BMJ

*BMJ* 2011;342:d2193 doi: 10.1136/bmj.d2193



EDITORIALS

# Angiotensin receptor blockers and cardiovascular outcomes

## Robust evidence refutes previous suggestions of an increased risk

F D Richard Hobbs *professor of primary healthcare*

Department of Primary Health Care, University of Oxford, Oxford OX1 2ET, UK

In the linked systematic review and meta-analysis (doi:10.1136/bmj.d2234), Bangalore and colleagues assess cardiovascular and other outcomes associated with angiotensin receptor blockers (ARBs). They found firm evidence to refute previous concerns that these drugs increase the risk of myocardial infarction. They also found that compared with controls, ARBs reduce the risk of stroke, heart failure, and new onset diabetes.[1]

In balancing risk against benefit health systems commonly raise safety concerns about drugs in common use. Such concerns may stem from the clear demonstration of catastrophic risk, such as was identified for thalidomide, and result in immediate and essential withdrawal of the drug from the market. Withdrawal can also be voluntary, as for drugs that do not pose a specific risk but have no advantages over competitor products. The cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs rofecoxib and valdecoxib, which resulted in greater use of non-selective non-steroidal anti-inflammatory drugs plus proton pump inhibitors, provide such an example.[2]

Some drugs that were rapidly withdrawn on safety grounds would have best been withdrawn gradually or not at all. An example of this is the precipitate 1995 withdrawal of third generation oral combined contraceptives (because of a 1.7 relative risk but small increase in absolute risk of thrombosis), which triggered public panic that extended to "safer" established contraceptives and resulted in a huge temporary increase in unwanted pregnancies and 6198 more abortions (a 16% rise) in the United Kingdom in the three months after the scare.[3] Caution about recent evidence of a possible increased risk of thrombosis with combined oral contraceptives containing drospirenone compared with those containing levonorgestrol will hopefully avoid similar safety scares.[4]

There is even the irresponsible scenario of safety concerns without merit, as exemplified by the false link between triple immunisation and autism. Although all these concerns potentially result in a safer range of evidence based treatments, they also undermine public confidence in the ability of companies to produce safe drugs, of health systems to regulate drugs safely, and of doctors to prescribe safe drugs (only after fully discussing risks and benefits with their patients). The principle of "first do no harm" works both ways—clinicians need to be sure of safety as well as efficacy in presenting treatment choices, to avoid direct harm, but they also need to ensure that these decisions are based on reliable evidence, to avoid indirect harm.

So where does this leave the purported increased risk of myocardial infarction with ARBs? This risk was first suggested after the VALUE trial showed that the ARB valsartan, when compared with the long acting calcium channel blocker amlodipine, did not reduce mortality and morbidity from cardiovascular disease (the powered primary combined outcome of the study) but was associated with a significant 19% relative increase in the incidence of myocardial infarction.[5] This last under-powered observation (which more accurately may have shown that valsartan reduced myocardial infarction less than amlodipine, rather than necessarily increasing it) prompted negative comparisons between ARBs and angiotensin converting enzyme inhibitors in particular. A critical editorial in the *BMJ* used selective reporting of different secondary end points from six other ARB trials against differing comparators to support the main message that clinicians may need to discuss with patients "the unexpected effects of ARBs on myocardial infarction" before prescribing them.[6]

It has taken seven years for a reliable assessment of this specific risk to emerge in the *BMJ*,[1] in a series of meta-analyses of the main ARB trials. The authors have conducted a rigorous systematic review, with appropriate inclusion and exclusion criteria. They have also subjected the data synthesised from these trials to standard meta-analytical methods and controlled for their multiple interim analyses using trial sequential monitoring. Their results from 37 trials and nearly half a million patient years of follow-up provide reassurance that these earlier observations from single trials were probably spurious, with the pooled data showing no increased risk for myocardial infarction against controls (relative risk 0.99, 95% confidence interval 0.92 to 1.07), whether against active comparators or placebo. The data on this outcome are reliable even down to a relative risk increase as low as 7.5%. Similarly, ARBs were not associated with a relative increase risk of death, cardiovascular

f.d.r.hobbs@bham.ac.uk

death, or angina compared with controls, again whether active or placebo. In contrast, ARBs were associated with a 10% reduced risk of stroke, 13% reduced risk of heart failure, and 15% reduced risk of new onset diabetes compared with controls.

It would be interesting to know how many clinicians have debated the speculative risk of myocardial infarction related to ARBs with their patients since the controversy emerged. These new data, along with earlier meta-analyses,[7 8 9 10] should provide reassurance that ARBs are no better or worse than their comparators with regard to death and myocardial infarction. However, they seem to offer additional benefits in terms of reduced risk of stroke, heart failure, and incidence of diabetes. These modest relative benefits can be reliably discussed alongside patient preferences without cost implications because the most commonly prescribed ARBs are already generic or will be by 2012. Although clinicians need guidance on which drugs are the most cost effective treatments of choice, most notably from the National Institute for Health and Clinical Excellence in the UK, better information on relative benefits or limitations of drugs within and between classes will continue to be of value.

Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; he has received occasional fees and expenses from companies that market products for treating cardiovascular disease (including Takeda, Astra-Zeneca, Merck, and Novartis), including ARBs, and for speaking at a variety of scientific congresses; these talks have been on general matters relating to risk of cardiovascular disease, and where talks have included data on ARBs this has been in relation to their licensed indications in heart failure; he has been involved with generating guidelines on cardiovascular disease risk reduction for various medical societies.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. *BMJ* 2011;342:d2234.
2 Sun SX, Lee KY, Bertram CT, Goldstein JL. Withdrawal of cox-2 inhibitors rofecoxib and valdecoxib: impact on NSAID and PPI prescriptions and expenditures. *Curr Med Res Opin* 2007;8:1859-66.
3 Drife JO. The third generation pill controversy ("continued"): the risks are still small compared with those of pregnancy. *BMJ* 2001;323:119-20.
4 Dunn N. The risk of deep venous thrombosis with oral contraceptives containing drospirenone. *BMJ* 2011;342:d2519.
5 Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al; 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;363:2022-31.
6 Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. *BMJ* 2004;329:1248-9.
7 Turnbull F, Neal B, Algert C, Chalmers J, Woodward M, MacMahon S. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527-35.
8 Blood Pressure Lowering Treatment Trialists Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;356:1955-64.
9 Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. *Ann Intern Med* 2008;148:16-29.
10 Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007;369:201-7.

Cite this as: *BMJ* 2011;342:d2193