Mineralocorticoid receptor blockade (MRB) has been shown to improve survival and reduce hospitalizations for heart failure (HF) in patients with chronic severe HF (New York Heart Association class III to IV) because of systolic left ventricular dysfunction and HF. The role of MRB in patients with mild-to-moderate HF (New York Heart Association class II) because of systolic left ventricular dysfunction is currently under investigation in a large-scale prospective, randomized study (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure [EMPHASIS-HF]). MRB has also been shown to improve echocardiographic indices of diastolic function in patients with diastolic HF and is currently under investigation in a large-scale prospective, randomized study in patients with HF and preserved left ventricular function, Treatment of Preserved Cardiac function heart failure with an Aldosterone ant agonist (TOPCAT).

Costello-Boerrigter et al, in this issue of Hypertension, shift our focus to the potential role of MRB in asymptomatic left ventricular dysfunction (ALVD). The Studies Of Left Ventricular Dysfunction (SOLVD) prevention trial has shown the benefit of an angiotensin-converting enzyme (ACE) inhibitor and a β-adrenergic receptor blocking agent to improve survival and to reduce hospitalizations for HF in patients with ALVD. There is, however, reason to believe that MRB will add to the beneficial effects of an ACE inhibitor and/or an angiotensin receptor blocker and a β-adrenergic receptor blocking agent. Although an ACE inhibitor and/or an angiotensin receptor blocker can transiently decrease the production of aldosterone from the adrenal gland, they cannot prevent its production over the long run, because stimuli other than aldosterone II (Ang II), such as corticotropin and extracellular potassium, are also important for the production of aldosterone. Furthermore, some of the adverse effects of Ang II have been shown to be mediated by aldosterone, and spironolactone has been shown to prevent some of the effects of Ang II. Blockade or inhibition of both Ang II and aldosterone results in greater benefit than either alone. Similarly, whereas β-adrenergic receptor blocking agents decrease renin, and, thus, Ang II, they cannot prevent the production of aldosterone from the adrenal gland. In contrast, there is evidence that some of the adverse effects of β-adrenergic stimulation on the myocardium can be prevented by MRB. In spontaneously hypertensive rats given a continuous infusion of the β-adrenergic agonist isoproterenol, MRB prevented ventricular dilatation, wall thinning, pump dysfunction, and collagen formation and, thus, the transition from compensated left ventricular hypertrophy to ventricular dilatation and pump dysfunction.

Myocardial damage and ventricular dilatation result in activation of the local renin-angiotensin-aldosterone system (RAAS) and an increase in the tissue levels of both Ang II and aldosterone, as well as an increase in endothelin and norepinephrine. Once the renin-angiotensin-aldosterone system is activated, a vicious cycle begins. An increase in Ang II can cause the local and eventually the adrenal production of aldosterone and an increase in MR expression in the myocardium. Stimulation of the mineralocorticoid receptor results in an upregulation of tissue ACE and the angiotensin II type-1 (AT1) receptor resulting in its further activation.

MRB has been found to be effective in preventing ventricular dilatation, myocardial fibrosis, and hypertrophy and to prevent an increase in metalloproteinases 2 and 9, as well as to prevent a decrease in capillary density in an animal model of ALVD. MRB has also been shown to lower blood pressure, prevent the progression of left ventricular hypertrophy, and to reduce the incidence and degree of microalbuminuria in patients with essential hypertension. An increase in aldosterone and/or an upregulation of the MR as a result of myocardial damage and ventricular dilatation is associated with an increase in oxidative and nitrosative stress; a decrease in NO availability; stimulation of the nuclear factor xB and activator protein-1 signaling pathways; an immunostimulatory state; an increase in myocardial cytokine production including cyclooxygenase-2, membrane cofactor protein-1, and osteopontin; microvascular inflammation and injury; and perivascular and myocardial fibrosis, with subsequent diastolic dysfunction and coronary lesions. Activation of the MR eventually results in left ventricular hypertrophy, both pressure dependent and independent. An increase in serum aldosterone and/or upregulation of myocardial MRB resulting from myocardial damage is also associated with an increase in myocyte action potential duration and an increase in myocyte calcium concentration, which could predispose to ventricular arrhythmias and sudden cardiac death.

Thus, MRB, in addition to an ACE inhibitor and/or an angiotensin receptor blocker and a β-adrenergic receptor blocking agent, soon after the development of ALVD, might prevent progressive myocardial fibrosis, hypertrophy, apoptosis, and ventricular remodeling and delay the onset of
aldosterone-induced sodium retention and renal damage and, thus, the transition to symptomatic HF, as well as its consequences sudden cardiac death and death because of progressive HF.

Although the promise of MRB in patients with ALVD to prevent the development of symptomatic HF and death is great, it will be essential to further understand the natural history of ALVD and to carefully evaluate the net risk/benefit and cost/benefit of this strategy in large-scale adequately powered, prospective, randomized studies before applying it to clinical practice.

Disclosures
B.P. has a significant relationship to Pfizer, Novartis, and AstraZeneca. He is on the consultant/advisory boards and is part of the speakers bureau.

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Promise of Mineralocorticoid Receptor Blockade in Asymptomatic Left Ventricular Dysfunction
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