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Scientific Update™

Novel Insights into the Renin Cascade and Heart Disease: Pursuing Excellence in Blood Pressure Control and Cardioprotection

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The renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathogenesis of cardiovascular disorders. Angiotensin-converting enzyme (ACE) inhibition is the most studied approach to inhibit the RAAS and constitutes standard therapy in many patients with cardiovascular disorders. However, inhibition of the RAAS may be incomplete with the use of ACE inhibitors alone and some patients may not tolerate their side effects. This issue of *Cardiology Scientific Update* reviews the increasing therapeutic role of angiotensin receptor blockers (ARBs) and potentially new approaches to RAAS inhibition.

The RAAS is well-recognized for its importance in the regulation of blood pressure, electrolyte balance, and cardiac and vascular growth.[1-3] In addition, the RAAS plays an important pathophysiologic role in almost every cascade along the cardiovascular disease (CVD) continuum,[1,4] from mediating the impact of risk factors (eg, insulin resistance,[5,6] hypertension, and obesity[7]) to the development of atherosclerosis, myocardial infarction (MI), heart failure, and end-stage heart disease. Pharmacological strategies to suppress the RAAS – through ACE inhibition, angiotensin receptor blockade (ARB) and, to a lesser extent, aldosterone receptor blockade – have been proven effective in the treatment of a range of cardiovascular disorders.

Benefits of RAAS inhibition for the post-MI patient: Turning evidence into action

Survivors of acute MI complicated by heart failure and/or resulting in left ventricular (LV) dysfunction are at particularly high risk for subsequent death and major nonfatal cardiovascular events.[8-10] The initial rationale for the use of ACE inhibitors in patients with MI was derived from rat studies demonstrating that, for comparable MI size, therapy could attenuate long-term changes in ventricular remodeling, as well as prolong survival.[11] It was subsequently demonstrated that, in patients following anterior MI, progressive ventricular enlargement was attenuated by treatment with the ACE inhibitor, captopril.[12] In the landmark, Survival And Ventricular Enlargement (SAVE) trial,[6] in patients with asymptomatic LV dysfunction after MI, long-term administration of captopril was associated with an improvement in survival, as well as a reduction in cardiovascular morbidity and mortality. These benefits were observed in patients who received thrombolytic therapy, aspirin, or ß-blockers, as well as those who did not, suggesting that treatment with ACE inhibition led to additional improvement in outcome.

A series of international, large-scale, randomized, placebo-controlled clinical trials involving >100,000 patients, have subsequently definitively established the survival benefit from ACE inhibitors in patients with acute MI, whether the agent was administered early or later, following

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Figure 1: ACE inhibitor and myocardial infarction mortality trials

Broad (short-term) Total = 96,635 patients	Selective (higher risk, long-term) Total = 7,522 patients
CONSENSUS II	SAVE (EF ≤40%)
GISSI-3	AIRE (clinical heart failure)
ISIS-4	TRACE (wall motion score, EF ≤35%)
Chinese-Captopril	SMILE (anterior MI, no lytic)
5 lives saved/1000 over 6 weeks	**60 lives saved/1000 over 3 years**

MI (Figure 1).[8,13] The greatest relative and absolute benefits, however, were observed in trials that selected patients at higher risk, based on evidence of LV dysfunction or the presence of heart failure.[14] In studies such as SAVE, AIRE (Acute Infarction Ramipril Efficacy), and TRACE (Trandolapril Cardiac Evaluation), the odds ratio for ACE-inhibitor attributed reduction in all-cause mortality was 0.74% (95% confidence interval [CI], 0.66%-0.83%), with comparable benefits achieved when major, nonfatal cardiovascular events (eg, hospitalization for heart failure 0.73%, 99.5% CI, 0.63%-0.85%; and recurrent MI 0.80%, 99% CI, 0.69%-0.94%) were evaluated (Figure 2).[6,8,15,16]

ARBs provide an alternative approach for blocking the RAAS,[17] potentially providing a more complete blockade of the actions of angiotensin II, but without the theoretically beneficial bradykinin-preserving effect of ACE inhibition.[18,19]

The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) was the first attempt to compare an ARB with an ACE inhibitor in patients following MI.[20] In OPTIMAAL, the ARB, losartan, at a dose of 50 mg/day, was compared with the ACE inhibitor, captopril, 150 mg/day, in high-risk patients with acute MI. There was a strong trend in favour of captopril in the primary endpoint of total mortality (p = 0.07). A similar trend in favour of the same dose of captopril over the same dose of losartan was observed in patients with chronic heart failure in the Evaluation of Losartan in the Elderly II (ELITE-II) trial.[21]

The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared the effects of the ARB, valsartan, the ACE inhibitor, captopril, and the combination of valsartan and captopril in a population of high-risk patients with clinical or radiologic evidence of heart failure, evidence of LV systolic dysfunction, or both, after acute MI.[22] A total of 14,808 patients underwent randomization in a 1:1:1 ratio to receive valsartan (titrated to 160 mg twice daily), captopril (titrated to 50 mg 3 times daily), or the combination of valsartan (titrated to 80 mg twice daily) and captopril (titrated to 50 mg 3 times daily), beginning 12 hours to 10 days after an MI. The primary endpoint of the study was death from any cause. Importantly, a pre-specified analysis was designed to demonstrate the noninferiority or equivalence of valsartan to captopril, in the event that valsartan was not clearly shown to be superior in the primary analysis.

During a median follow-up of 24.7 months, mortality was 19.9% in the valsartan group, 19.5% in the captopril group, and 19.3% in the valsartan-and-captopril group (Figure 3). The hazard ratio for death in the valsartan group, as compared with the captopril group, was 1.00 (97.5% CI, 0.90 to 1.11; *P*=0.98), and the hazard ratio for death in the valsartan-and-captopril group, as compared with the captopril group, was 0.98 (97.5% CI, 0.89 to 1.09; *P*=0.73). The number of patients reaching target dose after 1 year was 56%

Figure 2: All-cause mortality in the SAVE, AIRE, and TRACE studies

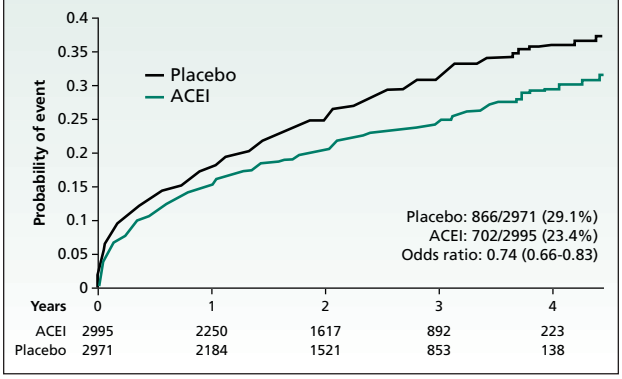


Figure 3: All-cause mortality in VALIANT

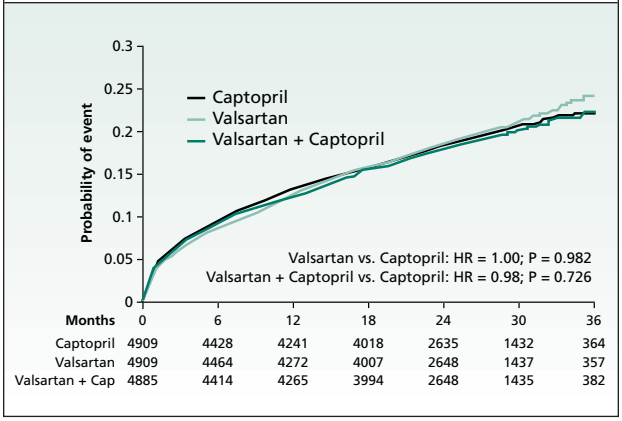
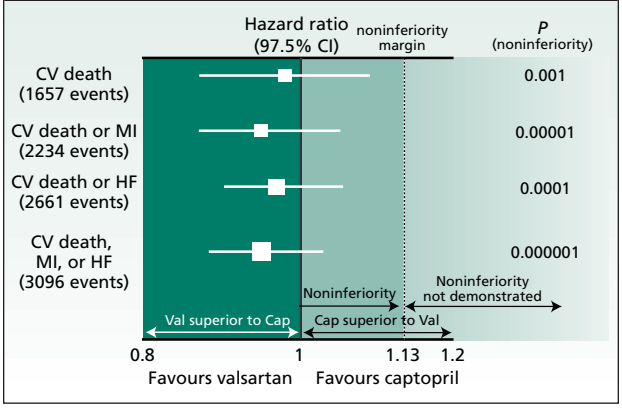


Figure 4: VALIANT – Cardiovascular (CV) mortality and morbidity



in the valsartan arm, 47% in the captopril arm, and 56% for the combination. The comparison of valsartan with captopril revealed that these 2 agents were equivalent in terms of overall mortality (Figure 4) and in the rate of the composite endpoint of fatal and nonfatal cardiovascular events.

Results of the VALIANT study reveal that the ARB, valsartan (titrated to a dose of 160 mg BID), is as effective as a proven ACE inhibitor, captopril, (titrated to 50 mg TID) in reducing all-cause mortality in high-risk patients with acute MI.[6] In this patient population, the combined use of an ACE inhibitor and an ARB does not produce additional benefit. Based on the results of the VALIANT trial, valsartan is now approved by Health Canada to reduce cardiovascular death in high-risk patients following MI when the use of an ACE inhibitor is not appropriate.

The promise of renin inhibition: A new approach to blood pressure control and beyond

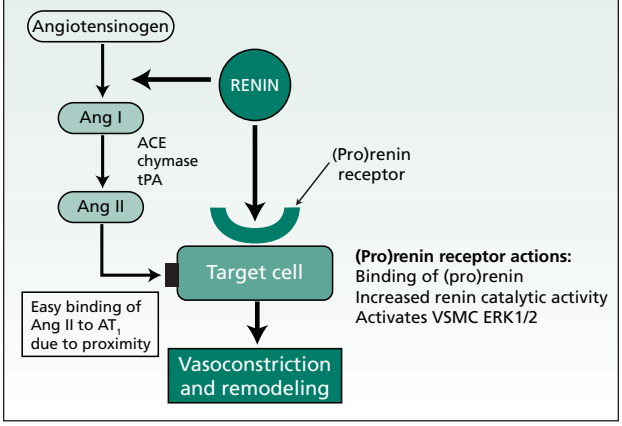
A substantial proportion of tissue angiotensin II (Ang II) is, however, generated from angiotensin I (Ang I) via non-ACE dependent pathways, primarily in the heart and kidney, and are not blocked by ACE inhibition.[23-25] The "ACE escape" phenomenon of ACE inhibition[26] may reflect the reflex increase in renin release following the interruption of normal Ang II feedback inhibition, which then increases Ang I and also Ang II through these alternate pathways.

Renin is an aspartic protease that consists of 2 homologous lobes. The cleft between the lobes contains the active site with 2 catalytic aspartic residues.[27] Renin has also been called "active" renin to underline the fact that an enzymatically-inactive form of renin exists. In 1971, Lumbers found that amniotic fluid, left at low pH in the cold, acquired renin activity.[28] It was later postulated that an inactive "big" renin – its molecular weight being 5 kDa higher than that of renin and with the potential to be activated – was the biosynthetic precursor of renin. Hence, it was named "prorenin." With the cloning of the renin gene in 1984,[29] prorenin was proven to be the precursor of renin. Unlike other aspartic proteases, such as pepsin or cathepsin D, renin *specifically* catalyses the first and *rate-limiting step* of the renin-angiotensin cascade, namely the cleavage of the peptide bond between leu10 and val11 in human angiotensinogen.

In 2002, Nguyen et al first reported the expression cloning of the human renin/prorenin [(Pro)renin] receptor complementary DNA, encoding a 350-amino acid protein with a single transmembrane domain and no homology with any known membrane protein.[30] The transfected cells stably expressed the receptor showed renin- and prorenin-specific binding. The binding of renin induced a 4-fold increase in the catalytic efficiency of angiotensinogen conversion to Ang I, as well as an intracellular signal with phosphorylation of serine and tyrosine residues associated with activation of extracellular, signal-related, MAP kinases, ERK1 and ERK2. Receptor mRNA was detected in the heart, brain, placenta, kidney, and liver. Indeed, early data support the possibility of a direct functional role for prorenin and renin. Renin has been reported to bind to human mesangial cells in culture and this binding causes cell hypertrophy and increased levels of plasminogen activator inhibitor-1.[31,32] The discovery of the renin/prorenin receptor has, therefore, opened new perspectives on tissue RAAS, as well as renin effects, including those that may be *independent* of Ang II (Figure 5).

The application of direct renin inhibition may, therefore, potentially offer more complete inhibition of the RAAS.

Figure 5: Actions of (pro)renin receptor

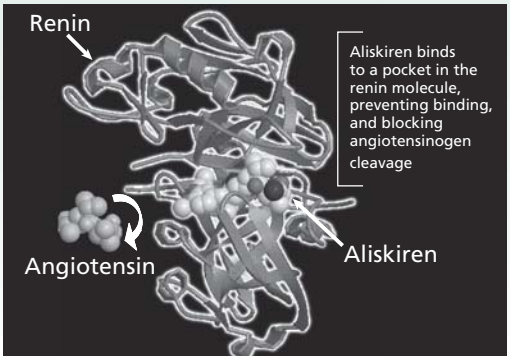


However, the clinical development of the early renin inhibitors was confounded by poor pharmacokinetic and oral bioavailability, limiting their effectiveness following oral administration.[33] Fortunately, with computational molecular modeling and crystallographic structure analysis, a number of highly potent, selective, non-peptidic, low-molecular-weight inhibitors of human renin, have been synthesized.[34-36]

Aliskiren

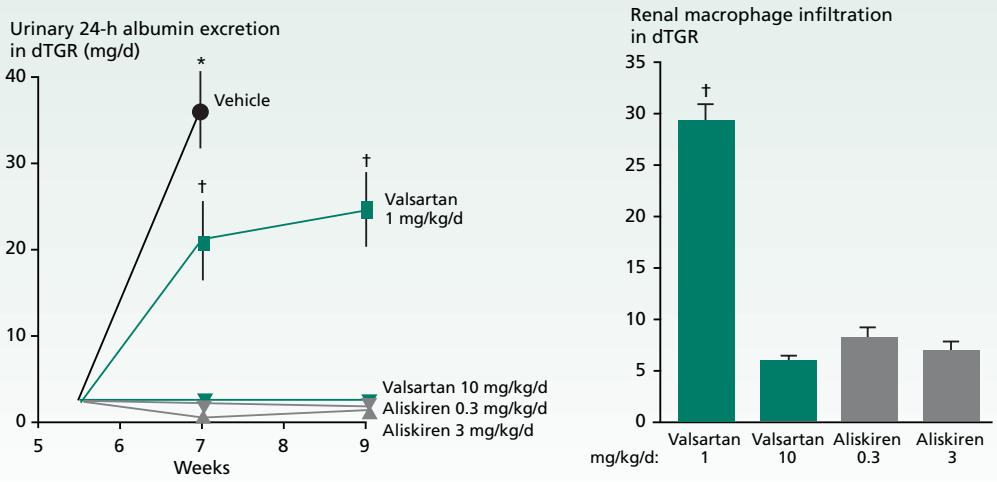
Aliskiren is a third-generation, orally active nonpeptide renin inhibitor, a substituted octanoyl amide with a 50% inhibitory concentration (IC50) in the low nanomolar range (0.6 nM).[35] In place of the peptide backbone of previous compounds, aliskiren was designed with lipophilic moieties that interact with the large hydrophobic S1/S3-binding pocket of renin. In addition, aliskiren interacts with a previously unrecognized, large, distinct subpocket of renin that extends from the S3-binding site toward the hydrophobic core of the enzyme. Binding to this S3 subpocket is responsible for the high-affinity binding of aliskiren to renin (Figure 6).[35,36] Because of its properties of potent and specific *in vitro* inhibition of human renin, as well as good oral absorption in mammals, aliskiren is the only renin inhibitor currently at an advanced phase of development for clinical use.[33,37] In pre-clinical studies, aliskiren produces dose-dependent reductions in plasma renin activity (PRA) and blood pressure in marmosets and spontaneous hypertensive rats,[38] and reduces albuminuria and LV hypertrophy in rats transgenic for human renin and angiotensin genes.[39] These observations are consistent with organ protective effects (Figure 7).

Figure 6: Renin inhibition with aliskiren



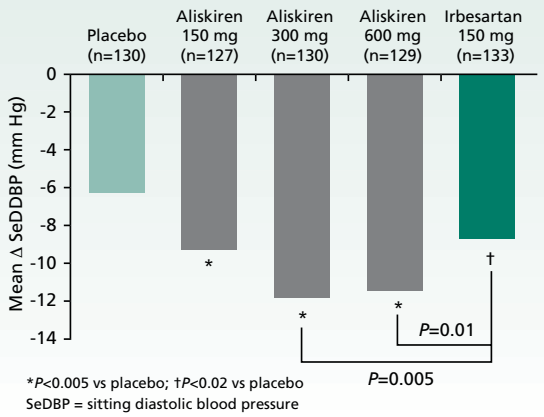
In a study comparing aliskiren with the ACE inhibitor, enalapril and placebo in healthy normotensive volunteers, aliskiren effected a dose-dependent suppression of the RAAS (as evidenced by decreased PRA, plasma Ang I, Ang II, and aldosterone) while increasing plasma-active renin.[40] Aliskiren inhibited PRA, while enalapril increased PRA. Aliskiren at 160 mg inhibited Ang II levels to a similar degree as enalapril; at 640 mg, aliskiren was more potent than enalapril.

Figure 7: Effects of aliskiren on albuminuria and renal inflammation in double-transgenic rats



*P<0.05 vs other groups; †P<0.05 vs other groups
dTGR = double-transgenic rats. Untreated rats died by week 8.

Figure 8: Renin inhibition with aliskiren



*P<0.005 vs placebo; †P<0.02 vs placebo
SeDBP = sitting diastolic blood pressure

In a double-blind, active comparator trial in patients with mild-to-moderate hypertension, 226 subjects were randomized to receive 37.5-300 mg aliskiren or 100 mg losartan daily for 4 weeks.[41] Dose-dependent reductions in daytime ambulatory systolic blood pressure and PRA were observed with aliskiren. The change in daytime systolic blood pressure with 100 mg losartan was not significantly different from that observed with 75, 150, and 300 mg of aliskiren.

In a recent randomized, multicentre, double-blind, placebo-controlled, active-comparator, 8-week trial in patients with mild-to-moderate hypertension, the antihypertensive effect of aliskiren 150 mg was comparable to that of irbesartan 150 mg. Aliskiren at 300 and 600 mg lowered blood pressure significantly more than irbesartan 150 mg (Figure 8).[42] In all of these comparison studies, aliskiren appears extremely well tolerated.

Summary

In spite of the success of ACE inhibition, patients with hypertension and heart failure remain at high risk for adverse clinical events that may be related, in part, to incomplete blockade of the RAAS using conventional agents. In addition, a considerable number of patients cannot tolerate ACE inhibitor therapy. In post-MI patients, the ARB, valsartan, has been shown to represent an alternative therapy that provides equivalent cardiovascular protection to ACE inhibitors. Combined ACE and renin inhibition or combined ARB and renin inhibition represents a novel and attractive approach that is currently being actively explored.

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