

## Section 14: Managing Patients with Hypertension and Heart Failure

### Overview

Blood pressure is a simple measurement that assesses the interaction of heart function with vascular impedance. When heart function is normal, the impedance is the main determinant of blood pressure. Therefore, pressure (systolic and mean) becomes a powerful risk factor for development of left ventricular (LV) hypertrophy, increased myocardial oxygen consumption, coronary atherosclerosis, and subsequent heart failure (HF).<sup>1,2</sup> Control of blood pressure in this setting is critical to prevent the development and progression of LV dysfunction.<sup>3</sup>

When LV function is impaired, however, the relationship between impedance and cardiac function becomes more complex. Increases of impedance may impair LV emptying and thus not be reflected in a higher pressure. Under those circumstances therapy is aimed at the impedance, not at the blood pressure. Indeed, blood pressure may rise in response to effective therapy that improves LV emptying or reverses remodeling even if the impedance is reduced.

### Recommendation for Patients with Hypertension and Preserved Left Ventricular Ejection Fraction (LVEF) and Asymptomatic Left Ventricular Hypertrophy (LVH), or for Patients with Hypertension and HF with Preserved LVEF (Stage B)

**14.1 It is recommended that blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be <130/<80 mm Hg, if tolerated. (Strength of Evidence = A)**

### Recommendations for Patients with Hypertension and Asymptomatic LV Dysfunction With LV Dilation and a Low LVEF

**14.2 Prescription of an angiotensin converting enzyme (ACE) inhibitor (dose equivalent to 20 mg daily enalapril) is recommended (Strength of Evidence = A)**

**14.3 Addition of a beta blocker (dose equivalent to HF trials) is recommended even if blood pressure is controlled. (see Table 7.1) (Strength of Evidence = C)**

**14.4 If blood pressure remains > 130/80 mm Hg then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) or other antihypertensive drugs. (Strength of Evidence = C)**

### Recommendations for Patients with Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF

**14.5 Prescription of target doses of ACE inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended, based on doses used in large-scale outcome trials (see Table 7.1). (Strength of Evidence = A)**

**14.6 If blood pressure remains > 130/80 mm Hg, a dihydropyridine calcium antagonist (eg, amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. (Strength of Evidence = C)**

### Background

**Target Blood Pressure in HF.** In hypertensive patients with evidence for LV dysfunction, therapy should be aimed at blood pressure reduction to the lowest levels that can be achieved without side effects, particularly when the LV dysfunction is associated with signs and symptoms of HF and preserved LV chamber dimension and LVEF. Most guidelines agree that a systolic pressure <130 mmHg or even lower may be optimal.<sup>4-7</sup> All effective antihypertensive drugs can reverse LV hypertrophy, but clinical trial data suggest that inhibition of the renin-angiotensin-aldosterone system with ACE inhibitors or ARBs may be most effective.<sup>8,9</sup> Adequate pressure reduction usually requires two or more drugs with different and complementary mechanisms of action.<sup>5,6</sup>

In hypertensive patients with HF and a dilated ventricle, therapy is aimed not predominantly at the pressure but at the vascular impedance and the cardiac structural remodeling.<sup>10,11</sup> Previously hypertensive patients respond similarly to drugs such as ACE inhibitors or ARBs, whether their pretreatment pressure is elevated, normal, or low.<sup>12,13</sup> In the patient population studied in the African-American Heart Failure Trial (A-HeFT), patients with lower systolic blood pressure (SBP) had a similar relative benefit from the use of isosorbide dinitrate/hydralazine as those with a higher SBP. The treatment did not reduce SBP that was already low.<sup>14</sup>

**J-Shaped Curve.** Several investigations suggest a link between excessive blood pressure lowering and an increased risk of clinical events. Data from the Hypertension Optimal Treatment (HOT) trial were modeled to evaluate the relationship between the level of blood pressure achieved and clinical risk.<sup>13</sup> In this analysis, more intensive diastolic blood pressure (DBP) lowering was associated with a lower risk of cardiovascular events among several subgroups, including diabetes, patients with ischemic heart disease, women, older patients, and patients classified as high or very high risk. In contrast, current smokers who

achieved greater levels of DBP lowering ( $\leq 80$  mmHg) had a higher risk of all types of cardiovascular events, except for myocardial infarction. These data minimize the clinical concern associated with lowering blood pressure, and suggest that the potential benefits on ventricular structure and function may outweigh the potential risks of a J-curve.

It is difficult to draw definitive conclusions about the existence of a J-curve and the optimal blood pressure for HF patients from these data derived in a non-HF hypertensive population; low blood pressure in HF patients, particularly in the acute setting, often reflects a low output state due to severe LV dysfunction, and may merely be a marker of poor outcome rather than a cause of poor outcome. Nonetheless, these data emphasize the need for more research to determine the optimal level of blood pressure for patients with HF.

**Blood Pressure Change and Outcome in HF.** Reviewing the data concerning the relationship of blood pressure change to outcome in HF reveals a complex relationship. On the positive side, large ACE inhibitor trials demonstrate a reduction in cardiovascular events and an improvement in ventricular structure associated with modest reductions in blood pressure.<sup>15–17</sup> In the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients who received enalapril had final measured blood pressures averaging 120/78 mmHg, 5/3 mmHg lower than the placebo arm. An echocardiographic substudy demonstrated improved ventricular structure and reduction in LV hypertrophy in symptomatic or asymptomatic patients with LV systolic dysfunction.<sup>18</sup>

However, agents demonstrated to lower blood pressure have not always conferred a mortality benefit, and the degree of blood pressure reduction has not necessarily correlated with the degree of clinical benefit. Strong mechanistic arguments can be made that in some cases these drugs were associated with other adverse effects that would be very likely to limit any benefit from blood pressure reduction. Neurohormonal activation may occur in response to rapid or excessive drops in blood pressure; agents that reduce blood pressure by direct vasodilation mechanisms without neurohormonal inhibitory effects may lack the ability to reduce morbidity and mortality.<sup>19–23</sup>

On the whole it appears that benefits of lowering blood pressure in hypertensive patients with asymptomatic and symptomatic LV dysfunction are dependent on the resting blood pressure and the type of agents used. Drugs that lower blood pressure and produce neurohormonal blockade have produced the best results. When such agents can be used with additional drugs that lower blood pressure further without neurohormonal activation, achievement of aggressive blood pressure goals seems likely to confer additional risk reduction in patients with HF.

## References

- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
- Vasan RS, Larson MG, Leip EP, Evans JC, O'donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–7.
- Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. *J Am Coll Cardiol* 1999;33:951–8.
- K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;43: S1–290.
- Arauz-Pacheco C, Parrott MA, Raskin P. Hypertension management in adults with diabetes. *Diabetes Care* 2004;27(Suppl. 1):S65–7.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–52.
- Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004;18:139–85.
- Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de FU, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995–1003.
- Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, et al. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation* 2001;104:1615–21.
- Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E. Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 1995;13:1091–5.
- Schlaich MP, Schmieder RE. Left ventricular hypertrophy and its regression: pathophysiology and therapeutic approach: focus on treatment by antihypertensive agents. *Am J Hypertens* 1998;11:1394–404.
- Zanchetti A, Hansson L, Menard J, Leonetti G, Rahn KH, Warnold I, et al. Risk assessment and treatment benefit in intensively treated hypertensive patients of the hypertension Optimal Treatment (HOT) study. *J Hypertens* 2001;19:819–25.
- Zanchetti A, Hansson L, Clement D, Elmfeldt D, Julius S, Rosenthal T, et al. Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? *J Hypertens* 2003;21: 797–804.
- Anand IS, Tam SW, Rector TS, Taylor AL, Sabolinski ML, Archambault WT, et al. Influence of blood pressure on the effectiveness of a fixed-dose combination of isosorbide dinitrate and hydralazine in the African-American Heart Failure Trial. *J Am Coll Cardiol* 2007;49:32–9.
- Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782–8.
- SOLVD Investigators. The effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
- Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53.
- Quinones MA, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, et al. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. *Studies of Left Ventricular Dysfunction*. *J Am Coll Cardiol* 2000;35:1237–44.

19. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325:303–10.
20. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation* 1997;96:856–63.
21. Lip GY. Regression of left ventricular hypertrophy and improved prognosis: some hope now... or hype? *Circulation* 2001;104:1582–4.
22. Messerli FH, Mehra MR. Crumbling of left ventricular hypertrophy as a surrogate end point (the Losartan for Intervention for Endpoint Reduction in Hypertension [LIFE] Study). *Am J Cardiol* 2002;90:1133–4.
23. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med* 1996;335:1107–14.