European Heart Journal (2011) **32**, 19–22
doi:10.1093/eurheartj/ehq382

CURRENT OPINION

Twisting arms to angiotensin receptor blockers/antagonists: the turn of cancer

Massimo Volpe[1,2]*, Michel Azizi[3,4,5], A.H. Jan Danser[6], Genevieve Nguyen[7], and Luis M. Ruilope[8]

[1]Division of Cardiology, Department of Clinical and Molecular Medicine, 2nd Faculty of Medicine, University of Rome 'La Sapienza', Sant'Andrea Hospital, Via di Grottarossa, 1035-39, 00189 Rome, Italy; [2]IRCCS Neuromed, Pozzilli, Italy; [3]Université Paris Descartes, Faculté de Médecine, Paris F-75006, France; [4]Assistance Publique des Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris F-75015, France; [5]INSERM, CIC 9201, Paris F-75015, France; [6]Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands; [7]Institut National de la Santé et de la Recherche Médicale (INSERM, Unit 833 and Collège de France, Experimental Medicine Unit, 11 place Marcelin Berthelot, 75005 Paris, France; and [8]Hypertension Unit, Hospital 12 de Octubre, Madrid, Spain

Received 21 July 2010; revised 24 August 2010; accepted 7 September 2010; online publish-ahead-of-print 21 October 2010

Introduction

Treatment of cardiovascular disease has achieved spectacular targets in the last 30 years, significantly contributing to the dramatic increases in life expectancy. In contrast, in the recent years, very few pharmacological innovations have been proposed, most likely because of the escalating costs of drug clinical development and by the reduced needs of innovation in this field.

Angiotensin receptor blockers/antagonists (ARBs) have represented one of the major novel class of drugs reaching the therapeutic use for cardiovascular disease indication. Given the extremely high prevalence of hypertension, the leading indication for ARBs, prescription of this class of drugs has increased to very high levels. It is calculated that about 200 million individuals are treated with ARBs on our planet and that this class covers ~25% prescription of antihypertensive agents. Even though this may be due to intensive marketing activity, it is also related to their 'friendly' use recognized by both doctors and patients, being the best tolerated class among cardiovascular drugs,[1,2] and to rigorous and impressive clinical development. In fact, beyond the 15-year clinical experience by physicians and the consequent long-term drug surveillance by the authorities of healthcare systems worldwide, until today more than 300 000 patients have been strictly monitored for periods averaging from 3 to 5 years in clinical trials performed in numerous different clinical settings [including hypertension, high cardiovascular risk, diabetes, heart failure, myocardial infarction (MI), renal failure, stroke, and atherosclerosis].[3,4] In all these studies, adverse reactions ascribed to ARBs have generally been less than any comparator, and similar to placebo. Besides the setting of clinical trials, these drugs have been extensively investigated as indicated by more than 12 100 scientific publications on PubMed at the date of 3 July 2010, using only the keywords Angiotensin Receptor Antagonists and Angiotensin Receptor blockers.

Angiotensin receptor blockers/antagonists clinical development: a long and winding road

During their clinical development and progressive application in therapy, several questions have been raised about the efficacy and safety of ARBs. An initial doubt, which has been only partially answered, relates to their equivalence/superiority to angiotensin-converting enzyme-inhibitor (ACE-I) in the treatment of congestive heart failure (CHF) and post-MI; the results of the ELITE I[5] and II studies[6] that compared a low-dose ARB (losartan 50 mg o.d.) with a very high dose of the ACE-I captopril (50 mg t.i.d.), showed no difference in efficacy but less side effects with the ARB in CHF. Similar results were obtained in post-MI in the OPTIMAAL[7] and VALIANT[8] studies, in which relatively low dosages of ARBs (losartan 12.5–50 mg and valsartan 20–160 mg daily, respectively) were used as compared with the dosages of captopril (50–150 mg daily). Finally, in Val-Heft[9] and CHARM,[10] some specific benefits of ARBs were described. These observations were not considered convincing enough to replace ACE-I, as the 'gold standard' therapy for these conditions, especially in view of the long-term and vast experience with ACE-I and their lower cost, as well as because, for ethical reasons, no direct comparisons between ARBs and ACE-I were performed.

The turn of myocardial infarction

A second, much more serious, hurdle for ARBs and especially for their safe use in clinical therapy was raised with regard to a

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +39 06 3377 5654, Fax: +39 06 3377 5061, Email: massimo.volpe@uniroma1.it

presumed increased risk of MI due to their use. This alarm appeared in the *British Medical Journal* with a subtitle 'these drugs may increase myocardial infarction and patients may need to be told,' which generated significant concern and disappointment in both physicians and patients, and received significant diffusion in the media.[11] Unsurprisingly, this was amplified by healthcare authorities in some countries, probably with the good intention to 'jeopardize' an expensive drug class and indirectly support other less expensive antihypertensive drugs. This alarm, based on an incomplete meta-analysis,[11] has been diminished by thorough meta-analyses,[12,13] as well as by direct comparisons with ACE-I,[14] and even, by the same author, by a vast analysis of a database.[15] Also the claim of clinical incompatibility of ARBs with beta-blockers in heart failure, based on a relatively small subgroup in Val-Heft,[9] was denied by the much larger experience of CHARM.[10]

The turn of cancer

In spite of these difficulties as well as of a series of mega trials with ARBs that generated substantially neutral results, especially in high-risk patients,[14,16] ARBs are prescribed worldwide for a number of indications beside hypertension with no major safety concerns, apart from being contraindicated in pregnancy, renovascular hypertension, and very severe chronic kidney disease. However, on the basis of some isolated experimental reports, suggesting a role of AT_1 receptors and AT_2 receptors in processes involved in carcinogenesis (cellular proliferation, angiogenesis, and tumour progression) and the unexpected findings of significantly higher death rate by cancers in the candesartan arm of the CHARM programme,[10] Sipahi *et al.*[17] undertook and published a meta-analysis based on the evaluation only of studies with ARB reporting cancer data, to gain insights on their effect on the development of solid cancers and cancer death. The conclusion of this study, published a few weeks ago in Lancet Oncology,[17] suggested that ARBs are associated with a 'modest increase' (1–2% absolute risk) of new cancers as compared with the control group (7.2 vs. 6.0%, RR 1.08, CI 1.01–1.15, $P = 0.016$).

Given the high emotional impact that this initial and preliminary report on such a sensitive endpoint may have on physicians currently prescribing ARBs, we felt that it is important to critically discuss some aspects of this report and, most of all, examine the biological data that support the assertion that ARBs may increase cancer risk.

With all due respect to a 'stand-alone' report, based on a limited meta-analytical approach, we cannot refrain from making a few general comments before discussing biological validity: (i) studies with a follow-up of 1 year and arbitrarily including at least 100 patients were considered. The longest follow-up was 5 years. Now, if one considers the time-course of cancer onset in response to well-known carcinogenic agents, this appears as a major conceptual limitation for a reasonable interpretation of a relatively short-term treatment with ARBs. There is little, if any, biological plausibility that a drug exposure of a few years only would increase the risk of new cancer diagnosis. Cigarette smoking, which is one of the most powerful risk factors for lung cancer, will require 10 years or longer exposure to significantly increase the risk of lung cancer. Thus, it is very unlikely that the short-term drug exposure over the course of a clinical trial ARBs would have a clinically meaningful effect; (ii) the lack of information on individual patient data from any of the trials considered and on the timing of cancer, as acknowledged by the authors, is a major drawback of the analysis. This limitation is aggravated by the consequent lack of information on sex, age, smoking, and previous neoplastic history; (iii) in the studies used for the analysis, adjudication of cancer diagnosis was not uniform; (iv) the increased risk of cancer found by Sipahi in their meta-analysis is completely driven by ONTARGET, and within this study, only by the telmisartan/ramipril combination vs. ramipril.[14] In contrast, telmisartan did not increase cancers as compared with ramipril. In the studies comparing telmisartan with placebo (TRANSCEND and the PROFESS), cancer rates were equivalent. These observations raise reasonable doubts in the interpretation, also in view of the fact that the rates of new cancers in these studies were quite consistent with that of the general population; and (v) in none of the studies considered, there was a higher risk of cancer death in the ARBs groups compared with the control groups with the exception of a borderline significance in CHARM-overall.[10]

As mentioned before, the authors recognize most of these limitations of their study, and other important methodological aspects would deserve to be discussed thoroughly. One important flaw of this meta-analysis is that the majority of large international trials involving ARBs (at least 16)[4] have not been considered. These data which represent thousands of patients treated with ARBs should now be made available to perform a state-of-the-art meta-analysis. The simple addition of VALUE data, for instance, eliminates the reported difference in cancer incidence between ARBs and controls (http://www.theheart.org/article/1091359.do#bib_3). Nonetheless, the authors suggest that their findings should prompt a prospective 'ad-hoc' study. Even more, the accompanying editorial[18] states that 'in the interim we should use great caution in the use of ARB' which are 'overprescribed as a result of aggressive marketing'. This kind of conclusions and statements may obviously generate anxiety, if not panic, among millions of patients regularly taking ARBs as well as among doctors.

This type of alarming situation is not new in the history of antihypertensive drugs, ever since the use of reserpine was associated with an increased risk of breast cancer more than 30 years ago, the question of antihypertensive drugs and cancer has not come to rest. Indeed, the cancer–hypertension connection has been discussed for a long time. Cancer is frequently occurring in the aging population in which hypertension is also more frequently present. In addition, hypertension has been associated with an excess rate of cancer mortality related to all types of tumours [adjusted pooled OR (95% CI): 1.23 (1.10–1.36)].[19] Over the past decades, antihypertensive drugs have been often associated with cancer.[20] Beta-blockers have been associated with lung cancer, calcium-channel blockers with cancer in general, and thiazide diuretics with renal cell carcinoma and colon cancer. The use of antihypertensive drugs was even reported to be associated with an increased risk of glioma. In most instances, the excess risk is small, does not persist after adjustment on confounding factors, and is not supported by biochemical experimental or epidemiological data.

Since a retrospective study[21] showed that the use of ACE-inhibitors potentially protects against cancer, albeit controversial,[22] blockers of the renin-angiotensin system have experienced a remarkably favourable record in this regard. In most studies and meta-analyses, the risk of cancer with renin-angiotensin system (RAS) blockers was either equal or lower than with their comparators including placebo.[22] Thus, the report by Sipahi *et al.*[17] showing a modestly increased risk of new cancer diagnosis with ARBs, is unexpected and certainly warrants scrutiny and further investigation.

Angiotensin receptor blockers/antagonists and cancer: a closer look at potential mechanisms

An important aspect to discuss, therefore, is whether there is sufficient biological plausibility to support the hypothesis that ARBs favour cancer development, and whether the postulated mechanism advocated by Sipahi *et al.*[17] in their discussion has any solid basis. This mechanism proposes that the rise in angiotensin (Ang) II during ARB treatment will activate the non-blocked AT_2 receptors, thereby inducing tumour angiogenesis.

Indeed, several tumoural cell types have been reported to express Ang II receptors.[23] These include melanoma, brain, lung, pancreatic, renal, breast, ovarian, bladder, and prostate cancer. Moreover, in high-grade astrocytomas, tumour Ang II receptor expression was associated with a high grade of malignancy, increased cellular proliferation, and angiogenesis, and thus predicted poor prognosis.[24]

As demonstrated in the Matrigel model in mice, Ang II induces angiogenesis via activation of the vascular endothelial growth factor (VEGF)/endothelial NO synthase (eNOS) pathway.[25] This involves AT_1 rather than AT_2 receptors, since only ARBs blocked this process.[25] In line with this observation, ACE-I,[26] ARBs,[27] and a recombinant antibody (R6313/G2) against the AT_1 receptor[28] displayed antineoplastic activity and inhibited angiogenesis in various tumoural experimental models.

With regard to the potential significance of the stimulation of unopposed AT_2 receptors in patients treated with ARBs, the role of the AT_2 receptor in cancer is controversial. This may depend on the experimental model and the cancer type. In the model of subcutaneously transplanted syngeneic xenografts pancreatic ductal carcinoma cells, tumour growth was more rapid and the tumour vasculature was significantly enhanced in AT_2 receptor knock-out mice than in wild-type animals.[29] In addition, the growth of pancreatic ductal carcinoma cells *in vitro* was decreased when cultured with AT_2 receptor gene transfected fibroblasts.[29] Furthermore, overexpression of AT_2 receptor induced cell death in lung adenocarcinoma cells via activation of apoptosis.[30] Taken together, these data suggest that AT_2 receptors stimulation results in an antitumour effect. This may be due to the fact that AT_2 receptors exert anti-angiogenic effects by interfering with VEGF/eNOS-mediated endothelial cell migration and tube formation.[31] Yet, AT_2 receptor gene deficiency attenuated susceptibility to tobacco-specific nitrosamine-induced lung tumourigenesis by down-regulating the level of transforming growth factor β,[32] thus supporting a pro-tumour effect of AT_2 receptors. A possible explanation for these contradicting observations is that AT_2 receptors may achieve an AT_1 receptor-like phenotype under pathological conditions, e.g. inducing vasoconstriction/angiogenesis rather than vasodilation/anti-angiogenesis.[33] Finally, studies with the AT_2 receptor agonist compound C21 so far have not produced any alert for cancer, although it should be acknowledged that this has been generally involved in short-term studies only.

Angiotensin receptor blockers/antagonists as well as ACE-I increase plasma and tissue concentrations of Ang (1–7). In a human lung tumour xenograft model, athymic mice with tumours treated with Ang-(1–7) by osmotic mini pumps for 28 days had a 30% reduction in tumour volume associated with reduced tumoural cyclooxygenase-2 expression and a decreased vessel density.[34] Angiotensin (1–7) has anti-angiogenic effects in the chick chorioallantoic membrane model and reduces VEGF-A expression in tumours.[35] *In vitro*, Ang-(1–7) inhibits lung cancer cell growth through the activation of the MAS receptor and this effect cannot be prevented by either AT_1 nor AT_2 receptor antagonists.[36]

Angiotensin receptor blockers/antagonists and ACE-I differently affect the level of *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), induced in plasma and tissues. *N*-acetyl-seryl-aspartyl-lysyl-proline is a natural inhibitor of pluripotent haematopoietic stem cell proliferation,[37] is formed *in vivo* by enzymatic cleavage of the N-terminus of thymosin beta4 by prolyl oligopeptidase (POP), and is physiologically degraded by the N-terminal domain of ACE.[37,38] Its accumulation during ACE inhibition may partially mediate the cardioprotective effect of ACE-inhibitors. However, Ac-SDKP has also been suggested to be pro-angiogenic: Ac-SDKP stimulates endothelial cell proliferation, migration, and tube formation in a dose-dependent manner and increases myocardial capillary density in rat hearts with MI.[39] It also stimulates an angiogenic response in the chicken embryo chorioallantoic membrane,[40] in the abdominal muscle of the rat, and in a model of surgically induced hind-limb ischaemia.[41] *N*-acetyl-seryl-aspartyl-lysyl-proline levels are increased in haematologic and solid malignancies (breast, colon, head and neck, kidney, lung, skin, ovary, and prostate) and enhanced activity of POP is also detected in cancer tissues.[42] Thus, in theory at least, ARBs (which do not alter Ac-SDKP concentrations) should not stimulate angiogenesis via this pathway, whereas ACE-I could.

Finally, the rise in renin per se, as occurring during any type of RAS blockade, may have detrimental consequences. Indeed, renin as well as its precursor prorenin bind to the (pro)renin receptor [(P)RR] and trigger intracellular signalling in an Ang II-independent manner. Interestingly, the (P)RR has recently been shown to be a component of the Wnt receptor complex and to be essential for the signalling of the canonic Wnt-β-catenin pathway although not necessarily in a (P)RR-dependent manner.[43] Since the Wnt-β-catenin pathway is essential in embryonic and adult stem cell biology and therefore in cancer, one could imagine that the increased levels of renin and prorenin, as occurring during ARB therapy (as well as during any other type of RAS blockade!), are responsible for augmented Wnt-β-catenin signalling and cancer. However, up to now, the role of the (P)RR in the Wnt-β-catenin signalling has only been demonstrated in *Xenopus*[43] and clearly,

more work is needed to substantiate these findings in higher mammals.

Conclusions and perspectives

Unfortunately, blood pressure still remains uncontrolled in many patients and exposes them to the risk of having a heart attack or stroke. To get blood pressure under control, we need to extensively use for long term all available antihypertensive drug classes, particularly those better tolerated by patients. The news that some of these antihypertensives potentially could cause cancer is alarming for patients who are on these drugs and could motivate them to abruptly discontinue treatment.

In any event, although we cannot avoid nor want to avoid this information being shared with our patients, it should be done prudently and with sufficient balance by responsible news media. A similar emphasis is often not given to the beneficial effects of these drugs. Thus, drawing the line between the benefits and the risks at the individual patient level may leave the prescribing physician and the patient in total perplexity!

The alarming conclusions of the paper by Sipahi *et al.*[17] and of the related commentary[18] do not seem appropriate, especially in consideration of the fact that the meta-analysis was neither thorough nor based on a systematic selection of the cancer endpoint in the included studies. At this time, we do not think that the data of the analysis of Sipahi *et al.*[17] are sufficient to undertake a prospective study exploring a causal link between ARBs (or a specific ARB) and cancer, especially in consideration of the lack of consistent biological mechanisms and the predicted duration of the study. At the same time, we believe a detailed scrutiny of all available databases by health authorities and scientific groups should be encouraged.

In this regard, very recently, the Food and Drug Administration (FDA) in US drug safety communication on ongoing safety review of the ARBs and cancer (online available on http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218845.htm), has not concluded that ARBs increase the risk of cancer. At this time, FDA believes that the benefits of these medicines continue to outweigh the potential risks. Food and Drug Administration recommends that these drugs continue to be used as indicated in their approved labels and that the patients should not stop their use unless told by physicians.

Disclosures

The authors wish to clearly state that this article was projected and written independently of any kind of support or influence from any other parties, including pharmaceutical industries. Furthermore, they have no active financial conflict of interest that may have affected the content of the article.

Acknowledgements

The authors wish to thank Francesca Palano, MD, for the precious help in preparing the manuscript.

Conflict of interest: M.V.: active research grant from Novartis; participation to international advisory boards of Bayer Schering Pharma and Daichii-Sankyo; honoraria lectures in symposia by Daichii-Sankyo and sanofi-aventis. M.A. has consulted for and has received research funding and honoraria from Novartis, sanofi-aventis, and Actelion within the past 2 years. A.H.J.D. has received lecture fees and research grants from Novartis and Vitae Pharmaceuticals. G. N. has received lecture fees and research grants from Novartis and Institut de Recherche Servier. L.M.R. is advisor/speaker for Astra-Zeneca, Bristol Myers Squibb, Bayer, Novartis, Menarini, Recordati, Takeda, Daiichi-Sankyo, Otsuka.

References

1. Elliott WJ, Plauschinat CA, Skrepnek GH, Gause D. Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. *J Am Board Fam Med* 2007;**20**:72–80.
2. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly treated patients: a population-based study in Italy. *J Hypertens* 2008;**26**:819–824.
3. Zanchetti A, Mancia G, Black HR, Oparil S, Waeber B, Schmieder RE, Bakris GL, Messerli FH, Kjeldsen SE, Ruilope LM. Facts and fallacies of blood pressure control in recent trials: implications in the management of patients with hypertension. *J Hypertens* 2009;**27**:673–679.
4. Tocci G, Sciarretta S, Volpe M. Development of heart failure in recent hypertension trials. *J Hypertens* 2008;**26**:1477–1486.
5. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan vs. captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;**349**:747–752.
6. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000 May 6;**355**:1582–1587.
7. Dickstein K, Kjekshus J. OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;**360**:752–760.
8. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
9. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
10. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall Programme. *Lancet* 2003;**362**:759–766.
11. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. *BMJ* 2004;**329**:1248–1249.
12. Volpe M, Tocci G, Sciarretta S, Verdecchia P, Trimarco B, Mancia G. Angiotensin II receptor blockers and myocardial infarction: an updated analysis of randomized clinical trials. *J Hypertens* 2009;**27**:941–946.
13. Verdecchia P, Angeli F, Gattobigio R, Reboldi GP. Do angiotensin II receptor blockers increase the risk of myocardial infarction? *Eur Heart J* 2005;**26**:2381–2386.
14. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
15. Verma S, Mamdani MM, Al-Omran M, Melo M, Rouleau JL. Angiotensin receptor blockers vs. angiotensin converting enzyme inhibitors and acute coronary syndrome outcomes in elderly patients: a population-based color study (UMPIRE study results). *J Am Soc Hypertens* 2007;**1**:286–294.
16. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.

17. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 2010;**11**:627–636.
18. Nissen SE. Angiotensin-receptor blockers and cancer: urgent regulatory review needed. *Lancet Oncol* 2010;**11**:605–606.
19. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? *Am J Med* 2002;**112**:479–486.
20. Grossman E, Messerli FH, Goldbourt U. Antihypertensive therapy and the risk of malignancies. *Eur Heart J* 2001;**22**:1343–1352.
21. Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL, Meredith PA, Murray LS, Reid JL, Robertson JW. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; **352**:179–184.
22. Rosenthal T, Gavras I. Angiotensin inhibition and malignancies: a review. *J Hum Hypertens* 2009;**23**:623–635.
23. Ager EI, Neo J, Christophi C. The renin-angiotensin system and malignancy. *Carcinogenesis* 2008;**29**:1675–1684.
24. Arrieta O, Pineda-Olvera B, Guevara-Salazar P, Hernandez-Pedro N, Morales-Espinosa D, Ceron-Lizarraga TL, Gonzalez-De la Rosa CH, Rembao D, Segura-Pacheco B, Sotelo J. Expression of AT1 and AT2 angiotensin receptors in astrocytomas is associated with poor prognosis. *Br J Cancer* 2008;**99**:160–166.
25. Tamarat R, Silvestre JS, Durie M, Levy BI. Angiotensin II angiogenic effect *in vivo* involves vascular endothelial growth factor- and inflammation-related pathways. *Lab Invest* 2002;**82**:747–756.
26. Volpert OV, Ward WF, Lingen MW, Chesler L, Solt DB, Johnson MD, Molteni A, Polverini PJ, Bouck NP. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. *J Clin Invest* 1996;**98**:671–679.
27. Kosugi M, Miyajima A, Kikuchi E, Horiguchi Y, Murai M. Angiotensin II type 1 receptor antagonist candesartan as an angiogenic inhibitor in a xenograft model of bladder cancer. *Clin Cancer Res* 2006;**12**:2888–2893.
28. Redondo-Müller MA, Stevanovic-Walker M, Barker S, Puddefoot JR, Vinson GP. Anti-cancer actions of a recombinant antibody (R6313/G2) against the angiotensin II AT1 receptor. *Endocr Relat Cancer* 2008;**15**:277–288.
29. Doi C, Egashira N, Kawabata A, Maurya DK, Ohta N, Uppalapati D, Ayuzawa R, Pickel L, Isayama Y, Troyer D, Takekoshi S, Tamura M. Angiotensin II type 2 receptor signaling significantly attenuates growth of murine pancreatic carcinoma grafts in syngeneic mice. *BMC Cancer* 2010;**10**:67.
30. Pickel L, Matsuzuka T, Doi C, Ayuzawa R, Maurya DK, Xie SX, Berkland C, Tamura M. Overexpression of angiotensin II type 2 receptor gene induces cell death in lung adenocarcinoma cells. *Cancer Biol Ther* 2010;**9**:277–285.
31. Benndorf R, Böger RH, Ergün S, Steenpass A, Wieland T. Angiotensin II type 2 receptor inhibits vascular endothelial growth factor-induced migration and *in vitro* tube formation of human endothelial cells. *Circ Res* 2003;**93**:438–447.
32. Kanehira T, Tani T, Takagi T, Nakano Y, Howard EF, Tamura M. Angiotensin II type 2 receptor gene deficiency attenuates susceptibility to tobacco-specific nitrosamine-induced lung tumorigenesis: involvement of transforming growth factor-beta-dependent cell growth attenuation. *Cancer Res* 2005;**65**:7660–7665.
33. Moltzer E, Verkuil AV, van Veghel R, Danser AH, van Esch JH. Effects of angiotensin metabolites in the coronary vascular bed of the spontaneously hypertensive rat: loss of angiotensin II type 2 receptor-mediated vasodilation. *Hypertension* 2010;**55**:516–522.
34. Menon J, Soto-Pantoja DR, Callahan MF, Cline JM, Ferrario CM, Tallant EA, Gallagher PE. Angiotensin-(1-7) inhibits growth of human lung adenocarcinoma xenografts in nude mice through a reduction in cyclooxygenase-2. *Cancer Res* 2007;**67**:2809–2815.
35. Soto-Pantoja DR, Menon J, Gallagher PE, Tallant EA. Angiotensin-(1-7) inhibits tumor angiogenesis in human lung cancer xenografts with a reduction in vascular endothelial growth factor. *Mol Cancer Ther* 2009;**8**:1676–1683.
36. Gallagher PE, Tallant EA. Inhibition of human lung cancer cell growth by angiotensin-(1-7). *Carcinogenesis* 2004;**25**:2045–2052.
37. Azizi M, Junot C, Ezan E, Menard J. Angiotensin I-converting enzyme and metabolism of the haematological peptide N-acetyl-seryl-aspartyl-lysyl-proline. *Clin Exp Pharmacol Physiol* 2001;**28**:1066–1069.
38. Azizi M, Ezan E, Reny JL, Wdzieczak-Bakala J, Gerineau V, Menard J. Renal and metabolic clearance of N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) during angiotensin-converting enzyme inhibition in humans. *Hypertension* 1999;**33**: 879–886.
39. Wang D, Carretero OA, Yang XY, Rhaleb NE, Liu YH, Liao TD, Yang XP. N-acetyl-seryl-aspartyl-lysyl-proline stimulates angiogenesis *in vitro* and *in vivo*. *Am J Physiol Heart Circ Physiol* 2004;**287**:H2099–H2105.
40. Liu JM, Lawrence F, Kovacevic M, Bignon J, Papadimitriou E, Lallemand JY, Katsoris P, Potier P, Fromes Y, Wdzieczak-Bakala J. The tetrapeptide AcSDKP, an inhibitor of primitive hematopoietic cell proliferation, induces angiogenesis *in vitro* and *in vivo*. *Blood* 2003;**101**:3014–3020.
41. Waeckel L, Bignon J, Liu JM, Markovits D, Ebrahimian TG, Vilar J, Mees B, Blanc-Brude O, Barateau V, Le Ricousse-Roussanne S, Duriez M, Tobelem G, Wdzieczak-Bakala J, Levy BI, Silvestre JS. Tetrapeptide AcSDKP induces postischemic neovascularization through monocyte chemoattractant protein-1 signaling. *Arterioscler Thromb Vasc Biol* 2006;**26**:773–779.
42. Liu JM, Kusinski M, Ilic V, Bignon J, Hajem N, Komorowski J, Kuzdak K, Stepien H, Wdzieczak-Bakala J. Overexpression of the angiogenic tetrapeptide AcSDKP in human malignant tumors. *Anticancer Res* 2008;**28**:2813–2817.
43. Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, Niehrs C. Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt signaling. *Science* 2010; **327**:459–463.