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Effects of RAS inhibitors on diabetic retinopathy: a systematic review and meta-analysis

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Summary

Background Results of several studies have shown a possible beneficial effect of renin-angiotensin system (RAS) inhibitors on diabetic retinopathy, but the findings were contradictory. We did a systematic review and meta-analysis to assess the effect of RAS inhibitors on diabetic retinopathy.

Methods We identified relevant publications in PubMed, Embase, Cochrane Library Central Register of Controlled Trials, and abstracts from main annual meetings. Only randomised controlled trials comparing angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) monotherapy with other antihypertensive drugs or placebo in type 1 or type 2 diabetes were eligible for inclusion in the analysis. The primary outcomes were progression and regression of diabetic retinopathy in all patients and several subgroups. Risk ratios (RRs) with corresponding 95% CIs were pooled. We also did a network meta-analysis to assess the effect of different antihypertensive drugs on diabetic retinopathy by ranking order. This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42013004548.

Findings 21 randomised clinical trials with 13 823 participants were included in the meta-analysis. RAS inhibitors were associated with reduced risk of progression (absolute risk difference –3%, 95% CI –5 to –1; pooled RR 0·87, 95% CI 0·80–0·95; p=0·002) and increased possibility of regression of diabetic retinopathy (8%, 1–16; RR 1·39, 95% CI 1·19–1·61; p=0·00002). In normotensive patients, RAS inhibitors decreased risk of diabetic retinopathy progression (0·81, 0·69–0·94; p=0·007) and increased possibility of regression (1·43, 1·14–1·79; p=0·002). In hypertensive patients, RAS inhibitors were not associated with difference in risk of progression of diabetic retinopathy (0·93, 0·79–1·10; p=0·42) or possibility of diabetic retinopathy regression (2·21, 0·92–5·31; p=0·08). ACE inhibitors were associated with reduced risk of diabetic retinopathy progression (0·84, 0·75–0·94; p=0·002) and higher possibility of disease regression (1·50, 1·20–1·86; p=0·0003). ARBs were associated with a higher possibility of diabetic retinopathy regression (1·32, 1·07–1·61; p=0·008), but had no effect on disease progression (0·92, 0·80–1·06; p=0·25). Network meta-analysis showed the association of antihypertensive drugs with risk of diabetic retinopathy progression was lowest for ACE inhibitors, followed by ARBs, β blockers, calcium channel blockers, and placebo in rank order. The association of antihypertensive drugs with possibility of diabetic retinopathy regression was highest for ACE inhibitors, followed by ARBs, placebo, and calcium channel blockers in rank order.

Interpretation In patients with diabetes, RAS inhibitors reduce the risk of diabetic retinopathy, and increase the possibility of diabetic retinopathy regression. ACE inhibitors might be better than ARBs for treating diabetic retinopathy, and might exert the most beneficial effect on diabetic retinopathy of all widely used antihypertensive drug classes.

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Introduction

Diabetic retinopathy is a sight-threatening and chronic microvascular complication in patients with diabetes, and it remains the leading cause of vision loss in adults worldwide.[1,2] At diagnosis, nearly 40% of patients with type 2 diabetes already have retinopathy and another 20% will develop the disease within 6 years of diagnosis.[3,4] Worldwide, there are about 93 million people with diabetic retinopathy, including 21 million people with diabetic macular oedema, and 17 million people with proliferative diabetic retinopathy.[5] Present guidelines mainly recommend optimised glycaemic control and optimised blood pressure control to reduce the risk or slow the progression of diabetic retinopathy.[6,7]

Intensive glucose control is the main and proven intervention to reduce diabetic retinopathy progression. However, optimised glucose control is difficult to achieve and intensive glucose control increases incident hypoglycaemia, which is associated with increased risks of cardiovascular events and all-cause mortality.[2,8] Results of previous studies suggested that intensive control of blood pressure in patients with diabetes could substantially reduce progression of diabetic retinopathy,[9,10] but results of recent studies[11–13] did not confirm the beneficial effect of intensive blood pressure control on progression. Various antihypertensive drugs were used in previous studies, and the different effects of antihypertensive drugs on diabetic retinopathy might be the reason for these conflicting findings.[11–13]

The results of several studies showed that blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-

receptor blockers (ARBs) might provide a beneficial effect on diabetic retinopathy; however, the findings were contradictory.[14–21] We did a systematic review and meta-analysis to assess the possible beneficial effect of RAS inhibitors on diabetic retinopathy, and a network meta-analysis to identify which antihypertensive drug class has the most beneficial effect on diabetic retinopathy incidence, progression, and regression.

Methods

Search strategy and selection criteria

Between Jan 1, 1980, and June 20, 2014, we searched PubMed, Embase, and the Cochrane Library Central Register of Controlled Trials. We searched Google scholar and ClinicalTrials.gov for unpublished relevant studies. We also searched abstracts from 2012 and 2013 meetings of the American Diabetes Association and the European Association for the Study of Diabetes. We combined key words and MeSH terms; the search terms and strategies for PubMed were (angiotensin-converting enzyme inhibitors, angiotensin-converting enzyme inhibitor, ACE inhibitors, ACE inhibitor, ACEI, captopril, enalapril, cilazapril, enalaprilat, fosinopril, lisinopril, perindopril, ramipril, angiotensin receptor blockers, angiotensin receptor blocker, angiotensin receptor antagonists, angiotensin receptor antagonist, ARBs, ARB, candesartan, irbesartan, losartan, telmisartan, valsartan, olmesartan, or eprosartan), (proliferative diabetic retinopathy, diabetic retinopathy, diabetic macular edema, diabetic maculopathy, retinal disorders, diabetic eye disease, retinal disease, or vision loss), and (random, randomized, randomised, double blind, placebo controlled, or randomized controlled trial). We updated our search on Nov 25, 2014, but did not find any new trials. We had no language restrictions for the literature search. We also searched for any additional studies in the reference lists of identified trials or reviews. Two investigators (BW and FW) reviewed study titles and abstracts independently, and studies that met inclusion criteria were retrieved for full-text assessment. There was an agreement value of 94% in the studies selected by these investigators for detailed analysis. Disagreements were resolved by a third investigator (YZ).

Studies meeting the following selection criteria were included: randomised controlled trial; individuals with type 2 diabetes or type 1 diabetes; comparison of ACE inhibitor or ARB monotherapy with other antihypertensive drugs (eg, β blockers, calcium channel blockers, or diuretics) or placebo; had at least one of incidence, progression, or regression of diabetic retinopathy as outcomes, and reported number of patients and events in each treatment group or reported the risk ratio (RR) with corresponding 95% CI; time of follow-up was more than 3 months; and appropriate initial doses of RAS inhibitors (ranging from a quarter of the recommended dose to the maximum recommended dose) for blood pressure control. There was no limitation on age, and children and adolescents with type 1 diabetes were also included in the meta-analysis. Studies were excluded if they were crossover trials, quasi experiments, non-randomised trials, or used dual therapies.

Outcomes

The primary endpoints were progression and regression of diabetic retinopathy. The secondary endpoint was incidence of diabetic retinopathy. Although progression and regression of diabetic retinopathy were not defined uniformly in the relevant studies, the endpoints defined according to the criteria used in individual trials were usually taken into consideration in meta-analyses, and in this meta-analysis we used the endpoints defined as per the criteria from the original trials. For studies in which outcomes of at least two step and at least three step changes were reported according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grading,[22] we first used the data of at least two step changes according to ETDRS grading because that was least likely to miss minor lesions and most studies with ETDRS grading used at least two step changes as a criterion. In the sensitivity analysis, we re-analysed the data when the data were for at least three step changes according to the grading system. Also, we did subgroup analyses by the different definitions of incidence, progression, or regression of diabetic retinopathy to improve the specificity of the assessment.

Data extraction and quality assessment

We extracted data into Microsoft Excel for first author's name, year of publication, type of diabetes, drugs, doses, hypertensive or normotensive status, number of participants, mean age, sex distribution, blood pressure, HbA_{1c}, duration of follow-up, adjusted estimates of relative effects, dropout rates, and number of events in the intervention groups.

Risk of bias in individual trials was assessed with the Cochrane Collaboration's method[23] that had six domains: sequence generation, allocation concealment, masking of participants or outcome assessors, incomplete outcome, selective outcome reporting, and other bias.[23] Intention-to-treat analysis was important for the assessment of the quality of clinical trials and it was regarded as one of the main potential sources of other bias.

The quality of the overall evidence for each outcome was summarised by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.[24] The quality was summarised as very low, low, moderate, or high to indicate the confidence in the effect estimate.[24] Reasons for downgrading the evidence included study limitations, indirectness of evidence, inconsistency of results, publication bias, and imprecision.[24] Reasons for upgrading the evidence included a dose-response relation, a large effect, or the

	Diabetes type	Hypertensive or normotensive	Sample size*	Diabetic retinopathy	Intervention	Baseline characteristics				Dropout	Follow-up	Diabetic retinopathy outcomes
						Age (years)	SBP (mm Hg)	DBP (mm Hg)	HbA_{1c} (%)			
Menne et al (2014)[43]	2	Mixed	881	Not all data available	Olmesartan (ARB)	57·8 (8·4)	137 (16)	81 (10)	7·7 (1·6)	NA	6·5 years	Incidence
			877		Placebo	57·9 (8·3)	136 (15)	80 (9)	7·8 (1·6)			
Wang et al, 2012)[36]	2	Normotensive	202	180 (56·8%)	Captopril (ACE inhibitor)	64·7 (9·1)	128 (13)	78 (8)	8·2 (1·7)	43 (11·9%)	2 years	Progression and regression
			115		Placebo	63·2 (8·5)	127 (15)	77 (8)	8·3 (1·6)			
Ruggenenti et al (2011)[37]	2	Hypertensive	127	50 (19·4%)	Delapril (ACE inhibitor)	61·9 (7·8)	147 (14)	87 (8)	6·2 (1·7)	21 (8·1%)	3·8 years	Incidence
			127		Placebo	60·4 (7·5)	147 (14)	86 (10)	6·2 (1·7)			
Mauer et al (2009)[38]	1	Normotensive	94	188 (65·9%)	Enalapril (ACE inhibitor)	30·6 (10·0)	120 (13)	71 (8)	8·6 (1·6)	<7%	5 years	Progression
			96		Losartan (ARB)	29·3 (10·2)	120 (11)	70 (8)	8·7 (1·7)			
			95		Placebo	29·1 (9·1)	119 (11)	70 (8)	8·3 (1·4)			
Ruggenenti et al (2010)[21]	2	Hypertensive	19	67 (100%)	Trandolapril (ACE inhibitor)	61·5 (7·7)	161 (15)	92 (8)	6·6 (1·4)	NA	3 years	Regression
			27		Verapamil (CCB)	60·8 (8·4)	154 (15)	90 (8)	6·6 (1·7)			
			21		Placebo	NA	NA	NA	NA			
DIRECT-Protect 2 (2008)[14]	2	Mixed	951	1905 (100%)	Candesartan (ARB)	56·9 (7·6)	123 (9)/ 139 (13)	75 (6)/79(7)	8·2 (1·6)	298 (15·6%)	4·7 years	Progression and regression
			954		Placebo	56·8 (7·9)	123 (9)/ 139 (12)	76 (6)/80(7)	8·2 (1·6)			
DIRECT-Prevent 1 (2008)[35]	1	Normotensive	711	0	Candesartan (ARB)	29·6 (8·0)	116 (10)	72 (7)	8·0 (1·7)	198 (13·9%)	4·7 years	Incidence
			710		Placebo	29·9 (8·1)	116 (10)	72 (7)	8·2 (1·7)			
DIRECT-Protect 1 (2008)[35]	1	Normotensive	951	1905 (100%)	Candesartan (ARB)	31·5 (8·5)	117 (10)	74 (7)	8·5 (1·6)	297 (15·6%)	4·8 years	Progression
			954		Placebo	31·9 (8·5)	117 (10)	73 (7)	8·5 (1·6)			
Estacio et al (2006)[46]	2	Normotensive	66	53 (41·1%)	Valsartan (ARB)	56·7 (7·7)	126 (9)	84 (2)	8·2 (2·3)	10 (7·7%)	1·9 years	Progression and regression
			63		Placebo	55·5 (7·7)	126 (9)	84 (2)	8·2 (2·1)			
Knudsen et al (2003)[42]	2	Hypertensive	12	24 (100%)	Losartan (ARB)	61·8 (5·6)	144 (17)	85 (11)	8·3 (1·1)	0	4 months	Progression
			12		Placebo	60·3 (9·5)	141 (21)	83 (8)	8·5 (1·7)			
Schrier et al (2002)[15]	2	Normotensive	246	238 (49·6%)	Enalapril (ACE inhibitor)	59·4 (0·5)	137 (1)	85 (1)	11·5 (0·2)	144 (30·0%)	5·3 years	Progression
			234		Nisoldipine (CCB)	59·1 (0·5)	135 (1)	84 (1)	11·6 (0·2)			
Parving et al (2001)[41]	1	Normotensive	15	32 (100%)	Captopril (ACE inhibitor)	32 (8)	128 (3)	78 (2)	9·5 (1·6)	1 (2·8%)	8 years	Progression
			17		Placebo	30 (8)	127 (2)	79 (1)	8·7 (0·8)			
HOPE (2000)[19]	Mixed	Mixed	1808	Not all data available	Ramipril (ACE inhibitor)	65·3 (6·4)	142 (19)	80 (11)	NA	1195 (33·4%)	4·5 years	Progression
			1769		Placebo	65·6 (6·6)	142 (19)	79 (11)	NA			
Estacio et al (2000)[20]	2	Hypertensive	235	282 (60·0%)	Enalapril (ACE inhibitor)	58·1 (8·4)	156 (17)	98 (7)	11·5 (3·2)	141 (30·0%)	5·3 years	Progression
			235		Nisoldipine (CCB)	57·6 (8·2)	155 (19)	98 (7)	11·7 (3·1)			
Ravid et al (1998)[39]	2	Normotensive	77	11 (7·1%)	Enalapril (ACE inhibitor)	55·5 (3·1)	NA	NA	9·3 (1·8)	27 (14·7%)	6 years	Incidence
			79		Placebo	54·4 (2·9)	NA	NA	9·2 (2·1)			
UKPDS (1998)[18]	2	Hypertensive	400	188 (24·8%)	Captopril (ACE inhibitor)	56·3 (8·1)	159 (20)	94 (10)	6·9 (1·6)	173 (22·8%)	8·4 years	Progression
			358		Atenolol (β blocker)	56·0 (8·2)	159 (19)	93 (10)	7·0 (1·8)			
Chaturvedi et al (1998)[16]	1	Normotensive	175	220 (62·1%)	Lisinopril (ACE inhibitor)	34 (9)	123 (10)	81 (5)	6·9 (1·9)	34 (8·3%)	2 years	Progression, incidence, and regression
			179		Placebo	35 (8)	123 (11)	81 (5)	7·3 (1·9)			
Patel et al (1998)[40]	Mixed	Hypertensive	22	43 (95·5%)	Perindopril (ACE inhibitor)	46·8 (9·7)	152 (14)	97 (7)	8·9 (2·4)	0	1 year	Progression
			23		Atenolol (β blocker)	46·3 (11·3)	159 (23)	97 (7)	8·2 (2·1)			

(Table 1 continues on next page)

	Diabetes type	Hypertensive or normotensive	Sample size	Diabetic retinopathy	Intervention	Baseline characteristics				Dropout	Follow-up	Diabetic retinopathy outcomes
						Age (years)	SBP (mm Hg)	DBP (mm Hg)	HbA_{1c} (%)			
(Continued from previous page)												
Ravid et al (1993)[37]	2	Normotensive	49	11 (11·7%)	Enalapril (ACE inhibitor)	43·5 (3)	NA	NA	10·4 (2·1)	14 (12·9%)	5 years	Incidence
			45		Placebo	44·8 (3·5)	NA	NA	10·4 (2·6)			
Chase et al (1993)[45]	1	Normotensive	7	13 (81·3%)	Captopril (ACE inhibitor)	22·0 (8·4)	118 (10)	78 (6)	8·8 (1·6)	0	2 years	Progression, incidence, and regression
			9		Placebo	19·9 (4·4)	113 (10)	78 (7)	8·0 (1·1)			
Larsen et al, (1990)[44]	1	Normotensive	10	20 (100%)	Captopril (ACE inhibitor)	29 (8)	125 (10)	77 (7)	9·5 (1·5)	1 (5·0%)	1·5 years	Progression
			9		Placebo	32 (5)	129 (11)	81 (6)	8·8 (1·3)			

Data are number (%) or mean (SD) unless otherwise indicated. ARB=angiotensin receptor blocker. ACE=angiotensin-converting enzyme. CCB=calcium channel blocker. SBP=systolic blood pressure. DBP=diastolic blood pressure. NA=not available. *Number of patients assessed.

Table 1: **Characteristics of the 21 trials included in the meta-analysis**

existence of plausible confounders that would result in an underestimation of the treatment effects.[24]

Statistical analysis

The pooled RRs with corresponding 95% CIs were used to compare treatment effects. The significance of the pooled RR was determined by the *Z* test and a p value of less than 0·05. Absolute risk difference in the actual event rates between the two treatment groups was also pooled in the meta-analysis. We used the Cochran's *Q* test to assess heterogeneity of the studies, with a threshold p value of less than 0·10 for significance.[25] We also did an I^2 test to assess the magnitude of heterogeneity between studies, with values more than 25%, 50%, and 75% defined as low, moderate, or high heterogeneity.[26] If heterogeneity was present or I^2 was greater than 50%, the random-effects model (DerSimonian-Laird method) was applied,[27] otherwise, the fixed-effects model (Mantel-Haenszel method) was used.[28]

We first used the data of at least two step changes as per the ETDRS grading, and then did a sensitivity analysis with data for at least three step changes. The adjusted RRs for incidence, progression, and regression of diabetic retinopathy were pooled in the sensitivity analyses. Subgroup analyses by the different definitions of incidence, progression, or regression of diabetic retinopathy were also done. The definitions of outcomes were classified as at least two step changes according to ETDRS grading, and at least three step changes according to ETDRS grading, or other definitions. For progression of diabetic retinopathy, the RRs for the development of proliferative diabetic retinopathy were pooled. We also did subgroup analyses by type of diabetes, hypertensive or normotensive status, comparison drugs (active comparator or placebo), follow-up (≥3 years or <3 years), number of study participants (≥100 or <100), endpoint (primary or secondary), and analysis (prespecified or post-hoc).

See Online for appendix

Potential publication bias was assessed with the funnel plot. We used the Egger's linear regression test at p<0·05 level of significance to assess the asymmetry of the funnel plot; an asymmetric plot suggested possible risk of publication bias.[29] In presence of bias, trim-and-fill computation was used to estimate the effect of publication bias on interpretation of the results.[30]

We undertook a network meta-analysis with a full Bayesian evidence network, which accounted for both direct and indirect comparisons to generate one integrated estimate of effects of antihypertensive drugs on the incidence, progression, and regression of diabetic retinopathy by rank order.[31–33]

Statistical analyses were done mainly with Review Manager (version 5.1.0) and Stata (version 12.0). The network meta-analysis was done with the online software ADDIS (version 1.16.5).[34] Any p values of less than 0·05 were regarded as significant, except p<0·10 for the test of heterogeneity.

This study is registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42013004548.

Role of the funding source

There was no funding source for this study and no commercial organisation was involved. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 229 studies through electronic searches and eight studies through manual searches (appendix). 197 studies were excluded on the basis of their titles and abstracts and 40 publications were retrieved for detailed assessment. 20 publications were further excluded: 11 did not meet inclusion criteria, two had data that could not be used, and seven had overlapping or other

data from trials that were already included (appendix). One of the included publications was a report of two individual trials.[35] Therefore, 21 randomised clinical trials from 20 publications with 13 823 participants were eligible for inclusion in our meta-analysis.[14–21,35–46] The characteristics of these studies are described in table 1. There were 12 studies of patients with type 2 diabetes, seven studies of patients with type 1 diabetes, and two studies of patients with either type 2 or type 1 diabetes (table 1). 12 of 21 trials were done in normotensive participants, six in hypertensive participants, and three in either normotensive or hypertensive participants (table 1). Data for diabetic retinopathy incidence were reported in seven trials, progression in 15 trials, and regression in six trials (table 1). The criteria for disease progression or regression were different (appendix; ETDRS Grading was used in nine trials and other criteria were used in the other trials). Ten trials were designed to assess the effects of RAS inhibitors on diabetic retinopathy and the other trials reported diabetic retinopathy as secondary outcomes (appendix). Only one trial used post-hoc analysis.[43] The bias risk assessment of the 21 studies included was shown (appendix), and there was no obvious risk of bias.

Table 2 is a summary of the main results of the meta-analysis of the effect of RAS inhibitors on diabetic retinopathy. There was no obvious heterogeneity in the studies included in the meta-analysis (table 2). Groups receiving RAS inhibitors had significantly lower risk of diabetic retinopathy incidence (absolute risk difference –7%, 95% CI –12 to –1; pooled RR 0·73, 95% CI 0·63–0·85, p=0·00006), lower risk of progression of diabetic retinopathy (absolute risk difference –3%, 95% CI –5 to –1; pooled RR 0·87, 95% CI 0·80 to 0·95, p=0·002), and higher possibility of disease regression (absolute risk difference 8%, 95% CI 1 to 16; pooled RR 1·39, 95% CI 1·19 to 1·61, p=0·00002; figure 1) than did those receiving other drug classes. When using data of at least three step changes according to ETDRS grading, RAS inhibitors were still associated with significantly reduced risks of incidence and progression of diabetic retinopathy, and higher possibility of disease regression than other drug classes (table 2). These pooled estimates changed little in most subgroup analyses (table 2). When random effect was used in all the analyses, there was no obvious change in the pooled RRs (appendix).

Subgroup analyses in normotensive people showed that RAS inhibitors significantly reduced risks of incidence (absolute risk difference –7%, 95% CI –11 to –3; RR 0·77, 95% CI 0·66 to 0·90; p=0·001) and progression of diabetic retinopathy (–5%, –8 to –1; 0·81, 0·69–0·94; p=0·007), and increased probability of disease regression (absolute risk difference 11%, 95% CI 5 to 18; RR 1·43, 95% CI 1·14 to 1·79; p=0·002; table 2 and figure 2). In hypertensive patients, effects of RAS inhibitors were not significant; table 2 and figure 2). However, subgroup analyses did not show a significant difference in the effect of RAS inhibitors

	Number of studies	Events/ participants	Risk ratio (95% CI)	p value	p_h	I^2
Diabetic retinopathy incidence						
Total studies	7	504/3705	0·73 (0·63–0·85)	0·00006	0·16	35%
Three step data	7	297/3705	0·58 (0·46–0·72)	0·000001	0·58	0%
Type 2 diabetic patients	4	78/2134	0·41 (0·25–0·65)	0·0002	0·83	0%
Type 1 diabetic patients	3	426/1571	0·81 (0·68–0·95)	0·009	0·55	0%
Hypertensive patients	1	15/126	0·61 (0·23–1·60)	0·31	NA	NA
Normotensive patients	5	458/1821	0·77 (0·66–0·90)	0·001	0·28	21%
Placebo comparison	7	504/3705	0·73 (0·63–0·85)	0·00006	0·16	35%
Excluding post-hoc analysis	6	473/1947	0·76 (0·65–0·89)	0·0007	0·38	6%
Primary end-point	3	426/1571	0·81 (0·68–0·95)	0·009	0·55	0%
Second end-point	4	78/2134	0·41 (0·25–0·65)	0·0002	0·83	0%
Follow-up (≥3 years)	5	473/3555	0·55 (0·34–0·87)	0·01	0·09	51%
Follow-up (<3 years)	2	31/150	0·65 (0·35–1·24)	0·19	0·32	0%
Number of participants (≥100)	4	469/3439	0·77 (0·65–0·90)	0·001	0·20	35%
Number of participants (<100)	3	35/266	0·36 (0·18–0·73)	0·005	0·85	0%
At least two steps of ETDRS	2	423/1555	0·81 (0·69–0·96)	0·01	0·79	0%
At least three steps of ETDRS	1	188/1421	0·65 (0·49–0·85)	0·002	NA	NA
Other definition	5	81/2150	0·39 (0·25–0·63)	0·00008	0·88	0%
Diabetic retinopathy progression						
Total studies	16	1537/9580	0·87 (0·80–0·95)	0·002	0·37	8%
Three step data	16	1463/9580	0·89 (0·81–0·97)	0·01	0·26	17%
Type 2 diabetic patients	7	806/3382	0·87 (0·78–0·98)	0·02	0·43	0%
Type 1 diabetic patients	6	371/2576	0·85 (0·71–1·03)	0·09	0·15	37%
Hypertensive patients	4	320/839	0·93 (0·79–1·10)	0·42	0·37	4%
Normotensive patients	9	518/3259	0·81 (0·69–0·94)	0·007	0·24	22%
Antihypertensive drugs	4	396/1052	0·89 (0·76–1·04)	0·14	0·65	0%
Placebo comparison	11	1141/8528	0·87 (0·78–0·96)	0·008	0·21	24%
Primary end-point	8	773/4829	0·77 (0·61–0·97)	0·02	0·07	45%
Second end-point	7	764/4751	0·89 (0·79–1·01)	0·06	0·96	0%
Follow-up (≥3 years)	8	1443/8710	0·89 (0·81–0·98)	0·01	0·51	0%
Follow-up (<3 years)	7	94/870	0·60 (0·41–0·87)	0·007	0·53	0%
Number of participants (≥100)	8	1420/9034	0·89 (0·81–0·98)	0·01	0·29	18%
Number of participants (<100)	7	117/546	0·66 (0·48–0·90)	0·009	0·77	0%
At least two steps of ETDRS	6	500/1672	0·81 (0·70–0·93)	0·003	0·20	29%
At least three steps of ETDRS	4	810/4577	0·93 (0·82–1·05)	0·22	0·13	44%
Other definition	8	643/4568	0·86 (0·75–0·99)	0·03	0·61	0%
Diabetic retinopathy regression						
Total studies	6	552/2624	1·39 (1·19–1·61)	0·00002	0·71	0%
Three step data	6	552/2624	1·39 (1·19–1·61)	0·00002	0·71	0%
Type 2 diabetic patients	4	489/2391	1·38 (1·18–1·62)	0·00007	0·51	0%
Type 1 diabetic patients	2	63/233	1·40 (0·92–2·14)	0·12	0·42	0%
Hypertensive patients	1	15/40	2·21 (0·92–5·31)	0·08	NA	NA
Normotensive patients	4	221/679	1·43 (1·14–1·79)	0·002	0·67	0%
Antihypertensive drugs	1	12/46	7·11 (1·75–28·82)	0·006	NA	NA

(Table 2 continues on next page)

	Number of studies	Events/ participants	Risk ratio (95% CI)	p value	p_h	I^2
(Continued from previous page)						
Placebo comparison	6	552/2624	1·39 (1·19–1·61)	0·00002	0·71	0%
Primary end-point	5	549/2495	1·39 (1·20–1·62)	0·00001	0·71	0%
Second end-point	1	3/129	0·48 (0·04–5·13)	0·54	NA	NA
Follow-up (≥3 years)	2	331/1945	1·36 (1·11–1·66)	0·003	0·27	19%
Follow-up (<3 years)	4	221/679	1·43 (1·14–1·79)	0·002	0·67	0%
Number of participants (≥100)	3	532/2442	1·37 (1·17–1·59)	0·00005	0·80	0%
Number of participants (<100)	3	20/182	1·88 (0·87–4·06)	0·11	0·42	0%
At least two steps of ETDRS	1	61/220	1·34 (0·87–2·05)	0·18	NA	NA
At least three steps of ETDRS	1	316/1905	1·33 (1·08–1·63)	0·006	NA	NA
Other definition	4	175/499	1·53 (1·19–1·97)	0·001	0·54	0%

p_h=p value of Cochran's *Q* test. NA=not applicable. ETDRS=Early Treatment Diabetic Retinopathy Study.

Table 2: **Effects of renin-angiotensin system inhibitors on diabetic retinopathy in the meta-analysis**

on diabetic retinopathy incidence, progression, or regression between hypertensive patients and normotensive patients (test for subgroup difference p=0·64, p=0·23, and p=0·35, respectively; figure 2).

There were nine trials (eight trials with placebo, one with active comparator) of progression of diabetic retinopathy in normotensive patients (table 1 and table 2). Further subgroup analysis by the type of comparator did not show a significant difference in the effect of RAS inhibitors on progression of diabetic retinopathy between trials with different types of comparators in normotensive patients (test for subgroup difference p=0·90).

There were seven trials in which estimates were adjusted for baseline or follow-up characteristics (appendix).[14,16,21,35,37,38,43] Meta-analysis of these studies suggested that RAS inhibitors were associated with a reduced risk of disease progression (RR 0·67, 95% CI 0·45–0·98; p=0·04; four trials with 4356 patients and 670 events) and increased possibility of disease regression (1·37, 1·11–1·69; p=0·003; three trials with 2155 patients and 392 events; appendix). There were six studies of the effect of RAS inhibitors on the development of proliferative diabetic retinopathy.[14,16,17,35,39,41] Meta-analysis of the data suggested that RAS inhibitors were not associated with a reduced risk of developing diabetic retinopathy (0·98, 0·85–1·13; p=0·78; six trials with 4404 patients and 633 events). ACE inhibitors tended to reduce the risk of developing proliferative diabetic retinopathy (0·53, 0·28–1·02; p=0·06; four trials with 594 patients and 31 events), whereas ARBs did not have a similar effect (1·01, 0·87–1·17; p=0·90; two trials with 3810 patients and 602 events; appendix).

Figure 3 shows the effects of ACE inhibitors and ARBs on retinopathy in patients with type 1 or type 2 diabetes. ACE inhibitors were associated with significantly reduced risks of incidence and progression, and higher possibility of regression of diabetic retinopathy than were antihypertensive drugs or placebo (appendix). ARBs were associated with a higher possibility of disease regression, but had no effect on disease progression (figure 3 and appendix).

The appendix shows the eligible comparisons in the network meta-analysis. Network meta-analysis showed that the association of antihypertensive drugs with diabetic retinopathy progression was lowest for ACE inhibitors, followed by ARBs, β blockers, calcium channel blockers, and placebo in rank order, whereas the association of antihypertensive drugs with regression was highest for ACE inhibitors, followed by ARBs, placebo, and calcium channel blockers in rank order (figure 4). The association of antihypertensive drugs with incidence of diabetic retinopathy was lowest for ACE inhibitors, followed by ARBs and placebo (ACE inhibitors *vs* placebo RR 0·45, 95% CI 0·16–0.86; ACE inhibitors *vs* ARBs 0·72, 0·19–2·67; and ARBs *vs* placebo 0·64, 0·18–1·45).

The shape of the funnel plots in the meta-analyses of disease progression and regression did not show obvious asymmetry, and the Egger's test p values were more than 0·05 (appendix). There was evidence of asymmetry in the funnel plot of diabetic retinopathy incidence (Egger's test p=0·009), but no additional study was added in the trim-and-fill analyses (appendix). One study was added in the meta-analysis of disease regression, but there was no obvious change in the pooled RR (1·39, 95% CI 1·20–1·61; p=0·00002).

The appendix shows the summary of the overall evidence for each outcome by the GRADE method. Generally, quality of evidence was high for the effect of ACE inhibitors on progression of diabetic retinopathy and was moderate for the effects of ACE inhibitors on incidence and regression of diabetic retinopathy. Additionally, the quality of evidence was moderate for the effect of ARBs on disease regression, and low for the effect of ARBs on disease incidence. However, the quality of evidence was moderate for the absence of effect of ARBs on disease progression.

Discussion

21 randomised clinical trials with a total of 13823 participants were included in the meta-analysis.[14–21,35–46] The large number of participants pooled in the meta-analysis ensured enough statistical power to detect the difference across studies and to obtain a precise estimation of the effect of RAS inhibitors on diabetic retinopathy. These inhibitors were associated with significantly reduced risks of incidence and progression of diabetic retinopathy, and higher possibility of disease regression (figure 1). The pooled estimates changed little in most subgroup analyses, the consistency of which further supported the credibility of the meta-analysis (table 2). Additionally, ACE inhibitors were associated with significantly reduced risks of incidence and progression, and higher possibility of disease regression,

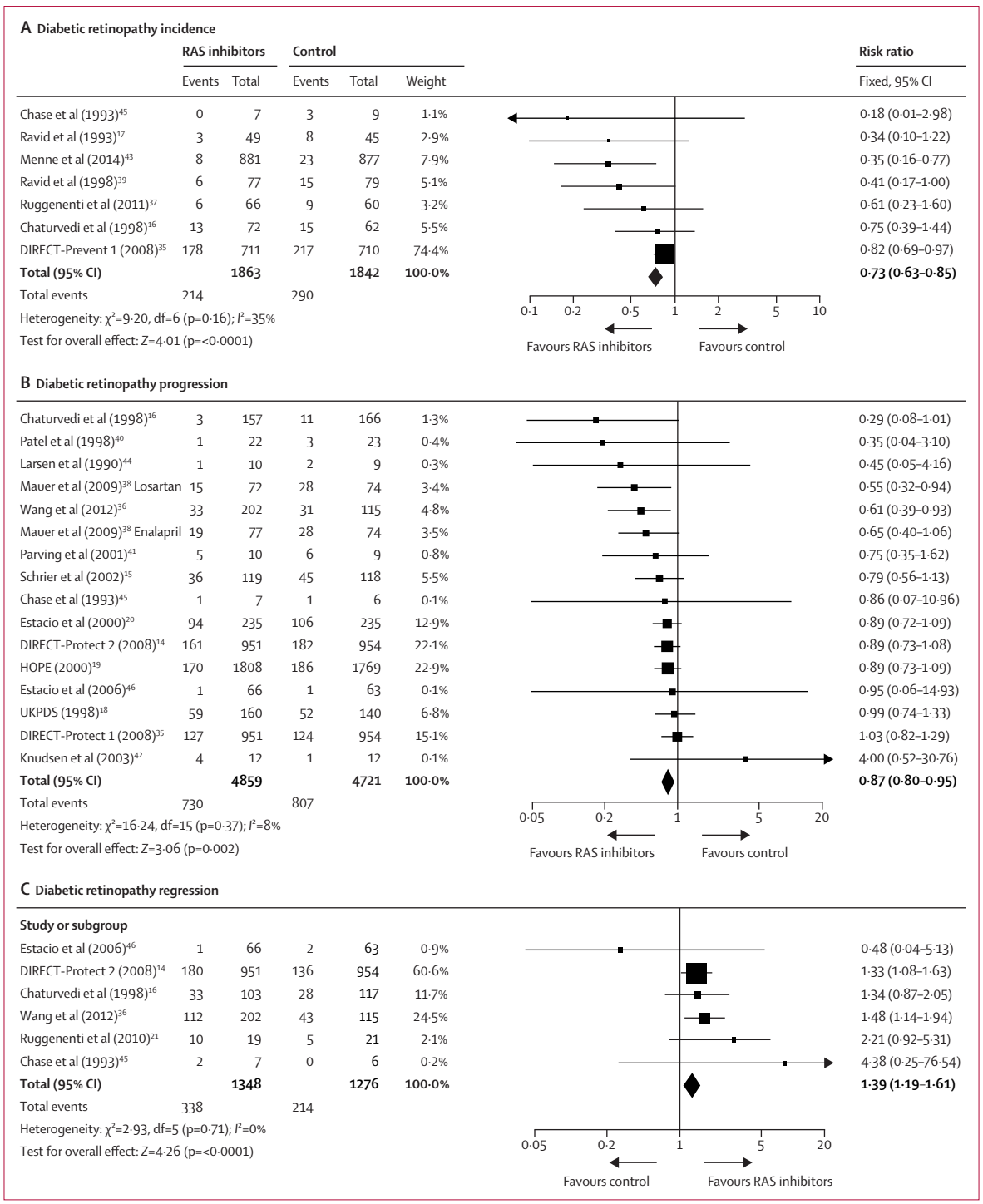

Figure 1: **Effects of renin-angiotensin system inhibitors on diabetic retinopathy incidence (A), progression (B), and regression (C) in the meta-analysis**

whereas ARBs only significantly increased possibility of disease regression (figure 3). ACE inhibitors tended to be better than ARBs in reducing risks of diabetic retinopathy incidence and progression, and increasing possibility of regression (figure 3). Thus, RAS inhibitors have beneficial effects on retinopathy in patients with diabetes, and ACE inhibitors seem to be more effective than are ARBs.

Our network meta-analysis incorporated both direct and indirect comparisons of treatments, including those that had never been compared directly. The findings

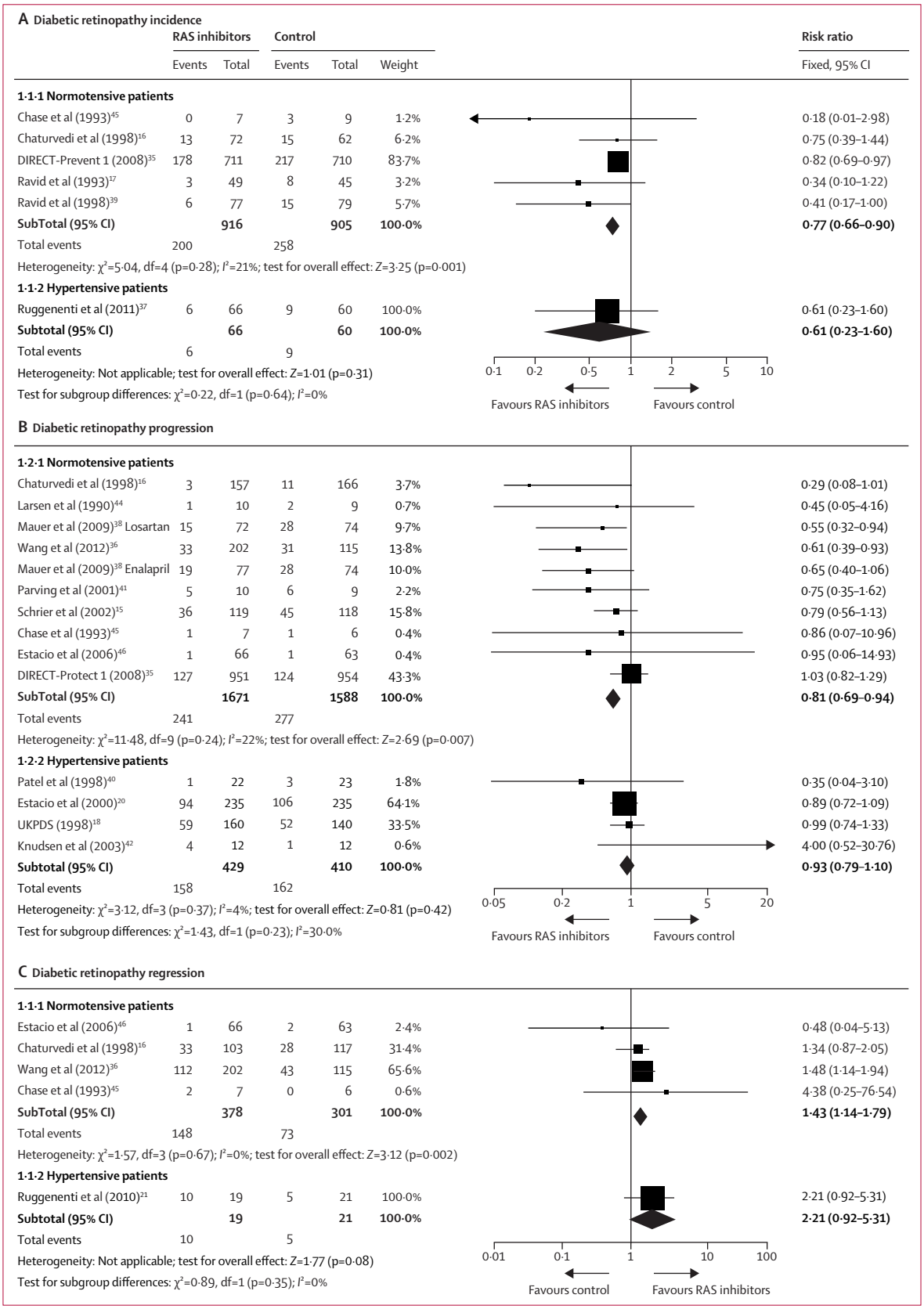

Figure 2: **Effects of renin-angiotensin system inhibitors on diabetic retinopathy incidence (A), progression (B), and regression (C) in the subgroup analysis of hypertensive and normotensive patients**

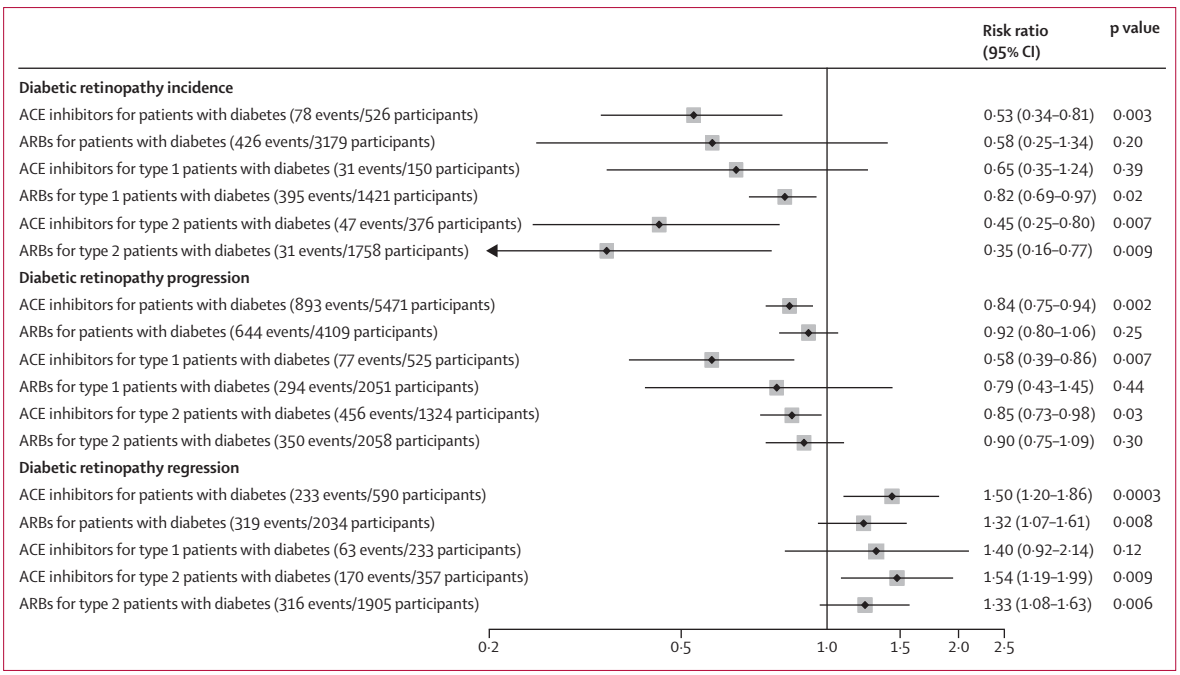

Figure 3: **Effects of ACE inhibitors and ARBs on diabetic retinopathy in the meta-analysis**
ACE=angiotensin-converting enzyme. ARBs=angiotensin receptor blockers.

from the network meta-analysis further identified the better effect of ACE inhibitors on diabetic retinopathy in comparison with ARBs, and ACE inhibitors consistently had higher probabilities of being in the superior ranking positions for incidence, progression, and regression (figure 4). Additionally, calcium channel blockers seemed to worsen the outcome of retinopathy as compared with placebo (figure 4), although this result was not significant. This finding is in line with findings of previous studies[47,48] of microvascular disease, which showed that ACE inhibitors had a potentially, although not significant, better effect on diabetic nephropathy than ARBs, whereas calcium channel blockers seemed to worsen the outcome of nephropathy compared with placebo. Evidence for the direct comparisons between ACE inhibitors and ARBs for diabetic retinopathy is still incomplete.

The criteria used to define progression or regression of diabetic retinopathy were not uniform in the studies included in the meta-analysis. Additionally, even in the studies with ETDRS grading, the definitions for progression and regression were not consistent. The different definitions were the main methodological limitation in our study. However, treating different definitions of progression and regression as different treatment outcomes would not be feasible because of insufficient numbers of participants and events to perform a meta-analysis or form a well-connected network meta-analysis. Also, there was no significant heterogeneity in the conventional meta-analyses, and no substantial inconsistency in the network meta-analyses, which indicated that the different definitions of disease

ACE inhibitors	1·64 (0·46–18·17)	**13·45 (1·83–166·80)**	..	2·15 (0·99–8·04)
0·79 (0·42–1·28)	**ARBs**	7·88 (0·43–103·46)	..	1·27 (0·24–4·07)
0·77 (0·43–1·35)	0·97 (0·47–2·34)	**CCBs**	..	0·16 (0·02–1·48)
0·90 (0·39–1·81)	1·15 (0·45–2·96)	1·18 (0·42–2·82)	**β blockers**	..
0·69 (0·41–0·98)	0·88 (0·57–1·31)	0·90 (0·41–1·67)	0·77 (0·32–1·78)	**Placebo**

Figure 4: **Effects of all antihypertensive drugs on diabetic retinopathy progression (blue) and regression (pink) in the network meta-analysis**
Comparisons between treatments should be read from left to right and the estimate is reported in the cell in common between the column-defining treatment and the row-defining treatment.ACE=angiotensin-converting enzyme. ARBs=angiotensin receptor blockers. CCBs=calcium channel blockers.

progression or regression did not cause obvious heterogeneity and inconsistency in the effect of RAS inhibitors across the included studies. Additionally, there was no obvious change in the pooled estimates when we used at least three step changes according to ETDRS grading. There was also no obvious change in the pooled RRs in the subgroup analysis by the different definitions of progression or regression (table 2). Thus, the different definitions for disease progression and regression were acceptable in the current context, and allowed us to obtain a precise assessment of the effect of RAS inhibitors on diabetic retinopathy.

Previous studies have suggested that dysfunction of metabolic pathways, reactive oxygen species in endothelial cells, and enhanced expression of vascular endothelial growth factor (VEGF) might be involved in the development of diabetic retinopathy.[49–51] There are several

possible mechanisms that might be the reason for the beneficial effect of RAS inhibitors on diabetic retinopathy. First, these drugs can inhibit the RAS in the eye, potentially improving retinal perfusion, and play a part in improving retinal blood flow, which further reduces disease progression.[52] Second, these inhibitors have been shown to inhibit mitochondrial reactive oxygen species and decrease the expression of VEGF in the retina,[53,54] whereas β blockers did not affect retinal VEGF expression.[55] Therefore, RAS inhibitors might have beneficial effects on diabetic retinopathy through reductions in VEGF overexpression, reducing vascular permeability, and alleviating the retinal vascular damage in patients with diabetes.[53,54] Last, RAS inhibitors can improve β-cell secretory function, insulin sensitivity, and reduce insulin resistance in patients with type 2 diabetes.[56–58] The dual effects of improved glucose metabolism and alleviated oxidative stress in the eye could thus reduce progression of diabetic retinopathy in people with diabetes.

There was no significant effect of RAS inhibitors on diabetic retinopathy in hypertensive patients in the meta-analysis, which might be the effect of lowering blood pressure on progression of diabetic retinopathy. In our meta-analysis, most studies in the subgroup analysis of hypertensive patients used active comparators. The effect of RAS inhibitors on disease progression in the hypertensive group might be reduced versus that of active comparators. However, previous trials of the effect of intensive blood pressure control on progression of diabetic retinopathy in patients with diabetes showed conflicting results,[10–12,20] and although results were not significant, results of the ACCORD trial showed that intensive blood pressure control was associated with increased hazard ratios for disease progression (1·28, 95% CI 0·84–1·79; defined as at least three-step ETDRS) and for moderate vision loss (1·27, 0·99–1·62). Previous meta-analysis also showed that intensive blood pressure control did not reduce the risk of progression (RR 0·93, 95% CI 0·83–1·05).[59] Thus, the effect of lowering the blood pressure on progression of diabetic retinopathy might not be sufficient to fully explain the absence of a significant effect of RAS inhibitors on progression of diabetic retinopathy in patients with hypertension. Another possible explanation for the absence of a significant effect of RAS inhibitors on diabetic retinopathy in hypertensive patients was the low statistical power from the small sample size because there were few eligible trials of hypertensive patients.

Our results from the meta-analysis suggest that RAS inhibitors reduce the risks of incidence and progression of diabetic retinopathy, and increase the possibility of regression in normotensive people with diabetes. Additionally, data from the meta-analysis also suggests that ACE inhibitors might be better than ARBs for diabetic retinopathy and, of all the antihypertensive drug classes, have the most beneficial effect. However, treatment decisions about the use of RAS inhibitors in normotensive people with diabetic retinopathy also need to take into account the effect of these drugs on other systems in the patient with diabetes.[60]

The findings in the meta-analysis are not generalisable to all patients with diabetes, and it is unclear whether treatment effects of RAS inhibitors on diabetic retinopathy differ between patients with type 2 and type 1 diabetes. There was a tendency of RAS inhibitors to have a larger effect on the incidence of retinopathy in patients with type 2 than in those with type 1 diabetes, the effect size was same for progression of retinopathy between patients with type 2 and those with type 1 diabetes (table 2).

There were several other limitations in the meta-analysis. First, there were only seven studies on incidence and six studies on regression of diabetic retinopathy. Some subgroup analyses had small numbers of participants, which could result in poor precision of estimates. Additionally, because of the small number of relevant studies, funnel plot and Egger's test had little power to correctly detect the risk of publication bias. Second, the findings from the meta-analysis are not generalisable to all RAS inhibitors. It is therefore also possible that the effects of ACE inhibitors on diabetic retinopathy might also depend on drug subtypes or dose. Third, few of the included studies reported additional stratification by glycaemic control or blood pressure control, and few studies reported estimates adjusted for follow-up blood pressure control. Fourth, the success of masking and dropouts were not fully assessed because some of the studies included were published many years ago and we were unable to obtain this information from authors. Fifth, the safety of the RAS inhibitors in patients with diabetic retinopathy was not fully assessed in the included trials. Although the investigators of several trials stated that there were no serious adverse events in the RAS inhibitors group, there was insufficient reliable evidence. Last, few trials assessed whether there was any difference in the effect of RAS inhibitors on diabetic retinopathy by severity of retinopathy. The effect of RAS inhibitors on diabetic retinopathy in patients with proliferative diabetic retinopathy or macular oedema remains unclear. More large-scale randomised controlled trials with rigorous definitions of progression and regression of diabetic retinopathy are needed to further clarify the effect of RAS inhibitors on retinopathy in diabetes. Additionally, more trials of the effect of ACE inhibitors and ARBs on diabetic retinopathy in normotensive patients with antihypertensive comparators are needed.

Contributors

BW and Y-GW had the idea for the study. BW, FW, and YZ selected and reviewed studies identified through the literature search, did the Cochrane risk of bias, and abstracted data from included articles. BW, FW, and Y-GW contributed to the statistical analysis and data synthesis of outcomes, and drafted and edited the final paper. S-HZ, W-JZ, and S-LY contributed to the writing of the methods and discussion sections, and edited the paper. BW, FW, and Y-GW critically revised the paper for important intellectual content. All authors have confirmed and agreed to submit the manuscript.

Declaration of interests
We declare no competing interests.

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