



## **Angiotensin Receptor Blockers and the Risk of Cancer**

### **Statement from the British Hypertension Society July 2010**

Angiotensin receptor blockers (ARBs) are a commonly used medication to treat hypertension, heart failure and renal disease, with millions of patients treated with these medications world-wide. The ARBs have been extensively studied in cardiovascular and renal outcome trials and have been found to have broadly similar efficacy to angiotensin converting enzyme inhibitors (ACE-inhibitors) at preventing cardiovascular and renal events but with the advantage of better tolerability. Consequently, current guidance in the U.K. recommends the use of ARBs for the treatment of hypertension in patients intolerant of ACE-inhibitors<sup>1</sup>.

A recent publication in the journal *Lancet Oncology*<sup>2</sup> has reported that ARBs may be associated with a modestly increased risk of incident cancer. This finding has received much publicity and has caused alarm for physicians and their patients. The *Lancet Oncology* report was based on a meta-analysis of some of the randomised clinical outcome trials evaluating ARBs versus other drugs or placebo. The authors noted that in patients randomised to treatment with ARBs, there was an 8% increased risk of new cancers versus patients randomised to alternative therapies and/or placebo (confidence interval 1.01 – 1.15). In studies where cancer was a pre-specified clinical trial end-point, the increased risk of new cancer was reported to be 11% (CI 1.04 – 1.18). Analysis of solid organ cancers suggested that only lung cancer was significantly higher in patients receiving ARBs (relative risk 1.25, CI: 1.05 – 1.49).

At face value, these findings are alarming but there are several important factors to consider before accepting them as sufficiently robust and important to warrant a change in the clinical use of ARBs. Clinical trials are designed and powered to assess very specific and focussed clinical questions. There is a real danger in subsequently interrogating data-bases to examine alternative hypotheses. Put simply, the more analyses you do, the greater the chance of finding a statistical difference between treatment groups. Doctors may recall earlier reports of increased incidence risk cancer and gastrointestinal bleeding associated with treatment with beta-blockers and later with calcium channel blockers that was subsequently shown to be erroneous by later large scale trials. Similar concerns emerged regarding statins which were also allayed by large scale trials. This is not to belittle the importance of continued vigilance with regard to drug safety, even for established treatments. Drug safety is of paramount importance and it is reassuring that the data from large clinical trials regarding efficacy and safety is carefully reviewed by international regulatory agencies. To date, this rigorous analysis has indicated no signal of harm related to incident cancers associated with ARB therapy in specific trials.

There are also the mechanistic aspects to consider. The suggestion that ARBs might “cause cancer” in the typical duration of a clinical trial (usually less than 5 years) is a surprise, mindful of the fact that there is usually considerable latency in the evolution of cancer such that many recognised causes of cancer (e.g. smoking) would not be expected to exert their effect in such a short time frame. One

might also have expected a signal of cancer risk to have emerged from the many toxicity studies undertaken with these agents prior to studies in man.

The Lancet Oncology report did not contain all of the available data on incident cancer from clinical trials with ARBs and analyses are now ongoing to comprehensively assess all available data. This will no doubt lead to further publications and more robust clarification in the near future. Precedent (e.g. CCBs and statins, see above) suggests such improved analyses often remove original spurious concerns.

In the meantime, what should doctors and their patients do? The authors of the Lancet Oncology paper acknowledge the limitations of their analysis and uncertainty regarding the significance of their findings. Our recommendation is that until more comprehensive analyses have been completed, this single study alone is not sufficient to warrant any change in current clinical recommendations of practice regarding the use of ARBs.

#### **References:**

1. Clinical guideline 34: hypertension: management of hypertension in adults in primary care: partial update: <http://www.nice.org.uk/CG034guidance>.
2. Ilke Sipahi, et al. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet, online publication 14<sup>th</sup> June 2010;