Direct Renin Inhibition: A New Option for End-Organ Protection

Renin-angiotensin-aldosterone system (RAAS) inhibitors reduce the risk of new-onset diabetes, microalbuminuria, and other adverse clinical outcomes in patients with hypertension. Matthew R. Weir, MD, University of Maryland School of Medicine, Baltimore, Maryland, USA, described new options for RAAS blockade in preventing end-organ damage in patients with elevated cardiovascular (CV) risk.

Several major clinical trials have demonstrated the benefits of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) in slowing the progression of vascular disease and reducing markers of CV risk (Table 1) [Weir MR et al. *J Clin Hypertens 2006*]. Despite the use of traditional RAAS inhibitors, many hypertensive patients continue to have an increased risk for CV morbidity and mortality. Treatment with ACE-Is and ARBs only partially block RAAS, with a compensatory rise in other RAAS hormones, such as angiotensin I. Residual RAAS activation, as shown by elevated plasma renin activity (PRA) in patients on ACE-I or ARB therapy, may leave patients vulnerable to adverse outcomes.

Table 1. Major Trials of RAAS Inhibition and End-Organ Protection.

	HOPE (n=9297)	ALLHAT (n=33,357)	LIFE (n=9193)	VALUE (n=15,245)	ASCOT (n=19,342)
Age (years)	66	67	67	67	63
Known CAD (%)	80	25	16	45	17
Diabetes	39	36	13	33	22
SBP Difference	-10 mm Hg ABPH -3 mm Hg Office	-3 to -5 mm Hg	-1.3 mm Hg	-2 to -4 mm Hg	-2.9 mm Hg
BP Advantage	RAAS Regimen	Non-RAAS Regimen	RAAS Regimen	Non-RAAS Regimen	RAAS Regimen
CV Death	-22%	No Difference	-13%	No Difference	-24%
LVH Regression	NR	NR	Yes	NR	NR
MAU Reduction	Yes	NR	Yes	NR	NR
Reduction in new DM	-32%	-43%	-25%	-23%	-32%
Reduction in CHF	Yes	Yes	No	Yes	NR

CAD=coronary artery disease; CV=cardiovascular; CHF=congestive heart failure; DM=diabetes mellitus; LVH=left ventricular hypertrophy; MAU=microalbuminuria; RAAS=renin-angiotensin-aldosterone system; SBP=systolic blood pressure.

Although investigators hoped that dual RAAS blockade with combination ACE-I/ARB therapy would provide greater CV risk reduction than single-agent RAAS inhibition, several trials have shown that this is not an effective strategy. In the Valsartan in Acute Myocardial Infarction (VALIANT) trial, the combination of valsartan and captopril failed to improve survival compared with captopril monotherapy (19.3% vs 19.5%; p=0.73), but increased the rate of discontinuation due to poor tolerability (19.0% vs 16.8%; p=0.007) [Pfeffer MA et al. N *Eng J Med* 2003]. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), combination with telmisartan and ramipril did not reduce the primary endpoint of death from CV causes, MI, stroke, or heart failure hospitalizations compared with ramipril alone (16.3% vs 16.5%; HR, 0.99; 95% CI, 0.92 to 1.07) [The ONTARGET Investigators. N *Eng J Med* 2008].

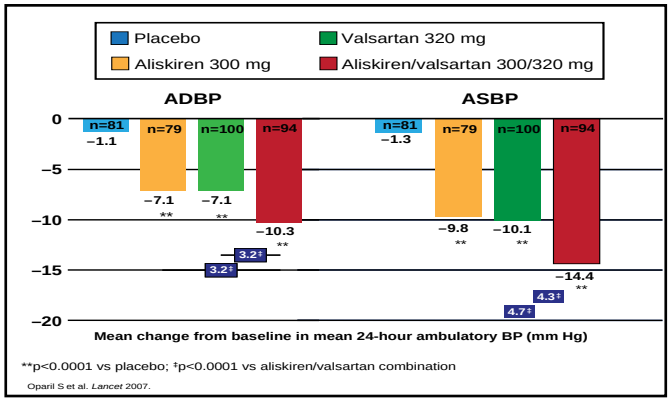
The benefits of ACEIs and ARBs might be enhanced by addressing incomplete RAAS suppression with another form of RAAS blockade. Directly targeting renin is a new option for blocking RAAS at the point of activation without interfering with other metabolic pathways. Aliskiren, the first oral direct renin inhibitor, provides effective blood pressure control in patients with hypertension, reducing the systolic blood pressure by up to 15.7 mm Hg when given as high-dose (300 mg) monotherapy [Villamil A et al. *J Clin Hypertens* 2006].

Treatment with aliskiren monotherapy effectively reduces PRA and, when used in combination with hydrochlorothiazide, blocks the rise in PRA that is seen during diuretic treatment (eg, mean reduction in baseline PRA, 46% to 64%) [Calhoun D et al. *J Clin Hypertens* 2006]. Therefore, aliskiren is an attractive candidate for RAAS inhibitor-based combination therapy. The potential benefits of dual RAAS blockade with aliskiren and an ARB were explored in a trial of 1797 patients with mild-to-moderate hypertension. After 8 weeks of treatment, combination therapy with aliskiren and valsartan provided significantly greater blood pressure reduction than either agent alone (Figure 1) [Oparil S et al. *Lancet* 2007].

The ASPIRE HIGHER clinical study program is currently underway to assess the incremental benefits of end-organ protection and CV event reduction with aliskiren alone or in combination with other antihypertensive agents, including RAAS inhibitors. Preliminary findings from the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial suggest that aliskiren significantly reduces BNP levels compared with placebo (-61% vs -12.2%; p=0.016) in patients who are already on optimal heart failure therapy [McMurray JJV et al. ESC 2007]. Additional trials in the ASPIRE HIGHER program will evaluate direct renal

inhibition in patients with hypertension, diabetes, and other CV risk factors. These studies may show whether combining a renin inhibitor with other RAAS blockers provides additional incremental benefits in blood pressure control and CV risk reduction.

Figure 1. Combination Therapy with Aliskiren and Valsartan Improves Blood Pressure Control Compared with Either Component as Monotherapy.



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A New Focus on Genetics and Individualized Management Approaches for CAD

There are many factors that increase the risk of developing coronary artery disease (CAD), including hypertension, dyslipidemia, inflammation, health behaviors, and genetics. Robert Chilton, DO, FACC, Professor of Medicine, University of Texas Health Science Center, San Antonio, Texas, USA, highlighted recent evidence concerning CAD treatment and described the clinical shift in therapeutic concentration from vulnerable plaque to genomics and metabolomics to improve drug risk benefit.

Recent studies have revealed an association between certain genetic phenotypes and CAD risk. In a meta-analysis by Schunkert and colleagues, genetic variants at chromosome 9p21.3 were associated with a 30% increase in CAD per copy of the 9p21.3 risk allele for heterozygote mutation [Schunkert H et al. *Circulation* 2008]. This study supported previous findings that mutations within this genetic locus conveyed a higher risk of CAD [Nilesh J et al. *N Engl J Med* 2007]. Additionally, a Trp719Arg polymorphism within the KIF6 gene, which encodes for a kinesin, also predicts development of CAD [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. These results begin to elucidate the role of genetics in the risk of developing CAD and may prove to be useful predictive markers in the future.

In a population-based study, reductions in short-term fatality rates from myocardial infarction (MI) between 1999 and 2008 were associated, in part, with the use of effective therapeutics, such as statins, renin angiotensin aldosterone system (RAAS) blockers, and β-blockers [Yeh RW et al. *N Engl J Med* 2010]. However, genes also play a role in treatment response, and more individualized strategies may be warranted, based on varying gene polymorphisms and therapeutic interactions. In the PROVE IT-TIMI 22 trial, carriers of 719Arg demonstrated significantly greater benefit from intensive statin therapy compared with noncarriers (41% relative risk reduction [RRR] in death/MI; p=0.018) [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. Similar evaluations that were performed in the CARE and WOSCOPS trials also showed that pravastatin therapy effectively reduced the risk of coronary events in KIF6 719Arg carriers, with a 54% RRR in coronary heart disease and a 41% RRR in acute MI [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. Alternatively, variants that were identified within SLCO1B1 (rs4363657) were strongly associated with an increased risk of statin-induced myopathy [SEARCH Collaborative Group. *N Engl J Med* 2008]. Thus, the need to consider genetics when determining an appropriate treatment strategy has become more apparent.

There has been increasing evidence of interactions between gene polymorphisms and therapies that are associated with variability in coronary risk. Pharmacogenomics and variable therapeutic responses have altered views on treatment approaches and may lead to more emphasis on genetic predictors of risk and therapeutic response moving forward. While previous strategies have focused on factors, such as inflammation, lipids, glucose, and other risk measurements, future approaches may incorporate additional factors, such as individual risk profile, genomics, and biomarkers.

Stroke Prevention in Atrial Fibrillation: Novel Agents Versus the Gold Standard

Stroke prevention is a priority for clinicians who treat patients with atrial fibrillation (AF). Warfarin has been the gold standard therapy for patients with AF who are at moderate or high risk of stroke. However, there are concerns about the limitations of warfarin, such as adherence issues, bleeding risk, narrow therapeutic window, vigilant monitoring requirements, and drug-drug/food-drug interactions that make it difficult to