Cardiovascular
CONGRESS REPORTER
A Summary of Recent International Meetings

RAS Blockade Across the CV Continuum

New Evidence Presented at the 2009 Congress of the European Society of Cardiology (August 29-September 2, Barcelona)

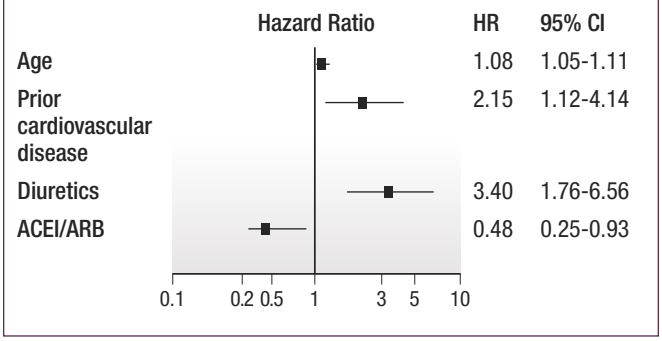
The renin-angiotensin system (RAS) plays an important role in the regulation of a number of key processes within the cardiovascular (CV) system. Overactivation of the RAS has been associated with deleterious effects in the vasculature, heart, brain and kidneys. Pharmacologic agents that block the activity of the RAS (*e.g.*, angiotensin converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]) have been shown to have protective effects in a number of different populations across the continuum of CV and renal diseases. Our understanding of the benefits of these agents continues to evolve as new data are added to the already substantial evidence base.

At the 2009 Congress of the European Society of Cardiology (ESC), researchers presented evidence from trials and subgroup analyses investigating the benefits of ACE inhibitors, ARBs, aldosterone antagonists and direct renin inhibitors (DRIs) across the continuum of CVD. The following report summarizes these presentations, including reviews of the Barbanza Diabetes Study, the VART trial, the KYOTO HEART trial, post-hoc JIKEI HEART sub-analyses, the ACTIVE-I trial, the SPIR-AF trial, an ALOFT sub-analysis, a trial of ACE inhibition in heart failure (HF), and a meta-analysis of combined ACE inhibitor + ARB therapy in HF.

Benefits of RAS blockade in Patients with CV Risk Factors

Several trials presented at the 2009 ESC Congress assessed the protective properties of RAS-inhibiting agents among populations of patients with major CV risk factors (*e.g.*, hypertension, dyslipidemia, diabetes).

Figure 1
Independent Predictors of Mortality Among Patients with Diabetes (Barbanza Diabetes Trial)[1]



Barbanza Diabetes Study. The benefits of ACE inhibitors and ARBs for the treatment of hypertension in diabetes are well known. The authors of clinical practice guidelines already recommend these agents as preferred first-line therapy in hypertensive patients with diabetes. A poster presented at the 2009 ESC Congress lent further support to these recommendations. Spanish investigators undertook a prospective cohort trial of 1,423 consecutive patients with diabetes and examined the impact of various factors on mortality risk.[1] They found that the use of ACE inhibitors or ARBs was an independent predictor of mortality, with a hazard ratio (HR) of 0.48 (95% CI 0.25-0.93) compared to no use of a RAS-blocking agent. The use of

diuretics, by contrast, was associated with an HR of 3.40 (95% CI 1.76-6.56) (Figure 1).

VART Trial. The VART trial was a randomized, prospective, double-blind comparison of the ARB, valsartan, and the calcium channel blocker (CCB), amlodipine, among 1,021 Japanese patients with hypertension. Over the three-year follow-up, there were no significant differences in terms of blood pressure (BP) reduction between the groups. For the primary composite endpoint of mortality, CV and renal events, there was no significant difference between the two study arms (events occurred in 4.1% of patients in each group). However, the investigators reported that there were benefits associated with valsartan therapy for several secondary endpoints, including changes from baseline in left-ventricular (LV) mass, plasma norepinephrine, heart:mediastinum ratio and urinary albumin:creatinine ratio. Although fewer patients in the valsartan arm had a new diagnosis of diabetes during the trial (1.7%, vs. 3.4% in the amlodipine arm), this finding was not statistically significant.

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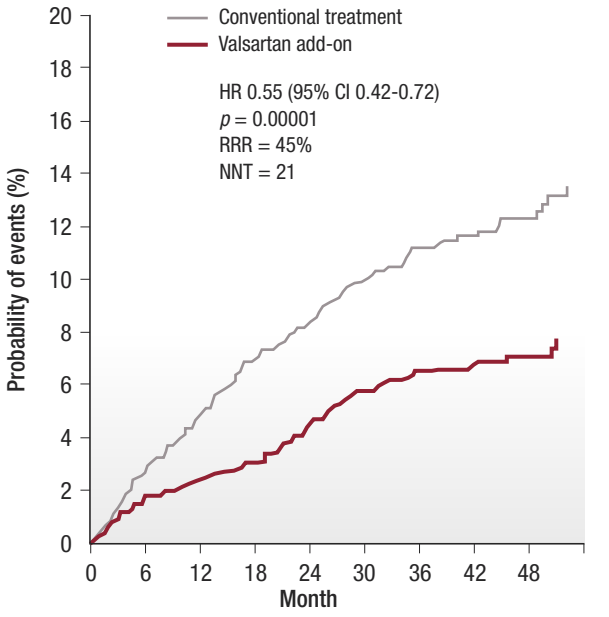
KYOTO HEART Trial. Delegates at the 2009 ESC Congress were also able to attend a presentation of the results of a Japanese trial involving valsartan: the KYOTO HEART trial.[3] These results have simultaneously been published in the *European Heart Journal*.[4] The objective of the trial was to assess the effect of valsartan added to conventional treatment (vs. conventional treatment excluding ARBs) among patients with high-risk hypertension (n = 3,031). The primary endpoint was a composite of fatal and non-fatal CV events.

Figure 2
Reduction in Cardiovascular Morbidity and Mortality with Valsartan (KYOTO HEART Trial Primary Endpoint)[4]

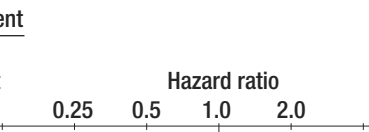


At risk (n)										
Valsartan	1517	1355	1289	1217	1084	901	768	647	380	220
Convent'l	1514	1377	1262	1167	1048	868	749	631	351	179

Mean BP at baseline was 157/88 mmHg. BP control (< 140/90 mmHg) was achieved in both groups within the first year of the four-year trial (median follow-up 3.27 years) and there were no significant inter-group differences in BP. At the trial's conclusion, the mean BP in both groups was 133/76 mmHg. The proportion of patients experiencing a primary-endpoint event was 10.2% (155 of 1,514 patients) in the conventional-treatment group and 5.5% (83 of 1,517 patients) in the valsartan add-on arm (HR 0.55; 95% CI 0.42-0.72; p = 0.00001; Figure 2). For each of the components of the composite endpoint, there were fewer events in the valsartan add-on arm, although not all comparisons were statistically significant (Figure 3). The endpoints in which valsartan therapy was associated with statistically significant risk reduction were angina (HR 0.51; 95% CI 0.3-0.9; p = 0.0106;) and stroke (HR 0.55; 95% CI 0.3-0.9; p = 0.0149). In addition, there was a statistically significant 33% reduction (p = 0.0282) in new-onset diabetes in the valsartan add-on arm compared to conventional treatment.

Figure 3
Hazard Ratios for Efficacy Endpoints in the KYOTO HEART Trial (Valsartan vs. Non-ARB)[4]

	Valsartan add-on		Conventional treatment				
	Patients with events, n (%)	/1000 patient years	Patients with events, n (%)	/1000 patient years	HR	95% CI	*p* value
Primary endpoint	**83 (5.5%)**	**18.7**	**155 (10.2%)**	**35.1**	**0.55**	**0.4-0.7**	**0.00001**
Acute myocardial infarction	7 (0.5%)	1.6	11 (0.7%)	2.5	0.65	0.2-1.8	0.39466
Angina pectoris	22 (1.5%)	4.9	44 (2.9%)	10.0	0.51	0.3-0.9	0.01058
Heart failure	12 (0.8%)	2.7	26 (1.7%)	5.9	0.65	0.3-1.3	0.20857
Stroke	25 (1.6%)	5.6	46 (3.0%)	10.4	0.55	0.3-0.9	0.01488
Dissecting aneurysm of aorta	3 (0.2%)	0.7	5 (0.3%)	1.1	0.60	0.1-2.5	0.69987
Lower-limb arterial obstruction	11 (0.7%)	2.5	12 (0.8%)	2.7	0.99	0.4-2.4	0.98106
Transition to dialysis or doubling of serum creatinine level	6 (0.4%)	1.3	14 (0.9%)	3.2	0.43	0.2-1.1	0.34666
All-cause mortality	22 (1.5%)	4.9	32 (2.1%)	7.2	0.76	0.4-1.3	0.32851
Cardiovascular death	8 (0.5%)	1.8	13 (0.9%)	2.9	0.66	0.3-1.6	0.37121
New-onset diabetes	58 (5.2%)	51.6	86 (7.7%)	76.7	0.67	0.5-0.9	0.02817



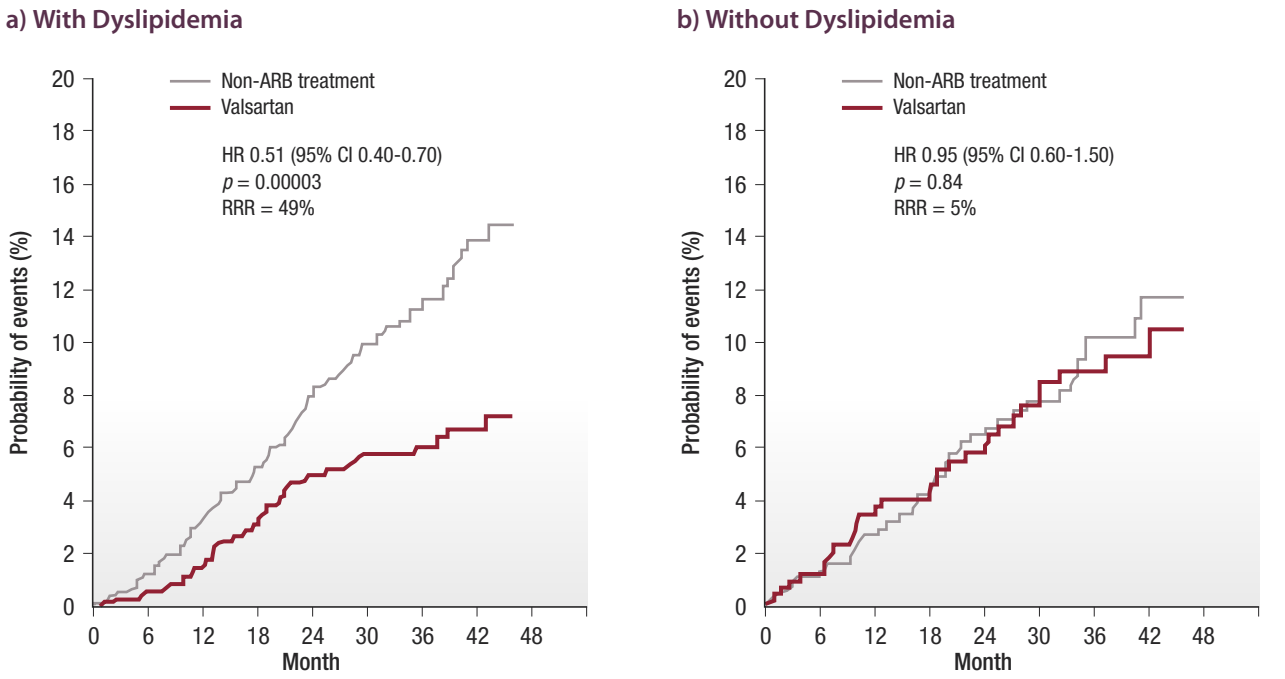
JIKEI HEART Sub-analyses. The primary findings of the JIKEI HEART trial were published in the *Lancet* in 2007.[5] The trial involved 3,081 Japanese patients with hypertension, coronary heart disease, heart failure, or a combination of these disorders. They were randomized to treatment with valsartan or to other, non-ARB treatment. The primary finding was that patients treated with add-on valsartan had a significant 39% reduction in risk for the composite primary endpoint of CV morbidity and mortality.

At the 2009 ESC Congress, two sets of investigators presented post-hoc analyses of the JIKEI HEART database. The first of these analyses focused on the large subgroup of patients from the database with dyslipidemia (n = 2,218 of 3,081).[6] The investigators found that the relative risk reduction in favor of valsartan in this subgroup was a statistically significant 49% ($p = 0.00003$; Figure 4a), whereas among those patients who did not have dyslipidemia, there was a nonsignificant risk reduction of 5% in favor of valsartan ($p = 0.84$; Figure 4b). Furthermore, within the group of patients with dyslipidemia, the risk reduction in favor of valsartan was of a greater magnitude among those being treated with statin therapy (69%, $p < 0.0001$) than among those not receiving statin therapy (28%, $p = 0.126$). These findings led the investigators to speculate that valsartan and statins exert synergistic, cardioprotective functions.

Another sub-analysis of the JIKEI HEART database investigated the sex-specific effects of valsartan vs. conventional therapy.[7] The investigators of this sub-analysis reported that the incidence of the primary composite endpoint was higher among men than among women, but that the benefits of valsartan therapy were identical (relative risk reduction 39%) in men aged 45 years or older and women aged 55 years or older.

The benefits of ACE inhibitors and ARBs for the treatment of hypertension are well known. The authors of clinical practice guidelines already recommend these agents as preferred first-line therapy in hypertensive patients with diabetes.

Figure 4
JIKEI HEART Sub-analysis: Effect of Valsartan in Patients With or Without Dyslipidemia[6]



Benefits of RAS Blockade in Atrial Fibrillation

Two trials presented at the 2009 ESC Congress examined the effects of RAS-blocking agents among patients with atrial fibrillation (AF).

ACTIVE-I Trial. The ACTIVE-I trial involved 9,016 patients with a history of documented AF and at least one other CV risk factor.[8] They were randomized to placebo or treatment with the ARB, irbesartan. The primary efficacy endpoint was a composite of stroke, myocardial infarction (MI) or vascular death. The incidence of this primary endpoint was 5.4% in both groups. Although there was no significant difference in terms of the primary endpoint, the investigators observed that irbesartan therapy was associated with benefits relative to placebo for several secondary endpoints. The risk of hospitalization for heart failure, for example, was 14% lower for irbesartan-treated patients than for those who received placebo (p = 0.018; Figure 5). Irbesartan also lowered the risk of cerebrovascular events (composite of stroke, transient ischemic attack or non-CNS embolism) in this patient population, with a statistically significant 13% relative risk reduction (p = 0.024). Irbesartan-treated patients also had significantly fewer hospital admissions for CV reasons.

RAS-blocking agents have an extensive clinical-trial database in patients with heart failure and LV dysfunction. At the 2009 ESC Congress, additional data were added to this evidence base.

SPIR-AF Trial. In this trial, 158 patients with a history of AF were randomized to receive one of four open-label treatments: beta-blocker alone; beta-blocker + ACE inhibitor; beta-blocker + spironolactone; or beta-blocker + ACE inhibitor + spironolactone.[9] The investigators found that, among the two groups whose regimens included spironolactone, the incidence of AF episodes was significantly reduced at 3, 6, 9 and 12 months compared to those groups that did not receive spironolactone (p < 0.05). Similarly,

the incidence of AF was lower in the two groups that received ACE-inhibitor therapy than among the two groups that did not ($p < 0.05$).

Benefits of RAS Blockade in Heart Failure

RAS-blocking agents have an extensive clinical-trial database in patients with heart failure (HF) and LV dysfunction. At the 2009 ESC Congress, additional data were added to this evidence base.

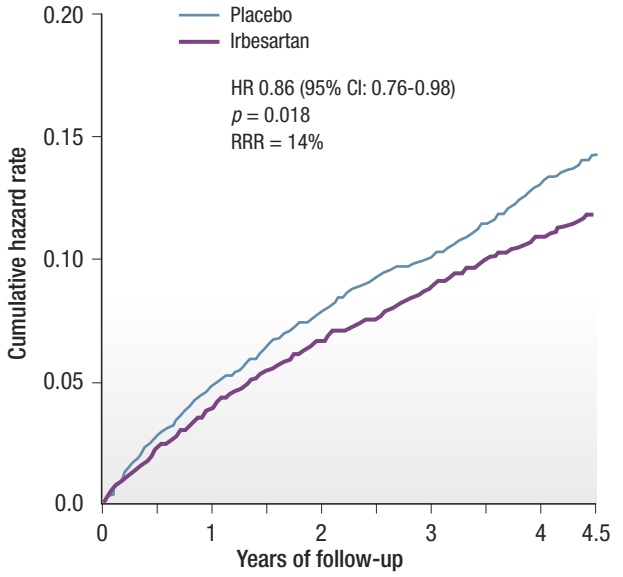
Dose-dependent Effect of ACE Inhibition. One trial evaluated the effects of two doses of the ACE inhibitor, perindopril, on markers of LV diastolic dysfunction in 130 patients with New York Heart Association class III HF and with normal or mildly abnormal LV systolic function.[10] The investigators found that, compared to perindopril 10 mg daily, a 20-mg daily dose was associated with improvements in left-atrial volume index (LAVI), left atrial ejection fraction (LAEF) and a reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP). The investigators hypothesized that the differences in terms of these parameters suggest that perindopril's ability to modulate the myocardial RAS is dose-dependent.

Combined ACE-inhibitor + ARB Therapy. A group of Swiss researchers sought to evaluate the utility of combined ACE inhibitor + ARB therapy among patients with HF.[11] To this end, they conducted a meta-analysis of all randomized, controlled trials comparing the combination to ACE inhibition alone with a minimum follow-up of six months. They identified eight such trials, comprising a total of 18,061 patients. Overall, there was no significant difference between the ACE inhibitor + ARB combination and ACE inhibitors alone in terms of overall mortality (HR 0.97; 95% CI 0.92-1.03). The combination was, however, associated with a reduced risk of hospitalization for HF (HR 0.81; 95% CI 0.72-0.91). On the other side of the risk:benefit equation, however, the ACE inhibitor + ARB combination was associated with a significantly increased risk of worsening renal function (HR 1.91; 95% CI 1.4-2.6).

The investigators of this meta-analysis concluded that the combination of ACE inhibitors and ARBs should be reserved only for those HF patients who have persistent symptoms despite therapy with a beta-blocker and an ACE inhibitor.

ALOFT Sub-analysis. While combination RAS blockade with an ACE inhibitor and an ARB has not produced consistently beneficial results, the ALOFT trial has shown that the addition of a DRI, aliskiren, to standard HF therapy (including an ACE inhibitor or ARB) is associated with significant benefit in terms of surrogate markers of CV risk.[12] At the 2009 ESC Congress, researchers presented a post-hoc analysis of the ALOFT database, investigating the safety, tolerability

Figure 5
Risk of Hospitalization for Heart Failure in Patients with AF (Secondary Endpoint of the ACTIVE-I Trial)[8]



At risk (n)						
Placebo	4498	4132	3841	3609	2691	2125
Irbesartan	4518	4179	3896	3654	2769	2161

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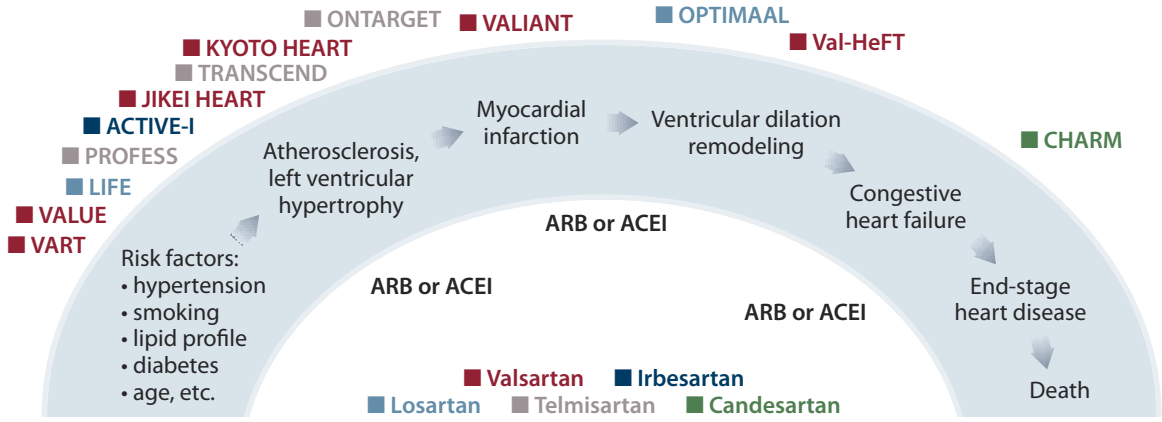
Figure 6
Major ARB Mortality and Morbidity Trials



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

and efficacy of add-on aliskiren therapy in elderly (aged 65 to 75 years) and very elderly (aged ≥ 75 years) patients.[13]

Of the 302 patients in the ALOFT trial, 127 (42.1%) fell into the elderly category and 85 (28.1%) were classified as very elderly. There were no apparent differences in terms of safety and tolerability between the age groups. In their analysis of the primary efficacy endpoint (change in NT-proBNP), the ALOFT investigators observed a significant benefit of add-on aliskiren therapy vs. placebo overall, with even more marked benefit vs. placebo in patients in the elderly and very elderly subgroups (with the greatest reduction relative to placebo being observed in the very elderly subgroup.)

Conclusion

Pharmacologic inhibition of the RAS (*i.e.*, with ACE inhibitors, ARBs, aldosterone antagonists and DRIs) has been consistently shown to be beneficial through the continuum of CV disease (for example with ARBs specifically, see Figure 6). The research presented at the 2009 ESC Congress has added to the growing evidence base for these agents, and has further confirmed their role as essential components of risk-reduction strategies in patients at risk of CV events.

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