Opinions in Hypertension Management

ARBs and risk of cancer: international and South African expert comment

The suggestion from a recent meta-analysis that angiotensin receptor blockers (ARBs) are associated with an increase in new cancer occurrence but not cancer deaths, has resulted in the initiation of a safety review of this class of drugs by both the FDA (Federal Drug Administration) and the EMA (European Medicines Authority) in accordance with good regulatory practice. This was also advocated by Dr Steve Nissen in his editorial comment. In the interim, a review of the published meta-analysis plus input from Boehringer-Ingelheim is pertinent to clinical practice.

Meta-analysis of randomised control trials

This meta-analysis pooled the published randomised, controlled trials of ARBs and found that ARB use may be associated with a modest increased risk of new cancers – predominantly lung cancer. Patients who were randomly assigned to receive ARBs had an increased risk of new cancer occurrence compared with patients in the control groups (7.2 vs 6.0%, risk ratio 1.08, 95% CI, 1.01–1.15). When analysis was limited to those trials (LIFE, ONTARGET and TRANSCEND) where cancer was a pre-specified endpoint, the risk ratio was 1.11 (95% CI, 1.04–1.18, p = 0.001). The authors concluded that the findings of the meta-analysis warrant further investigation.

The meta-analysis reviewed 60 trials and included published and available FDA data from nine different trials (Table 1) to assess overall cancer risk and risk of specific solid-organ cancers associated with ARBs plus ACE inhibitor therapy, compared with ACE inhibitors alone. Cancer was a pre-specified endpoint of special interest in three of the five trials that included new cancer data for analysis of cancer occurrence (LIFE, ONTARGET and TRANSCEND).

In the ONTARGET and TRANSCEND trials, information on the occurrence of malignancies was also collected prospectively in more detail than usual for trials of cardiovascular outcomes, thereby placing the spotlight on telmisartan which was the study drug in 30 014 (85.7%) of the ARB-treated patients included in the meta-analysis. The association of ARBs with the occurrence of solid-organ cancers, new lung, prostate and breast cancer from the meta-analysis is summarised in Table 2.

Comment from Boehringer Ingelheim

Boehringer-Ingelheim commented that peer-reviewed meta-analyses of aggregate published data such as that of Sipahi et al. have their appropriate place in scientific research. However, these publications have well-recognised limitations, including the following:

- the analyses did not include the individual patient data for any of the trials
- the trials were not designed to explore cancer outcomes
- the adjudication of cancer diagnoses was not uniform among included studies
- the analyses did not consider the latency for the malignancies

### TABLE 1. RANDOMISED CONTROLLED TRIALS OF ANGIOTENSIN RECEPTOR BLOCKERS THAT REPORTED CANCER DATA

| Trials with data on new cancer, new specific solid-organ cancers, and cancer death | Mean or median duration, years | Number of patients | Study drug | Control | History of cancer at baseline (%) |
|---|---|---|---|---|---|
| LIFE (2002) Hypertension | 4.8 | 9 193 | Losartan up to 100 mg (n = 4605) | Atenolol up to 100 mg (n = 4588) | NA NA |
| ONTARGET (2008) Cardiovascular disease* or diabetes with end-organ damage | 4.7 | 25 620 | Telmisartan 80 mg (n = 8542) or Telmisartan 80 mg + ramipril 5 mg (n = 8502) | Ramipril 5 mg (n = 8576) | 6.3 6.3 |
| TRANSCEND (2008) ACE inhibitor-intolerant patients with cardiovascular disease* or diabetes, with end-organ damage | 4.7 | 5 926 | Telmisartan 80 mg (n = 2954) | Placebo (n = 2972) | 4.9 4.9 |
| PROFESS (2008) Recent (< 90 days) ischaemic stroke | 2.5 | 20 332 | Telmisartan 80 mg (n = 10146) | Placebo (n = 10186) | NA NA |

**Table continued...**

ACE = angiotensin converting enzyme. NA = not available. *Includes coronary, peripheral, or cerebrovascular disease
Breast cancer†

With background ACE-inhibitor treatment

All available trials

Without background ACE-inhibitor treatment

With background ACE-inhibitor treatment

All available trials

Prostate cancer*

Without background ACE-inhibitor treatment

With background ACE-inhibitor treatment

Lung cancer

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The Cardiovascular Journal of Africa obtained comment from Dr Carl Lombard, director of the Biostatistics Unit at the South African Medical Research Council (MRC) and Dr Adam Nosworthy, senior specialist physician and medical oncologist, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, and clinical advisor to the South African Oncology Consortium. They reviewed the published and Boehringer-Ingelheim data for the Journal, and their comments are presented on the study participants of these trials (Fig. 1, Table 3).

Comment from Dr Carl Lombard on Boehringer-Ingelheim analysis

Systematic reviews, which evaluate different trials around the same question often lead to a formal analysis of the relevant information through a meta-analysis. This is often a crude analysis since only the summarised data from trials are available from the publications.

The methodology of meta-analysis is well established and is a useful tool to pick up small signals of benefit or risk across trials with varying levels and direction of effect sizes. Sipahi et al. utilised the meta-analysis methodology to look at the risk of solid-organ cancers involving patient-level information on the anal yses did not take into account the effect of gender, age, smoking or other known risk factors for malignancies.

Boehringer-Ingelheim had conducted a comprehensive internal safety data analysis including internal malignancy data, which has formed part of the submission package to regulatory bodies since 2008. This analysis includes patient level time-to-event data, which are presented as malignancies per 100 patient years, and no statistically significant difference was observed.

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The information provided across the three trials is differential and limited, which does not allow an appropriate pooled analysis across them. For the TRANSCEND and ONTARGET trials for example, the patient years of follow up is absent, whereas it is provided for the PROFESSION trial. The report reviews the findings published by Sipahi et al. in the 14 June issue of the Lancet, which does not allow an appropriate pooled analysis for overall malignancies, similar to that done by Sipahi et al., the following was found:

1. In all three trials [PROFESSION (telmisartan vs placebo), ONTARGET (telmisartan vs placebo), ONTARGET (telmisartan + ramipril, telmisartan vs ramipril)], the incidence rate ratio was 1.07; 95% CI: 0.99–1.14.

2. With background ACE inhibitor treatment [ONTARGET (telmisartan + ramipril vs ramipril)], the incidence rate ratio was 1.14; 95% CI: 1.03–1.16.

3. Without background ACE inhibitor treatment [PROFESSION (telmisartan vs placebo), TRANSCEND (telmisartan vs placebo), ONTARGET (telmisartan vs ramipril)], the incidence rate ratio was 1.03; 95% CI: 0.96–1.12.

These analyses still have some limitations in that they utilise only patient follow up and do not adjust for latency and other confounders. However, the comparisons are between large groups of patients that have been properly randomised, and with the same intensity of follow up and malignancy ascertainment.

From analysis 3 in which monotherapy telmisartan was compared to either placebo or ramipril, there is no evidence of risk for overall malignancy with regard to this product. With regard to the telmisartan/ramipril combination arm, there is evidence of risk with regard to the incidence of overall malignancies.

The conclusion made by Boehringer-Ingelheim in their safety report is therefore objective: ‘There was a modest imbalance in malignancies seen in some of the recently completed cardiovascular outcome studies with telmisartan. This imbalance was primarily in the telmisartan/ramipril combination arm, there is evidence of risk with regard to the incidence of overall malignancies.

The findings published by Sipahi et al. in the 14 June issue of the Lancet raise the concern of most doctors involved in clinical trials. (1) Do the treatments intended to offer benefit result in long-term harm to patients? (2) The latest trend of regulatory bodies to grant fast-track approval to new medications needs to be carefully reviewed.

In an attempt to offer patients the latest

![Fig. 1. Fatal and non-fatal malignancies: ONTARGET and TRANSCEND](image-url)
benefits, are we doing more harm than good in the long run? Having said that, the inferences made from the Sipahi et al.1 study that the risk of cancer is increased in patients taking ARBs is concerning to say the least.

The most important tenant of clinical trials is to determine which statistical endpoints need to be defined prior to commencing any study, and any post-hoc analysis needs to be treated with the contempt that it deserves. To group a number of studies involving the ARBs (meta-analysis) and to extrapolate that there is an increased incidence of cancer in certain groups of patients is bad medical practice. Randomised evidence in patients using ARBs in a retrospective analysis of numerous studies, yet a medication that is used widely and is known to have far greater impact on the development of breast cancer in women is prescribed in far greater numbers on a daily basis by doctors around the world – oestrogen replacement therapy – without as much as a mention in widely read medical journals!

C Lombard, Biostatistics Unit, Medical Research Council; Dr Adam Nosworthy, oncologist, Donald Gordon Oncology Centre; J Aalbers, Special Assignments Editor

4. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang J. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Published online June 14, 2010 DOI:10.1016/j.heart.2010.05.008.

5. Nissen SE. Comment: Angiotensin-receptor blockers and cancer: urgent regulatory review needed. Published online. June 14 2010;DOI:10.1016/j.heart.2010.05.008.

Drug Trends in Cardiology

FDA committee unanimously recommends approval of dabigatran etexilate for stroke prevention in atrial fibrillation

The US Food and Drug Administration (FDA) Cardiovascular and Renal Drugs Advisory Committee recently voted 9 to 0 in favour of recommending dabigatran etexilate for stroke prevention in patients with atrial fibrillation (AF).

For decades, vitamin K antagonists such as warfarin have been the most efficacious therapeutic option for stroke prevention in AF. Current recommendations for patients with non-valvular atrial fibrillation treated with warfarin recommend maintaining an international normalised ratio (INR) in the range of 2.0–3.0 through frequent blood monitoring and dose adjustments, which can be challenging for physicians and patients.

In RE-LY®, dabigatran etexilate demonstrated efficacy without the need for ongoing INR monitoring or dose adjustments. Furthermore, there were no food restrictions on those taking dabigatran in RE-LY®. A total of 6.3 million people in the USA, Japan, Germany, Italy, France, UK and Spain were living with AF in 2007 and this is expected to increase to 7.5 million by 2017, primarily due to the ageing population.1

‘We are pleased with the committee’s recommendation, which marks an important step in advancing care for patients with atrial fibrillation’, said Prof Klaus Dugi, Corporate Senior Vice President Medicine, Boehringer Ingelheim. ‘We believe dabigatran etexilate will offer patients and doctors the first new treatment option for stroke prevention in atrial fibrillation in more than 50 years. We look forward to working with the FDA as it finalises its review of dabigatran.’

Pradaxa (75 and 110 mg) is currently only registered in South Africa for the prevention of venous thromboembolic events in patients who have undergone hip- and knee-replacement surgery. For full prescribing information refer to the package insert approved by the Medicines Regulatory Authority.

For more information visit www.boehringer-ingelheim.com, or contact Sue Thomas, Medical Information Manager on tel: +270(11) 348-2514 or e-mail: sue.thomas@boehringer-ingelheim.com

J Aalbers, A Bryer, E Klug

1. Benyoucef S, Hughes M, Mehta N. Atrial fibrillation. Decision Resources, December 2008.