

Drug Trends in Cardiology

ARBs for cardiovascular and renal protection in high-risk patients

The contribution of recent trials such as the extensive ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) 'a thorough, double-blind, prospective, randomised trial, which documents the equal-outcome efficacy of an ARB (telmisartan) and an ACE inhibitor in a high-risk population' is noted in a recent meta-analysis of ARBs.¹

Among ARBs, telmisartan is further differentiated by both its pharmacokinetic and pharmacodynamic properties.² It has a longer half-life and higher lipophilicity than other agents in the class.

Focus on ONTARGET: cardiovascular protection in high-risk patients without heart failure

The findings from the ONTARGET study showed that telmisartan 80 mg per day was as efficacious as the proven dosage of ramipril (10 mg/day) in reducing the risk of cardiovascular death, myocardial infarction, stroke and hospitalisation for heart failure in a broad cross-section of high-risk cardiovascular patients. It achieved these results with far fewer side effects, resulting in significantly fewer patients discontinuing therapy.³

The ONTARGET study was designed to measure the effects of ramipril, telmisartan or a combination of the two drugs in patients over the age of 55 years. It recruited and randomised 25 620 patients over 18 months at 733 centres in 40 countries, including South Africa. These patients all had coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage.

Characteristics of the patients were similar in the three groups, which included 27% women, 75% of patients had coronary artery disease, 69% had hypertension, 38% had diabetes and 21% had stroke or transient ischaemic attack. The mean age was 66.4 years. Interestingly, while the majority of patients (70%) were Caucasian/European, there was a good

representation of patients of Asian (15%), Latin (9%) and black African (2%) origins.

Prof Yusuf, professor of Medicine and director of the Population Health Research Institute at McMaster University, Ontario, Canada, pointed out when the ONTARGET results were announced, that this comparative head-to-head trial of telmisartan 80 mg and ramipril 10 mg was designed to establish equivalence firstly (in statistical terms referred to as non-inferiority), and to provide clinically relevant data by choosing the usual dose of telmisartan and the proven dose of ramipril, based on the HOPE study. In addition, ONTARGET sought to answer the provocative question of whether the combination of an ACE inhibitor and an angiotensin receptor blocker would work for these high-risk patients and provide further benefit, as it does for patients with heart failure.

Comparison of telmisartan and ramipril

The ONTARGET results showed that telmisartan (Micardis) therapy was as effective as ramipril in each component of the composite outcome, which included death from cardiovascular causes, myocardial infarction, stroke or hospitalisation for heart failure. The composite outcome occurred in 1 412 (16.5%) patients in the ramipril-alone treated group compared to 1 423 (16.7%) patients in the telmisartan-alone treated group.

There was no significant difference in the total number of deaths between the ramipril and telmisartan groups; 1 014 and 989 deaths, respectively. 'Telmisartan was clearly non-inferior, as the confidence interval for the relative risk of the primary outcome was well below the prior established upper boundary of equivalence', Prof Yusuf stressed. With regard to secondary outcomes, there were also no significant differences in the telmisartan-alone compared to the ramipril group.

Telmisartan therapy did, however,

result in slightly improved blood pressure control, with somewhat lower blood pressure levels than those achieved in the ramipril-alone group. Before the run-in period, the mean blood pressure was 141.8/82.1 mmHg. At six weeks, the mean blood pressure was reduced by 6.4/4.3 mmHg in the ramipril-alone group, compared to 6.9/5.2 mmHg in the telmisartan-alone group. Although the blood pressures in the telmisartan group remained slightly lower throughout the study, the difference was not significant, and adjustment for this did not affect outcomes.

'This study is of significant clinical importance because it demonstrates that telmisartan is an effective and safe alternative to ramipril. This means both patients and physicians have choices and can use telmisartan where appropriate with a high degree of confidence. While we cannot be sure what we will see with other ARBs, with telmisartan, clinicians now know its efficacy and its tolerability', Prof Yusuf concluded.

Renal protection

The evidence supporting RAS blockade, and especially the use of ARBs in patients with type 2 diabetes and incipient and overt nephropathy continues to grow.

The Incipient to Overt Angiotensin II receptor blocker, Telmisartan, Investigation On type 2 diabetic Nephropathy (INNOVATION)⁴ study has shown that telmisartan delayed the transition from incipient to overt nephropathy in Japanese type 2 diabetes subjects, an effect that was only partly related to blood pressure control.

A clinical study conducted in patients with type 2 diabetes and overt proteinuria compared the renoprotective effect of telmisartan with that of losartan on a background of antihypertensive intervention as required to ensure similar blood pressure control [A trial to compare telmisartan 40 mg titrated to 80 mg versus losartan 100 mg in hypertensive type 2

Diabetic patients with Overt nephropathy (AMADEO)].⁵ In this one-year, prospective, double-blind study, telmisartan provided greater reduction in proteinuria compared with losartan.

Prof George Bakris of the Department of Medicine, Rush University Centre, Illinois, USA, pointed out that the ultimate test of the benefit of an antihypertensive agent is its ability to reduce renal and cardiovascular endpoints.⁶

J Aalbers, Specialist Assignments Editor

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. *Br Med J* 2011; **342**: d2234. DOI: 10.1136/bmj.d2234.
 2. Munger MA. Use of angiotensin receptor blockers in cardiovascular protection. Current evidence and future directions. *Pharmacy Therapeut* 2011; **36**(1): 22–40.
 3. ONTARGET proves telmisartan efficacy compared to ramipril in cardiovascular protection of patients at high risk and without heart failure. *Cardiovasc J Afr* 2008; **19**(2): 108–109.
 4. The Innovation Study Group. Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. *Diabetes Care* 2007; **30**(60): 1–2.
 5. Bakris G, *et al.* Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. *Kidney International* May 2008. DOI: 10.1038/ki.2008.204.
 6. Renal and stroke protection in hypertensive patients at CV risk. *Cardiovasc J Afr* 2007; **18**: 337–340.
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