A review of clinical studies on angiotensin II receptor blockers and risk of cancer

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ABSTRACT

Angiotensin II receptor blockers (ARBs) are one of the most frequently used antihypertensive drugs with good tolerability and are indicated for treatment of many cardiovascular morbidity. Findings from clinical studies conducted in the past decade, suggest a possible relationship between some ARB-active substances, and certain malignancies cannot be excluded. Despite a lack of agreement, clinical results do not rule out the possibility that type 2 angiotensin II receptor stimulation during ARB therapy may also have unfavorable consequences, such as the development of certain malignancies. However, according to the current official position of FDA, the cardiovascular benefits of ARB therapy far outweigh the risks. Based on the limited information available, this review aims to provide medical practitioners with a clearer view on the balance of the benefits and risks of ARBs.

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1. Introduction

Products blocking type 1 angiotensin II receptor (AT1R), known as angiotensin II receptor blockers (ARBs), represent a group of medicines used for a wide range of indications. ARBs are successful primarily in the therapy of hypertension, but may also be beneficial in patients with intolerance to angiotensin-converting enzyme (ACE) inhibitors for the treatment of several cardiovascular diseases, such as stable coronary heart disease, the state after acute myocardial infarction, and heart failure [1–4]. ARBs are used widely in everyday clinical practice because of their well-known effectiveness and proven good tolerability [5]. Approximately 25% of hypertensive patients worldwide are taking ARBs.

The number of patients treated with products belonging to this group of medicines is approximately 200 million worldwide [6].

In addition to losartan, introduced nearly 20 years ago, there are seven other active substances (valsartan, candesartan, irbesartan, telmisartan, olmesartan, eprosartan, and azilsartan), which have been used in several major clinical studies in recent years. Based on safety data obtained in these trials, a favorable image has been formed on the tolerability of ARBs, confirmed also by the results of long-term adherence studies.

However, experimental studies in the recent decade have shown yet unmapped areas of the renin–angiotensin–aldosterone system (RAAS) with certain effects and clinical consequences, which cannot be disregarded in the use of ARBs. The RAAS, as well as AT1R and type II angiotensin II receptor (AT2R), play a role in the regulation of cell proliferation and neoplastic progression. Therefore, evaluating these effects might be desirable for medicines, which exert their effect directly on these receptors [7]. Clinical studies evaluating ARB-active substances primarily examined the cardiovascular endpoints, and usually did not report on the incidence of various cancers.

The first data on cancers were shown by the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) study. The CHARM study showed that the incidence of neoplastic diseases was increased by candesartan to a significant extent compared with the placebo group in patients with heart failure [8]. This study was also the first to show an increased incidence of myocardial infarction (57%) during the use of ARBs, which caused concern, and has been debated since this study.

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In this review, results are discussed that may help clarify this issue for the practicing physician and may dispel some misconceptions. Mainly the results of clinical studies with a large number of subjects and a long follow-up period are discussed, including studies that recorded the incidence of neoplastic diseases.

2. Incidence of cancerous diseases in clinical studies during the use of ARBs

2.1. CHARM-Overall study

An increased incidence of some neoplastic diseases during the use of ARBs was first shown by the CHARM study (n = 7,601), which compared candesartan with placebo in patient with chronic heart failure (CHARM-Overall program) in 2003 [8,9]. Although the candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure during the follow-up of 37.7 months, this study showed a significant increase (42%) in the risk of developing a fatal cancer in patients treated with candesartan upon randomization compared with the placebo group (absolute risk [AR] 2.3% vs. 1.6%; relative risk [RR] 1.42; n = 86 vs. 59; p = 0.038). At the time of this study, the investigators considered this imbalance as accidental, and then explained it with differences in risks between the groups.

2.2. LIFE study

In the LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study the losartan and atenolol therapies were compared in 9193 hypertensive patients with LVH. During the mean follow-up of 4.8 years losartan prevents more cardiovascular morbidity and mortality than atenolol for a similar reduction in blood pressure and is better tolerated. This study also reported data on losartan related to cancer [9,10]. The risk of neoplastic diseases was increased by 12% compared with the control group (p = 0.01). Pulmonary carcinoma also occurred at a high rate in ARB groups in other studies, but this was below the level of significance in most of the studies [8]. Prostate cancer, another type of tumor correlated with the use of ARBs [8], showed a 38% increase in its incidence in the losartan group. However, because of the low number of subjects, this was proven to be non-significant (AR 2.7% vs. 2.0%; RR 1.38; n = 58 vs. 42; p = 0.11).

2.3. ONTARGET and TRANSCEND studies

Five years after the LIFE study, the results of the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) studies, were published [11,12]. In the ONTARGET study the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs were compared in patients with vascular disease or high-risk diabetes (n = 25,620). Based on the results of primary endpoint (composite of death from cardiovascular causes, myocardial infarction, stroke and hospitalization for heart failure), telmisartan was equivalent to ramipril, and the combination of the two drugs was associated with more adverse events without an increase in benefit. In the TRANSCEND study telmisartan did not show any additional cardiovascular benefit over the placebo in patients unable to tolerate ACE inhibitors (HR 0.92, p = 0.216). A report on the increased incidence of malignant tumors observed among patients treated with telmisartan in these studies was presented to the advisory board of the Food and Drug Administration (FDA) on cardiovascular and renal medicines in July 2009 [13].

In the ONTARGET study, the incidence of neoplastic diseases was increased by 9% in patients taking ARBs compared with the control treatment arm (9.3% vs. 8.6%; RR 1.09; p = 0.054), but this difference was not significant [9]. However, for malignant tumors, there was a significantly higher risk of development of cancer in patients treated with the combination of telmisartan + ramipril compared with ramipril monotherapy; either a malignancy was present or not present at baseline (AR 9.7% vs. 8.6%; RR 1.14; n = 824 vs. 735; p = 0.011).

In the TRANSCEND study, the incidence of cancerous diseases was increased by 16% in the telmisartan group compared to placebo, but this was not significant (AR 8.0% vs. 6.9%; RR 1.16; n = 236 vs. 204; p = 0.099). However, the risk of developing malignancies in patients who were free of cancer at baseline (95% of all participants) was significantly increased by 24% in patients treated with telmisartan compared with those who received placebo (AR 7.3% vs. 6.0%; RR 1.24; n = 206 vs. 169; 95% confidence interval [CI] 1.01-1.52) [9].

2.4. ProFESS study

In the ProFESS (Prevention Regimen For Effectively avoiding Second Strokes) study telmisartan did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes in patients with previous ischemic stroke compared to placebo (n = 20,332, mean follow-up 2.5 years). The study of the most common malignancies, including lung cancer, prostate cancer, and breast cancer, showed a non-significant increase of 24, 12% and 36% in the ARB (telmisartan) group compared to placebo, a non-significant 4% decrease in the total number of cancers was reported by the investigators (AR 3.3% vs. 3.4%; RR 0.96; n = 326 vs. 340; p = 0.610). Unfortunately, no data showing the background of this contradiction can be found in publications [9,14].

2.5. VALUE and VALIANT studies

With regard to valsartan, inconsistent data are available as shown in the VALUE study. The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study compared valsartan- and amlodipine-based therapies in 15,245 hypertensive patients at high cardiovascular risk, and the primary endpoint (time to first cardiac event) did not differ between the treatment groups during the mean follow-up of 4.2 years. The study showed a significant 15% decrease in neoplastic diseases in the ARB group (AR 0.7% vs. 0.8%; odds ratio [OR] 0.85; n = 510 vs. 591; 95% CI 0.75-0.96) [15,16]. The VALIANT (Valsartan in Acute Myocardial Infarction Trial) study did not find any significant differences in the effects of captopril, valsartan, and their combination on atherosclerotic events (fatal and non-fatal AMI) in patients who had acute myocardial infarction (n = 14,703). This study showed a non-significant increase of 22% for cancer-related mortality in the valsartan group compared with the captopril group (AR 1.1% vs. 1.4%; OR 1.22; n = 67 vs. 55; 95% CI 0.85–1.74) [16,17].

3. Pooled analysis of the various studies

The results from the above-mentioned studies, except for the ProFESS and VALUE trials, show that a newly developed cancer occurs in a higher number of patients treated with ARBs than those not treated with ARBs in all surveyed studies (Fig. 1). However this result was non-significant in most of the studies because of the low number of cases. In this regard the various, correctly compiled analyses especially useful, because they make powerful tendencies and observations experienced in single studies less ambiguous.

The first prominent analysis which drew attention to a potential correlation between ARB therapy and neoplastic diseases was published by Coleman in 2008 [18]. They processed the data of 126,137 patients from 27 studies (subjects with hypertension, cardiac failure, coronary heart disease, or renal disease). Although the analysis has come to the basic conclusion that neither of the five large groups of antihypertensive
medicines (diuretics, beta blockers, calcium channel blockers, ACE inhibitors, ARBs) increased the risk of neoplastic diseases to a significant extent, nevertheless noteworthy trend-like differences could be recognized in the effects of the individual groups. While ARBs (based on the data of RENAAL, CHARM, LIFE and TROPHY studies) influenced the risk of cancerous diseases, although not significantly, but to an unfavorable direction (OR 1.12; CI 0.87–1.47), the other four groups of medicines showed neutral or slightly favorable effects as compared to the placebo/untreated control group (Fig. 2).

A meta-analysis published by Sipahi et al. in 2010 investigated the data of LIFE, CHARM-Overall, TRANSCEND, ONTARGET, and PRoFESS studies [9]. This meta-analysis showed a significantly increased risk of newly developed cancer in patients treated with ARBs compared with control therapy (AR 7.2% vs. 6.0%; RR 1.08; n = 67 vs. 55; 95% CI 1.01–1.15; p = 0.016) [8]. When the analysis was limited to three studies where the development of cancer was a pre-defined endpoint, and data related to cancer were collected according to a strict order (LIFE, ONTARGET, and TRANSCEND), the risk of cancer was also significantly higher with the use of ARBs compared with control therapy (RR 1.11; 95% CI 1.04–1.18; p = 0.001). However, notably, a neutral effect for the whole group of ARBs could have been demonstrated if the analysis had included the results of the VALUE study, which were favorable for the valsartan group [19]. With regard to this criticism, Sipahi et al. gave a reasonable explanation for why some studies were intentionally omitted or left out from the analysis [20].

The analysis by Sipahi et al. also included the incidence of specific types of cancer [9] (Fig. 3). A meta-analysis of the above-mentioned five major ARB studies detected a significant 25% increase in the risk of newly developed pulmonary carcinoma among patients treated with ARBs compared with the control arm (AR 0.9% vs. 0.7%; RR 1.25; p = 0.01). Similarly, the incidence of prostate cancer increased in the separate ARB groups of the reviewed studies (7–32%, non-significant). Pooled analysis demonstrated a 15% higher incidence in the ARB-treated groups compared with controls, but this difference was non-significant (AR 1.7% vs. 1.3%; RR 1.15; p = 0.076). For breast cancer, an increase in risk of 4% in the ARB group was non-significant compared with the control arm (AR 1.2% vs. 1.1%; RR 1.04; p = 0.74).

Interestingly, an increased incidence of tumors resulted in no significant increase in mortality of cancer in all of the studies. This is not surprising because the development and growth of tumors and then failure of anti-cancer treatment, leading to a fatal outcome, is often a slow process, even in the case of failure of oncological therapy.

Another important meta-analysis (ARB Trialist Collaboration) was published in 2011 [21]. The results of 138,769 patients of 15 major clinical studies with ARBs were analyzed, and some interesting conclusions were reached. The pooled results showed no correlation between ARBs and certain types of cancer, suggested by earlier meta-analyses. However, they also showed potential differences between effects of the active substances of individual ARBs. This meta-analysis showed a non-significant increase of neoplastic diseases with the use of candesartan, losartan, and telmisartan, while the incidence of neoplastic diseases was significantly decreased with valsartan, and non-significantly decreased with irbesartan (Fig. 4).

An analysis of a subgroup in this meta-analysis focused on studies where, besides ARB therapy, the control group received ACE inhibitor treatment. In all of the five such ARB studies (ACTIVE, I-PRESERVE, ONTARGET, VALIANT, and PRoFESS) a uniform, but non-significant increase in the risk of neoplastic diseases was observed (RR 3–15%) compared with ACE inhibitor treatment (Fig. 5).

The discussion of a potential correlation between ARBs and neoplastic diseases continued also in 2012, when a further interesting cohort analysis was published by Bhaskaran et al. [22]. They examined the data of 377,649 hypertensive patients who had taken ARB or ACEI for one year at least in the period between 1995 and 2010 (General Practice
Research Database, UK). The mean duration of the treatment with ARB (10%) or ACEI (90%) was 4.6 years, and 45% of patients had taken the examined medicine for 5 years at least. During the analyzed period, 20,203 neoplastic diseases were registered, the most frequent ones included prostate cancer (n = 3025), breast cancer (n = 2411), lung cancer (n = 2144) and colorectal cancer (n = 1516).

According to the results, although there was no significant increase in the incidence of any neoplastic disease during ARB therapy (HR 1.03, CI 0.99–1.06, p = 0.10) compared those patients who never had taken ARB before, however significant differences could be observed in the incidences of the individual tumor types. The incidence of lung cancer was significantly lower in patients who took ARB (RR 0.84, CI 0.75–0.94, p = 0.003), while the risk of breast cancer and prostate cancer was significantly higher with ARB therapy as compared to the data of patients taking ACEI (HR 1.11, CI 1.01–1.21, p = 0.02 and HR 1.10, CI 1.00–1.20, p = 0.04). The highest increase in the risk of breast cancer was observed with telmisartan (RR 1.36, CI 1.00–1.86), while an increased risk of prostate cancer was seen primarily with candesartan therapy (RR 1.32, CI 1.13–1.54). Although colorectal cancer showed no significant change for the whole examined period (HR 1.02, CI 0.91–1.16, p = 0.70), at the same time an abrupt and significant increase of colonic tumors among patients taking ARB was observed between months 49 and 60 of the examined period (HR 1.32, CI 1.00–1.75). However, the investigators excluded the codes for borderline and suspected malignancies. As a result of screening tests the major part of colon tumors are detectable in an early phase, when this disease is not yet reported as malignancy, and early treatment is available. In this study the real risk of the colon cancer may significantly be underestimated.

Thus, the analysis may be a further confirmation to the concept that the correlation between ARBs and neoplastic diseases is not "homogeneous"; it may strongly depend on tumor type, on the duration of medication and on the active substance of the used ARB as well.

4. Conclusion

The data presented in this review suggest that the use of some medicines, which belong to the group of ARB-active substances, might be associated with a moderately increased risk of newly developed cancer. The increase in risk, which occurred in the individual studies, was often not significant because of the relatively short follow-up periods in relation to neoplastic diseases and the low number of cases. However, the trend-like differences have been consistent in most instances. If a conclusion is attempted by pooling the results of these studies, the differences become clearly significant for some types of cancer. Nevertheless, oncological data are not available for certain ARB-active substances (olmesartan and eprosartan).

The mechanism of the occasional increase in the incidence of newly developed cancer during ARB therapy has not been fully elucidated. While the well-known effects of angiotensin II (e.g., vasoconstriction and aldosterone synthesis) are mediated primarily by the AT1R, the function of the AT2R is not as well clarified [23]. The role of angiotensin II in cell proliferation, cell migration, and angiogenesis suggests a role in certain steps of tumor genesis and tumor progression [24,25]. ARBs exert their main clinical effects by inhibiting AT1R, and they have an inhibitory effect on tumor growth [24]. However, some studies have demonstrated continuing tumor growth despite AT1R blockade [25]. Results of experimental studies have shown that increased stimulation of free AT2R during ARB therapy results in increased tumor progression [24,26]. Therefore, evidence has shown in vivo enhancement of tumor vascularization by inhibition of AT1R by ARBs (accompanied by stimulation of AT2R, which remain with no counterbalance) and direct stimulation of AT2R [27]. Because of the incomplete information available, varying follow-up periods, and other differences, the effects of individual ARB-active substances on the risk of cancer cannot be accurately determined. When studies on telmisartan, where the occurrence of cancer was a separate endpoint (TRANSCEnd, ONTARGET, and PROFEss), were evaluated in a separate meta-analysis, the increase in the risk of cancer became significant (RR 1.07; 95% CI 1.00–1.14; p = 0.05) [9].

The relationship between RAAS inhibition and malignancies has already emerged in relation to ACE inhibitors and other antihypertensive medicines approximately one decade ago. ACE inhibitors are neutral in relation to cancerous diseases, and might even represent protection to some extent. The first study that assessed the risk of cancer retrospectively was...
performed in 1559 hypertensive patients treated with ACE inhibitors for more than 15 years [28,29]. The relative risk of cancer was decreased by 28%, and even up to 37% in female patients treated with ACE inhibitors compared with the control group.

In three other retrospective, case–control studies, where the correlation between ACE inhibitors and esophageal, pancreatic, and rectal carcinoma was assessed in 783,733 patients, the use of ACE inhibitors was associated with a significant reduction in the risk of all three types of cancer [30]. In this retrospective study, Heinzlerling et al. observed a decreased incidence of metastasis formation in patients with colorectal carcinoma who were treated with ACE inhibitors compared with the control group [31]. Among the major studies, the HOPE (Heart Outcomes Prevention Evaluation) study and its extended HOPE-TOO trial (with 7 years of follow-up) showed no effect of ramipril/vitamin E on the incidence of newly diagnosed cancer [32]. Experimental data have demonstrated that perindopril in the therapeutic dose range inhibits tumor growth and angiogenesis, and hinders the expression/synthesis of various tumor factors/vascular endothelial growth factor [33].

Notably, individual ARB studies were not designed for studying the development of cancer as a primary endpoint. However, in studies that only analyzed cancer as a pre-defined endpoint and cancer–related data were collected according to strict viewpoints, the risk of cancer showed a significant increase with the use of ARBs.

Meta-analyses are considered less convincing compared with large prospective studies designed for the assessment of specifically defined outcomes. Nevertheless, meta-analyses may be useful for identifying any deficiencies in the safety of treatment and rare undesirable events. Based on the available data, there appears to be a moderately increased risk of various cancerous manifestations during the use of some ARB-active substances. However, the benefits associated with the administration of ARBs (reduction of certain cardiovascular events) exceed the equivocal ‘undesired side effects’. This issue was raised by the recent European Society of Hypertension guideline (ESH 2013), which stated that no clear-cut correlation can be demonstrated between ARB therapy and neoplastic diseases [34]. Although this issue generated debate in the FDA, their final official position statement was also formulated according to the ESH guideline [35]. All these support the need for an appropriate level of pharmacovigilance. This viewpoint is also shared by the Italian Hypertension Society (SIIA), which did not recommend the issue of any warning in relation to antihypertensive therapy with ARBs [36]. Further studies and data collection are required to precisely identify the ARB-active substances and the types of cancer, as well as to establish exact correlations.

As regards minimizing the – possibly increased – risk associated with the use of ARBs, I would suggest the colleagues to implement the following two, practical measures:

– Focus on the differential use of the individual ARBs. Whenever possible, avoid those active substances, which have been shown to be associated with a significant increase in malignancy (such as telmisartan and candesartan), and prefer those for which reassuring findings are available (e.g. valsartan).
– Comply with the recommendations on the management of the most common cardiovascular disorders (such as stable coronary artery disease, post-AMI, chronic CHF, PAD). These prefer the use of ACEIs in the first place, and reserve ARBs for patients who cannot tolerate the former.

Conflict of interest

The author declares that he have no conflict of interest.

References


