



New Frontiers in

CARDIOLOGY

New Perspectives on Cardiovascular Event Prevention in High-risk Patients

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Toronto - In individuals with stable coronary, cerebral or peripheral arterial disease, or end-organ damage related to diabetes, inhibition of the renin angiotensin system (RAS) provides blood pressure-independent protection against cardiovascular (CV) events. The importance of adding a RAS inhibitor to routine therapy in such patients was initially demonstrated with an ACE inhibitor. However, the recent ONTARGET trial demonstrated that the ARB telmisartan is equivalent to ramipril, the index ACE inhibitor, in achieving reductions in this population. Both are effective for reducing CV death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure. It provides a better tolerated alternative to ACE inhibitors, to which 20% to 25% of individuals are intolerant.

Three recently completed trials investigating the vasculoprotective impact of the angiotensin receptor blocker (ARB) telmisartan, collectively including more than 50,000 patients, contributed a wealth of data to the knowledge base on renin-angiotensin system (RAS) inhibition, according to Dr. Salim Yusuf, Professor of Medicine and Director, Population Health Research Institute, McMaster University, Hamilton, Ontario.

The new data provide guidance for managing individuals with stable coronary, cerebral or peripheral arterial disease or end-organ damage related to diabetes. In this population, the expected rate of clinical events such as cardiovascular (CV) death, myocardial infarction (MI), and stroke is about 3% per year. These end-stage events are actually partially driven by activation of RAS, which promotes atherosclerosis and renal impairment through vasoconstriction, sodium retention, smooth muscle cell growth and oxidative stress. Inhibitors of RAS prevent these effects. ACE inhibitors were the first RAS inhibitors, but ARBs achieve similar effects by blocking the AT₁ receptor, which is the final common pathway by which RAS exerts end-stage pathophysiology.

ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) has now proven that either an ACE inhibitor or the ARB telmisartan can be added on top of other proven pharmacological strategies including antiplatelet agents and statin therapy. Beta blockade should be added for patients post-MI or who have heart failure (HF), stressed Dr. Gilles Dagenais, Professor Emeritus and cardiologist, Heart and Lung Institute, Université Laval, Quebec. Intensive lifestyle modification is also recommended.

In high-risk patients without HF or left ventricular (LV) systolic dysfunction, ACE inhibitors significantly reduce all-cause and CV mortality, non-fatal MI, stroke, HF, and coronary artery bypass surgery. A recent meta-analysis of trials including patients with and without HF or LV systolic dysfunction determined ACE inhibitors and ARBs had similar positive effects leading to a reduced risk of stroke, coronary heart disease and HF (Blood Pressure Lowering Treatment Trialists' Collaboration. *J Hypertens* 2007;25(5):951-8).

Until ONTARGET, there was debate over the relative efficacy of ACE inhibitors and ARBs against coronary heart disease. According to Dr. Dagenais, "On the one hand, in the CHARM study, the ARB candesartan was better than placebo in reducing MI. On the other hand, several meta-analyses showed that in contrast to ACE inhibitors, ARBs did not seem to reduce the incidence of MI." A large prospective trial was needed to resolve this issue. The ONTARGET study was undertaken to address the issue of whether an ACE inhibitor, an ARB, or the combination provided greater protection against clinical events in high-risk patients without HF or LV systolic dysfunction.

Evidence from ONTARGET

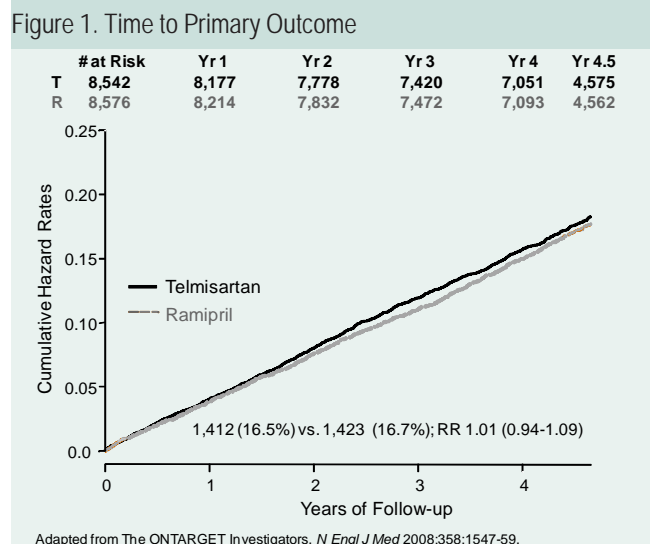
The primary objective of the multinational ONTARGET was to determine whether the ARB telmisartan 80 mg/day would be as effective as ramipril 10 mg/day in reducing the incidence of a composite of first clinical CV events (CV death, nonfatal MI, stroke, or hospitalization for HF) in a high-risk population. Its

second objective was to establish whether the two agents used in combination would be more effective than ramipril alone in reducing the composite end point. To ensure the robustness and clinical relevance of a finding of non-inferiority, the trial design and population were similar to those of the HOPE (Heart Outcomes Prevention Evaluation) trial. Dr. Dagenais explained that the margin of non-inferiority was set at RR 1.13 to mirror the impact of ramipril vs. placebo in the HOPE trial. A randomization of 26,620 high-risk patients ensured that ONTARGET was the largest study ever conducted with an ARB. Patients who were screened for ONTARGET but were deemed unable to tolerate ACE inhibitors were assigned to a parallel trial comparing telmisartan and placebo (i.e. TRANSCEND).

The telmisartan, ramipril and combination therapy arms of the study each included more than 8500 subjects. Most subjects were receiving additional preventive therapies including diuretics (>30%), beta blockers (>50%), statins (>60%) and antiplatelet agents (>80%). Blood pressure was decreased by an average of 6/4.6 mm Hg in the ramipril arm and by 6.9/5.2 mm Hg with telmisartan. A high adherence rate was key to successful completion of the study, Dr. Dagenais added. At the end of the trial, 84.7% and 85.6% of patients in the ramipril and telmisartan groups, respectively, were taking their study medication. At two years, 81.7% of ramipril-treated patients and 88.6% of telmisartan-treated patients were receiving the full dose of their medication.

Establishing Non-Inferiority

CV protection, as measured by the composite primary outcome, was equivalent in patients receiving telmisartan or ramipril over the 56-month study period, Dr. Dagenais stated. As shown in Figure 1, 16.5% of the ACE-inhibitor-treated patients (n=1412) and 16.7% of the ARB-treated individuals (n=1423) experienced a first CV event (RR 1.01, CI: 0.94-1.09, P=0.8). “The 95% upper limit of the CI is 1.09, which is well within the 1.13. So telmisartan was clearly non-inferior to ramipril and, according to the design of the study, this is highly significant.”



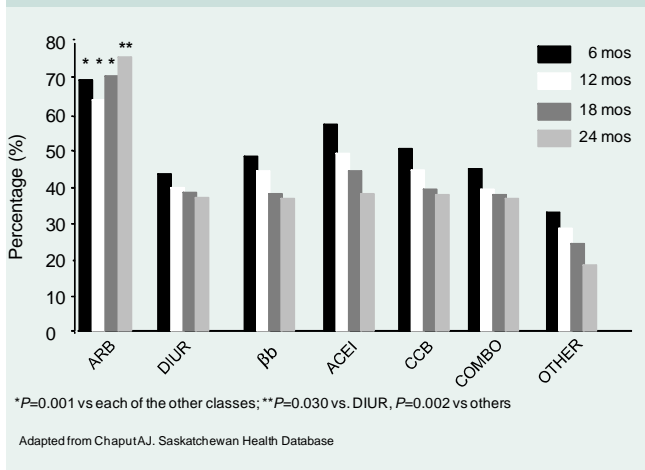
Telmisartan and ramipril also achieved similar reductions in the HOPE composite end point of CV death/MI /stroke. In addition, for each component of the primary end point, “there was no difference [between telmisartan and ramipril] regarding CV mortality, MI, stroke [or] HF hospitalization,” Dr. Dagenais confirmed. Further evidence of the two agents’ clinical equivalence was the similarity in rates of hospitalization for angina, worsening or new angina, revascularization, new atrial fibrillation, development of LV hypertrophy, renal impairment and new-onset diabetes. The ONTARGET results were consistent across prespecified patient subgroups, including patients of both genders, younger patients and the very elderly, those with/without diabetes or hypertension and irrespective of concomitant medications. “This trial is robust because you have a consistent result [in primary and secondary outcomes] and the same thing in the subgroups,” he emphasized. Interestingly, significantly more patients in the telmisartan arm experienced regression of LV hypertrophy by the study’s end (incidence 42.6% vs. 47.5%, P=0.021) and reversion to normoglycemia (22.6% vs. 27.5%, P=0.0256).

Adherence Rates

Given the similarity in clinical outcomes in ONTARGET, the selection of an ACE or ARB for high-risk patients will depend on various factors such as the patient’s condition, physician and patient preference, and tolerability, Dr. Dagenais indicated. Numerous reports, including a recent assessment from the Saskatchewan Health Database (Figure 2), have confirmed that ARBs are more easily tolerated than ACE inhibitors and other antihypertensive agents, and are associated with greater long-term adherence. In ONTARGET, the discontinuation rate was significantly greater in the ramipril arm despite a design that screened patients for ACE inhibitor intolerance. In ONTARGET, only 4.2% of patients on ramipril (1.1% on telmisartan) discontinued therapy for cough, which was dramatically lower than the 15% to 20% reported in other trials and typically seen in clinical practice, Dr. Dagenais remarked. In addition, angioedema, a potentially life-threatening adverse event, occurred in 0.3% of patients receiving ramipril vs. 0.1 of those receiving telmisartan. Hypotension was significantly more common on telmisartan (2.7% vs. 1.7%, RR 1.54, P=0.0001), but serious hypotensive events, such as syncope (RR 1.27, P=0.4850) did not differ significantly.

The actual rates of adherence and, potentially, of outcome might differ outside of a clinical trial. In ONTARGET, physicians were encouraged to monitor their patients closely for adherence and were provided with a protocol for restarting therapy in those who discontinued treatment. In clinical practice, such strategies to encourage adherence are less common, a disadvantage for the less well tolerated therapy. Moreover, both arms were titrated to full assigned doses, while current prescribing practices in Canada suggest that the average dose of ramipril be less than 10 mg, presumably as a result of intolerance.

Figure 2. Adherence Rates of Antihypertensive Medication during Six to 24 Months in Saskatchewan



Combine with Care

The rationale for employing both an ACE inhibitor and an ARB is the prospect of more complete renin-angiotensin-aldosterone system (RAAS) blockade and more effective suppression of clinical events. Some suggestion of benefit was noted in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, in which the combination produced a 15% reduction in the relative risk of CV death and HF hospitalization over ACE inhibitor alone in patients with chronic HF or LV systolic dysfunction. In the VALIANT (Valsartan in Acute MI) study, however, patients with recent MI who received an ARB/ACE inhibitor combination did not experience a greater reduction in CV death, MI or HF over those using only an ACE inhibitor. Similarly, in ONTARGET, the patients receiving both telmisartan and ramipril did not experience a greater reduction in clinical events than those receiving ramipril alone. This group also had a higher incidence of adverse events leading to discontinuation of treatment, including hypotension (RR 2.75, $P<0.001$), syncope (RR 1.95, $P=0.032$), renal impairment (RR 1.59, $P<0.0047$) and diarrhea (RR 3.28, $P<0.001$).

Dr. Koon Teo, Professor of Medicine, McMaster University, and cardiologist, Hamilton Health Sciences Centre, observed that the study investigators tried to ensure patients received maximal doses of both agents; this may have contributed to the adverse event profile. He added that an ACE inhibitor/ARB combination remains an option in patients with HF, but is not recommended for patients at high risk of CV events due to vascular disease or diabetic end-organ damage. In patients in whom combination therapy is employed, careful monitoring of renal function and blood pressure is mandatory.

ACE-intolerant Patients

Performed concurrently with ONTARGET and employing the same composite outcome, TRANSCEND (Telmisartan Randomized Assessment Study in ACE-intolerant Subjects with

Cardiovascular Disease) was designed to determine if telmisartan (80 mg/day) would offer superior CV protection over placebo in 5926 patients identical to the ONTARGET population but unable to tolerate ramipril. As with ONTARGET patients, these subjects were similar to those in the landmark HOPE study; however, TRANSCEND included much larger proportions of women, individuals with hypertension, and patients with a history of stroke/transient ischemic attack, remarked Dr. Jeffrey Probstfield, Professor of Medicine and Director, Clinical Trials Unit, University of Washington, Seattle.

After 56 months, ARB-treated patients had a significantly lower incidence of events constituting the primary outcome in HOPE; the reduction in CV death/MI/stroke was 13% vs. 14.8% ($P=0.048$). This result was primarily driven by reductions in MI (21%) and stroke (17%). The 8% reduction in the primary composite outcome produced by telmisartan was not statistically significant (15.8% vs. 17%, $P=0.216$). Stroke and MI were reduced by 17% and 21%, respectively, in treated patients although these results did not reach statistical significance.

A possible explanation for the rather surprising results was that the trial was underpowered due to a substantially lower event rate than was initially projected (3.7% vs. 5.1% per year). Furthermore, comprehensive background therapy for risk reduction (especially antihypertensive and lipid-lowering agents) was more common during TRANSCEND than HOPE; statin therapies were prescribed almost twice as often in TRANSCEND. As might be expected, patients in the placebo group received more antihypertensive agents (diuretics, beta blockers and calcium channel blockers) than those in the telmisartan arm. The trial’s duration may also have been a factor. A difference in primary outcome rates between the two groups could be observed after about three years of follow-up, Dr. Probstfield indicated. The effect of treatment on HOPE outcomes was evident before two years of follow-up. “From then on, there seemed to be a progressive separation between placebo and telmisartan.”

An interesting finding in TRANSCEND was that fewer patients discontinued telmisartan than placebo. This benefit was attributed to its ability to prevent or delay the addition of less well tolerated agents by participating physicians attempting to control disease risk. The study confirmed that the ARB could be considered for use in patients with high CVD risk who cannot tolerate an ACE inhibitor, he concluded.

RAAS Inhibition in Stroke Patients

The increasing epidemiologic burden and high human costs of stroke and related disease processes are under-recognized, according to Dr. Philip Teal, Professor of Neurology, University of British Columbia, and Director, Stroke Program, Vancouver General Hospital. The incidence of nonfatal stroke is much higher than that of nonfatal MI and hypertension-related small-vessel disease is also contributing to a “tsunami of dementia” in the aged, he indicated.

“There is a lot of evidence for using drugs that act on the RAAS both in primary and secondary prevention of stroke,” Dr. Teal stated. The LIFE (Losartan Intervention for Endpoint Reduction) study showed that over five years, treatment with an ARB reduced the risk of stroke, CV death and MI significantly more than a beta-blocker, despite comparable blood pressure reduction. In ONTARGET, telmisartan was at least as effective as ramipril in reducing stroke incidence (4.3% vs. 4.7%). Secondary prevention has been largely guided by the PROGRESS (Perindopril Protection Against Recurrent Stroke) study, in which perindopril with or without indapamide produced a 28% reduction in recurrent stroke, while combination treatment reduced the risk by 43%. The same two-drug regimen was shown to be safe and effective in reducing stroke and death in the HYVET (Hypertension in the Very Elderly Trial) of patients aged >80 with systolic blood pressure >160 mm Hg. The MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention) trial confirmed that as compared with a calcium channel blocker, an ARB produced a 25% reduction in the relative risk of cerebrovascular events over 3.5 years of follow-up.

In the recent PROFESS (Prevention Regimen For Effectively Avoiding Second Strokes) trial, there was a trend favouring telmisartan over placebo (stroke incidence 8.7% vs. 9.2%) after a relatively short follow-up of 2.5 years. Similar trends were observed for cardiac events and new-onset diabetes, noted Dr. Teal. Post-hoc analysis indicated that telmisartan reduced stroke incidence more effectively over time: after the first six months of the study, the relative risk reduction with treatment increased to 13% ($P=0.004$). Similar to

TRANSCEND, plausible reasons for the lack of statistically significant benefit of the ARB was the relatively greater use of additional antihypertensive medication in the placebo group and the low CV risk of the population studied, Dr. Teal suggested. A positive finding in PROFESS was an 11% reduction in intracranial hemorrhage with the ARB.

All these trials have been taken into account in current Canadian Hypertension Education Program guidelines and inform the clinical management of hypertension in stroke patients, Dr. Teal indicated. “An ARB is a very reasonable alternative [to an ACE inhibitor] in patients with previous stroke.”

Suggestions for Future Research

The ONTARGET trial demonstrated that telmisartan is as effective as ramipril for reducing CV events in high-risk patients. Despite missing their primary end point, the results of TRANSCEND and PROFESS are consistent and promising. TRANSCEND, in particular, demonstrated benefit on the HOPE end point from telmisartan in ACE inhibitor-intolerant patients even on top of modern standards, which have raised the bar for risk reduction. “In the contemporary era it is hard to get a 20% or 30% risk reduction such as we got with HOPE or PROGRESS,” Dr. Yusuf stated. Indeed, as a result of the consistent application of global risk-reducing strategies, Dr. Yusuf suggested that trials must have a longer follow-up than was necessary in the past. “Once we start people on a blood pressure-lowering agent or ASA or statin, we don’t treat them just for five years... Five-year trials are just far too short. The real answer we want is what happens over a lifetime.” □

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