [18], CAPP [20] and IMAGINE [17] failed to reach statistical significance. However, results did show a trend favoring use of ACEIs for prevention of DM. The total number of patients developing DM in this sub-group was 3,675 (1,665 in ACEIs group and 2,010 in placebo/ /other group). RR ratio was 0.78, 95% CI 0.70–0.88 and $p < 0.0001$ (Fig. 2).

Trials involving ARBs i.e. Anti-hypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) [23], Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity (CHARM) [24], Losartan Intervention For Endpoint Reduction in hypertension study (LIFE) [25], Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) [26], Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) [27], Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) [28], The Study on Cognition and Prognosis in the Elderly (SCOPE) [29] and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [30] had a total number of 51,530 patients. Four trials in the ARBs group i.e. ALPINE [23], CASE [27], VALUE [30] and PRoFESS [28] had incidence of new onset DM as a pre-specified end point, while the rest were again post-hoc analysis. PRoFESS [28] had the largest number of patients, while ALPINE [23] had the

Table 1. Summary of clinical trials with angiotensin converting enzyme inhibitor (ACEI).

ACEI trials	Name of ACEI	Total no. of patients	Follow up (years)	Mean age (years)	BMI [kg/m^2]	Event rate ACEI group (%)	No. of patients ACEI group	Event rate control group (%)	No. of patients control group	Risk ratio (95% CI)*
SOLVD [13]	Enalapril	4,228	3.4	56.45	N/A	9 (5.8)	153	31 (22)	138	0.26 (0.13–0.53)
AASK [15]	Ramipril	1094	4.1	55	31	45 (10.9)	410	70 (17.2)	405	0.64 (0.45–0.90)
HOPE [16]	Ramipril	9,297	5	66	28	102 (3.59)	2837	155 (5.3)	2883	0.67 (0.52–0.85)
ANBP2 [22]	Enalapril	6.083	4.1	71.9	27	138 (4.92)	2800	200 (7.0)	2826	0.70 (0.56–0.86)
ALLHAT [19]	Lisinopril	33,357	4.9	66.9	29.76	119 (2.9)	4096	154 (3.8)	3954	0.75 (0.59–0.94)
IMAGINE [17]	Quinapril	2,553	2.95	61	N/A	28 (2.4)	1159	35 (3.0)	1141	0.79 (0.48–1.29)
PEACE [21]	Trandolapril	8,290	4.8	64	N/A	335 (9.7)	3432	399 (11.4)	3472	0.85 (0.74–0.97)
CAPPP [20]	Captopril	10,985	6.1	52.55	27.95	337 (6.5)	5183	380 (7.2)	5230	0.89 (0.78–1.03)
DREAM [18]	Ramipril	5,269	3	54.7	30.9	449 (17.1)	2623	489 (18.4)	2646	0.93 (0.82–1.04)
STOP-2 [14]	Enalapril/ /Lisinopril	6,614	5	76	27.8	93 (4.7)	1970	97 (4.9)	1960	0.95 (0.72–1.26)

*Risk ratios may have been derived from sub-group analysis and do not necessarily equal crude incidence ratios; BMI — body mass index; CI — confidence interval

Table 2. Summary of clinical trials with angiotensin receptor blocker (ARB).

ARB Trials	Name of ARB	Total no. of patients	Follow up (years)	Mean age (years)	BMI [kg/m^2]	Event rate ARB group (%)	No of patient ARB group	Event rate control group (%)	No of patients control group	Risk ratio (95% CI)*
ALPINE [23]	Candesartan	392	1	54.95	27.95	1 (0.5)	196	8 (4.0)	196	0.13 (0.02–0.99)
CASE-J [27]	Candesartan	4,703	3.2	63.85	24.55	38 (2.8)	1343	58 (4.3)	1342	0.65 (0.44–0.98)
LIFE [25]	Losartan	9,193	4.8	66.9	28	242 (6.0)	4020	320 (8.0)	3979	0.75 (0.64–0.88)
CHARM [24]	Candesartan	7,599	3.2	64.5	27.85	163 (6.0)	2715	202 (7.4)	2721	0.81 (0.66–0.99)
SCOPE [29]	Candesartan	4,937	3.7	76.4	26.95	93 (4.2)	2167	115 (5.2)	2175	0.81 (0.62–1.06)
VALUE [30]	Valsartan	15,245	4.2	67.25	28.65	690 (13.5)	5087	845 (16.6)	5074	0.81 (0.74–0.89)
PRoFESS [28]	Telmisartan	20,332	2.5	66.15	26.8	125 (1.7)	7306	151 (2.0)	7283	0.83 (0.65–1.04)
TRANSCEND [26]	Telmisartan	5,926	4.6	66.9	28.15	209 (7.0)	2954	245 (8.2)	2972	0.86 (0.72–1.02)

*Risk ratios may have been derived from sub-group analysis and do not necessarily equal crude incidence ratios; BMI — body mass index; CI — confidence interval

smallest number of patients in this sub-group. Three trials i.e. SCOPE [29], PRoFESS [28] and TRANSCEND [26] failed to reach statistical significance. However, results did show a trend favoring use of ARB for prevention of DM. The total number of patients developing DM in this sub-group was 3,505 (1,561 in the ARB group and 1,944 in the placebo/other group). RR was 0.80, 95% CI 0.75–0.86 and $p < 0.00001$ (Fig. 2).

The mean duration of follow-up ranged from one year to 6.1 years. ACEIs/ARBs in the current meta-analysis were compared with other anti-hypertensive agents including beta-blockers, calcium channel blockers, and diuretics as well as with a placebo. Cumulative data from both sub-groups show a total of 100,848 patients. Incidence of new onset DM was 7,170 (7.1%) in total, with 3,216 patients in the ACEIs/ARBs group (6.37%) against 3,954 patients in the placebo/other group (7.84%). RR was 0.80, 95% CI 0.75–0.86 (Fig. 2). Reduction in risk of new onset DM was 22% for the ACEI group, 20% for the ARBs group and ~20% for the ACEIs/ARBs group. The absolute risk reduction associated with ACEIs therapy to prevent new onset DM was 0.01 (1%) while the absolute risk reduction associated with ARBs therapy to prevent new onset DM was 0.02 (2%). Thus treating 100 patients with ACEIs or 50 patients with ARBs prevents one case of new onset diabetes.

On further sub-analysis of the data, the total number of patients in ACEIs/ARBs trials reporting the incidence of new onset DM as a pre-specified end point was 33,096. The total number of patients with new onset DM was 2,854 (8.6%) with 1,303 (7.87%) in the ACEIs/ARBs group and 1,551 (9.37%) in the placebo/other group. RR with ACEIs/ARBs for new onset DM was calculated to be 0.83 with 95% CI 0.74–0.94 (Fig. 3).

On further breakdown of data for trials reporting the incidence of new onset DM as a part of post-hoc analysis, there were 67,752 patients. The total number of patients with new onset DM was 4,316 (6.3%) with 1,913 (5.6%) in the ACEIs/ARBs group and 2,403 (7.0%) in the placebo/other group. RR for ACEIs/ARBs studies with incidence of DM reported as a part of post-hoc analysis: the RR was for new onset DM with ACEIs/ARBs was calculated to be 0.78 with 95% CI 0.72–0.85 (Fig. 4).

The test for heterogeneity showed some difference in effect among the studies as evident by I^2 estimates for different outcomes ($I^2 > 50\%$), while it was not evident for the ARBs sub-group ($I^2 < 50\%$). Sensitivity analysis was done with respect to ACEIs *vs* ARBs use, follow-up duration ≤ *vs* ≥ 4 years, age ≤ *vs* ≥ 65 years, tissue specific ACEIs use *vs*

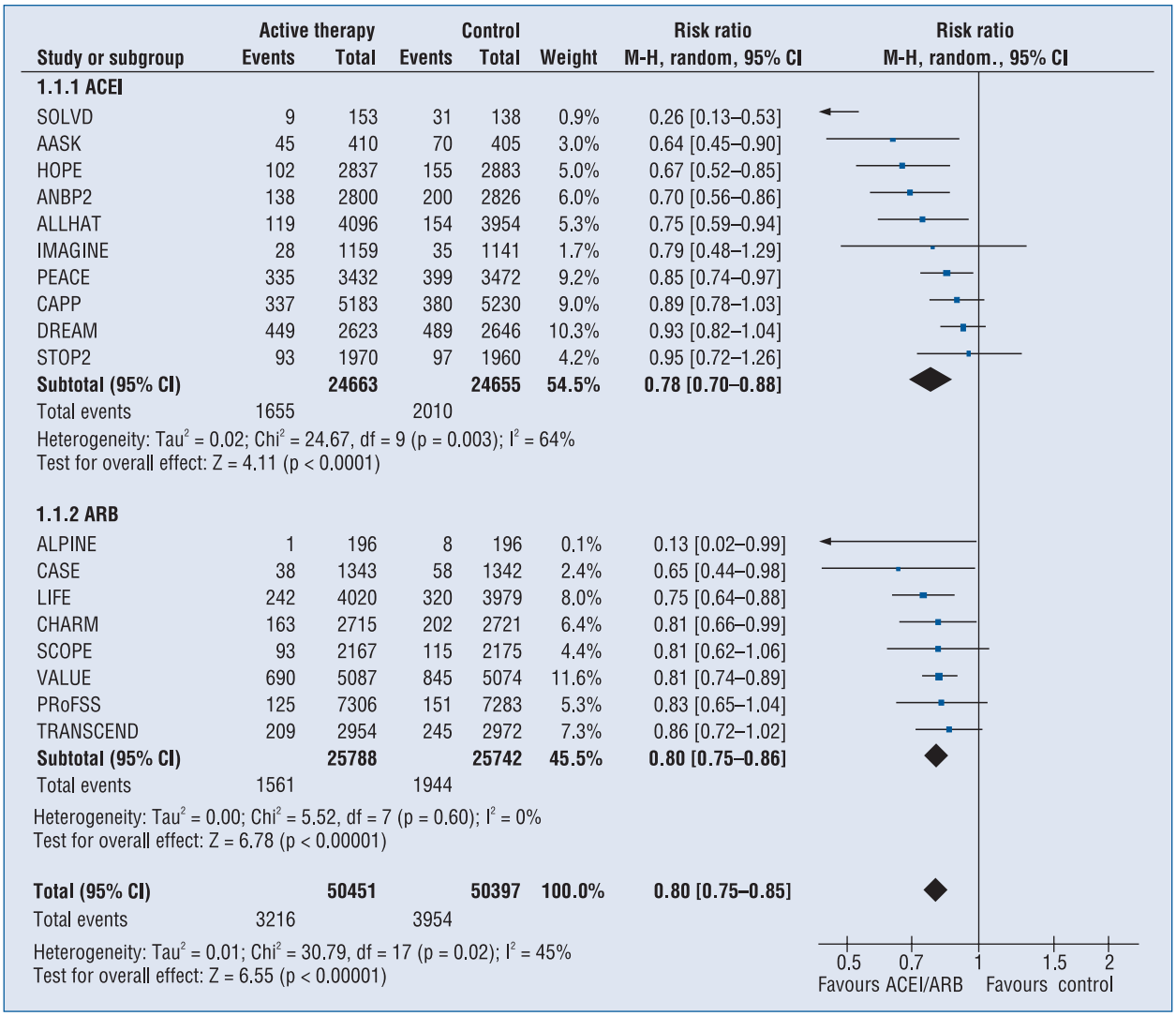

Figure 2. Forest plot of the meta-analysis. Angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use was associated with a decrease in the incidence of diabetes mellitus; M-H — Mantel-Haenszel; CI — confidence interval.

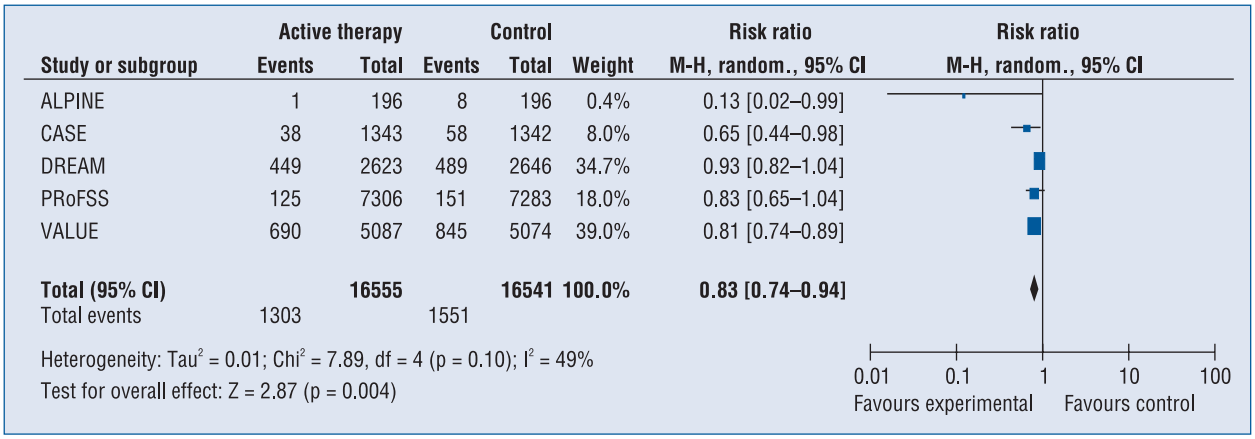

Figure 3. Forest plot of comparison with diabetes mellitus as a pre-specified end-point (ACEI/ARB); CI — confidence interval; ACEI — angiotensin converting enzyme inhibitor; M-H — Mantel-Haenszel; ARB — angiotensin receptor blocker.

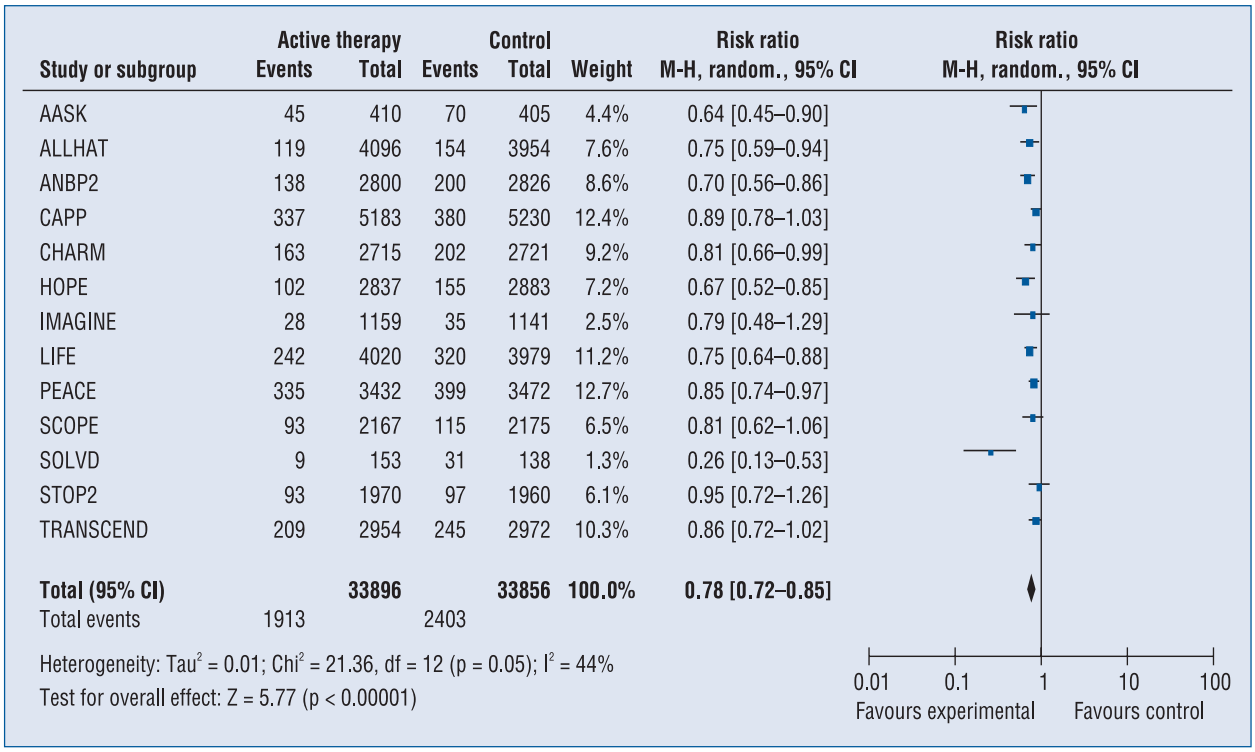

Figure 4. Forest plot of comparison with diabetes mellitus incidence as post-hoc analysis (ACEI/ARB); CI — confidence interval; ACEI — angiotensin converting enzyme inhibitor; M-H — Mantel-Haenszel; ARB — angiotensin receptor blocker.

Table 3. Sensitivity analysis.

Variables	Yes RR, M-H, randomization (95% CI)	No RR, M-H, randomization (95% CI)	P
ACEI *vs* ARB (Yes *vs* No)	0.78 (0.70–0.88)	0.80 (0.75–0.86)	0.710
Follow up ≤ 4 years (Yes *vs* No)	0.76 (0.64–0.91)	0.80 (0.75–0.86)	0.590
Age ≤ 65 years (Yes *vs* No)	0.75 (0.62–0.90)	0.80 (0.76–0.85)	0.505
Tissue specific ACEI (Yes *vs* No)	0.80 (0.70–0.92)	0.79 (0.73–0.86)	0.878
Candesartan use (Yes *vs* No)	0.77 (0.63–0.93)	0.80 (0.75–0.86)	0.712
Pre-specified endpoint *vs* post-hoc analysis	0.83 (0.74–0.94)	0.78 (0.72–0.85)	0.431

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; RR — relative risk; M-H — Mantel-Haenszel; CI — confidence interval

others, pre-specified endpoint or post-hoc analysis, and candesartan use *vs* use of other medications among ACEIs/ARBs. There was no statistically significant difference with all the p values more than 0.05 as shown in Table 3. The funnel plot analysis showed asymmetrical distribution of RR estimates with evidence of publication bias as shown in Figure 5.

Discussion

This meta-analysis of 100,848 patients shows a statistically significant 20% cumulative relative risk reduction in the incidence of new onset diabetes with the use of ACEIs or ARBs. These results are consistent with previous analyses of smaller samples, showing the beneficial effects of ACEIs and ARBs in preventing new onset diabetes [10, 11].

Insulin mediated glucose uptake in skeletal muscles is important for the regulation of blood glucose levels. ACEIs, by suppressing angiotensin II and/or increasing bradykinin (BK), have been shown to increase insulin sensitivity in skeletal muscles [31]. ACEIs increase BK levels by inhibition of kininase II mediated degradation [32]. This leads to an increased production of prostaglandins and nitric oxide which improves exercise induced

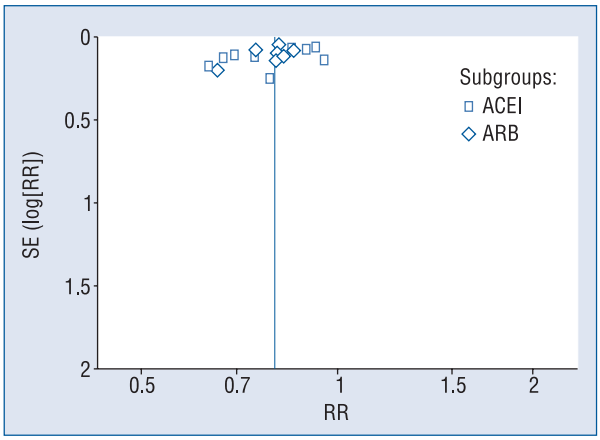

Figure 5. Funnel plot for publication bias.

glucose metabolism and muscle sensitivity to insulin, thereby increased glucose uptake [33, 34]. It was reported that ACEIs and physical activity have additive effects on lowering serum insulin concentrations and improving HOMA-R (insulin resistance); this indicates that ACEIs may improve insulin sensitivity in hypertensive patients with insulin resistance.

ARBs, with partial PPARγ agonist activity, have also been shown to improve insulin sensitivity in non-modulating hypertensive patients. Unlike modulating hypertensive patients, who normally handle high salt intake, non-modulating hypertensive patients are salt sensitive and develop insulin resistance as well as oxidative stress [35, 36].

ACEIs have been shown to be beneficial in the secondary prevention of microvascular complications. Low-dose ramipril significantly improved capillary refill velocity during post-occlusive hyperemia in hyperglycemic patients without established complications [37]; this demonstrates that ACEIs improve microcirculation in hyperglycemic patients and are of benefit in preventing microvascular complication in diabetic patients.

When compared, ACEIs and ARBs have been proven to be equally effective in treating hypertension in DM. Comparison was made between losartan (ARB) and fosinopril (ACEI) with respect to blood pressure (BP), creatinine clearance (Ccr) and urinary albumin excretion (UAE), as well as metabolic parameters. Ccr was similar in both groups. UAE was lower in both groups at 1 and 6 months, although the antiproteinuric effect of losartan was somewhat decreased at 6 months [38]. Thrombomodulin (TM) has been shown to be a marker of endothelial cell damage, along with an increased urinary albumin excretion in patients with DM. Treatment with ACEIs decreased both UAE and TM [39].

Congestive heart failure (CHF) is found in 10––15% of diabetics and is an independent risk factor for DM and *vice versa*. Insulin resistance has been shown to be directly responsible for diastolic dysfunction of the heart [40]. CHF in patients with DM has a poor prognosis and good glycemic control improves its prognosis [41]. ACEIs and ARBs provide an added benefit for CHF patients by preventing diabetes.

Results of Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) are expected to be released later this year [42]. This was a multinational, double blind and randomized trial that enrolled patients from January 2002 until January 2004. One of the three primary end points of this trial was to look for reduction in the incidence of new onset type 2 diabetes with reduction in post parandial hyperglycemia, blockade of RAAS, or both. The results of this trial will be a valuable addition.

This meta-analysis clearly shows a significant beneficial effect for ACEIs and ARBs in preventing diabetes. However, only one case would be prevented by treating 50–100 patients. It is therefore not justified to use these medications for simple prevention. However, the use of these medications to treat hypertensive and CHF patients at risk for diabetes is highly recommended, since there is the added benefit of diabetes prevention. Future cost-effectiveness analysis are needed to determine the cost-effectiveness of ACEI and ARB in preventing diabetes in a specific patient population including patients with pre diabetes or hypertension.

Limitations of the study

The current meta-analysis has some limitations. Four of the ten trials i.e. STOP2 [12], AASK [11], ANBP2 [20] and CAPP [14] in the ACEIs group were open label trials while six others were double blinded randomized controlled trials. Likewise, two of eight trials i.e. CASE [21] and PRoFESS [16] in the ARBs group were open label trials, while the rest were double blinded randomized controlled trials. As mentioned above, only the DREAM [13] trial in the ACEIs group had incidence of new onset DM as a pre-specified end point, while the others were post-hoc analysis.

Likewise, only four trials in the ARBs group i.e. ALPINE [17], CASE [21], VALUE [22] and PRoFESS [16] had incidence of new onset DM as a pre-specified end point, while the rest were again post-hoc analysis. Another potential limitation

would be differences between drugs in the same group that are ignored in this approach. A significant limitation of the study is the use of various antihypertensive drugs, especially thiazide diuretics and conventional beta-blockers, in the placebo arm which are well known for inducing impaired glucose metabolism and could have very likely affected the results of the study.

Conclusions

In summary, this meta-analysis of more than 100,000 patients clearly points towards a beneficial effect of ACEI and ARB in preventing new onset diabetes mellitus. Additional prospective double-blinded randomized controlled trials will be needed to confirm the importance of ACEI and ARB in preventing new onset diabetes.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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