

# Critical review of cancer risk associated with angiotensin receptor blocker therapy

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**Abstract:** The role of drugs in new cancer occurrence and cancer-related death is a major concern. Recently, a meta-analysis raised the possibility that angiotensin receptor blockers (ARBs) might have an adverse effect on patients. This generated a significant debate until the publication of two further meta-analyses, neither of which demonstrated an increased risk of new cancer occurrence or cancer-related death with the use of ARBs in patients with hypertension, heart failure, and/or nephropathy. This illustrates that the results of meta-analyses should be interpreted cautiously and critically as bias, such as selection bias, might lead to erroneous conclusions. Overall, the bulk of evidence today indicates that ARBs are not associated with increased cancer risk.

**Keywords:** hypertension, cancer, angiotensin receptor blocker, meta-analyses

## Introduction

Hypertension and cancer are both major health issues worldwide. They have stimulated research into pharmacological products to decrease the burden associated with the diseases. However, hypertension and cancer are not perceived the same way, as the negative image of cancer far outweighs that of hypertension.

Whenever approval is sought for a new drug, regulators from medical agencies such as the US Food and Drug Administration and the European Medicines Agency are faced with the difficult task of evaluating the risk–benefit ratio. This involves, on one hand, quantifying efficacy endpoints from controlled clinical trials and, on the other hand, quantifying harms reported from clinical trials and other sources such as spontaneous adverse event reports. However, the principles and methodology for risk–benefit assessment are currently lacking and quantitative risk–benefit assessment is not expected to replace qualitative evaluation according to the European Medicines Agency,<sup>1</sup> even if decision analysis is introduced.<sup>2</sup> Importantly, drugs are assessed at the population level, but patients and health professionals often focus their consideration on the risks and benefits for individuals.

In the case of hypertension, the availability of oral antihypertensive drugs has, according to findings from large controlled trials, decreased cardiovascular mortality and morbidity compared with placebo. These findings have been confirmed in several meta-analyses.<sup>3–5</sup> However, the safety of these drugs, with regard to cancer risk, has been questioned from the time they were first marketed. This has been the case for reserpine,<sup>6</sup> diuretics,<sup>7,8</sup> calcium channel blockers,<sup>9</sup> and angiotensin-converting enzyme inhibitors.<sup>10</sup> On each occasion, a debate, secondary to conflicting results, has followed the release of these publications, resulting in the generation of new reviews

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and meta-analyses.<sup>11–13</sup> More recently, the question of cancer occurrence in conjunction with the use of angiotensin II receptor blockers (ARBs) has also been addressed.

## Meta-analyses of ARBs and cancer

The first meta-analysis of the relationship between ARBs and cancer was released on June 14, 2010.<sup>14</sup> It included nine controlled randomized trials: five trials, with data from 61,590 patients, assessing new cancer risk as a primary objective,<sup>15–19</sup> and eight trials, with data from 93,515 patients, assessing the risk of cancer-related death<sup>15,17–23</sup> as a secondary objective.

Follow-up was at least 1 year and the number of patients included had to be at least 100. Of the patients included in the primary analysis, 85.7% were taking telmisartan. The analysis showed that the risk ratio (RR) of new cancer in patients randomized to ARBs compared with patients randomized to placebo was 1.08 (95% confidence interval [CI] 1.01–1.15). There was no significant difference in the risk of cancer death (RR 1.07, 95% CI 0.97–1.18) between patients randomized to ARBs and those randomized to placebo. The authors concluded that ARBs were associated with a modestly increased risk of new cancer occurrence. The absolute increase risk of cancer over a 4-year period was 1.2%, which had to be interpreted, according to authors, in the view of the estimated 41% lifetime cancer risk. Some limitations acknowledged were: the pooled results were taken from trials not designated to explore cancer outcomes as primary outcome measures, the adjudication of cancer diagnoses was not uniform among the included studies, the possibility of publication bias, and the absence of access to individual data. The authors encouraged further investigations of ARBs and cancer risk.

The second meta-analysis was released online in the same journal on November 30, 2010.<sup>24</sup> The authors undertook a traditional direct-comparison meta-analysis, a multiple-comparison or network analysis, and trial sequential analyses. The primary objectives were cancer risk and cancer-related deaths with antihypertensive drugs. Follow-up had to be at least 1 year and at least 100 patients had to be included in the trials. Of the 70 randomized control trials (324,168 participants), 23 included ARBs.<sup>15–22,25–39</sup> Of note, two of the trials (Valsartan Heart failure trial [Val-Heft] and Candesartan in Heart Failure Assessment of reduction in Mortality and Morbidity [CHARM]-added)<sup>20,33</sup> were considered as angiotensin-converting enzyme inhibitors (ACE-Is) plus ARB trials, because ARBs were given on top of ACE-Is. Therefore, 21 trials, enrolling more than 120,000 patients, were included in the meta-analyses on ARBs. The mean follow-up was 3.5 years and heterogeneity was low.

The results from the multiple-comparison meta-analyses showed that the risk of cancer for each individual antihypertensive agent did not differ significantly from placebo. In particular, there was no excessive risk of cancer with ARBs (odds ratio 1.01, 95% CI 0.93–1.09). However, the combination of ACE-Is and ARBs was associated with increased cancer risk when compared with placebo (odds ratio 1.14, 95% CI 1.02–1.28) in one model but not in other models (random effect models). No difference in risk of cancer-related death was observed between placebo and antihypertensive drugs. For ARBs, the death rate was 1.33% with no increased risk (odds ratio 1.00, 95% CI 0.87–1.15). Based on trial sequential analysis, results suggested that there was no evidence of a 5%–10% relative-risk increase of cancer and cancer-related death with any individual class of antihypertensive drugs studies. Limitations acknowledged by authors included: lack of adjustment for drug dosage or compliance to the assigned treatment, possible outcome measure reporting bias, and multiple testing. Since medications were grouped in classes, increase in cancer risk with an individual drug could not be excluded. The authors also pointed out that antihypertensive drugs are usually prescribed for decades and that the mean follow-up was only 3.5 years. They concluded that a clinically significant increase in cancer risk or cancer-related death was not observed in their large comprehensive analysis.

Finally, a third meta-analysis from the ARB Trialists Collaboration was published in April 2011 in the *Journal of Hypertension*.<sup>40</sup> It included 15 large parallel long-term double-blind clinical trials<sup>15–20,22,23,25,30,39,41–45</sup> involving 138,769 participants. More than 500 participants had to be included and the mean follow-up had to be at least 12 months. The primary objective of the study was cancer incidence in ARB versus non-ARB control treatment. The average follow-up ranged from 23 to 60 months.

Overall cancer incidence was 6.16% in participants allocated ARBs versus 6.31% in those assigned non-ARB treatment (odds ratio 1.00 with 95% CI 0.95–1.04). However, the test for heterogeneity was significant. In the secondary analysis, no excess of cancer was observed for each individual ARB (candesartan, irbesartan, losartan, valsartan, telmisartan). Data on cancer death were available in 13 trials. Death from cancer occurred in 1.85% of the patients randomized to ARBs and in 1.77% of the patients randomized to non-ARBs (odds ratio 1.03, 95% CI 0.95–1.12). The test for heterogeneity was not significant. No excess risk of cancer was observed with the combination of ACE-Is and ARBs. The main limitation acknowledged by authors was

the relatively short duration of exposure to antihypertensive drugs. The authors concluded that, in patients with cardiovascular disease, heart failure, hypertension, and diabetes, there is no significant excess in cancer with the long-term use of the ARBs included in their analysis.

### Can some meta-analyses be misleading?

Meta-analyses are often seen as the holy grail of evidence medicine, having the “strongest” level of evidence that can be obtained. However, they are and have been subject to criticism.<sup>46</sup> Meta-analyses have been developed in an attempt to resolve conflicting results from trials addressing similar issues. Those who believe in the efficacy of a given intervention tend to use positive (significant) trials to defend a point of view, and explain negative trials by a lack of statistical power. Conversely, those who do not believe that a given intervention has any efficacy will use negative trials as proof of inefficacy and will argue that positive (significant) trials are the result of chance. To draw conclusion from conflicting results, data have to be synthesized and must take into account the possibility of underpowered negative trials and the possibility of a type I error (false positive) in positive trials.

The main advantages of a meta-analysis over a single trial or several trials taken individually are: to increase power, to reconcile apparently discordant results, to increase the accuracy of the size of the effect of treatment, to test and increase the extent of the result to a large number of patients, to explain the variability of the results, and, in some cases, to notice the lack of reliable data. Key elements of meta-analyses are that the synthesis is exhaustive, rigorous, reproducible, and quantifiable. Table 1 summarizes some questions to be asked when reading a meta-analysis.

In the case of ARBs, critical reading of the meta-analyses available is essential, particularly when different meta-analyses provide divergent results. The conflicting results obtained by the three meta-analyses discussed are probably best explained by the clinical trials selected for the analyses

**Table 1** Some questions to be asked when reading a meta-analysis

Has the research of published trials been extensive?
Have unpublished trials been searched?
Have the trials been included independently of their results?
Have the reasons for exclusion of trials been specified?
Are the trials included in the analysis devoid of methodological flaws?
If heterogeneity was detected, has an explanation been sought?
Are the results of the analysis clinically relevant?
Can the analysis assess the benefit–risk balance?
Does the conclusion reflect the results of the analysis?

(Table 2), one of the most frequent reasons of discordance. Selection criteria and a time effect (new trials available) explain the different studies included in the meta-analyses.

Finally, the lack of evidence of a significant effect of ARBs on cancer incidence does not necessarily mean that there is no effect. This point is often raised in the concluding remarks of negative meta-analyses and was evident in the meta-analysis of Bangalore et al,<sup>24</sup> in which the authors refuted a 5.0%–10.0% relative increase in the risk of cancer or cancer-related death with the use of ARBs.

### Is there a plausible pathophysiological mechanism explaining a causal relationship between ARBs and cancer?

From a pathophysiological point of view, most of the evidence indicates that the inhibition of the renin angiotensin system is protective rather than deleterious with regard to the development of cancer. After the publication of a retrospective study suggesting lower than expected incidence of lung and breast cancer in hypertensive patients taking ACE-Is,<sup>47</sup> possible pathophysiological mechanisms for such a finding were explored.<sup>48</sup> So far, it has been shown that components of the renin angiotensin system are expressed in cancer cells from various tissues including the lungs, kidneys, breast, and prostate.<sup>49</sup> Further, angiotensin II has been shown to have a local effect on cell proliferation, angiogenesis, and inflammation, in addition to its well-known systemic effects on the cardiovascular system. These local effects are mediated by the angiotensin II type 1 receptor or the angiotensin II type 2 receptor, which have different tissue distribution. They can, respectively, activate or inhibit various cascades of intracellular protein kinases usually associated with growth factors.

The main effect of ARBs on cancer appears to be through inhibition of the release of pro-angiogenic factors from tumor cells *in vitro*.<sup>50</sup> This has been observed with candesartan in various cancer cell lines.<sup>51–53</sup> Decrease in the expression of the vascular endothelial growth factor receptor 1 has also been observed.<sup>51,53,54</sup> This effect could be mediated by an inhibitory effect of ARB on hypoxia-inducible-factor and ETS-1 induction, which has been reported in hormone refractory prostate cancer cell lines.<sup>55</sup> Hence, these studies provide a molecular basis suggesting that ARB has a protective effect against some cancers. However, a few studies have shown that ARBs may increase vascular density in cancer models, an effect possibly mediated by the angiotensin type 2 receptor stimulation.<sup>56,57</sup> In stroke models, ARBs

**Table 2** Trials included in the three meta-analyses

Trial	ARB	N	Sipahi <sup>a,14</sup>	Sipahi <sup>b,14</sup>	Bangalore <sup>24</sup>	ARB trialist <sup>40</sup>
LIFE <sup>15</sup>	Losartan	9193	x	x	x	x
TROPHY <sup>16</sup>	Candesartan	772	x		x	x
TRANSCEND <sup>18</sup>	Telmisartan	5926	x	x	x	x
ONTARGET <sup>19</sup>	Telmisartan	25,620	x	x	x	x
PROFESS <sup>17</sup>	Telmisartan	20,332	x	x	x	x
CHARM overall <sup>23</sup>	Candesartan	7599		x	x*	x
OPTIMAAL <sup>21</sup>	Losartan	5477		x	x	
VALIANT <sup>22</sup>	Valsartan	14,703		x	x	x
VAL-HEFT <sup>20</sup>	Valsartan	5010		x	x	x
i-PRESERVE <sup>39</sup>	Irbesartan	4128			x	x
ACTIVE-I <sup>42</sup>	Irbesartan	9016				x
IDNT <sup>25</sup>	Irbesartan	1715			x	x
VALUE <sup>30</sup>	Valsartan	15,245			x	x
NAVIGATOR <sup>41</sup>	Valsartan	9306				x
SCOPE <sup>16</sup>	Candesartan	4964				x
DIRECT <sup>43, 45</sup>	Candesartan	5231				x
ALPINE <sup>32</sup>	Candesartan	393			x	
E-COST <sup>37</sup>	Candesartan	2048			x	
GISSI-AF <sup>27</sup>	Valsartan	1442			x	
HJ-CREAT <sup>31</sup>	Candesartan	2049			x	
IRMA 2 <sup>35</sup>	Irbesartan	608			x	
JIKEI <sup>34</sup>	Valsartan	3081			x	
KYOTO Heart study <sup>36</sup>	Valsartan	3031			x	
RENAAL <sup>26</sup>	Losartan	1513			x	
ROAD <sup>29</sup>	Losartan	360			x	
Suzuki et al <sup>38</sup>	Valsartan, candesartan, losartan	366			x	

**Notes:** \*Only CHARM added<sup>33</sup> and CHARM alternative.<sup>28</sup> <sup>a</sup>Assessment of new cancer risk; <sup>b</sup>assessment of cancer-related death risk.

**Abbreviation:** ARB, angiotensin receptor blocker.

may play an angiogenic role.<sup>58,59</sup> Therefore, the angiogenic effect of angiotensin II receptor blockade may conceivably be organ specific. More basic studies are needed to explain the potential role of ARBs in local cell proliferation and angiogenesis in more detail.

## Risk of cancer in hypertensive patients

As previously mentioned, the potential cancer risk associated with antihypertensive drugs has been in question since these drugs first became available. One of the difficulties has been in the determination of the cancer risk associated with hypertension itself or to factors associated with hypertension, such as age, obesity, and blood pressure-lowering drugs.

Several epidemiological prospective studies have shown that high blood pressure is associated with increased cancer risk<sup>60</sup> and cancer mortality.<sup>61–63</sup> In the first of these prospective studies, which describes the association between blood pressure and cancer, Dyer et al observe that the increased risk of death from cancer was seen in both treated and untreated patients.<sup>62</sup> Some have suggested that the causal direction is from cancer to hypertension, because the increased risk of

malignancy is most pronounced among newly diagnosed hypertensive patients.<sup>60</sup> However, uncertainties persist, mainly concerning the effect of the duration of the disease, age and sex of patients, and cancer-site specificity.<sup>64</sup> For example, the effect of time is illustrated in a prospective study where a negative association between blood pressure and cancer during the first 5 years of follow-up changed into a positive association after 13 years of follow-up.<sup>65</sup> Of note, the mean follow-up of these prospective epidemiological trials studying the association between hypertension and cancer ranged from 9 to 20 years, in comparison with a shorter follow-up, usually of less than 5 years, in the controlled studies included in the meta-analyses previously discussed.<sup>14,24,40</sup>

Obesity is another example of a risk factor associated with both cancer<sup>66</sup> and hypertension.<sup>67</sup> When the risk of renal cell carcinoma was studied in a Swedish cancer registry, both higher body mass index and elevated blood pressure were independently associated with long-term risk of renal cell cancer in men.<sup>68</sup> This indicates that although obesity and hypertension are associated, they might influence renal cell cancer through different mechanisms.



## Conclusion

At a time when evidence-based medicine plays an increasing role in all fields of health care, meta-analyses have become an obligatory step in many areas of medicine. Their strength lies in compiling observations made in several trials, which provides increased power, secondary to the large number of participants included, to detect even small differences in outcomes. However, the selection or nonselection of trials within an analysis can strongly influence the results, as is illustrated in this review. For this reason, the search for trials has to be exhaustive and the selection criteria have to be well documented to avoid unrecognized selection bias.<sup>69</sup> Further, it has to be kept in mind that a population-level benefit observed in a meta-analysis does not necessarily apply to the individual patient.

The media buzz generated by the release of the first meta-analysis<sup>14</sup> that observed an increased cancer risk with ARBs, currently some of the most prescribed cardiovascular drugs, has, however, prompted the scientific community to respond with new meta-analyses<sup>24,40</sup> and the US Food and Drug Administration to release a statement<sup>70</sup> concluding that the proven benefits of ARBs continue to outweigh their potential risk.

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## Disclosure

The authors report no conflicts of interest in this work.

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