



Cardiovascular

CONGRESS REPORTER

A Summary of Recent International Meetings

Global Cardiovascular Risk Reduction: Focus on Inhibiting the Renin-Angiotensin System

Based on presentations from the 2008 Canadian Cardiovascular Congress (CCC 2008), October 25 - 29, Toronto, Ontario

REPORTER FOCUS:

Discussed New CHEP Recommendations for ACEI + ARB Combination Among the Highlights of CCC 2008

Managing Cardiovascular Risk and Metabolic Challenges: Treatment Strategies for CV Risk Reduction

Management of High-risk Patients: Recent Advances and Clinical Implications

Multifaceted Approach to Vascular Risks: Where are we Headed?

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The 2008 Canadian Cardiovascular Congress (CCC 2008) was held in Toronto in October. One of the recurrent themes at the Congress was the growing evidence base with agents inhibiting the renin-angiotensin system (RAS). One particular focus on RAS blockade was within the preliminary report of the Canadian Hypertension Education Program's (CHEP) 2009 recommendations.

The most notable change announced by CHEP for 2009 is the recommendation not to use the combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) for the treatment of hypertension, except for patients with concomitant left-ventricular (LV) dysfunction.

The impetus behind this new recommendation was provided by the results of the ONTARGET study,¹ which showed that, among patients who have vascular disease or high-risk diabetes without heart failure, the combination of an ACE inhibitor and an ARB did not confer additional protection against major cardiovascular (CV) events compared to ACE inhibition alone. The investigators also observed an increased risk of hypotensive symptoms, syncope and renal dysfunction with the combination. Although the combination of the two agents is no longer recommended as an option in treating most patients with hypertension, the proceedings of the CCC 2008 did reinforce the fact that ARBs and ACE inhibitors are each integral parts of global CV protection.

Also still an integral part of the CHEP recommendations is an emphasis on the importance of patient adherence to prescribed antihypertensive therapy. Among the recommended ways to enhance adherence to pharmacotherapy are the use of simplified medication regimens (*i.e.*, long-acting once-daily dosing), the use of fixed-dose combination pills to reduce the patient's pill burden, and the use of memory aids such as unit-of-use packaging. Another important consideration in promoting adherence to pharmacotherapy could be the side-effect profile of available agents (opting for agents that are less likely to cause adverse effects).

CCC 2008 satellite symposia: focus on global CV risk reduction. At the CCC 2008, there were three satellite events with similar themes, each of which included an in-depth discussion of the importance of blockade of the RAS. These symposia are reviewed on the following pages.

Managing Cardiovascular Risk and Metabolic Challenges: Treatment Strategies for CV Risk Reduction

This was an interactive learning session in which experts in the field of cardiology, endocrinology and nephrology were able to share their opinions on the appropriate management of four common contributors to global CV risk: dyslipidemia, diabetes, hypertension and renal disease.

Dyslipidemia. Dr. Robert Hegele emphasized that measures known to lower global CV risk have a significant positive impact on dyslipidemia. Smoking cessation and maintenance of a healthy body weight (through appropriate diet and regular physical exercise) were cited as key interventions. In terms of pharmacotherapy, Dr. Hegele

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emphasized that lowering of low-density lipoprotein cholesterol (LDL-C) remains the primary treatment goal for most patients with dyslipidemia. However, he also discussed the need to treat beyond LDL-C, as even patients whose LDL-C is well controlled by statin therapy may have significant residual CV risk.

Traditional risk factors used in the Framingham calculation of CV risk are important, he explained, but do not adequately account for all of the potential risk factors. Non-traditional risk factors, such as high-sensitivity C-reactive protein (hs-CRP), B:AI ratio and intimal-medial thickness (IMT) may also help stratify risk.

Diabetes. Dr. Lawrence A. Leiter used this opportunity to highlight the recommendations of the recently published Canadian Diabetes Association (CDA) 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada.²

Dr. Leiter emphasized that rapid glycemic control is an essential component of global CV risk reduction. He cited the results of long-term follow-up from the UKPDS study, in which patients were initially randomized to conventional or more intensive glycemic control. At a median of 8.5 years

Table 1

Vascular Protection in Diabetes: 2008 CDA Guidelines²

- Individuals with diabetes at high risk for CV events should receive an ACE inhibitor or ARB at doses that have demonstrated vascular protection.
- Low-dose ASA therapy (81-325 mg) may be considered in people with stable CVD. Clopidogrel (75 mg) may be considered in people unable to tolerate ASA. The decision to prescribe antiplatelet therapy for primary prevention of CV events should be based on individual clinical judgment.

after the conclusion of the study, long after early glycemic differences between the groups had been eliminated, those originally assigned to the intensive-control group had significantly lower risk of micro- and macrovascular events, including myocardial infarction (MI) and all-cause mortality, which were not significantly reduced in the initial trial period.

Dr. Leiter also discussed the 2008 CDA guidelines recommendation that all individuals with diabetes be targeted with vascular-protection strategies, including lifestyle modification, achievement and maintenance of a healthy body weight, healthy diet, regular physical activity, smoking cessation, optimization of blood-pressure (BP) control and optimization of glycemic control.

For those people with diabetes who are deemed to be at high risk for CV events, the 2008 CDA guidelines recommend an ACE inhibitor or an ARB at doses that have demonstrated vascular protection (Table 1). ARBs are now deemed to be as effective as ACE inhibitors in the vascular-protection setting largely due to the results of the ONTARGET study,¹ which showed that an ARB was as effective as an ACE inhibitor in protecting against major events among patients at high risk for vascular events.

Renal disease. Dr. Sheldon Tobe discussed the impact of nephropathy on global CV risk, highlighting the fact that deteriorating renal function is directly correlated with an increased risk for CV events.³ The 2008 CDA guidelines state that once global vascular-protection measures are implemented and BP is controlled to target (< 130/80 mmHg), if there is residual proteinuria despite these efforts, it needs to be treated. However, the first two steps should already have a significant impact on renal parameters. Dr. Tobe pointed out that the current recommendations for antihypertensive pharmacotherapy for patients with diabetic nephropathy state that an ACE inhibitor or ARB should be a component of therapy.⁴ In addition, the CDA guidelines recommend that all patients at high risk receive one of these agents.²

Figure 1
ONTARGET Study: Time to Primary Outcome (MI, Stroke, CV death or HF Hospitalization)¹

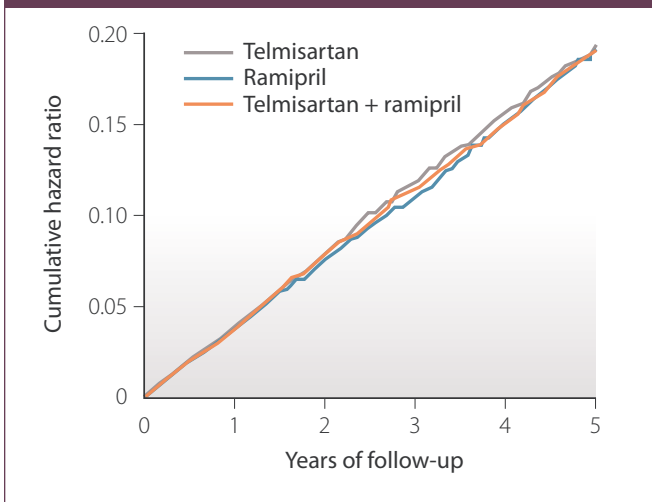
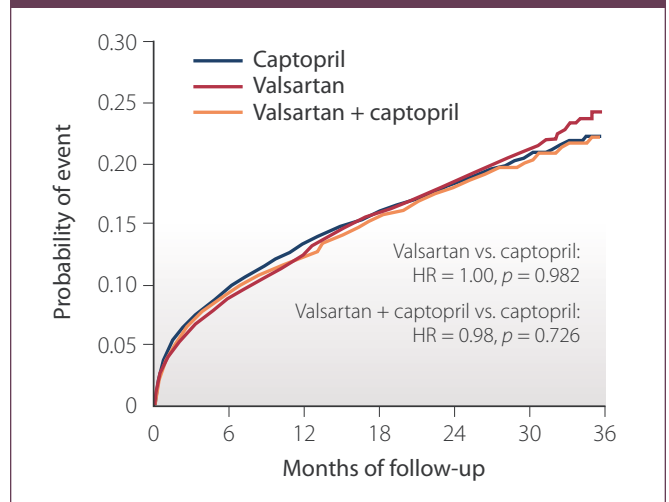


Figure 2
VALIANT: All-cause Mortality in Post-MI Patients with Captopril, Valsartan or their Combination⁹



As Dr. Tobe showed, data from clinical trials are conclusive that these agents are potent antiproteinuric agents in addition to their BP-lowering and vasculoprotective effects, as demonstrated in the IDNT and RENAAL trials.^{5,6} Of note, while the BP effects of ARBs plateau at lower dose levels, a dose-dependent effect on proteinuria continues at higher doses. In the SMART study, patients with diabetic nephropathy were randomized to ARB treatment at standard dose (candesartan 16 mg/d) or at significantly higher doses (64 mg or 128 mg). The investigators reported a significant additional, dose-dependent reduction of proteinuria with the higher doses compared to standard dose.⁷

Management of High-risk Patients: Recent Advances and Clinical Implications

This session's faculty focused on the evolution of evidence with ACE inhibitors and ARBs in a variety of clinical scenarios. The majority of the session was devoted to discussing two parallel studies, ONTARGET and TRANSCEND.

ONTARGET. Dr. Gilles Dagenais focused on the results of the ONTARGET study, which compared an ARB to an ACE inhibitor or the combination of both agents among patients with vascular disease or high-risk diabetes without heart failure.¹ There were two major and distinct analyses in the ONTARGET trial: 1) to determine whether the ARB telmisartan (80 mg daily) is non-inferior to the ACE inhibitor ramipril (10 mg daily); and 2) to determine whether the combination of both agents is more effective than ramipril alone. The primary outcome was a composite of CV death, MI, stroke or hospitalization for heart failure.

For the first analysis, as discussed above in the context of the new CDA recommendations for vascular protection, the results showed that telmisartan was indeed as effective as ramipril. At a median follow-up of 56 months, the primary outcome had occurred in 16.5% of ramipril patients and 16.7% of telmisartan patients. The difference between the groups was insignificant (relative risk [RR] 1.01; 95% confidence interval [CI] 0.94 to 1.09; Figure 1) and well within the prespecified margin for noninferiority of telmisartan vs. ramipril.

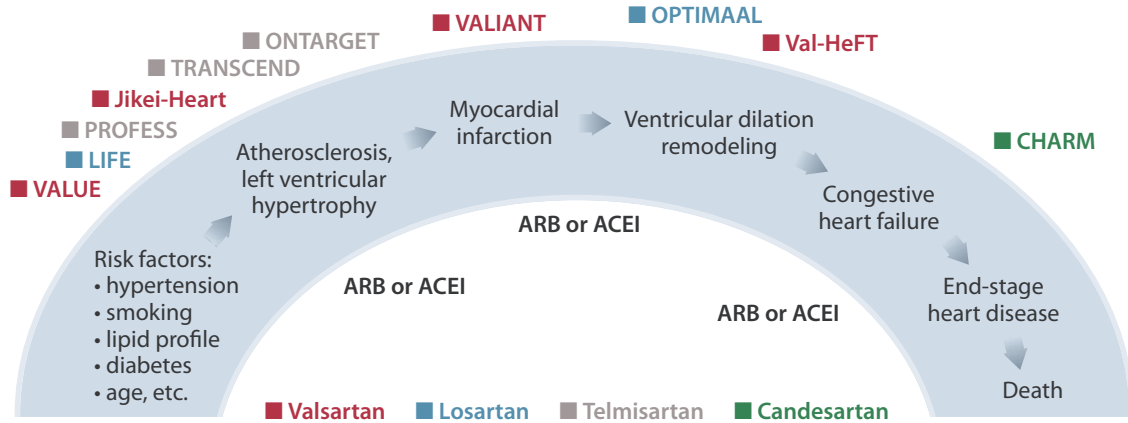
Dr. Dagenais also showed that there were no significant differences between groups for any of the individual components of the primary endpoint, any other prespecified secondary CV and renal endpoints or all-cause mortality.

With respect to the second analysis of the ONTARGET study—the efficacy of the ARB + ACE inhibitor combination compared to ACE inhibitor monotherapy—Dr. Koon Teo presented the results. First, he provided a brief review of other studies that have examined the combination of an ACE inhibitor with an ARB. In the CHARM-Added study, for example, adding candesartan to existing ACE inhibitor therapy significantly reduced the incidence of the primary outcome (CV death or hospitalization for heart failure) among patients with chronic heart failure.⁸

In VALIANT, a study of valsartan, captopril or their combination in post-MI patients, valsartan monotherapy was found to be as effective as captopril in offering CV protection (Figure 2).⁹ However, the combination of the two agents was not statistically different from captopril monotherapy.

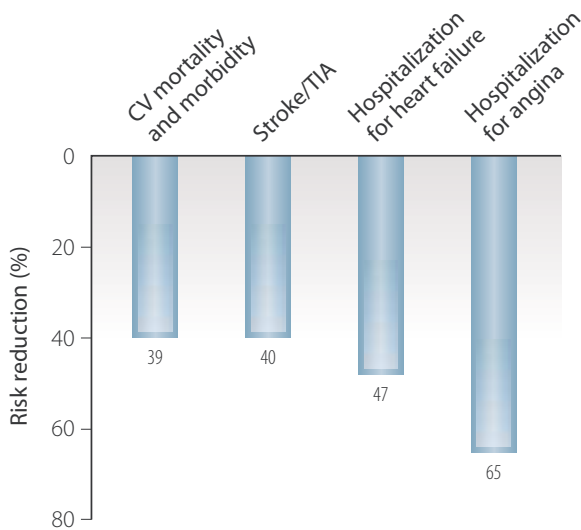
In ONTARGET, there was no significant difference between the two groups for the primary endpoint, which occurred in 16.3% of the combination arm and 16.5% of the ramipril arm (RR 0.99; 95% CI 0.92 to 1.07). Fur-

Figure 3
Major ARB Mortality and Morbidity Trials



Adapted from: Dzau V et al. Am Heart J 1991; 121:1244-63.

Figure 4
Jikei-Heart Study: Risk Reductions With Valsartan in Patients with Hypertension, CHD and/or HF



Adapted from: Mochizuki et al. Lancet 2007; 369:1431-9.

thermore, the investigators reported that the incidence of adverse events, namely hypotension, syncope, diarrhea and renal impairment, were significantly higher in the combination group.

TRANSCEND. ARBs have also been examined among patients who are intolerant of ACE inhibitors (approximately 15-20% of patients). Dr. Jeffrey Probstfield discussed

the evidence in this population, concentrating on the recently published TRANSCEND study¹⁰ (which was conducted among patients from the ONTARGET study who did not tolerate ramipril therapy during the run-in phase).

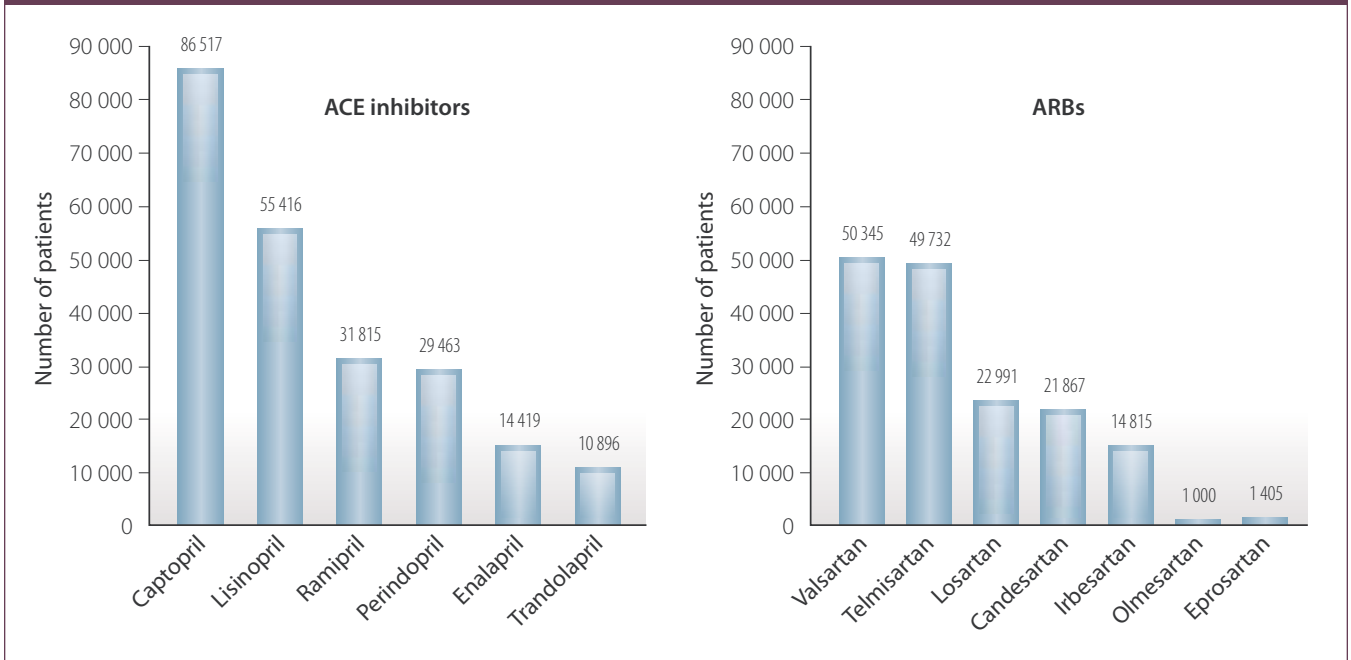
TRANSCEND was a comparison of telmisartan vs. active placebo among 5,926 patients at high risk of CV events. As Dr. Probstfield showed, there was no significant difference in primary-outcome events for telmisartan compared to active placebo, although the incidence was numerically lower (15.7% vs. 17.0%, respectively; HR 0.92, 95% CI 0.81 to 1.05).

When the investigators examined the pre-specified secondary composite endpoint of CV death, MI or stroke (the primary endpoint in the HOPE study¹¹), they found that ARB therapy was associated with a significant 13% relative risk reduction vs. active placebo.

Dr. Probstfield discussed some possible explanations for why the findings were not as robust for telmisartan in TRANSCEND compared to ramipril in HOPE. First, there was a lower event rate among placebo-treated patients in TRANSCEND than among placebo-treated patients in HOPE. This may be due to the fact that more patients in TRANSCEND received other proven therapies: lipid-lowering agents (55.2% of TRANSCEND patients vs. 28.6% of HOPE patients), diuretics (33.5% vs. 15.3%) and beta-blockers (58.3% vs. 39.5%). There is also the possibility that those patients who are intolerant of ACE inhibitors are physiologically different from those who are tolerant of these agents.

Figure 5

Numbers of Patients Evaluated in Mortality & Morbidity Trials with ACE Inhibitors and ARBs



Multifaceted Approach to Vascular Risks: Where are we Headed?

This session, co-chaired by Drs. Jean-Lucien Rouleau and Subodh Verma, included didactic presentations, a debate between expert presenters and a round-table discussion.

With respect to the inevitable comparisons between ACE inhibitors and ARBs in terms of which is better for providing cardioprotection, Dr. Verma cited the ONTARGET¹ and VALIANT⁹ studies as having clearly demonstrated non-inferiority of these two antihypertensive classes in certain populations.

Dr. Verma did, however, caution that one should not over-generalize in stating that the drugs are equivalent for all patients. Even among agents within each class, there may be differences. As shown in Figure 3, some agents among the ARB class have accumulated more evidence than others. Valsartan has compelling cardioprotection data from the Jikei-Heart (Figure 4), VALIANT and Val-HeFT studies; telmisartan from the ONTARGET study; and candesartan from the CHARM study. As observed in VALIANT and ONTARGET, respectively, valsartan and telmisartan are as effective as ACE inhibitors.

Dr. Verma also pointed out that there are marked differences in terms of numbers of patients studied in clinical trials (Figure 5).

He also reminded the session participants that, even among treated patients, there remains significant residual risk. Given that the RAS is known to play such a key role in the pathogenesis of CV and renal diseases, and given

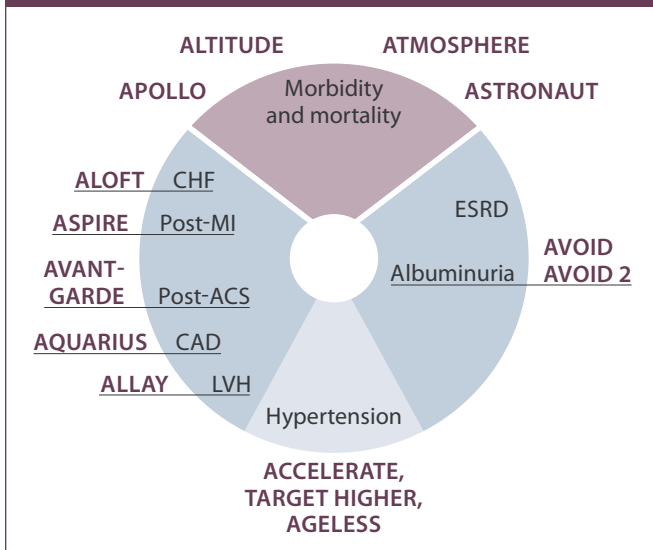
that the trials with combination ACE inhibition and ARB therapy have largely been disappointing, he postulated that blockade of the RAS with these therapies has been incomplete. As such, a new class of antihypertensive agents, direct renin inhibitors (DRIs), which have a mechanism of

As observed in VALIANT and ONTARGET, respectively, valsartan and telmisartan are as effective as ACE inhibitors. The results with other agents have been less encouraging.

action distinct from those of ACE inhibitors and ARBs, may provide additional benefits. As explained by Dr. Verma, the DRIs block renin's ability to cleave angiotensinogen to form angiotensin I, which is the rate-limiting first step within the RAS cascade.

Dr. Marc Pfeffer presented evidence for the antihypertensive efficacy of aliskiren, the first DRI approved in Canada. This agent has been shown to be efficacious and safe as an antihypertensive monotherapy or in combination with a diuretic, calcium channel blocker, ACE inhibitor or ARB.¹²⁻¹⁵ In addition to these hypertension trials, aliskiren has been studied as an add-on to an ARB and optimal antihypertensive therapy in diabetic patients with proteinuria (the AVOID study).¹⁶ As Dr. Pfeffer showed, the addition of aliskiren to this regimen led to a signifi-

Figure 6
ASPIRE HIGHER: Ongoing Program Studying the Effects of Aliskiren in > 35,000 patients



elderly patients at high risk for CV events. Figure 6 presents a schematic of the patient populations and/or disease states being investigated within the various studies comprising the ASPIRE HIGHER program.

Conclusions

Optimally lowering global CV risk requires a comprehensive, multifaceted approach. Lifestyle interventions are extremely important, and can have an impact on most of the modifiable risk factors for CV disease.

With respect to pharmacotherapy, it is essential to target all of a patient's relevant risk factors (*e.g.*, BP, A1C level, lipid levels), whenever possible using agents that have been shown to be protective for the vasculature.

Blockade of the RAS is an integral component of global CV risk reduction. Clinical trial data have shown that ACE inhibitors and ARBs provide significant protection against major events, independent of their BP-lowering abilities. Furthermore, the VALIANT and ONTARGET studies showed that ARBs are as effective as ACE inhibitors in terms of vascular protection in those trials' populations. The results of these studies have led the authors of evidence-based guidelines to recommend ACE inhibitors and ARBs as equivalent first-line agents in specific populations. While ARBs and ACE inhibitors will remain key components of risk-reduction regimens, the cardiorenal-protective properties of another means of inhibiting the RAS, DRI therapy, is also being investigated.

cant 20% reduction in urinary albumin:creatinine ratio compared to the addition of placebo.

The cardiorenal-protective properties of aliskiren are also under investigation in a large clinical trial program involving more than 35,000 patients (the ASPIRE HIGHER program). The major morbidity and mortality trials within this program are investigating the effect of aliskiren in type 2 diabetes patients at high risk for CV events, in patients with with heart failure (HF), and in

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