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Renin–angiotensin system blockade for the risk of cancer and death

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Abstract

Introduction: The effects of renin–angiotensin system blockade with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs) on cancer remain inconsistent.

Methods: We searched existing databases from 1960 to August 2015, for randomised controlled trials and observational studies (case–control studies and cohort studies) of ARB/ACEI therapy with a minimal one year of follow-up. Outcomes were incidence and mortality of cancer.

Results: We included 14 randomised controlled trials and 17 observational studies of 3,957,725 participants (350,329 ARB/ACEI users). The users had a lower incidence of cancer in the observational studies (RR 0.82, 95% CI 0.73–0.93) but not in the randomised controlled trials (RR 1.00, 95% CI 0.92–1.08). The protection persisted for lung cancer (RR 0.85, 95% CI 0.75–0.97) but not for other sites of cancer. The relative risk of cancer associated with renin–angiotensin system blockade was reduced along with time of follow-up. Mortality reduction with ARB/ACEI was marginally significant in the observational studies (RR 0.71, 95% CI 0.55–0.93) but not in the randomised controlled trials (RR 0.99, 95% CI 0.89–1.09).

Conclusions: The significant benefits of renin–angiotensin system blockade observed in case–control studies and cohort studies might diminish in randomised controlled trials. Clinical design, site of cancer and duration of follow-up may affect the clinical outcomes.

Keywords

Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, renin–angiotensin system, cancer, angiotensin-receptor blocker

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Introduction

The renin–angiotensin system (RAS) is a key therapeutic target for diabetes mellitus, chronic kidney disorders, hypertension, heart problems, chronic obstructive pulmonary disease and stroke. RAS blockers include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs). The impacts of RAS blockade on the incidence and mortality of cancer remain debated. Some studies suggest that the use of ACEIs and ARBs may increase the risk of cancer.[1] A meta-analysis showed an increased risk of cancer by ARBs compared with controlled therapy.[2] Intriguingly, the US Food and Drug Administration claims no increase in the risk of cancer with ARBs.[3]

Angiotensin II and angiotensin II type 1 receptors (AT1) play major roles in the development and progression of cancer.[4,5] Angiotensin II acts on the AT1 receptor to promote cell proliferation and angiogenesis.[6–8] The expression of AT1 receptors has been reported to be

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upregulated in hyperplasic and cancer tissues.[9,10] ACEIs prevent the generation of angiotensin II by inhibiting angiotensin-converting enzymes (ACEs) while ARBs selectively block angiotensin II binding to the AT1 receptor. These actions may have important implications for cancer development. However, the existing clinical evidence is inconsistent.[2,11,12] Therefore we conducted a systematic review and meta-analysis to evaluate the impact of an RAS blockade with ACEI/ARB therapy on the risk of cancer and death.

Materials and methods

Search strategy

Candidate studies were identified through electronic literature searches of PubMed, Cochrane Library databases, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases from 1960 to August 2015. We used the following MeSH terms and keywords: 'cancer', 'carcinoma', 'sarcoma', 'neoplasia' or 'malignancy' in combination with 'renin–angiotensin system', 'RAS' and 'angiotensin-receptor blocker', 'ARB' or 'angiotensin-converting enzyme inhibitor', 'ACEI'. A manual search of reference lists from reports of review articles, meta-analyses and original studies was performed to identify additional relevant studies.

Selection criteria

Our inclusion criteria were as follows: (a) clinical trials, including randomised controlled trials (RCTs), cohort studies and case–control studies; (b) use of ACEIs and/or ARBs in the participants; (c) incidence and/or mortality due to cancer as an outcome with detailed description of relative risk ratios (RRs), corresponding 95% confidence intervals (CIs), size of the baseline samples and years of follow-up; and (d) each study should have enrolled at least 200 participants. Literature meeting any of the following criteria was excluded: non-clinical nature, non-human studies, duplication, unclear outcome evaluation and non-original studies including reviews, letters, editorials and commentaries.

Data extraction

The extracted data included first author name, study title, year of publication date, country of origin, disease, demographic characteristics of participants, details of intervention, outcome measurements, intervention durations, incidence and mortality of cancer and RR for cancer with the corresponding 95% CI. All articles were read by two independent reviewers (JS and XZ) who extracted data from the articles according to a standardised data extraction form. Disagreements were resolved in all cases by discussion among our team members.

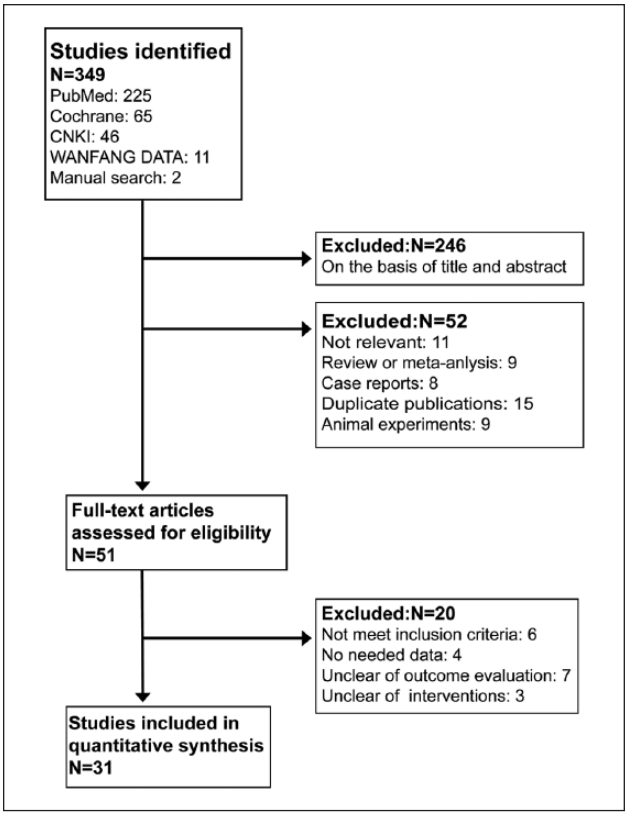

Figure 1. Flow chart of selection process in this study.

Quality assessment

The methodological quality of studies was assessed by the Newcastle–Ottawa scale (NOS). Using the NOS, a study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups and the ascertainment of the outcome of interest.[13] Studies with a score of less than 3 were considered as low quality, while scores of 4–6 were considered as moderate quality and 7–9 were considered as high quality. All studies were reviewed by two investigators (JS and X-NS). A third reviewer (H-LZ) served to resolve disputes.

Statistical analyses

This study is reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[14] Dichotomous outcome data from individual trials were analysed by using RR and corresponding 95% CI. Data were pooled using the random effects model or fixed effect model according to the heterogeneity between studies. Heterogeneity was assessed using the chi-square test, with values greater than 50% regarded as being indicative of moderate to high heterogeneity. For studies of moderate to high heterogeneity, a random effects meta-analysis model was used;[15] otherwise, we used the fixed effects meta-analysis model.[16] The possibility of

Table 1. Summary of the characteristics of the included trials.

First author, year	Study type	Country	Type of cancer	Age (year)	Participants	Intervention	Cancer outcome	Follow-up (years)
Makar et al.,[19] 2014	Observational studies	USA	Colorectal cancer	70	31,086	ARB, ACEI	Incidence	⩾5.0
Engineer et al.,[22] 2013	Observational studies	USA	Colorectal cancer	65	262	ARB, ACEI	Mortality	2.9
Cardwell et al.,[32] 2014	Observational studies	UK	Breast cancer	65	16,920	ARB, ACEI	Mortality	3.9
			Colorectal cancer	65	12,053	ARB, ACEI	Mortality	2.8
			Prostate cancer	65	12,188	ARB, ACEI	Mortality	3.8
Rao et al.,[21] 2013	Observational studies	USA	Lung cancer	62	1,228,960	ARB	Incidence	4.5
Rao et al.,[20] 2013	Observational studies	USA	Prostate cancer	65	543,824	ARB	Incidence	6.0
Koomen et al.,[43] 2009	Observational studies	Netherlands	Melanoma	67	6520	ARB	Incidence	2.7
Chae et al.,[23] 2011	Observational studies	USA	Breast cancer	59	703	ACEI	Incidence	4.6
Chiang et al.,[36] 2014	Observational studies	Taiwan	Hypertension	59	69,660	ACEI	Incidence	2.4
Sugiura et al.,[44] 2012	Randomised trials	Japan	Hypertension	65	2049	ARB	Incidence	4.2
							Mortality	
Bhaskaran et al.,[11] 2012	Observational studies	UK	Hypertension	64	377,649	ARB	Incidence	4.6
Julius et al.,[26] 2006	Randomised trials	USA	Hypertension	48	772	ARB	Incidence	3.6
Julius et al.,[27] 2004	Randomised trials	USA	Hypertension	67	15,245	ARB	Incidence	4.2
Huang et al.,[12] 2011	Observational studies	Taiwan	Hypertension	59	109,002	ARB	Incidence	5.7
Dahlof et al.,[41] 2002	Randomised trials	Sweden	Hypertension	67	9193	ARB	Incidence	4.8
Lindholm et al.,[42] 2001	Randomised trials	Sweden	Hypertension	76	6614	ACEI	Incidence	5.0
Lewis et al.,[29] 2001	Randomised trials	USA	Hypertension	59	1715	ARB	Incidence	2.6
Lever et al.,[35] 1998	Observational studies	UK	Hypertension	52	5207	ACEI	Incidence	6.6
NAVIGATOR[24] 2010	Randomised trials	USA	Cardiovascular disease	64	9306	ARB	Incidence	5.0
ONTARGET[25] 2008	Randomised trials	USA	Cardiovascular disease	66	23,994	ARB	Incidence	4.7
						ARB+ACEI		
TRANSCEND[34], 2008	Randomised trials	UK	Cardiovascular disease	67	5926	ARB	Incidence	4.7
Yusuf et al.,[45] 2008	Randomised trials	Canada	Cardiovascular disease	66	20,332	ARB	Incidence	2.5
						ARB+ACEI		
Massie et al.,[31] 2008	Randomised trials	USA	Cardiovascular disease	72	4128	ARB	Incidence	4.1
						ARB+ACEI		
Pfeffer et al.,[28] 2003	Randomised trials	USA	Cardiovascular disease	65	14,703	ARB	Incidence	2.1
						ARB+ACEI		
Dickstein et al.,[46] 2002	Randomissed trials	Norway	Cardiovascular disease	67	5477	ARB	Mortality	2.7
Cohn et al.,[30] 2001	Randomised trials	USA	Cardiovascular disease	63	5010		Incidence	1.9
						ARB+ACEI		
Chin et al.,[47] 2011	Observational studies	South Korea	Glomerulonephritis	41	3288	ARB	Incidence	2.5
							Mortality	
Chang et al.,[38] 2011	Observational studies	Taiwan	Type 2 diabetes mellitus	66	5104	ARB	Incidence	7.4
Wang et al.,[37] 2013	Observational studies	Taiwan	Breast, colon, lung, rectum cancer	62	85,842	ARB	Incidence	4.8
Azoulay et al.,[33] 2012	Observational studies	UK	Breast, colon, lung, rectum cancer	72	410,167	ARB	Incidence	6.4
Hallas et al.,[39] 2012	Observational studies	Denmark	Breast, colon, lung, rectum cancer	69	597,668	ARB, ACEI	Incidence	7.8
Pasternak et al.,[40] 2011	Observational studies	Denmark	Breast, colon, lung, rectum cancer	63	317,158	ARB, ACEI	Incidence	2.9

ARB: angiotensin II type 1 receptor blocker; ACEI: angiotensin-converting enzyme inhibitor.

publication bias was quantified using the Begg's and Egger's test.[17,18] A two-tailed $P>0.050$ was considered to be no publication bias, followed by confirmation using the visual inspection of Begg funnel plots in which relative risks were plotted against their standard errors (SE). All the analyses were carried out using Stata 11.0SE statistical software package (StataCorp, College Station, TX, USA).

Results

Study description

Figure 1 shows the study selection process. A total of 31 studies met our inclusion criteria and involved 3,957,725 participants with hypertension, cardiomyopathy, vascular disease, breast cancer, colon cancer, lung cancer, melanoma, type 2 diabetes mellitus and glomerulonephritis. The age of the participants ranged from 18 to 80 years. All the studies were published between 1998 and 2014 (Table 1). There were 17 observational studies and 14 RCTs. Seven studies tested dual blockade with ARBs and ACEIs, 24 studies assessed ARB monotherapy and eight studies focused on ACEI monotherapy. The duration of follow-up ranged from 1.9 to 7.8 years. Sites (number) of the studies were as follows: America (13),[19–31] England (5),[11,32–35] Taiwan (4),[12,36–38] Denmark (2),[39,40] Sweden (2),[41,42] Netherlands (1),[43] Japan (1),[44] Canada (1),[45] Norway (1)[46] and South Korea (1).[47] Table 1 shows

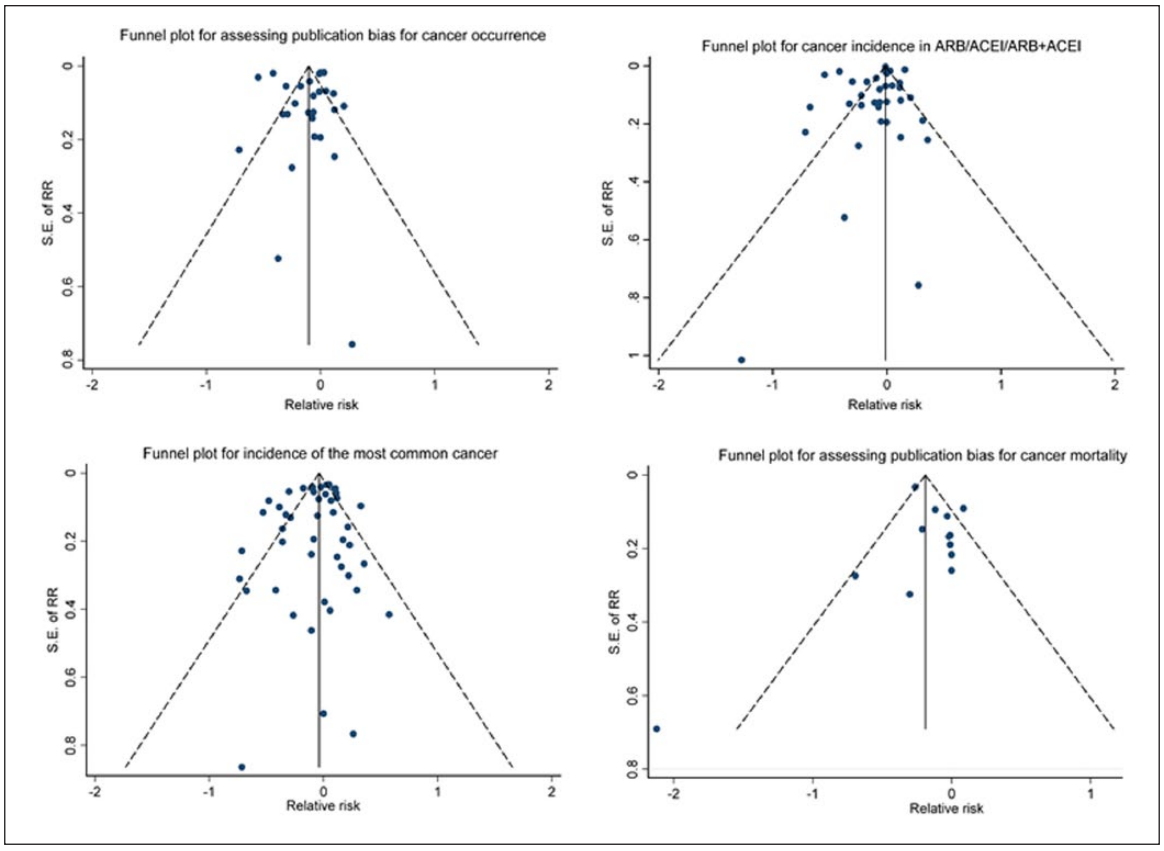

Figure 2. Funnel plots for assessing publication bias.

the characteristics of the 31 studies included in the meta-analysis.

Risk of bias within studies

As shown in Table 2, the range in the total NOS score for the 31 studies was 6 to 9 (theoretical range 0 to 9) and the mean (SD) was 7.7 (0.77). No publication bias was evident by Begg's test (P=0.160) and Egger's test (P=0.790). Consistently, all the funnel plots were symmetric, indicating no publication bias (Figure 2).

Outcomes

RAS blockade on incidence of cancer. There were 28 studies reporting the incidence of cancer (Table 1). Figure 3 shows incidence reduction with ARB/ACEI in the observational studies (RR 0.82, 95% CI 0.73–0.93, P=0.001). In the RCTs, incidence reduction with ARB/ACEI was not significant (RR 1.00, 95% CI 0.92–1.08, P=0.989).

In subgroup analysis by RAS blockers, ACEIs (RR 0.84, 95% CI 0.72–0.99, P=0.033) and ARBs (RR 0.91, 95% CI 0.84–0.99, P=0.022) consistently lowered the incidence of cancer in the observational studies (Figure 4). In the RCTs, no benefits were evident by ARBs (RR 1.00, 95% CI 0.92–1.10, P=0.964) or by combined therapy of ARBs and ACEIs (RR 1.05, 95% CI 0.87–1.27, P=0.603).

Figure 5 illustrates the pooled data of the observational studies and RCTs stratified by sites of cancer. The observational studies revealed significant incidence reduction with ARB/ACEI in lung cancer (RR 0.85, 95% CI 0.75–0.97, P=0.015) but not colorectal cancer (P=0.164), breast cancer (P=0.211) or prostate cancer (P=0.506). The RCTs showed no incidence reduction with ACEI/ARB in lung cancer, breast cancer or prostate cancer.

Although the pooled data of 28 studies in total disclosed significant incidence reduction with the RAS blockade (Figure 6(a)), the protective effects were not statistically significant with the duration of follow-up stratified into less than 3, 3–5 and over 5 years. Figure 6(b) demonstrates a trend of reduced RR along with the time of follow-up.

RAS blockade on mortality of cancer. Figure 7 shows mortality reduction with ARB/ACEI in the observational studies (RR 0.71, 95% CI 0.55–0.93, P=0.051). In the RCTs, mortality reduction was not significant (RR 0.99, 95% CI 0.89–1.09, P=0.765).

Differences in outcomes for cancer in observational studies and RCTs. Differences in the observational studies and RCTs included duration of follow-up and sample sizes

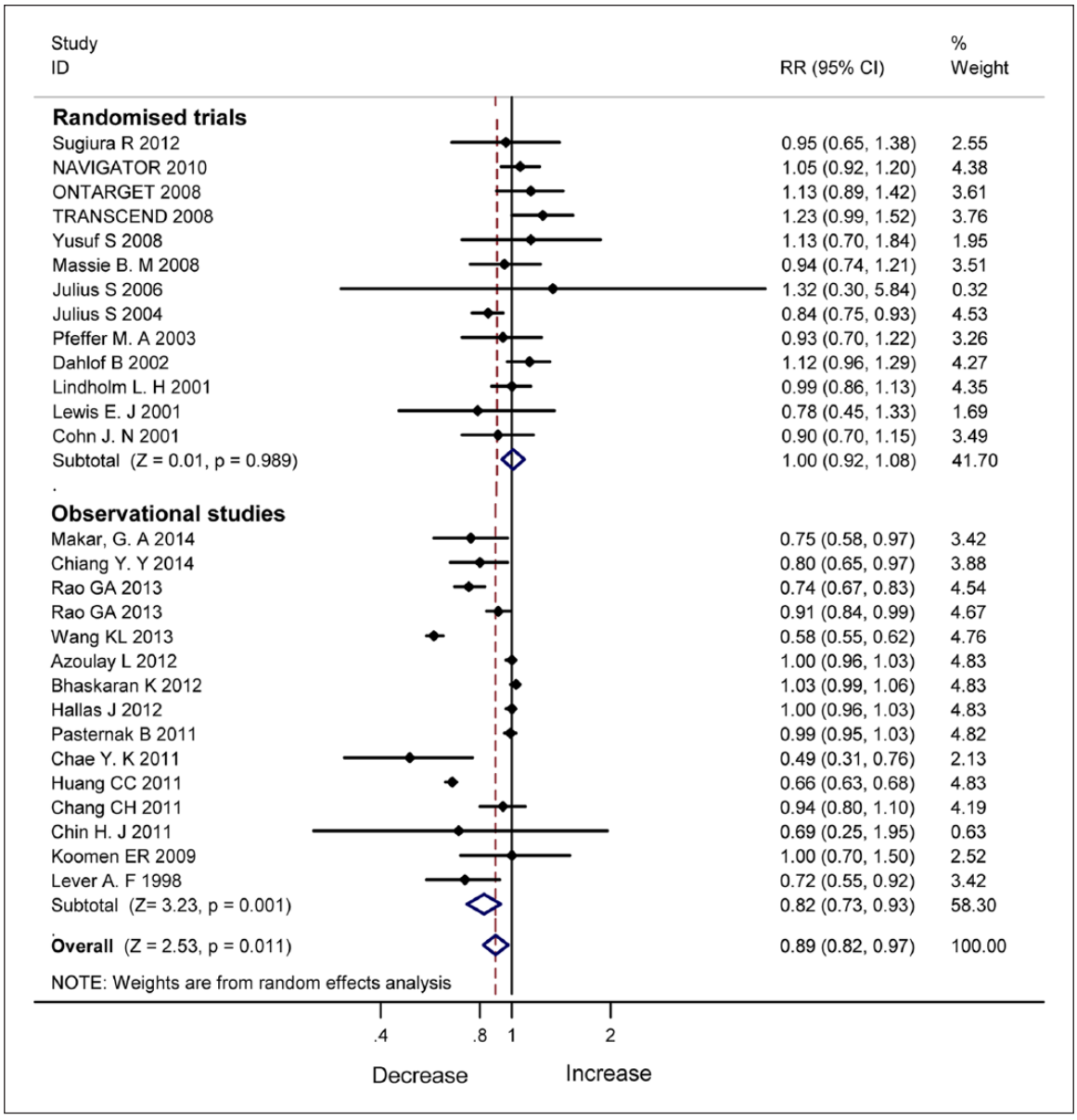

Figure 3. Incidence reduction with angiotensin-converting enzyme inhibitor/angiotensin II type I receptor blocker therapy in randomised controlled trials and observational studies.

(Table 3). The range of follow-up duration in observational studies was 2.4–7.8 years, compared to 1.9–5.0 years in RCTs. The mean duration of follow-up was 23% higher in observational studies than in RCTs. Moreover, the 17 observational studies had a sample size much larger than the 14 RCTs. The observational studies included 289,858 RAS blockade users and 3,833,261 participants, compared with 59,802 and 124,464, respectively, for the RCTs.

Discussion

This meta-analysis reveals that the significant benefits of the RAS blockade observed in case–control studies and cohort studies might diminish in RCTs. Monotherapy with ACEI/ARB might have protective effects on the incidence and mortality of cancer in the pooled analysis of observational studies. The claimed therapeutic benefits in observational studies could not be validated in RCTs. The observed benefits of RAS blockade against the risk of cancer and death could largely result from non-randomised clinical design with a prolonged period of follow-up.

Observational studies have shown that ACEI/ARB may reduce the incidence and mortality of cancer. Angiotensin II receptors AT1 and AT2 are widely distributed in the cardiovascular system, brain, liver, kidney, adrenal cortex, muscle and connective tissue.[48,49] Angiotensin II, the

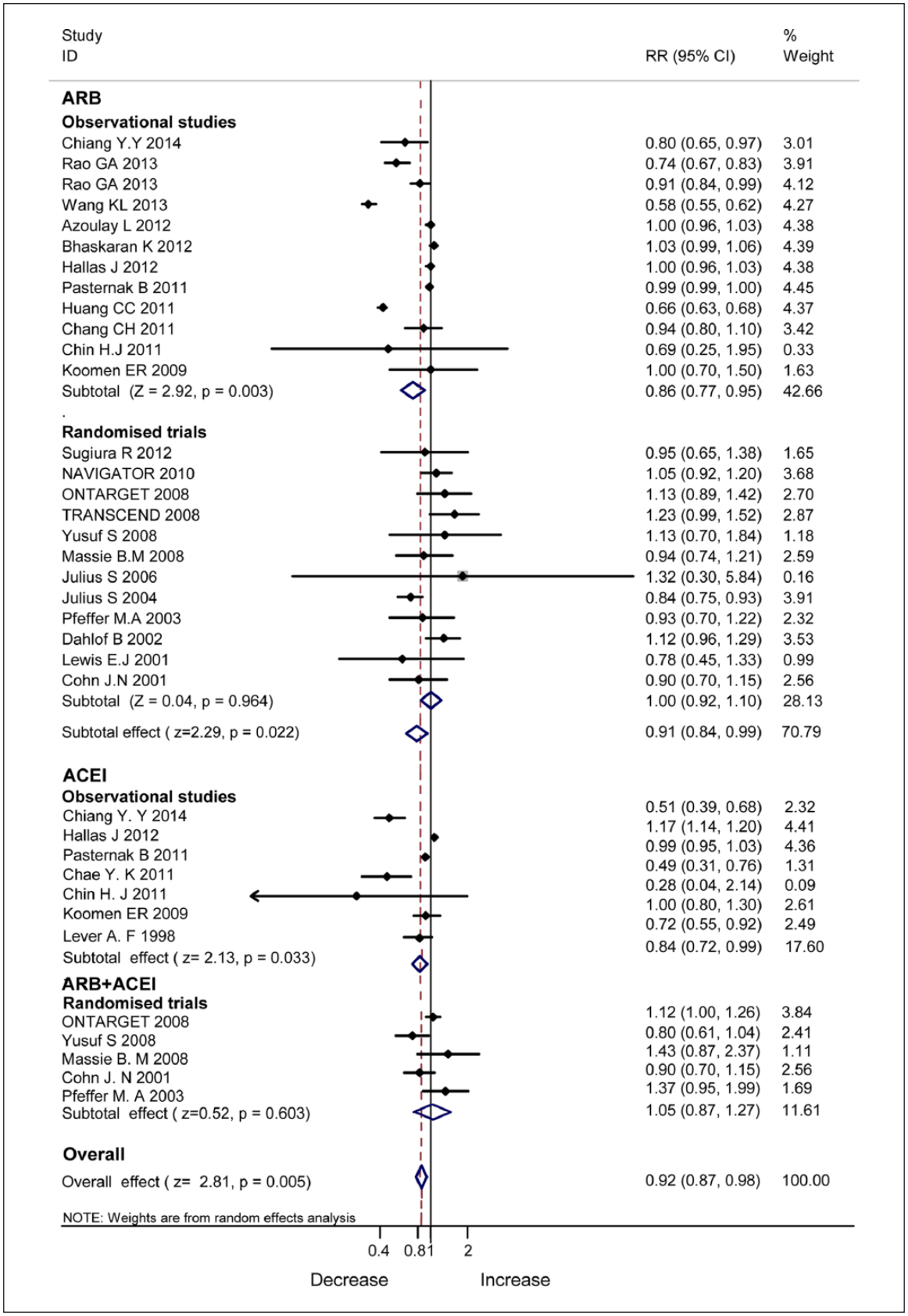

Figure 4. Subgroup analyses of monotherapy with angiotensin-converting enzyme inhibitor/angiotensin II type 1 receptor blocker therapy and dual renin–angiotensin system blockade.

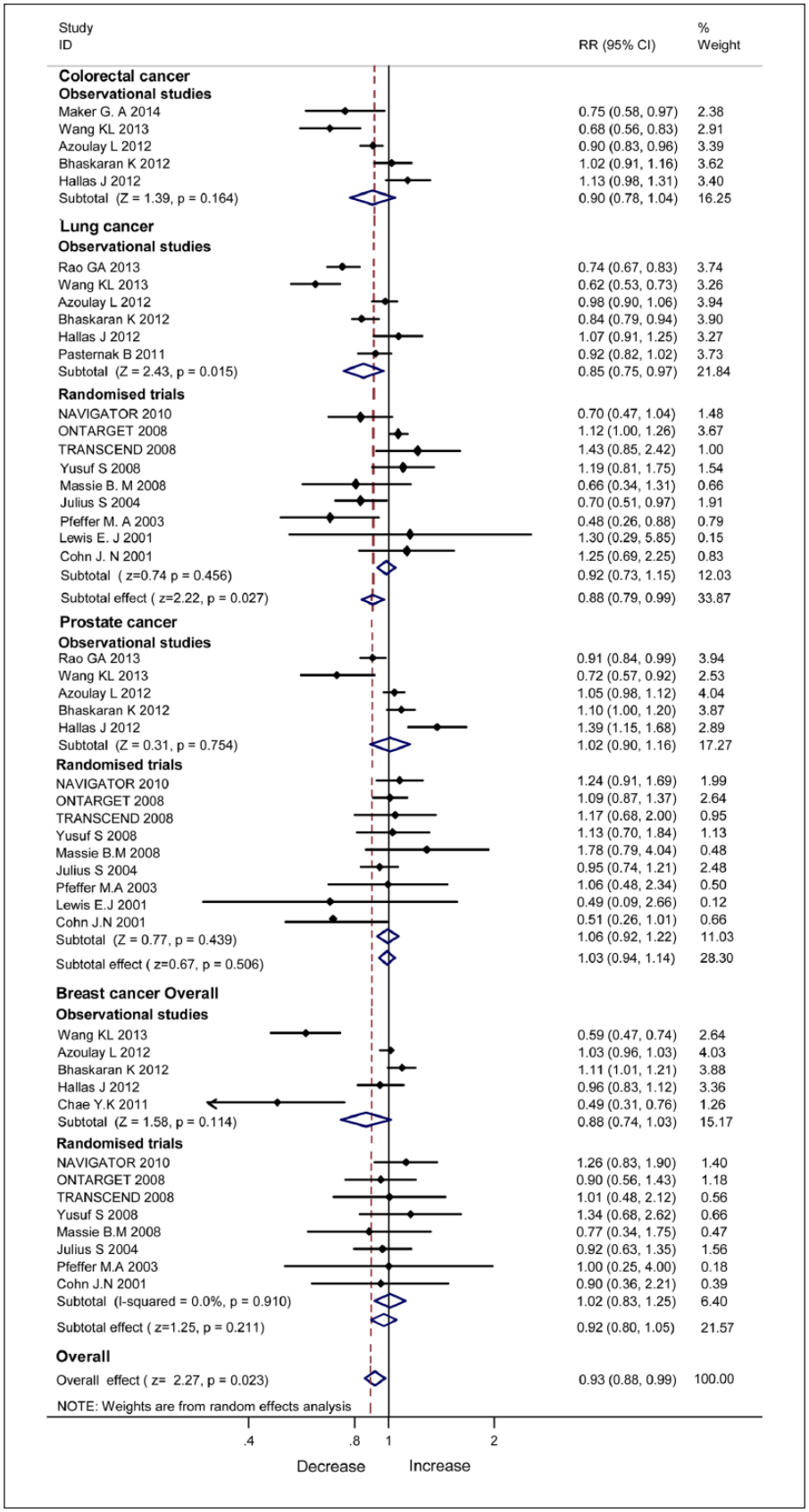

Figure 5. Incidence reduction with angiotensin-converting enzyme inhibitor/angiotensin II type I receptor blocker therapy in site-specific cancer.

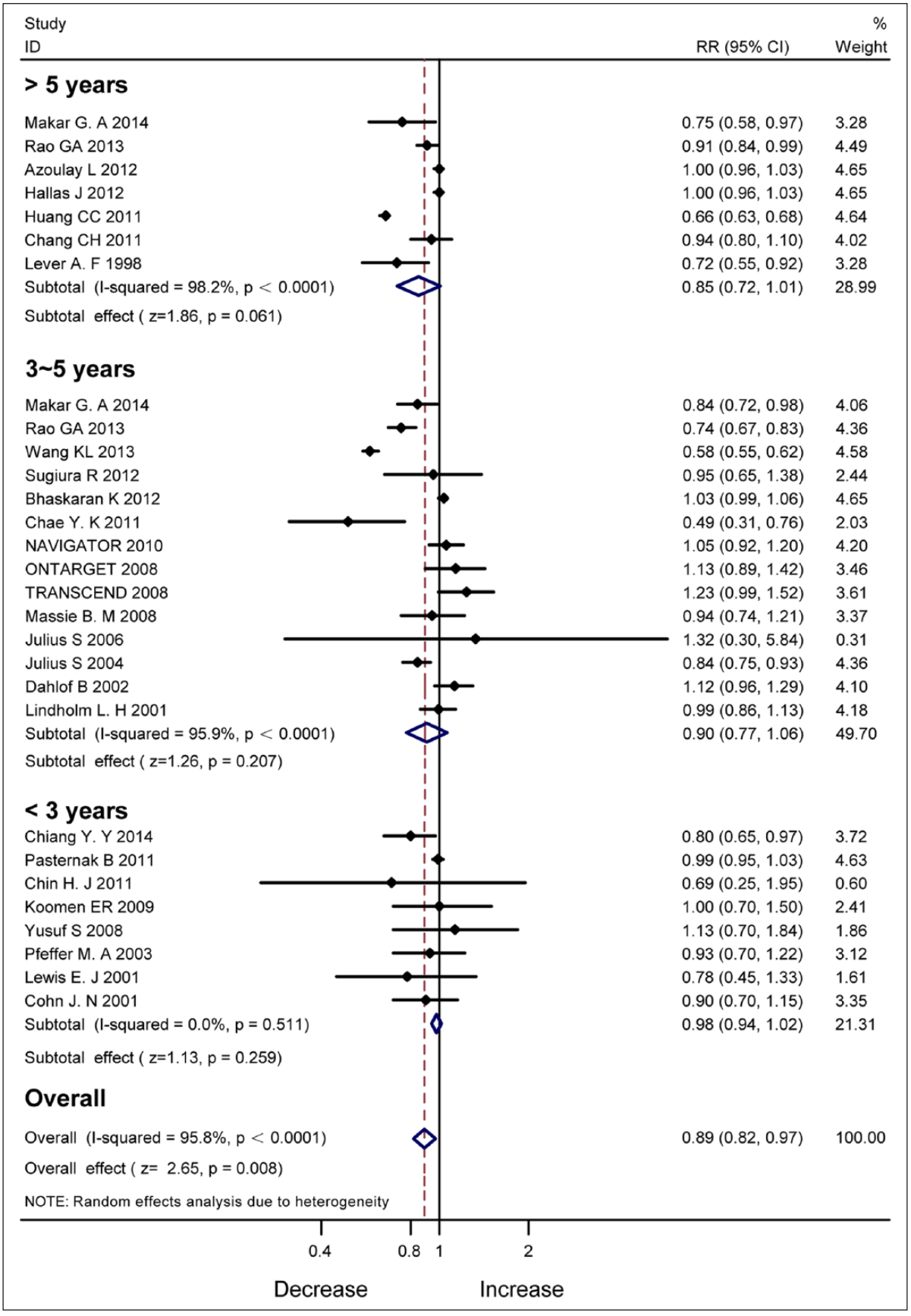

Figure 6 Contined

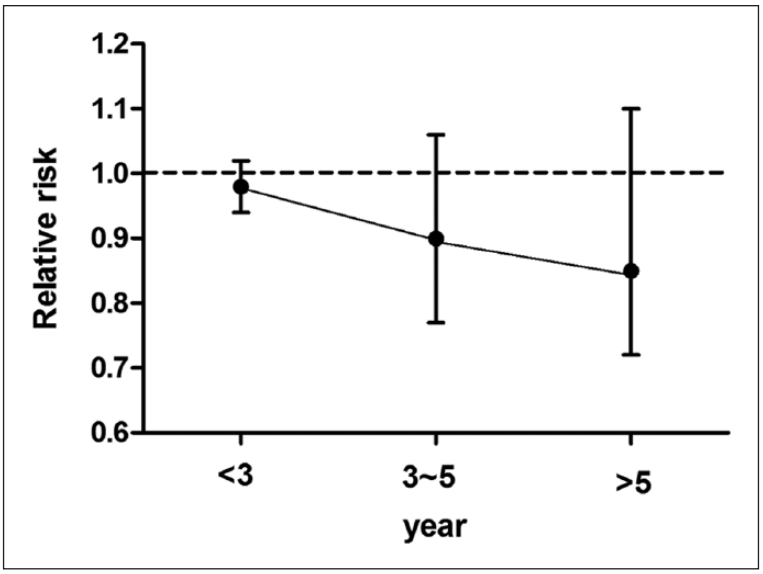

Figure 6. Incidence reduction with angiotensin-converting enzyme inhibitor/angiotensin II type I receptor blocker therapy stratified by the duration of follow-up. (a) Forest plot; (b) Relative risk ratios.

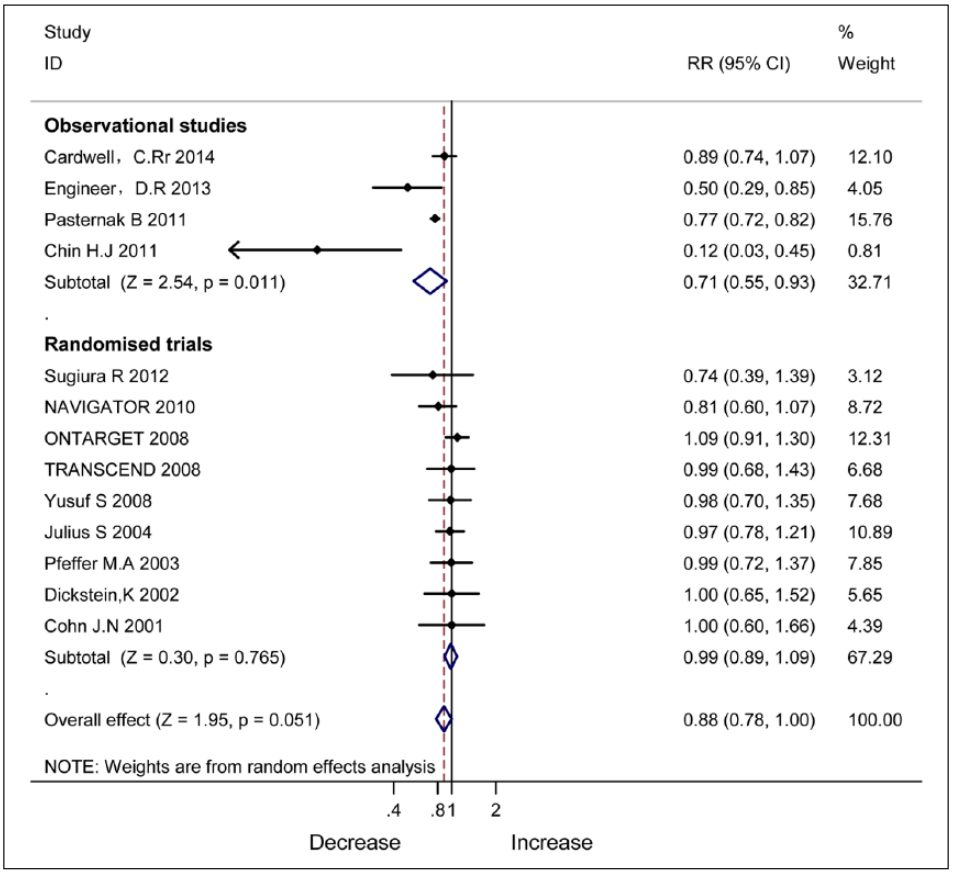

Figure 7. Mortality reduction with angiotensin-converting enzyme inhibitor/angiotensin II type I receptor blocker therapy in observational studies and randomised controlled trials.

known key active peptide of RAS, binds the AT1 receptor to promote the initiation and progression of cancer by stimulating cell proliferation, angiogenesis and inflammation[50–53] (Figure 8). The network regulation may

Table 2. Quality assessment of the 31 studies.

Authors	Year	Selection score	Comparability score	Outcome score	Total score
Makar et al.[19]	2014	4	2	2	8
Chiang et al.[36]	2014	4	2	2	8
Cardwell et al.[32]	2014	3	2	2	7
Rao et al.[21]	2013	3	2	3	8
Rao et al.[20]	2013	3	2	3	8
Wang et al.[37]	2013	4	1	2	7
Engineer et al.[22]	2013	3	1	2	6
Sugiura et al.[44]	2012	3	2	2	7
Bhaskaran et al.[11]	2012	4	2	3	9
Azoulay et al.[33]	2012	4	2	2	8
Hallas et al.[39]	2012	4	0	2	6
Pasternak et al.[40]	2011	4	2	2	8
Chae et al.[23]	2011	3	2	2	7
Huang et al.[12]	2011	4	2	3	9
Chin et al.[47]	2011	3	2	2	7
Chang et al.[38]	2011	4	2	3	9
NAVIGATOR[24]	2010	4	2	2	8
Koomen et al.[43]	2009	3	1	2	6
ONTARGET[25]	2008	4	2	3	9
TRANSCEND[34]	2008	4	2	3	9
Yusuf et al.[45]	2008	4	2	2	8
Massie et al.[31]	2008	4	2	3	9
Julius et al.[26]	2006	4	2	2	8
Julius et al.[27]	2004	4	2	2	8
Pfeffer et al.[28]	2003	3	2	3	8
Dahlof et al.[41]	2002	3	2	2	7
Dickstein et al.[46]	2002	4	2	2	8
Lindholm et al.[42]	2001	3	2	2	7
Lewis et al.[29]	2001	4	1	2	7
Cohn et al.[30]	2001	4	2	2	8
Lever et al.[35]	1998	4	1	2	7

Table 3. Differences in observational studies and randomised controlled trials (RCTs) included in this meta-analysis.

	Observational studies	RCTs
Study included	17	14
Follow up (mean, years)	4.59 (2.4–7.8)	3.72 (1.9–5)
User	289,858	59,802
Participant	3,833,261	124,464
ACEI	3	1
ARB	9	12
ARB+ACEI	0	5
ARB or ACEI	5	0

ARB: angiotensin II type 1 receptor blocker; ACEI: angiotensin-converting enzyme inhibitor.

explain the decreased risk of cancer incidence and mortality with RAS blockade.[54–56] Cancer cells are angiogenesis dependent, and thus blockade of angiogenesis could limit tumour growth.[57–60] Indeed, several studies have shown angiotensin II in the promotion of angiogenesis due to increased vascular endothelial growth factor expression by activation of the AT1.[61–63] In contrast to angiotensin II, the angiotensin-(1-7) inhibits both angiogenesis and cell proliferation.[64–66] It is well known that the ACE2–angiotensin-(1-7)–Mas axis serves as the principal counter-regulatory mechanism for the ACE–angiotensin II–AT1 axis.[67] An increased ACE/ACE2 activity ratio might lead to increased angiotensin II generation and increased catabolism of angiotensin (1-7). Monotherapy with ACEIs could upregulate ACE2 expression to lower the risk of cancer.[68] These findings might explain the consistent findings in the observational studies included in this meta-analysis.

The protection with RAS blockade against cancer in observational studies diminished in the pooled analysis of the RCTs. The difference in outcomes for cancer between the two types of studies is attributed to sample size and duration of follow-up (Table 3). The 17 observational studies included in this meta-analysis provided a larger sample size than the 14 RCTs, and had a longer average duration of follow-up. Although observational studies have inherent limitations, which might compromise real associations between tested drugs and outcomes, it is

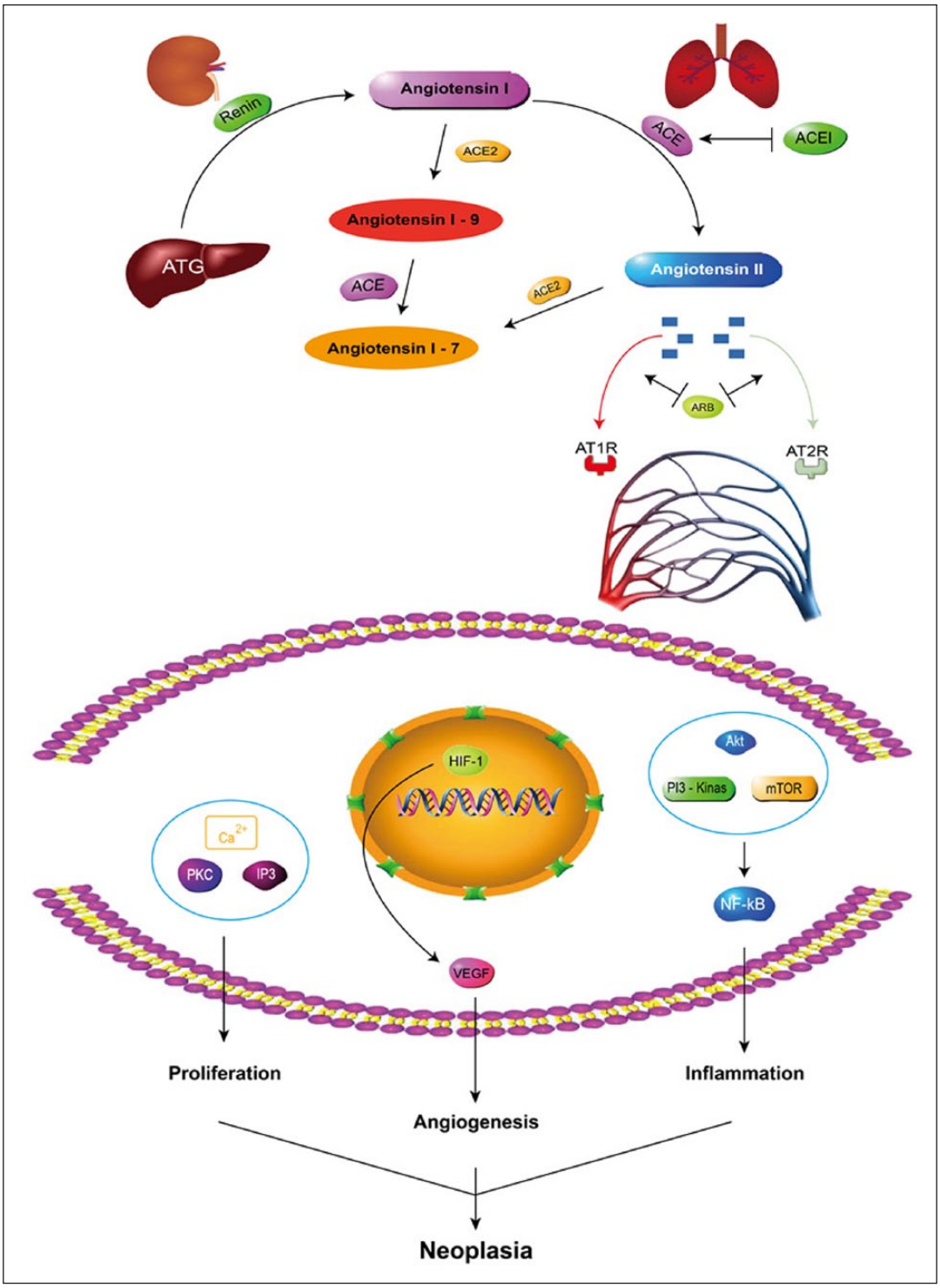

Figure 8. Current view of the renin–angiotensin system cascade.

difficult to implement RCTs in real clinical settings and lifetime treatment. In the present study, RCTs included in this analysis were not conducted to evaluate the effects of ARBs and ACEIs on the risk of cancer and cancer-related death as the primary endpoints. Concerning the differences in outcomes for cancer, here we have reported cancer incidence and mortality changes separately in RCTs and observational studies.

There are limitations in this study. First, the incidence and mortality of cancer were not the primary endpoints in some of the included case–control studies. Second, lack of the original data has prevented our direct evaluation of the

effects of ARB/ACEI on different ethnic groups. Finally, the exact doses and dosages were inconsistent in the 31 studies included. All these limitations might affect the implication and interpretation of the findings from the present study.

In summary, the therapeutic benefits with ACEIs and ARBs reported in case–control studies and cohort studies might diminish in RCTs. The clinical design, site of cancer and duration of follow-up may affect the clinical outcomes.

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Authors' contributions

The study was designed by JS, YMH, XNS, XZH, XZ and HLZ; YMH, JS, XNS were responsible for critical revision of the article for important intellectual content and draft the manuscript; YMH, MW, YHP, XZH conducted the collection and assembly of the data; MW, YMH and WL performed the statistical analyses; MHZ, XXZ, YS and HLZ interpreted the data; JS and YMH drafted the manuscript; HLZ had primary responsibility for the final content.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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