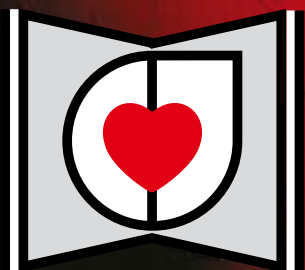


**PEER-REVIEWED JOURNAL FOR THE
PAN AFRICAN SOCIETY OF CARDIOLOGY AND FOR
ASSOCIATES WORKING IN CLINICAL AND
LABORATORY CIRCULATION DISORDERS**

CARDIOVASCULAR JOURNAL OF AFRICA

**ONTARGET LANDMARK TRIAL
PRIMARY RESULTS**



VOL 19, NO 2, MARCH/APRIL 2008
www.cvja.co.za

ONTARGET proves telmisartan efficacy compared to ramipril in cardiovascular protection of patients at high risk and without heart failure

Telmisartan now has the status of proven drug therapy in the prevention of cardiovascular events in patients at high risk for cardiovascular disease, and should be regarded as the drug of choice for these patients, considering both its efficacy and tolerability, according to the ONTARGET trial leader Prof Salim Yusuf. He released the results of this pivotal angiotensin receptor blocker (ARB) trial at the American College of Cardiology (ACC) meeting in Chicago yesterday.

The findings from the ONTARGET study show 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 (Fig. 1).

The ONTARGET study (the ONGoing

Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) 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 CAD, 69% had hypertension, 38% had diabetes and 21% had stroke or TIA. 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.

The results of the trial have been long awaited by the cardiovascular commu-

nity, as this is the first outcome-based study of the role of ARBs in this patient population. It was developed to further explore questions that emerged after the Heart Outcomes Prevention Evaluation trial (HOPE),¹ which showed that ramipril reduced cardiovascular death, myocardial infarction, stroke and heart failure in these high-risk patients. However, in HOPE and in subsequent ACE inhibitor studies, a significant number of patients were unable to tolerate these ACE inhibitors due to cough, hypotension or angioneurotic oedema.

Prof Yusuf, professor of Medicine and director of the Population Health Research Institute at McMaster University, Ontario, Canada noted at the outset of his presentation on ONTARGET at the late-breaking clinical trial session that ACE inhibitors are not tolerated by 15 to 25% of patients. 'It is important to note when looking at the fact that telmisartan was better accepted and tolerated from the start and

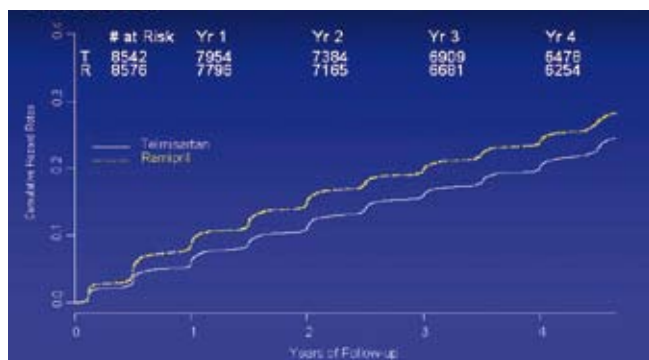


Fig. 1. Time to permanent discontinuation of study medication.

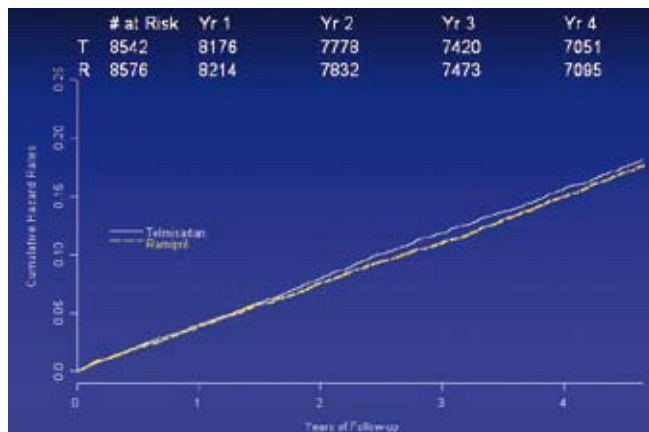


Fig. 2. Time to primary outcome.

TABLE 1. SECONDARY AND OTHER OUTCOMES²

Outcome	Ramipril (n = 8576)	Telmisartan (n = 8542)
Revascularisation	1269 (14.8%)	1290 (15.1%)
Hospitalisation for angina	925 (10.8%)	954 (11.2%)
Worsening or new angina	567 (6.6%)	536 (6.3%)
New diagnosis of diabetes	366 (6.7%)	399 (7.5%)
Any heart failure	514 (6.0%)	537 (6.3%)
New atrial fibrillation	570 (6.9%)	550 (6.7%)
Renal impairment	871 (10.2%)	906 (10.6%)
Renal failure requiring dialysis	48 (0.6%)	52 (0.6%)

Amended from *N Engl J Med* 2008; 358(15): 1554.

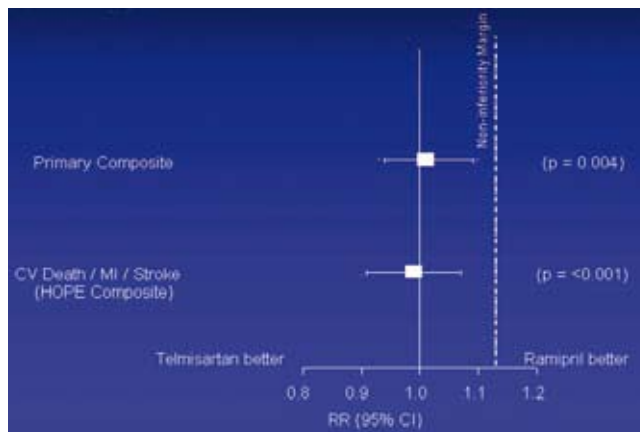


Fig. 3. ONTARGET non-inferiority comparison.

throughout the study, that the tolerability advantages over ramipril will be even better for telmisartan in everyday clinical practice because ACE-intolerant patients were excluded during the run-in period of ONTARGET and were then taken up in the TRANSCEND trial,' he stressed.

Prof Yusuf noted 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.

Telmisartan and ramipril comparison

The ONTARGET results show 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.² There was no signifi-

cant difference in the total number of deaths between the ramipril and telmisartan groups; 1 014 and 989 deaths respectively (Fig. 2).

'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 (Fig 3). With regard to secondary outcomes, there were also no significant differences in the telmisartan-alone compared to the ramipril group (Table 1).

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.

Combination therapy results

Surprisingly, the combination of the two drugs in dual renin-angiotensin blockade was associated with more adverse events without an increase in benefit.

'Contrary to our expectations there was no incremental benefit for the combination therapy and there were some concerns over safety related to renal impairment. Data relating to microalbuminuria with regard to some 3 000 patients are currently being analysed and results will be available within six weeks', Prof Yusuf promised. 'Currently, I would not recommend combination therapy using dual blockade of the renin-angiotensin system for these high-risk patients with cardiovascular, cerebrovascular or diabetic disease' he added.

Conclusion

'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.

1. Pfeffer MA, Mc Murray JJ, *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. *N Eng J Med* 2003; **349**: 1893–1906.
2. The ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Eng J Med* 2008; **358**(15): 1547–1559.

South African cardiologists comment on the study

Dr Shirley Middlemost
*Cardiologist, private practice,
Somerset West*

I find it very reassuring to know that this ARB is effective and provides comparable protection to the ACE inhibitor of choice for these patients. What really impressed me was the fact that telmisartan was better tolerated than ramipril, even in the patient population of this study, which excluded ACE-intolerant patients, and in fact was based on ACE tolerance as an inclusive criterion following the run-in period of the study.

Previously in my practice when I had to switch a patient from an ACE inhibitor to an ARB because of intolerance, I felt unsure as to whether the patient was getting optimal protection. This doubt has been convincingly removed from my mind with regard to telmisartan.

I also like the fact that the data from this trial are robust and, unlike HOPE where there was a great deal of discussion as to whether some of the benefit seen with ramipril was due to the better blood pressure lowering achieved with the drug, in ONTARGET we don't have

this confounding factor to deal with.

Certainly I will use telmisartan first for patients in this group, as the drug is better tolerated, and this will help to ensure better compliance.

It's interesting to note that ramipril was given in the evening in the HOPE study and it achieved a blood pressure lowering of 3/2 mmHg. In ONTARGET, ramipril was given in the morning, with greater BP reduction but with the same overall protective result as in the HOPE trial, removing a lingering doubt in one's mind about this aspect also.

Prof Brian Rayner

UCT Department of Medicine and director of the Hypertension Clinic, Groote Schuur Hospital

ONTARGET will influence clinical practice for years to come. It provides clear evidence that, in this group of patients, there is no difference in the benefits achieved with telmisartan as the selected candidate, or a proven ACE inhibitor, ramipril. The controversy surrounding the issue of the increased risk of myocardial infarction associated with ARBs has been resolved by the ONTARGET results and there is now no evidence that there is any difference between telmisartan and ramipril in this regard.

We must keep in mind the group of patients being treated in ONTARGET. They all had cardiovascular disease and most likely had extensive damage to their vascular systems. I am not surprised that the combination of an ARB and an ACE

inhibitor did not provide further benefit.

In this group of patients, there would have been numbers with renal arterial disease, for example. Aggressive blood pressure lowering in these patients with dual RAS blockade could have resulted in the renal impairment and hyperkalaemia seen in the trial. We must await the results of subgroup analysis, for example microalbumuria, before we finally assess the role of combination therapy. Also, we must take careful note of the fact that ONTARGET was not a hypertension trial and many of the patients on the combination therapy may have been overtreated.

The importance of telmisartan's PPAR-gamma agonist action is not covered in this study.

In conclusion, physicians may safely prescribe telmisartan as an alternative to an ACE inhibitor for patients at high cardiovascular risk and with the knowledge of increased tolerability. Combination therapy

must not be used in this population group.

Prof Jacques Snyman

Clinical business director at the Healthcorp, South Africa, and clinical pharmacologist and consultant at the University of Pretoria

The study provides solid evidence for the value of telmisartan as an equivalent therapy to ramipril, which is a tough competitor in the ACE inhibitor class. In my view, this is also important news as it will be difficult for funders to opt out of using telmisartan for this group of patients.

I have a high regard for telmisartan's blood pressure-lowering action from its pharmacokinetic properties, in particular its long half-life that ensures efficacy across the 24-hour period required. Now its long-term protective actions and excellent tolerability will place it at a further advantage as first choice for therapy in this high-risk population