



## Canadian Cardiovascular Congress

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### ACE Inhibitors and ARBs: Compelling Evidence for Rational Comparison Now Available

**Toronto** - Until recently, the debate about the relative value of ACE inhibitors and angiotensin receptor blockers in cardiovascular (CV) risk management has been largely hypothetical. Although both inhibit the renin-angiotensin system (RAS) and both have been associated with a reduced risk of CV events in high-risk patients, there are fundamental differences in their mechanisms of action and comparative data remain relatively limited. Now, after a series of major studies, there is a great deal more clarity about the relative role of these agents. At one of the most clinically useful symposia at this year's CCC, a panel of experts will explain what the controlled trials mean to daily clinical practice. The chair of the program is Dr. Salim Yusuf, professor at McMaster University, who has held a key role in several of the most important studies of RAS inhibition for reducing clinical risk.

***Toronto** – Jusqu'à tout récemment, le débat sur l'utilité relative des inhibiteurs de l'ECA et des antagonistes des récepteurs de l'angiotensine dans la prise en charge du risque cardiovasculaire (CV) était somme toute théorique. Certes, les deux classes inhibent le système rénine-angiotensine (SRA) et diminuent le risque d'événement CV chez les patients très vulnérables, mais il existe des différences fondamentales entre leurs modes d'action respectifs, et les données comparatives demeurent assez limitées. Plusieurs études d'envergure ont permis de mieux définir le rôle de chacun de ces agents. Des experts invités à un symposium – l'un des plus utiles du congrès sur le plan clinique – discuteront de la portée des essais comparatifs dans la pratique clinique quotidienne. Le symposium sera présidé par le Dr. Salim Yusuf, professeur titulaire, McMaster University, qui a joué un rôle clé dans plusieurs études d'importance sur la contribution de l'inhibition du SRA à la réduction du risque clinique.*

By Ted Bosworth

The largest study ever conducted of any kind with an angiotensin receptor blocker (ARB) was a direct comparison of telmisartan to the ACE inhibitor ramipril. Completed earlier this year, the study addressed a question that has been pending for almost a decade: is an ARB less effective, as effective, or more effective than a proven ACE inhibitor for preventing cardiovascular (CV) events in high-risk patients? The data generated by this study provide the latest and largest piece of a puzzle regarding the relative role of ARBs and ACE inhibitors. In this study, called ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), the ARB telmisartan was equivalent in efficacy to the ACE inhibitor ramipril but better tolerated.

“Many general practitioners who participated in the study thought that this was a great result,” reports Dr. Salim Yusuf, the senior ONTARGET investigator when the results were presented earlier this year. The reason is that ARBs are easier to administer than ACE inhibitors because they are better tolerated. Rather than a reasonable alternative in patients who are intolerant to ACE inhibitors, telmisartan joins ramipril as a first-line therapy for preventing CV events in high-risk patients. By confirming equivalent benefits, Dr. Yusuf explains that ONTARGET “tells clinicians they can use telmisartan with confidence.”

How this and other studies defines the relative role of ARBs and ACE inhibitors in CV risk management will be tackled by the lead-off speaker at the symposium, Dr. Gilles Dagenais, Quebec Heart Institute, Université Laval, Quebec City. As chair of the ONTARGET Adjudication Committee and one of the senior investigators of HOPE (Heart Outcomes Protection Evaluation), which provided the framework for ONTARGET, Dr. Dagenais is an appropriate expert. The important lesson of the study was that even though either approach to inhibition of the renin angiotensin system (RAS) was effective, the strategies were not indistinguishable because of the differences in tolerability.

Specifically, although the proportion of patients who reached the composite outcome of myocardial infarction (MI), stroke, death from a CV cause, and hospitalization for heart failure was statistically indistinguishable, the discontinuation rate over the course of the study was significantly greater on ramipril than on telmisartan ( $P=0.02$ ). The increased rate of discontinuations not only included the expected difference in cough (4.1% vs. 1.1%;  $P<0.001$ ), but also the potentially life-threatening effect of angioedema (0.3% vs. 0.1%;  $P=0.04$ ). In typical practice, the differences are likely to be far greater. Not only did the trial include formal guidelines to restart medications discontinued for any reason, but patients with intolerance to ACE inhibitors were excluded from the study.

Tolerability is a critical issue for agents that must be taken indefinitely to continue to provide protection against CV events. In the HOPE trial, which established ACE inhibitors as a standard of care in high risk patients, ramipril was associated with a 22% reduction ( $P<0.001$ ) in the composite outcome of MI, stroke, or death from CV causes relative to placebo in patients at high risk for CV events. The benefit was largely independent of effect on blood pressure, which was well controlled in both groups.

In ONTARGET, which randomized 25,620 patients with coronary artery disease or high-risk diabetes to telmisartan, ramipril, or the combination, the majority had a previous CV event, including a MI in almost half and a stroke in more than 20%. However, a substantial minority had no previous event, allowing telmisartan, ramipril, and the combination to demonstrate protection against primary as well as secondary events. The high-risk population of ONTARGET, like HOPE, is considered representative of the types of individuals commonly seen by general practitioners as well as specialists. Due to the difficulty of managing side effects and monitoring compliance in

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general practice, the identification of a better tolerated therapy is considered a major clinical advantage.

“For the clinician, particularly general practitioners who are often in the position of addressing multiple health issues simultaneously, a better tolerated therapy can be a meaningful advantage,” confirms Dr. Koon Teo, Professor of Medicine (cardiology), McMaster University. Another senior author of ONTARGET and another speaker at the Saturday symposium, Dr. Teo has been assigned to evaluate the evidence for combining an ARB and an ACE inhibitor. Much of his discussion is expected to be based on ONTARGET because it evaluated more than 8000 patients on this combination. There was no added benefit for the primary end point, and there was a significant increase in risk of adverse events even relative to ramipril alone.

“The combination is not considered viable because it produced the most adverse events without an increase in benefit,” Dr. Teo has stated. It has been speculated that the two distinct mechanisms of RAS inhibition might provide additive benefit, but this was not seen for the overall outcome or for any of the secondary outcomes, including protection against renal impairment. These results, especially for target organ damage that would be expected to be most strongly driven by upregulated RAS, were surprising, but they are also important because they provide an evidence-based answer to a long debated question. Some clinicians have been offering ARB/ACE inhibitor combinations in selected patients in anticipation of a favourable result.

“The rates of renal impairment in the telmisartan and ramipril groups did not differ significantly (10.6% vs. 10.2%), but the 13.5% incidence in the combination arm generated a 33% increased risk ( $P<0.001$ ) for this complication,” according to Dr. Teo, who notes that ONTARGET has not supported a combination of RAS inhibitors in any population so far evaluated.

The ONTARGET study demonstrated that telmisartan is as effective as ramipril in high-risk patients who are candidates for either, but a companion study to ONTARGET called TRANSCEND (Telmisartan Randomized Assessment in Study in ACE Intolerant Subjects with Cardiovascular Disease) specifically evaluated the efficacy of telmisartan in patients who are ACE inhibitor-intolerant. This is the topic of a presentation

to be made at the Saturday symposium by Dr. Jeffrey Probstfield, Professor of Medicine, University of Washington, Seattle. Not surprisingly, its benefit relative to placebo in the study population was significant, but Dr. Probstfield will place the results in context of HOPE, the study TRANSCEND most resembles.

On the basis of the HOPE composite outcome, patients randomized to telmisartan in TRANSCEND had a 13% (HR 0.87, 0.76-1.00;  $P=0.048$ ) risk reduction relative to placebo, despite the modifying effects of more aggressive risk management, particularly the use of statins, at baseline in the TRANSCEND population. While more than 50% of the TRANSCEND population were taking a statin at baseline and more than 60% by the end of the study, less than 30% were on statins in HOPE. In addition, 55% were taking beta blockers vs. less than 40% in HOPE, and more than 80% were taking antiplatelet drugs vs. only about 75% in HOPE. In his talk, Dr. Probstfield is expected to place the results of TRANSCEND vs. HOPE in the context of current treatment.

Several new studies, including PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes), have also provided new insight about the efficacy of ARBs and ACE inhibitors in the prevention of stroke. This is the topic of a presentation by Dr. Philip Teal, Professor of Neurology, University of British Columbia, Vancouver, who is expected to explain what the results mean for clinical choices. Indeed, the theme of the entire meeting is clinical relevance as exemplified by the last segment, led by Dr. Yusuf. The exact title is: “Overview of Management of the High-risk Patient with Vascular Disease: Use of Preventive Strategies – Which, When, and in Whom?”

#### Summary

Tonight’s symposium promises to be one of the most important sessions for practical management of high-risk patients. The session is topical because of the enormous quantity of new data that helps determine the relative roles of ARBs and ACE inhibitors in day-to-day practice. The session is not an overview of the data but a specific exercise in making practice-changing, evidence-based data clinically relevant by a panel that includes many of those at the front line of clinical trial design. □

#### Please plan to attend:

“Management of High-risk Patients: Recent Advances and Clinical Implications.” Saturday, October 25, 2008, 18:00-21:00, Room 701 AB.

*This symposium is accredited and co-developed as an Accredited Group Learning Activity under Section 1 of the framework of Continuing Professional Development options as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada (RCPSC).*

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