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Review Article

Systematic review and meta-analysis of randomised controlled clinical trial evidence refutes relationship between pharmacotherapy with angiotensin-receptor blockers and an increased risk of cancer☆

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ABSTRACT

Aims: The potential influence of angiotensin-receptor blockers (ARBs) on carcinogenesis is a much-debated topic. Both observational, as well as preclinical studies in rodent carcinogenic assays, suggest a major role of the Renin-Angiotensin-Aldosterone-System (RAAS) in cancer development. Therefore, a systematic review and meta-analysis with available study data on ARBs and carcinogenicity in general as primary outcome were conducted. Secondary outcomes were defined as tumour-specific mortality rates and the frequency of new cases of specific tumour types with particular emphasis on lung, breast, and prostate cancer.

Methods: A systematic literature research was performed in MEDLINE, EMBASE, Cochrane Library, and TOXLINE. We used a combination of MeSH terms, keywords and substance names of ARBs and searched between 1950 and 2016. At least 100 participants in each study arm and a minimum follow-up for one year were necessary for study inclusion. Odds ratios (OR) were calculated by a random-effects model.

Results: A total of 8818 potentially eligible publications were identified of whom seven randomised controlled trials, four case-control studies and one cohort study met our inclusion criteria. As a key result, we found no effect on carcinogenesis in randomised controlled trials for ARB usage. (OR 1.02, 95% CI 0.87–1.19; $p = .803$). Conflicting results with observational studies could be explained by poor reporting- and study qualities.

Conclusions: The results of our meta-analysis focusing only on high evidence levels and study designs (RCTs) did not reveal any relationship between pharmacotherapy with an ARB and an increased risk for cancer in general.

1. Introduction

Cardiovascular drugs were the most prescribed drugs in Germany in 2015 with 21,768,398 prescriptions. Among them, inhibitors of the renin-angiotensin system (RAS) are the most effective drugs for the therapy of hypertension, heart failure and kidney diseases. Their prescription volume amounted to 57% of antihypertensive agents [1,2].

Over the last decade, observational studies and preclinical research with carcinogenic assays have indicated that, besides its cardiovascular effects, the RAS also influences migration, angiogenesis and apoptosis as well as proliferation [3]. Angiotensin II (Ang II) acts via the Angiotensin Type 1 receptor (ATR1), which is upregulated in many cancer tissues (breast hyperplasia, pancreas carcinoma, lung cancer) and increases the level of Vascular Endothelial Growth Factor proteins (VEGF) [4]. Therefore, pharmacotherapeutic RAS modulation, theoretically, might have an influence on the incidence of specific cancers.

☆ The authors confirm that the PI for this paper is Christoph Schindler and that he had direct clinical responsibility for patients.

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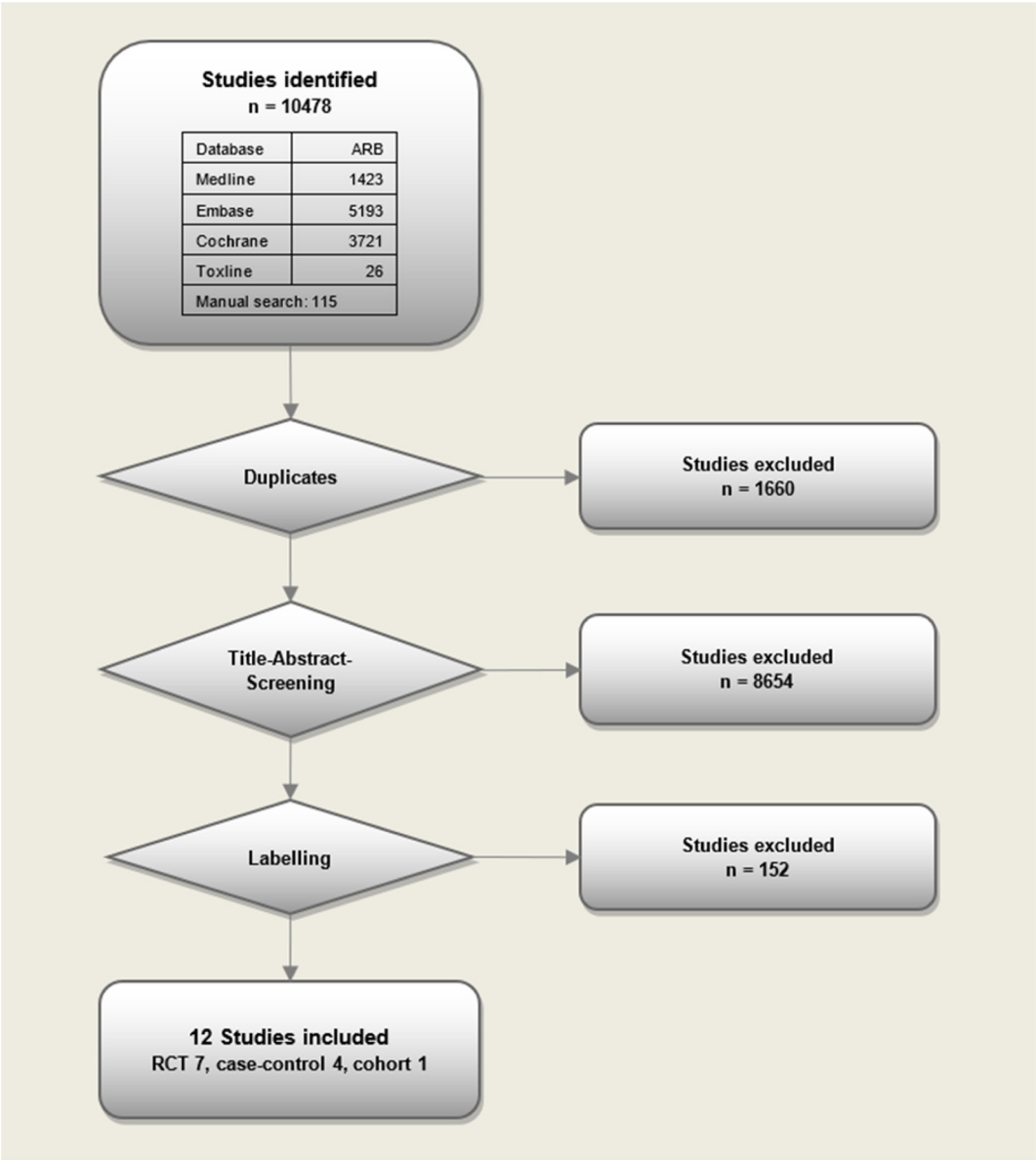

Fig. 1. Study selection process.

Initial controversial discussions suggesting that angiotensin-receptor blockers (ARBs) might increase tumour incidences developed in 2010, when Sipahi et al. [5] published results of a meta-analysis. This demonstrated that patients which were randomly assigned to receive ARBs had a significantly increased risk of new onset cancer compared with patients in respective control groups (Relative Risk - RR 1.08, 95% CI 1.01–1.15, p = .016, 7.2% vs. 6.0%). The risk was shown to be especially high in lung cancer patients (RR 1.25, 95% CI 1.05–1.49, p = .01).

Because of this disconcerting scientific evidence and the indisputable high importance of ARBs in the pharmacotherapeutic armamentarium for cardiovascular diseases [6], we conducted a systematic review on available randomised and observational study data on ARBs and carcinogenesis as the primary outcome.

2. Methods

Prior to the initiation of the systematic literature research, two separate study protocols were registered within the International Prospective Register of Systematic Reviews in 2013 (PROSPERO; CRD42013004749, CRD42013005321). One was for randomised controlled trials and the other was for observational studies. The protocols contain information about search string, selection criteria and data extraction procedures as well as statistical analyses. In 2016, the exclusion criteria were changed. Included studies had to compare the use of ARBs with medication without any influence on the RAS in the control group. Therefore, studies, which used angiotensin-converting-enzyme inhibitors (ACEi), beta blockers (BB), or thiazide diuretics in the control group, were not eligible.

This review was organized and reported by PRISMA and MOOSE Guidelines [7,8]. Eligible studies were identified through electronic searches in MEDLINE, EMBASE, Cochrane Library, and TOXLINE between January 1950 and February 2016. The search string was based on a combination of MeSH terms, keywords and substance names and was organized in four fields: population, intervention, outcome and study design (details under Appendix Table A1). The manual search was accomplished by searches in reference or citation lists of other reviews, meta-analyses [9–11] or clinical and observational studies until June 2017. Investigators were not contacted directly.

The frequency of new cancer cases in general was defined as the

Table 1
Baseline characteristics and quality appraisal of included studies.

Source, year	Study type	Participants	Intervention	Cohort	Age	Follow up (yrs)	Cancer outcome	Quality appraisal
Val-HEFT, 2001 [19,20]	RCT	5010	Valsartan	HF	62.7	1.9	No	High risk
TROPHY, 2006 [37]	RCT	772	Candesartan	HTN	48.5	3.6	No	Low risk
NAGOYA HEART, 2012 [17]	RCT	1150	Valsartan	HTN + GI	63	3.2	No	High risk
TRANSCEND, 2008 [38,39]	RCT	5926	Telmisartan	CVD or DM	66.9	4.7	Yes	Low risk
I-Preserve, 2010 [40,41]	RCT	4128	Irbesartan	HF, ↓ EF	72	4.1	No	Low risk
PRoFESS, 2008 [38,42]	RCT	20,064	Telmisartan	Stroke	66.1	2.5	No	Low risk
CASE-J ex, 2011 [18]	RCT	2066	Candesartan	CVD + DM	63.9	6.2	No	High risk
Hallas, 2012 [43]	CC	747,085	ARB	cancer	69.4	7.8	Incidence	Very high risk
Chang, 2011 [30]	CC	6385	ARB	DM	66.2	7.4	Incidence	Low risk
Kemppainen, 2011 [44]	CC	49,314	ARB	CaP	–	< 1 to > 6	Incidence	High risk
Li, 2013 [45]	CC	2851	ARB	CaB	–	< 5 to > 10	Incidence	High risk
Huang, 2011 [22]	cohort	109,002	ARB	HTN	58.6	5.7	Incidence	High risk

Numbers are presented as absolute values, mean or median; RCT = randomised controlled trial, CC = case-control study, yrs. = years.
HF = heart failure, AMI = acute myocardial infarction, HTN = Hypertension, GI = glucose intolerance, CVD = cardiovascular disease, DM = Diabetes mellitus, AP = Angina pectoris, EF = ejection fraction, CaP = Prostate cancer, CaB = Breast Cancer, Val-HEFT = Valsartan Heart Failure Trial, TROPHY = The Trial of Preventing Hypertension, TRANSCEND = The Telmisartan Randomised Assessment Study in ACE Intolerant subjects with cardiovascular disease, Preserve = The Irbesartan in Heart Failure With Preserved Ejection Fraction Study, PRoFESS = The Prevention Regimen for Effectively Avoiding Second Strokes Study, CASE-J ex = The Candesartan Antihypertensive Survival Evaluation in Japan Extension Study, Quality appraisal: Newcastle-Ottawa Scale 7–9 = low risk 4–6 = high risk 0–3 = very high risk (observational studies), Risk of Bias Tool for RCTs.

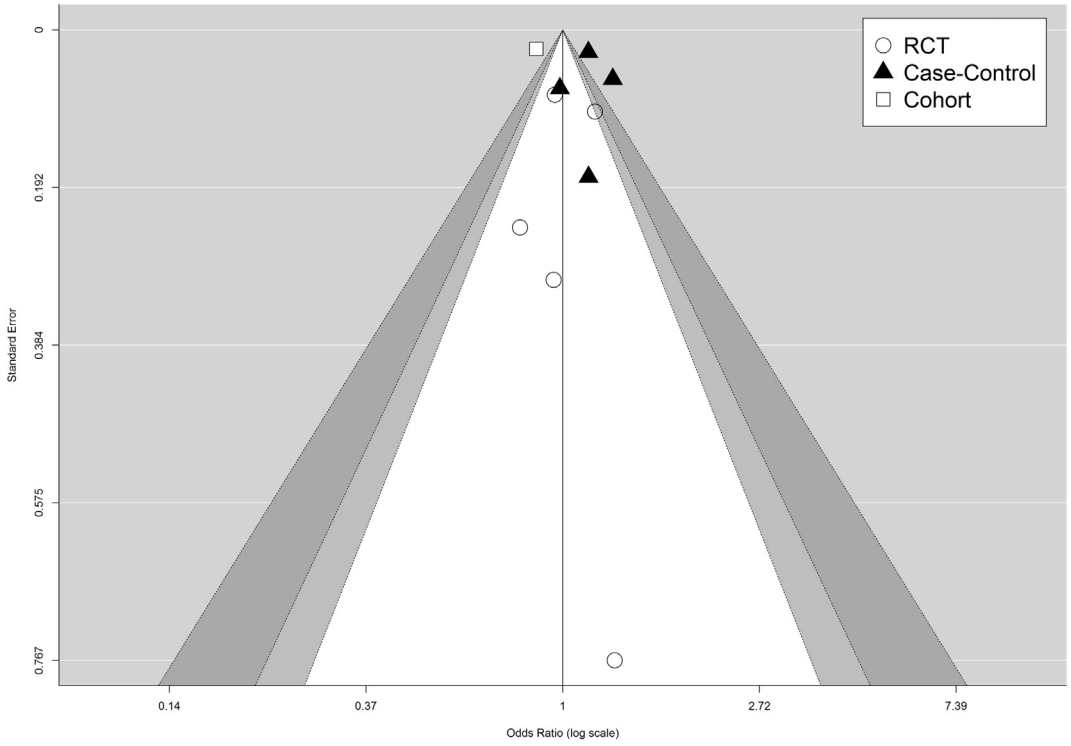

Fig. 2. Contour-enhanced funnel plot for assessing publication bias for RCTs and observational studies (90, 95, 99% CI).

primary outcome. We used tumour-specific mortality and new cases of different tumour types, i.e. lung, breast, and prostate cancer, as secondary outcomes. Eligible trials had to be double-blind, randomised, open-label extension studies or case-control and cohort studies published in English language with at least 100 patients in each study arm, a minimum follow-up of one year and treatment with an ARB. Potential studies had to publish their results regarding new tumour cases or tumour-specific mortality. Studies with the following criteria were excluded: participants under 18 years of age, having any cancer disease in baseline characteristics, cross-sectional studies and studies with RAS modulating medication in the control group;

The inclusion procedure was performed by two independent reviewers (SF and DA, interns) in three steps: (1) title-abstract-screening, (2) labelling according tumour data and (3) data synthesis. Disagreements were resolved by a 3rd advanced reviewer. Extracted data included baseline characteristics (e.g. age, smoking, comorbidities, ethnicity), intervention and control medication with dosages and duration of intake. Quality appraisal was undertaken with the Cochrane Collaboration tool for assessing risk of bias in RCTs and the Newcastle Ottawa Scale (NOS) for assessing bias risk in observational studies. Randomised trials with one high or unclear risk in the first four items (random sequence generation, allocation concealment, blinding of participants and personnel) were rated as studies with high risk of bias [12]. Other items were screened and presented (Table A3), but not used in the overall quality appraisal. Bias risk for observational studies was rated with the Newcastle-Ottawa Scale [9–13]. Here, 7–9 points correspond to “low risk”, 4–6 correspond to “high risk” and 0–3 to “very high risk”. All data was extracted with standardized evidence tables.

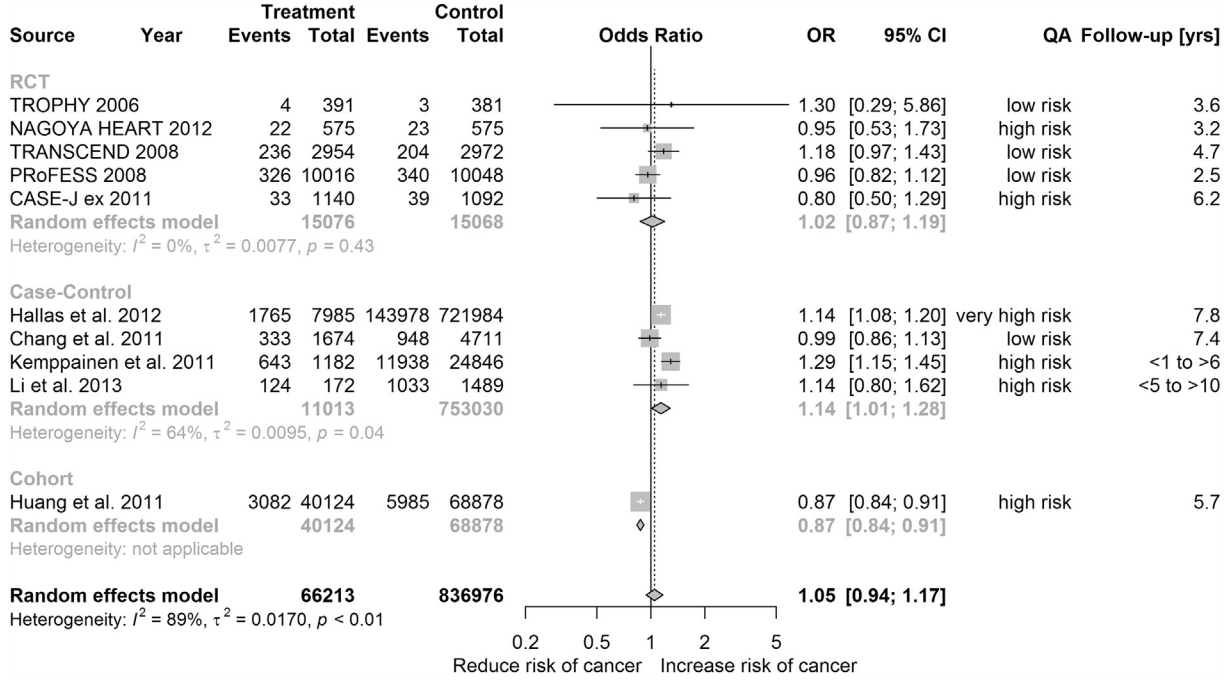

Fig. 3. Odds ratio for angiotensin-receptor blockers and frequency of new cancer cases in randomised controlled trials and observational studies.

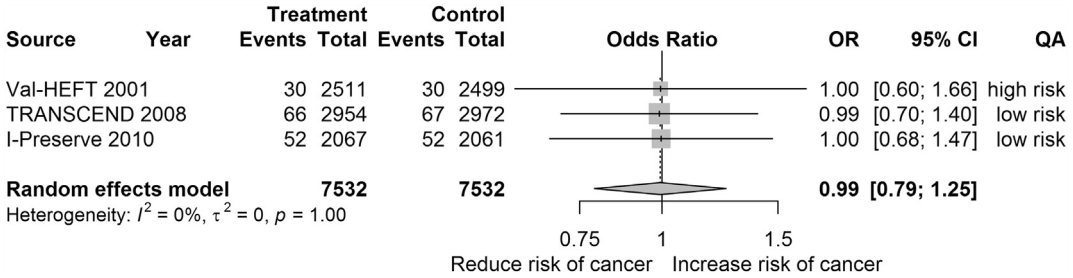

Fig. 4. Odds ratio for angiotensin-receptor blockers and tumour-specific mortality in randomised controlled trials.

Results of the meta-analyses are presented as odds ratios (OR) calculated by using a random-effects model (REML method). We used odds ratios to compare the studies among each other instead of relative risks, since we included also case-control designs. Nevertheless, we calculated relative risk estimates, where appropriate (for RCTs and cohort studies), and compared them with the odds ratio values (relative risk estimates not shown). No discrepancies between OR and RR results were discovered. As a measure of heterogeneity/consistency I-square (I^2) was used. Reporting bias (e.g. publication bias) was analysed graphically with the help of a funnel plot. A statistical bias test (e.g. Egger's test) for each study type was not carried out, as at least 10 studies are necessary to obtain sufficient power [14]. Subgroup analyses were done for lung-, breast-, and prostate cancer, respectively. To explain the observed heterogeneity between the case-control studies (Fig. 3) and also in the subgroup analyses (Fig. 5), meta-regressions were performed. However, no significant differences in baseline parameters (proportion of women, participants with hypertension, smokers and average age) were found between the studies that could explain the heterogeneity (results not shown).

Statistical analyses were conducted with the software R, version 3.4.3 (Vienna, Austria) R Core Team [15].

Key targets in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [16].

3. Results

A total of 10,478 studies were identified fulfilling the primary inclusion criteria. After 1660 duplicates had been excluded, 8818 studies were screened (Fig. 1). Twelve studies met the inclusion criteria: seven RCTs, four case-control and one cohort study. All studies were published between 2001 and 2012. Two of the seven included RCTs were open-label extension trials [17,18].

A total of 954,187 participants, with mean age 63.7 years, were included of which 43.8% were women. Patients ranged in age between 18 and 96 years with a mean duration of follow up between 1.9 and > 10 years (Table 1, A2). Complete information about concomitant medication was not systematically reported in all studies. Participants were additionally co-medicated with BB, CCB, ACEi or thiazide diuretics. In the Val-HEFT trial [19,20] 93% of patients were additionally on an ACEi (Table A2).

The judged quality of the included trials varied between low (most RCTs) and very high (one case-control study) bias risk (Table 1, Table A3, A4). There was no evidence for heterogeneity across randomised controlled trials measured by I^2 statistic (< 0.01%, p = .433), but across case-control studies (I^2 = 64.4%, p = .038) (Fig. 3). Further subgroup- (Fig. 5) and meta-regression analyses (not shown) could not explain the observed heterogeneity across the case-control studies.

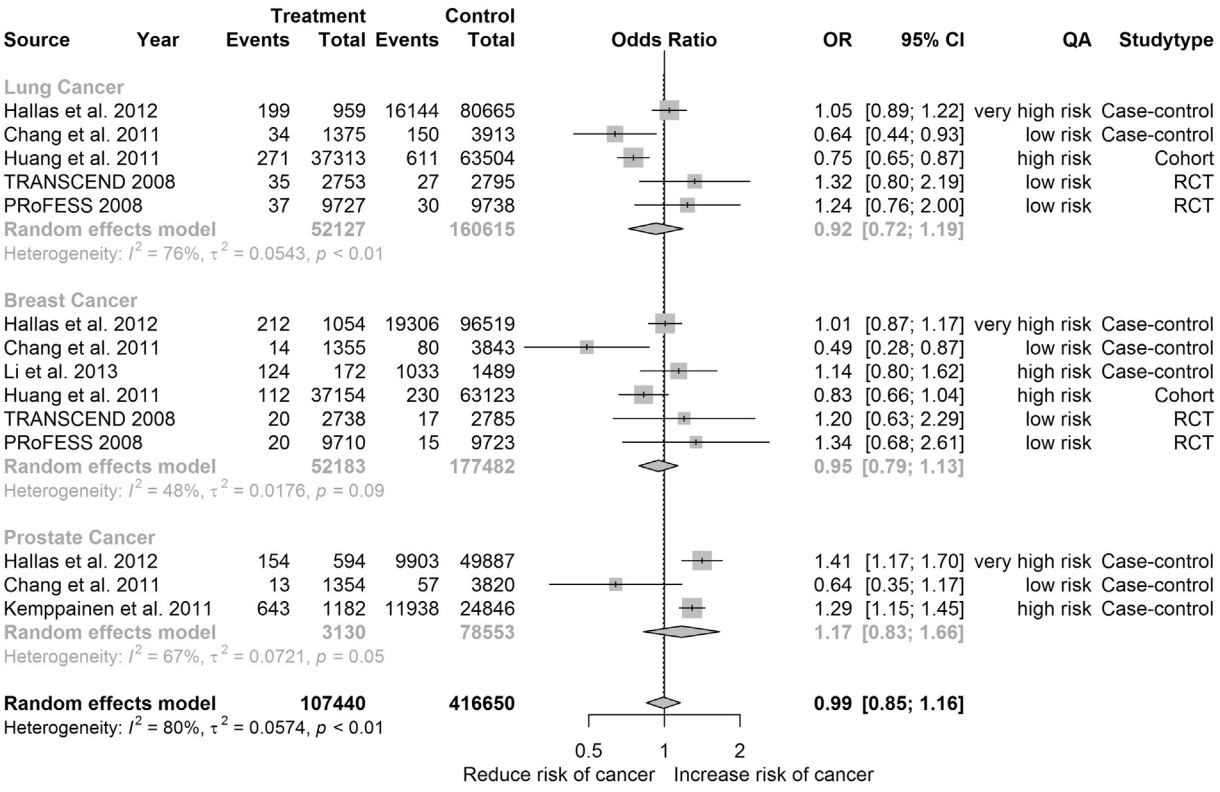

Fig. 5. Odds ratio for angiotensin-receptor blockers and lung, breast, as well as prostate cancer for all study designs included.

3.1. ARBs and carcinogenicity

No increased cancer risk for patients on ARBs was detected by the meta-analysis of high evidence randomised controlled trials (OR 1.02, 95% CI 0.87–1.19; p = .803). However, there are discrepancies in the observational studies (Fig. 3). While the cohort study of Huang suggests a protective effect of ARBs against cancer development (OR 0.87; 95% CI 0.84–0.91; p < .001), our meta-analysis of included case-control studies revealed an elevated risk (OR 1.14, 95% CI 1.01–1.28, p = .035).

Secondary outcomes were defined as tumour-specific mortality and frequency of different tumour cases i.e. lung, breast, and prostate cancer. An overall OR for tumour-specific mortality was exclusively calculated for RCTs (only three of the included RCTs reported tumour-specific mortality data) because the respective information was not given by observational studies. No effect, however, could be observed (OR 0.99, 95% CI 0.79–1.25, p = .958) (Fig. 4). Furthermore, the ORs for development of specific tumour types (lung-, breast-, and prostate cancer) were calculated in subgroup analyses but no significant deviation from OR = 1 could be observed (significance level 0.05). Specifically for lung cancer, (RR 0.92, 95% CI 0.72–1.19, p = .538) the analysis showed a slightly decreased risk (Fig. 5).

4. Discussion

Our meta-analysis focusing on high evidence levels and study designs reliably provides an unbiased assessment of the frequency of tumour development. The results refute a relationship between pharmacotherapy with ARBs and an increased risk of cancer development in general, as well as of specific tumour types and -mortality. This corresponds well with the results of other meta-analyses [9,10,21] and provides further evidence that routine clinical use of ARBs is safe.

Randomised controlled trials are the gold standard for efficacy assessments of pharmacotherapeutics and their safety concerns. Observational studies are less suitable for this task. In particular, incorrect selection of controls in case-control designs could introduce serious bias in effect estimates. In principal, large prospective cohort studies are well suited for the detection of (rare) adverse events and could be used for drug safety studies. Nevertheless, there is a high bias potential through elevated loss-to-follow-up in this study type. Furthermore, effect estimates must be adjusted for confounding and effect modifying factors in a specific manner. Otherwise, these effect estimates could be strongly biased, even in the opposite direction.

According to our quality appraisal, three out of five RCTs included in the primary analysis (Fig. 3, Table 1) had a low reporting bias risk. In contrast, all but one case-control study were assessed with a high bias risk. Altogether, we did not observe any small study effects (e.g. publication bias) as no sign for overall funnel plot asymmetry was present (Fig. 2). All case-control studies, however, lay in the uppermost right corner of Fig. 2. This likely indicated potentially biased publication of results, since it is feasible that case-control studies with an unincreased and insignificant cancer risk were not published at all. Additionally, the only included cohort study by Huang et al. [22] was assessed to have a high risk of bias, too. The cohort study was designed specifically to estimate the risk for newly diagnosed cancers arising from the use of ARBs in the treatment of hypertension. In this study, there was a mismatch in the medication of both groups, with co-medication (ACEi, BB, CCB, thiazide diuretics) being significantly higher in the treatment group compared to the control group (see Table 1 of Huang et al. [22]). But, the effect analysis has not been adjusted for this. Also, other important factors influencing cancer risk [23–26] were not assessed in the analyses. These included genetics, sunlight exposure, tobacco and alcohol use, obesity, pharmaceuticals, nutrition, virus infections, hormones, and environmental or occupational exposures to toxins. Therefore, effect estimates of this study are likely biased and should be interpreted with caution. The evidence from the four included case-control studies and the one cohort study must be seen critically in the light of causal inference for effectiveness and safety trials. RCTs are the gold choice; case-control studies are not really suited and cohort studies must be at least adjusted for serious confounders to achieve trustworthy

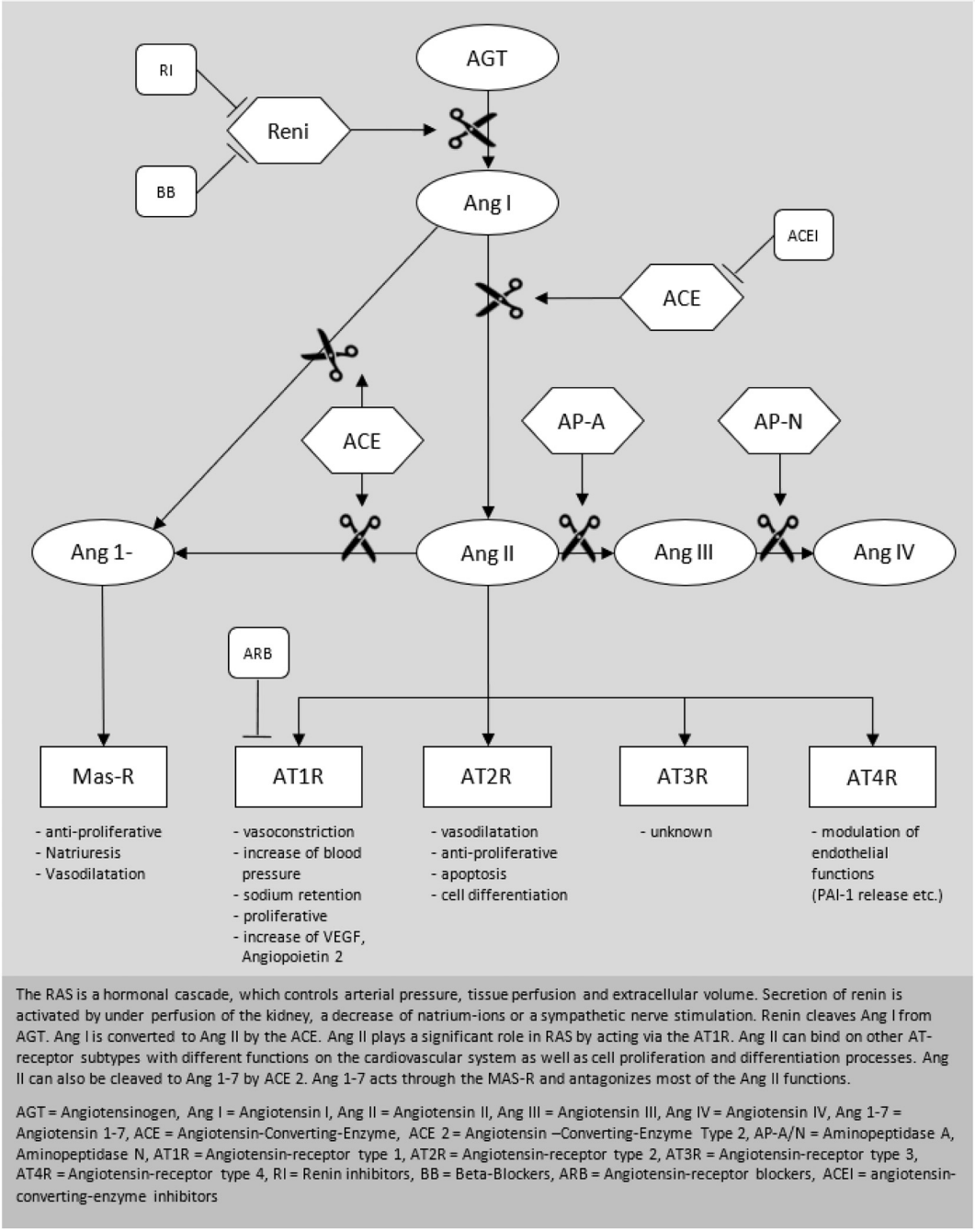

Fig. 6. The renin-angiotensin system (RAS).

estimates.

In vitro, ARBs have been shown to exert anti-proliferative effects on breast cancer cells [27], to trigger cell death in pancreatic cancer cells [28], and to restrain tumour growth in colon cancer liver metastases [29]. Furthermore, studies in preclinical animal models revealed suppressive effects on various tumour types [3]. The studies by Chang et al. [30] and Huang et al. [22] particularly showed a decreased OR for lung and breast cancer development in patients on ARB therapy (Fig. 5). Longer exposure to ARBs resulted in even greater benefit. Blocking the Angiotensin AT_1-Receptor (AT1R) with an ARB resulted in accumulated systemic angiotensin II levels which could not bind to the blocked AT1R. Therefore, the observed positive effects could have possibly been explained via mediation of beneficial pleiotropic effects by binding to the unopposed AT_2-Receptor (AT2R) and Ang(1-7) Mas-Receptors (MasR) [31,32] (Fig. 6). Whereas Ang- (1-7) acts via the MasR and inhibits proliferation, angiogenesis as well as migration [32], AT2R stimulation antagonizes the actions of the AT1R thereby promoting apoptosis and antiangiogenic effects hindering tumour growth [33]. Preclinical studies have provided compelling evidence that the AngII/AT1R axis is involved in the regulation of almost all hallmarks of cancer [34,35].

In summary, our meta-analysis supports the safety of ARB-therapy for cardiovascular indications. Based on the preliminary laboratory work and theoretical assumptions, we suggest that inhibiting the RAS with an ARB might even be a beneficial pharmacotherapeutic strategy to enhance anti-tumour treatment in oncology.

Although in general no effects of ARBs on carcinogenesis and cancer mortality have been demonstrated, certain ARBs could nevertheless increase the risk of certain forms of cancer. The analysis of specific tumour types revealed an indication of an increased risk of lung or

Table 2
Reasons of exclusion of studies, which were included by other reviews.

Source, year	Study type	Intervention	Control	Patients n	Cancer outcome	Reason of exclusion
ALPINE, 2003 [46]	RCT	Candesartan	HCTZ	393	No	Exposition vs. control
CHARM, 2003 [47]	RCT	Candesartan	Placebo	1831	No	History of cancer
E-COST, 2005 [48]	RCT	Candesartan	Conventional	2048	No	Unpublished data
GISSI-AF, 2009 [49]	RCT	Valsartan	Placebo	1442	No	History of cancer
HIJ-CREATE, 2009 [50]	RCT	Candesartan	Non-ARB	2049	No	Unpublished data
IDNT, 2003 [51]	RCT	Irbesartan	Amlodipine, Placebo	1715	No	Unpublished data
IRMA 2, 2001 [52]	RCT	Irbesartan	Placebo	608	No	Unpublished data
JIKEI, 2007 [53]	RCT	Valsartan	Conventional	3081	No	Control group
Kyoto Heart, 2009 [54]	RCT	Valsartan	Conventional	3031	No	Exposition vs. control
LIFE, 2002 [55]	RCT	Losartan	Atenolol	9193	No	Exposition vs. control
ONTARGET, 2008 [56]	RCT	Telmisartan	Ramipril, Telmisartan + Ramipril	25,620	Yes	Exposition vs. control
OPTIMAAL, 2002 [57]	RCT	Losartan	Captopril	5477	No	Exposition vs. control
RENAAL, 2001 [58]	RCT	ARB	Placebo	1513	No	Unpublished data
ROAD, 2007 [59]	RCT	Losartan	Benazepril	360	No	Exposition vs. control
Suzuki et al., 2008 [60]	RCT	ARB	Control	366	No	Control group
VALIANT, 2003 [61]	RCT	Valsartan	Captopril, Captopril + Valsartan	14,626	No	Exposition vs. control
VALUE, 2004 [62]	RCT	Valsartan	Amlodipine	15,245	No	Unpublished data[a]
Makar et al., 2014 [63]	CC	ARB, ACEi	–	31,086	Incidence	Exposition
Engineer et al., 2013 [64]	Cohort	ARB, ACEi, BB	No use	262	Survival	Cancer at baseline
Cardwell et al., 2014 [65]	Cohort	ARB, ACEi	–	16,920	Survival	Cancer at baseline
Rao et al., 2013 [66]	Cohort	ARB	No use	1,228,960	Incidence	Control group
Rao et al., 2013 [67]	Cohort	ARB	No use	543,824	Incidence	Control group
Koomen et al.,2009 [68]	CC	ARB, ACEi	–	6520	Incidence	Patients < 100/arm
Bhaskharan et al., 2012 [69]	Cohort	ARB	ACEi	377,649	Incidence	Exposition vs. control
Fryzek et al., 2005 [70]	Cohort	ARB, ACEi	Any antihypertensive use	113,298	Incidence	Exposition vs. control
Fryzek et al., 2006 [71]	Cohort	ARB, ACEi	Any antihypertensive use	19,284	Incidence	Exposition vs. control
Chin et al., 2011 [72]	Cohort	ARB, ACEi	No use	3288	Incidence	History of cancer
Wang et al., 2013 [73]	Cohort	ARB	Non ARB	85,842	Incidence	Control group
Azoulay et al., 2012 [74]	Cohort	ARB	Any antihypertensive use	410,167	Incidence	History of cancer
Pasternak et al., 2011 [75]	CC	ARB	ACEi	317,158	Incidence	Exposition vs. control
van der Knaap et al., 2008 [76]	Cohort	ARB, ACEi	–	4710	Incidence	Exposition
Chang et al., 2016 [77]	CC	ARB, ACEi, BB, diuretics, CCB	No use	46,985	Incidence	Exposition
Yang et al., 2010 [78]	Cohort	ARB, ACEi	No use	4750	Incidence	Exposition
Houben et al., 2006 [79]	CC	ARB, ACEi, BB, diuretics	Any antihypertensive use	1414	Incidence	Exposition
Assimes et al., 2008 [80]	CC	ARB, ACEi, CCB, HCTZ	Any antihypertensive use	128,667	Incidence	Exposition vs. control

Presentation of included studies by other meta-analyses which were excluded in this meta-analysis. CC = case-control studies, HTCZ = thiazide diuretic
Reason for exclusion: control group – there hasn't been any classification of medication in control groups, exposition vs. control - both groups took RAS-influencing medication, unpublished data – no tumour data could be officially found, exposition – no classification of medication

[a] Julius et al. [81] directly addressed a letter to Sipahi et al. [5], which presented results regarding tumour incidences. But also, they clearly formulated, that these data are not official and that there exists “a policy of providing data access only to its own investigators or to those with whom a formal joint project has been negotiated.” On this basis of policy, we decided not to include the results of the VALUE-Trial.

breast cancer in RCT studies using telmisartan in the intervention group. However, these studies showed insignificant results, maybe to due low study sample sizes, which could nevertheless be clinically relevant. Therefore, tumour- and medication-specific, large RCTs are needed to clarify the situation.

4.1. Strengths

Firstly, in contrast to other investigations, we included studies with different study designs. Whereas large cohort studies may be better suited for analysing carcinogenicity in the general population, randomised controlled studies were additionally included because they provide the highest evidence level and in principle the possibility of deciphering causal relationships. Secondly, due to very strict in- and exclusion criteria compared to other meta-analyses, we excluded many studies, which other meta-analyses had included, to gain a higher reliability of our results. For example, Bangalore et al. [10] undertook a network meta-analysis for randomised controlled trials of antihypertensive therapy (ARBs, ACEi, BB, CCB, thiazide diuretics) investigating the risk of cancer. They identified 70 trials, of which in only 23 studies patients were exposed to ARBs. Of these 23 included studies, we identified only five trials as suitable for our meta-analysis. We excluded trials due to certain medication in the control group or due to unpublished data as well as history of cancer in baseline characteristics (for more information see Table 2). Similarly, Shen and colleagues [11] evaluated the impact of RAS-blockade with ARBs/ACEi on the risk of cancer with randomised controlled and observational studies between 1960 and 2015. They included 31 studies (17 observational and 14 RCTs) comprising a total of 3,957,725 participants. We decided to exclude most of their included trials due to medical intervention in the control groups or cancer history at baseline (Table 2).

In our meta-analysis, most (6 out of 7) included RCTs were not designed to specifically analyse cancer outcomes, therefore avoiding selection bias of participants with regard to cancer predispositions or risk factors, which strengthens our results.

4.2. Limitations

We cannot completely exclude publication bias with respect to the file-drawer problem [36]. Authors were not contacted for missing information and we based the quality appraisal solely on officially reported data. We aimed to examine only available study data. Case-control studies showed a high heterogeneity, which could not be explained by meta-regression analyses regarding the proportion of women, patients with arterial hypertension, smokers or the average age. There could also have been a potential risk for recall bias in observational studies, because information about drug use, dosages or disease histories was collected in hindsight by questionnaires or interviews. Data on exact dosages or duration of intake was inconsistently reported. Finally, we tightened our exclusion criteria during the

screening process to include only studies with a high level of evidence. Overall, our study basis for answering safety questions on ARB deployment was therefore somewhat limited. More high quality, tumour- and medication-specific, large RCTs would be necessary to fully clarify the situation.

4.3. Conclusions

The available study evidence actually only contains very few studies originally designed to investigate a potential influence of ARB-therapy on carcinogenesis and tumour-specific mortality. The results of our meta-analysis, focusing only on high levels of evidence and study designs reliably providing an unbiased assessment of frequency of new cancer cases, support the safety of ARB-therapy for cardiovascular indications and suggest that inhibiting the RAS with an ARB might rather be a beneficial pharmacotherapeutic strategy to enhance anti-tumour treatment in oncology.

Authors' contributions

SF and DA conducted the literature search, selection, extraction and update of the study basis. TD designed and performed the meta-analysis and produced forest and funnel plots and contributed substantially to the interpretation of the results. SF, TD, and CS drafted the manuscript. JS critically revised the manuscript and contributed to the interpretation of the results. CS and BH initiated and monitored the study. All authors approved the submitted manuscript and agree to be responsible for this work.

Competing interests

Jochen Schmitt reports institutional funding for IITs from Sanofi, Novartis, ALK, and Pfizer. The other authors do not indicate any financial or non-financial competing interests.

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Appendix A. Supplementary data

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References

[1] Anlauf M, Weber F. Hemmstoffe des Renin-Angiotensin-Systems. Arzneiverordnungsreport Springer-Verlag; 2016. p. 209–35.
[2] Grandt D, Schubert I. Barmer GEK Arzneimittelreport 2016. Schriftenreihe zur Gesundheitsanalyse 2016;39:1–123.
[3] Link WT, De Felice A. An FDA overview of rodent carcinogenicity studies of angiotensin II AT-1 receptor blockers: pulmonary adenomas and carcinomas. Regul Toxicol Pharmacol 2014;70(2):555–63.
[4] Deshayes F, Nahmias C. Angiotensin receptors: a new role in cancer? Trends Endocrinol Metab 2005;16(7):293–9.
[5] Sipahi I, Debanne SM, Rowland DY, et al. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol 2010;11(7):627–36.
[6] Marquez DF, Ruiz-Hurtado G, Ruilope LM, et al. An update of the blockade of the renin angiotensin aldosterone system in clinical practice. Expert Opin Pharmacother 2015;16(15):2283–92.
[7] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[8] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. Jama 2000;283(15):2008–12.
[9] Arb Trialists C. Effects of telmisartan, irbesartan, valsartan, candesartan, and losartan on cancers in 15 trials enrolling 138,769 individuals. J Hypertens 2011;29:623–35.
[10] Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol. 2011;12(1):65–82.
[11] Shen J, Huang YM, Wang M, et al. Renin-angiotensin system blockade for the risk of cancer and death. J Renin Angiotensin Aldosterone Syst 2016;17(3):1470320316656679.
[12] Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[13] Lo CK, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol 2014;14(1):45.
[14] Chaimani A, Mavridis D, Salanti G. A hands-on practical tutorial on performing meta-analysis with Stata. Evid Based Ment Health 2014;17(4):111–6.
[15] R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
[16] Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucleic Acids Res 2018;46(D1):D1091–106.
[17] Muramatsu T, Matsushita K, Yamashita K, et al. Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART study. Hypertension 2012;59(3):580–126.
[18] Ogihara T, Ueshima K, Nakao K, et al. Long-term effects of candesartan and amlodipine on cardiovascular morbidity and mortality in Japanese high-risk hypertensive patients: the Candesartan Antihypertensive Survival Evaluation in Japan Extension Study (CASE-J Ex). Hypertens Res 2011;34(12):1295–301.
[19] Cohn JN, Tognoni G. Valsartan heart failure trial I. a randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667–75.
[20] Novartis. Diovan® (valsartan) congestive heart failure. Advisory briefing document. 2001. p. 37–62.
[21] Ioannidis JPA, Zhou Y, Chang CQ, et al. Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses. Ann Oncol 2014;25(1):16–23.
[22] Huang CC, Chan WL, Chen YC, et al. Angiotensin II receptor blockers and risk of cancer in patients with systemic hypertension. Am J Cardiol 2011;107(7):1028–33.
[23] Blackadar CB. Historical review of the causes of cancer. World J Clin Oncol 2016;7(1):54–86.
[24] Clapp RW, Jacobs MM, Loechler EL. Environmental and occupational causes of cancer: new evidence 2005-2007. Rev Environ Health 2008;23(1):1–37.
[25] Datzmann T, Markevych I, Trautmann F, et al. Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. BMC Public Health 2018;18(1):715.
[26] Perera FP. Environment and cancer: who are susceptible? Science 1997;278(5340):1068–73.
[27] Rhodes DR, Ateeq B, Cao Q, et al. AGTR1 overexpression defines a subset of breast cancer and confers sensitivity to losartan, an AGTR1 antagonist. Proc Natl Acad Sci 2009;106(25):10284–9.
[28] Fujimoto Y, Sasaki T, Tsuchida A, et al. Angiotensin II type 1 receptor expression in human pancreatic cancer and growth inhibition by angiotensin II type 1 receptor antagonist. Fed Eur Biochem Soc Lett 2001:197–200.
[29] Neo JH, Malcontenti-Wilson C, Muralidharan V, et al. Effect of ACE inhibitors and angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. J Gastroenterol Hepatol 2007;22(4):577–84.
[30] Chang CH, Lin JW, Wu LC, et al. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. J Clin Oncol 2011;29(22):3001–7.
[31] Wegman-Ostrosky T, Soto-Reyes E, Vidal-Millan S, et al. The renin-angiotensin system meets the hallmarks of cancer. J Renin Angiotensin Aldosterone Syst 2015;16(2):227–33.
[32] Xu JJ, Fan JS, Wu F, et al. The ACE2/angiotensin-(1-7)/Mas receptor Axis: pleiotropic roles in cancer. Front Physiol 2017;8:276.
[33] Pei N, Mao Y, Wan P, et al. Angiotensin II type 2 receptor promotes apoptosis and inhibits angiogenesis in bladder cancer. J Exp Clin Cancer Res 2017;36(1):77.
[34] Busby J, McMenamin U, Spence A, et al. Angiotensin receptor blocker use and gastro-oesophageal cancer survival: a population-based cohort study. Aliment Pharmacol Ther 2018;47(2):279–88.
[35] Pinter M, Jain RK. Targeting the renin-angiotensin system to improve cancer treatment: implications for immunotherapy. Sci Transl Med 2017;9(410).
[36] Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull 1979;86(3):638–41.
[37] Julius S, Nesbitt SD, Egan BM, et al. Trial of preventing hypertension (TROPHY) study investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006;354(16):1685–97.
[38] FDA. Micardis®. (Telmisartan) Cardiovascular and Renal Drugs. Advisory Committee Briefing Document. Boehringer Ingelheim; 2009.
[39] The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. 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(9644):1174–83.
[40] Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359(23):2456–67.
[41] Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in heart failure with preserved ejection fraction study (I-preserve) trial. Circulation

2010;121(12):1393–405.
[42] Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359(12):1225–37.
[43] Hallas J, Christensen R, Andersen M, et al. Long term use of drugs affecting the renin-angiotensin system and the risk of cancer: a population-based case-control study. Br J Clin Pharmacol 2012;74(1):180–8.
[44] Kemppainen K, Tammela TLJ, Auvinen A, et al. Antihypertensive drugs and prostate Cancer risk - a population-based case-control study. Eur Urol Suppl 2011;10(2). 35–35.
[45] Li CI, Daling JR, Tang MTC, et al. Use of antihypertensive medications and breast cancer risk among women aged 55 to 74 years. JAMA Intern Med 2013;173(17):1629–37.
[46] Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year i n newly detected hypertensives: results of the antihypertensive treatment and lipid profile in a North Sweden efficiacy evaluation (ALPINE) study. J Hypertens 2003;21:1563–74.
[47] Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. Lancet 2003;362(9386):759–66.
[48] Suzuki H, Kanno Y. Efficacy of candesartan on outcome in saitama trial G. effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. Hypertens Res 2005;28(4):307–14.
[49] Investigators G-A, Disertori M, Latini R, et al. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 2009;360(16):1606–17.
[50] Kasanuki H, Hagiwara N, Hosoda S, et al. 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(10):1203–12.
[51] Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan diabetic nephropathy trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003;138(7):542–9.
[52] Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345(12):870–8.
[53] Mochizuki S, Dahlof B, Shimizu M, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. Lancet 2007;369(9571):1431–9.
[54] Sawada T, Yamada H, Dahlof B, et al. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART study. Eur Heart J 2009;30(20):2461–9.
[55] Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):995–1003.
[56] Investigators O, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358(15):1547–59.
[57] Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet 2002;360(9335):752–60.
[58] Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345(12):861–9.
[59] Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol 2007;18(6):1889–98.
[60] Suzuki H, Kanno Y, Sugahara S, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 2008;52(3):501–6.
[61] Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349(20):1893–906.
[62] Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363(9426):2022–31.
[63] Makar GA, Holmes JH, Yang YX. Angiotensin-converting enzyme inhibitor therapy and colorectal cancer risk. J Natl Cancer Inst 2014;106(2):djt374.
[64] Engineer DR, Burney BO, Hayes TG, et al. Exposure to ACEI/ARB and β-blockers is associated with improved survival and decreased tumor progression and hospitalizations in patients with advanced colon cancer. Transl Oncol 2013;6(5):539–45.
[65] Cardwell CR, Mc Menamin UC, Hicks BM, et al. Drugs affecting the renin-angiotensin system and survival from cancer: a population based study of breast, colorectal and prostate cancer patient cohorts. BMC Med 2014;12(1):28.
[66] Rao GA, Mann JR, Shoaibi A, et al. Angiotensin receptor blockers: are they related to lung cancer? J Hypertens 2013;31(8):1669–75.
[67] Rao GA, Mann JR, Bottai M, et al. Angiotensin receptor blockers and risk of prostate cancer among United States veterans. J Clin Pharmacol 2013;53(7):773–8.
[68] Koomen ER, Herings RM, Guchelaar HJ, et al. Melanoma incidence and exposure to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cancer Epidemiol 2009;33(5):391–5.
[69] Bhaskaran K, Douglas I, Evans S, et al. Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. BMJ 2012;344:e2697.
[70] Fryzek JP, Poulsen AH, Johnsen SP, et al. A cohort study of antihypertensive treatments and risk of renal cell cancer. Br J Cancer 2005;92(7):1302–6.
[71] Fryzek JP, Poulsen AH, Lipworth L, et al. A cohort study of antihypertensive medication use and breast cancer among Danish women. Breast Cancer Res Treat 2006;97(3):231–6.
[72] Chin HJ, Oh SW, Goo HS, et al. Effect of RAAS inhibition on the incidence of cancer and cancer mortality in patients with glomerulonephritis. J Korean Med Sci 2011;26(1):59–66.
[73] Wang KL, Liu CJ, Chao TF, et al. Long-term use of angiotensin II receptor blockers and risk of cancer: a population-based cohort analysis. Int J Cardiol 2013;167(5):2162–6.
[74] Azoulay L, Assimes TL, Yin H, et al. Long-term use of angiotensin receptor blockers and the risk of cancer. PLOS One 2012;7(12):e50893.
[75] Pasternak B, Svanstrom H, Callreus T, et al. Use of angiotensin receptor blockers and the risk of cancer. Circulation 2011;123(16):1729–36.
[76] van der Knaap R, Siemes C, Coebergh JW, et al. Renin-angiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer: the Rotterdam study. Cancer 2008;112(4):748–57.
[77] Chang CH, Chiang CH, Yen CJ, et al. Antihypertensive agents and the risk of breast cancer in women aged 55 years and older: a nested case-control study. J Hypertens 2016;34(3):558–66. [discussion 566].
[78] Yang X, Ma RCW, So WY, et al. White blood cell count and renin–angiotensin system inhibitors for the risk of cancer in type 2 diabetes. Diabetes Res Clin Pract 2010;87(1):117–25.
[79] Houben MP, Coebergh JW, Herings RM, et al. The association between antihypertensive drugs and glioma. Br J Cancer 2006;94(5):752–6.
[80] Assimes TL, Elstein E, Langleben A, et al. Long-term use of antihypertensive drugs and risk of cancer. Pharmacoepidemiol Drug Saf 2008;17(11):1039–49.
[81] Julius S, Kjeldsen SE, Weber MA. Angiotensin-receptor blockade, cancer, and concerns. Lancet Oncol 2010;11(9):817–8.