REVIEW

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Treatment of Hypertension in Patients with Coronary Artery Disease. A Case-Based Summary of the 2015 AHA/ACC/ASH Scientific Statement

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ABSTRACT

The 2015 American Heart Association/American College of Cardiology/American Society of Hypertension Scientific Statement "Treatment of Hypertension in Patients with Coronary Artery Disease" is summarized in the context of a clinical case. The Statement deals with target blood pressures, and the optimal agents for the treatment of hypertension in patients with stable angina, in acute coronary syndromes, and in patients with ischemic heart failure. In all cases, the recommended blood pressure target is <140/90 mm Hg, but <130/80 mm Hg may be appropriate, especially in those with a history of a previous myocardial infarction or stroke, or at high risk for developing either. These numbers may need to be revised after the publication of the SPRINT data. Appropriate management should include beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and in the case of heart failure, aldosterone antagonists. Thiazide or thiazide-like (chlorthalidone) diuretics and calcium channel blockers can be used for the management of hypertension, but the evidence for improved outcomes compared with other agents in hypertension with coronary artery disease is meager. Loop diuretics should be reserved for patients with New York Heart Association Class III and IV heart failure or with a glomerular filtration rate of <30 mL/min.

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"To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."

William Osler, Books and Men, in *Aequanimitas* (p 32).[1]

July 2015 saw the publication of the Scientific Statement "Treatment of Hypertension in Patients with Coronary Artery Disease," sponsored by the American Heart Association, the American College of Cardiology, and the American Society of Hypertension.[2-5] The motivation for the Statement was clear: there is a strong epidemiologic association between hypertension and coronary artery disease; they have many pathophysiologic features in common and there are unique management challenges in these patients.

The Oslerian epigraph above provides a cue to structure this summary of the clinical sections of the Statement around a real patient.

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BLOOD PRESSURE TARGETS

A 62-year-old man has hypertension and coronary artery disease. His hypertension is currently treated with lisinopril 20 mg per day and hydrochlorothiazide 25 mg per day. His blood pressure at his latest clinic visit is 138/88 mm Hg. He had a myocardial infarction 5 years previously.

What Is an Appropriate Blood Pressure Target for This Patient?

A major section of the statement addresses blood pressure targets. The debate on this revolves around the issue of whether targets lower than the conventional <140/90 mm Hg are appropriate or even safe for patients with coronary artery disease. Because the diastolic blood pressure is the coronary perfusion pressure, the diastolic blood pressure is the critical value in this discussion (Figure 1).[6]

There are very few clinical trial data to help us. Some studies with surrogate outcomes support a "lower is better" blood pressure target. In one of these, the intravascular ultrasound substudy of CAMELOT,[7] those subjects with a sustained blood pressure of <120/80 mm Hg had a significant decrease in coronary atheroma volume.

However, we had to wait until the ACCORD study[8] to give us some more direct evidence on which to base decisions about blood pressure goals. In ACCORD there was no significant difference in the cardiovascular outcomes (except stroke) among subjects, all with type 2 diabetes and other risk factors for cardiovascular disease, treated to an intensive (systolic blood pressure <120 mm Hg) vs a standard (systolic blood pressure <140 mm Hg) blood pressure target. However, with a mean achieved diastolic blood pressure in the intensive-therapy group at 4-8 years after randomization in the range 60-65 mm Hg, there was a numerical but statistically nonsignificant decrease in cardiovascular events. This suggests that lower diastolic blood pressures are safe, at least in the 60-65 mm Hg range, and may protect against stroke.

Our Statement is somewhat flexible:

The <140/90 mm Hg blood pressure target is reasonable for the secondary prevention of cardiovascular events in patients with hypertension and coronary artery disease (Class IIa; Level of Evidence B), but a lower target blood pressure (<130/80 mm Hg) may be appropriate in some individuals with coronary artery disease, with previous myocardial infarction, stroke or transient ischemic attack, or coronary artery disease risk equivalents (carotid artery disease, peripheral artery disease, abdominal aortic aneurysm) (Class IIb; Level of Evidence B).

CLINICAL SIGNIFICANCE

- Blood pressure target for patients with hypertension or coronary artery disease is <140/90 mm Hg, or <130/80 mm Hg if high risk for myocardial infarction or stroke.
- Beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the mainstay of treatment, supplemented where appropriate by calcium channel blockers, or thiazide or thiazide-like diuretics. Loop diuretics should be reserved for those with severe heart failure or severe chronic kidney disease.
- Mineralocorticoid inhibitors (spironolactone and eplerenone) are effective in ischemic heart failure as well as resistant hypertension.

Even more compelling is the news[9] from SPRINT in nondiabetic subjects, with a design very close to that of ACCORD. In this study, those subjects randomized to the intensive group (systolic blood pressure goal <120 mm Hg), compared with the standard group (systolic blood pressure goal <140 mm Hg), had a reduction of 25% in the composite cardiovascular outcome measure and a 27% reduction in all-cause mortality.

The blood pressure target for our patient described above is either <140/90 mm Hg ("reasonable") or <130/80 mm Hg ("may be appropriate," especially with his history of a previous myocardial infarction). This flexibility restores to the physician and the patient the discretion to make personalized decisions on a topic about which there is no definitive consensus. It is possible that these numbers will be lowered even further when the SPRINT data are fully evaluated.

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH CORONARY ARTERY DISEASE AND STABLE ANGINA

Three months later, our patient, the 62-year-old man with hypertension and coronary artery disease, is still being treated with lisinopril 20 mg per day and hydrochlorothiazide 25 mg per day. His blood pressure today is 132/76 mm Hg. He had a myocardial infarction 5 years previously, and now reports that he has angina on exertion, after walking briskly for 4 blocks.

What Is the Appropriate Antihypertensive Drug Regimen for This Patient?

Management of hypertension in patients with chronic coronary artery disease and chronic stable angina is to prevent death, myocardial infarction, and stroke; reduce the frequency and duration of myocardial ischemia; and ameliorate symptoms.

Figure 2 is a summary of the pharmacologic treatment of hypertension in patients with stable angina, acute coronary syndrome and ischemic heart failure.

Beta-blockers. Beta-blockers are the drugs of first choice for the treatment of hypertension in patients with coronary artery disease and angina.[10,11] They reduce ischemia and angina primarily because of their negative inotropic and chronotropic actions. The decreased heart rate increases diastolic filling time for coronary perfusion, and the negative

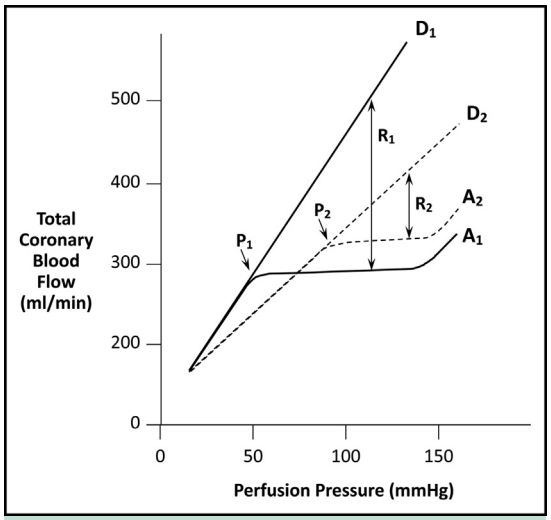

Figure 1 Autoregulation of coronary blood flow and myocardial flow reserve. Because coronary blood flow occurs almost entirely during diastole, the diastolic blood pressure can be regarded as the coronary perfusion pressure. The numbers on the 2 axes are purely hypothetical. A_1 represents the relationship of perfusion pressure (diastolic blood pressure) and total coronary blood flow. Within a range of diastolic blood pressures, flow is constant because of autoregulatory changes in coronary vascular resistance. For example, if the diastolic blood pressure decreases, there is dilatation of the coronary vascular bed, so that flow remains constant. However, there are limits to the extent to which coronary resistance vessels can dilate or constrict; thus, there are lower and upper limits to the autoregulatory capacity. P_1 is the lower limit of the autoregulatory range. D_1 is the pressure-flow relationship in the maximally dilatated vascular bed. At any given perfusion pressure, the coronary flow reserve is R_1. A_2, P_2, and R_2 represent corresponding values for patients with hypertension or left ventricular hypertrophy, or both. In these patients, the lower limit of coronary autoregulation is shifted to the right ($P_1 \rightarrow P_2$), increasing the vulnerability of the myocardium to a severe drop in blood pressure. Also, at any given perfusion pressure, the coronary flow reserve is less in the hypertensive/hypertrophied hearts, a further hazard, such as during exercise or any other situation requiring increased coronary flow. (Modified from Rosendorff C. Ischemic heart disease in hypertension. In: Black HR, Elliott WJ, eds. *Hypertension, A Companion to Braunwald's Heart Disease*. Philadelphia: Saunders Elsevier; 2007:327-339.[6])

inotropic and chronotropic actions reduce myocardial oxygen demand. Cardioselective (β_1-selective) agents without intrinsic sympathomimetic activity, such as metoprolol or bisoprolol, are recommended.

Angiotensin-converting Enzyme Inhibitors. The clinical trials that support the use of angiotensin-converting enzyme (ACE) inhibitors in hypertension and stable angina are the HOPE study (ramipril),[12] the EUROPA (perindopril),[13] and the SAVE trial (captopril).[14]

Angiotensin Receptor Blockers. Angiotensin receptor blockers (ARBs) are reasonable for patients with stable angina and hypertension who are intolerant of ACE inhibitors. In the VALUE trial,[15] and in VALIANT,[16] there was no difference in cardiac mortality and morbidity in patients with hypertension and high risk of cardiovascular events who were treated with a regimen based on valsartan vs amlodipine or captopril.

Calcium Channel Blockers. Although nondihydropyridine calcium channel blockers (CCBs), such as verapamil or diltiazem, are useful in the management of hypertension in patients with stable angina, there is no consensus about their role in preventing cardiovascular events in patients with established coronary artery disease.

INVEST[17] compared verapamil with the beta-blocker atenolol in >22,000 hypertensive patients with chronic coronary artery disease. There was no difference between the groups in the composite cardiovascular end point. Nondihydropyridine CCBs (verapamil or diltiazem) can be prescribed for relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects in patients with stable angina, but should not be prescribed if there is heart failure, and generally not together with beta-blockers, because of their potent negative inotropic and chronotropic actions.

Diuretics. Thiazide diuretics or thiazide-like diuretics, such as chlorthalidone or indapamide, reduce cardiovascular events, as demonstrated in early studies such as the Veterans Administration studies,[18] the MRC Trial,[19] and SHEP,[20] all with thiazides, and in later studies, in ALLHAT,[21] using chlorthalidone.

Therefore, according to the 2015 Statement, our patient should be treated as follows:

A beta-blocker, an ACE inhibitor (or ARB), and a thiazide or thiazide-like diuretic. He is on an ACE inhibitor and diuretic, so a beta-blocker should be added. The preferred beta-blockers are metoprolol or bisoprolol. Also, consideration could be given to changing his hydrochlorothiazide to chlorthalidone. If beta-blockers are contraindicated or produce intolerable side effects, a nondihydropyridine CCB (such as diltiazem or verapamil) may be substituted, but not if there is left ventricular dysfunction. The combination of a beta-blocker and either of the nondihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic coronary artery disease and hypertension because of the increased risk of significant bradyarrhythmias and heart failure.

If either the angina or the hypertension remains uncontrolled, a long-acting dihydropyridine CCB (such as amlodipine, felodipine, long-acting nifedipine) can be added to the basic regimen of beta-blocker, ACE inhibitor, and thiazide or thiazide-like diuretic.

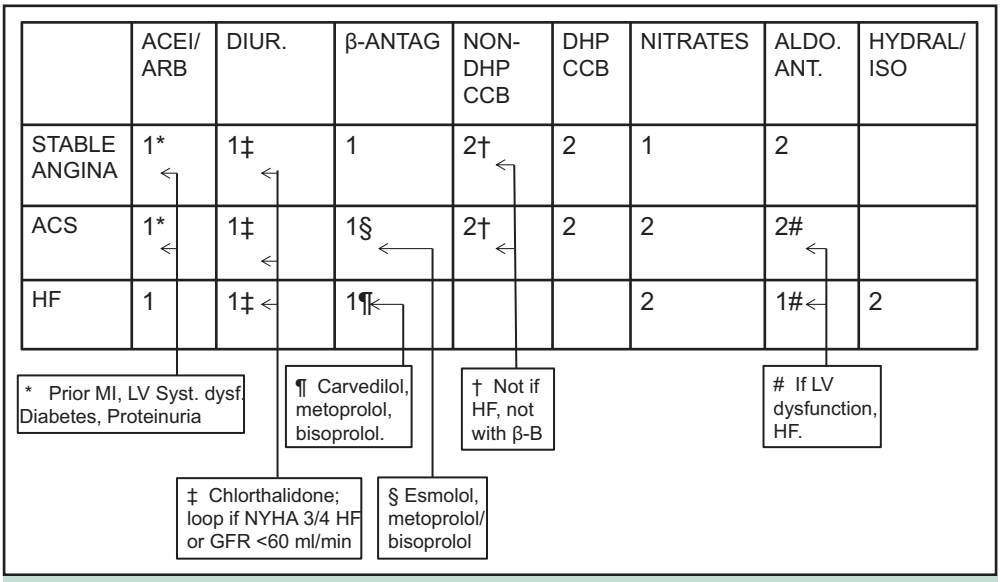

Figure 2 Drugs for the treatment of hypertension in patients with coronary artery disease. 1 and 2 represent drugs of first choice and alternate/second line choices, respectively. ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ALDO-ANT = aldosterone antagonist; β-ANTAG = β-antagonist; β-B = beta-blocker DHP CCB = dihydropyridine calcium channel blocker; DIUR = diuretic; GFR = glomerular filtration rate; HF = heart failure; HYDRAL/ISO = hydralazine and isosorbide; LV Syst.dysf. = left ventricular systolic dysfunction; MI = myocardial infarction; NON-DHP CCB = nondihydropyridine calcium channel blocker; NYHA = New York Heart Association. (Modified from Rosendorff et al.[2-5])

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH ACUTE CORONARY SYNDROMES

The same patient, the 62-year-old man, has a beta-blocker, aspirin, and a nitrate added to his regimen. In subsequent visits these drugs had their doses titrated to maintain the blood pressure at <130/80 mm Hg. At his last clinic visit his blood pressure was 124/74 mm Hg, heart rate was 64 beats per minute, sinus rhythm, and he was taking lisinopril 20 mg per day, chlorthalidone 25 mg per day, metoprolol succinate 50 mg per day, aspirin 81 mg per day, a statin, and sublingual nitroglycerin when required. He was feeling fine, and his angina attacks had stopped.

Two months later he is admitted to your hospital with chest pain and an anteroseptal non-ST-segment elevation myocardial infarction. His vital signs are stable, but his blood pressure is now 172/94 mm Hg. There is some pulmonary venous congestion on a chest radiograph, but he does not have any other signs of heart failure. His serum creatinine concentration is 1.0 mg/dL.

What Is the Appropriate Antihypertensive Drug Regimen for This Patient Now? What Is the Blood Pressure Goal?

Hypertension is common in patients with acute coronary syndromes. Hypertension is an independent predictor of death and recurrent myocardial infarction at 90 days. Uncontrolled hypertension is also a relative contraindication to fibrinolytic therapy because of the risk of hemorrhagic stroke. Specific trials of blood pressure lowering have not been performed in patients with acute coronary syndromes. Fortunately, drugs that have an established role in the treatment of hypertension are the same agents that have been shown to improve outcomes in acute coronary syndromes.

Beta-blockers. Beta-blockers are an important part of acute coronary syndrome treatment,[22,23] based upon their ability to reduce both heart rate and blood pressure, and therefore, myocardial oxygen demand. Beta-blockers reduce infarct size, and reduce early sudden death postmyocardial infarction, mainly via their antiarrhythmic effects. In patients with ST-elevation myocardial infarction, the long-term benefits of chronic postdischarge beta-blocker administration have been shown in many trials.

In general, short-acting β_1-selective agents are preferable, such as metoprolol or bisoprolol. Carvedilol, which also blocks β_2- and α_1-adrenergic receptors, is also a good choice for patients with acute coronary syndrome and severe hypertension.

ACE Inhibitors. ACE inhibitors are indicated for most patients with acute coronary syndrome. In ST-elevation myocardial infarction, ACE inhibitors reduce infarct

expansion, prevent left ventricular remodeling and chamber dilatation, ventricular arrhythmias, heart failure, or even myocardial rupture. A meta-analysis from the ACE Inhibitor Myocardial Infarction Collaborative Group[24] found a 7% lower relative mortality rate at 30 days in patients treated with ACE inhibitors. When started later post myocardial infarction among individuals with left ventricular dysfunction, and continued long term, the benefits of ACE inhibitors are even more robust.[25]

Angiotensin Receptor Blockers. The VALIANT trial[16] showed that valsartan was as effective as captopril for reducing cardiovascular events in high-risk patients through 2 years of follow-up after a myocardial infarction. On the other hand, in the OPtimal Trial In OPTIMAAL[26] there was a trend toward increased mortality in patients receiving 50 mg of losartan once daily over patients receiving captopril. These negative results may have been due to inadequate dosing of losartan. In general, due to the larger and more consistent evidence base for ACE inhibitors, these agents are preferred over ARBs for patients that can tolerate them, but ARBs are a first-line alternative for ACE inhibitor-intolerant patients.

Calcium Channel Blockers. CCBs have not been found to be useful in the management of acute coronary syndromes. The nondihydropyridine agents, diltiazem and verapamil, have been disappointing in the early-myocardial infarction setting and are recommended only if beta-blockers are contraindicated or cause intolerable side effects.[22,23] Among patients with left ventricular dysfunction, there is a detrimental effect on mortality.

Evidence for the use of dihydropyridine CCBs in acute coronary syndromes is limited.

Aldosterone Antagonists. Aldosterone, which is incompletely suppressed even among individuals on high dosages of ACE inhibitors, is thought to contribute both to adverse ventricular remodeling and myocardial fibrosis after myocardial infarction. Both the EPHESUS[27] (eplerenone) and RALES[28] trials showed benefit in patients with myocardial infarction and left ventricular dysfunction.

Diuretics. Although thiazide and thiazide-type diuretics (chlorthalidone, indapamide) play a major role in the long-term control of blood pressure, in the acute setting, diuretics are primarily used for patients with evidence of increased filling pressures, pulmonary venous congestion, or heart failure. Loop diuretics are preferred over thiazide and thiazide-type diuretics for patients with acute coronary syndrome who have heart failure (New York Heart Association [NYHA] Class III or IV) or for patients with chronic kidney disease and a glomerular filtration rate of <30 mL/min.

Blood Pressure Goal in Acute Coronary Syndromes

Therapeutic targets for blood pressure have not been established specifically for patients with acute coronary syndromes. The blood pressure may fluctuate early after acute coronary syndrome and thus, efforts should focus on pain control and clinical stabilization before blood pressure is specifically targeted. A blood pressure target of $<130/80$ mm Hg at the time of discharge from the hospital is a reasonable option.

Therefore, according to the 2015 Statement, our patient should be treated as follows:

If there is no contraindication to the use of beta-blockers, the initial therapy of his hypertension should include:

1. If hemodynamically stable, a short-acting β_1-selective beta-blocker without intrinsic sympathomimetic activity; metoprolol tartrate, followed by the longer-acting metoprolol succinate, or bisoprolol.
2. An ACE inhibitor; he has an anterior myocardial infarction and left ventricular dysfunction.
3. A thiazide or thiazide-like diuretic; he has pulmonary venous congestion.
4. Sublingual nitroglycerin: for the symptomatic relief of chest pain.
5. Other usual measures for the management of acute coronary syndrome as indicated, such as fibrinolytic therapy, percutaneous coronary intervention, antithrombotic therapy, and antiplatelet therapy.

His target blood pressure is $<140/90$ mm Hg, but a target of $<130/80$ mm Hg at the time of discharge from the hospital is a reasonable option.

MANAGEMENT OF HYPERTENSION IN ISCHEMIC HEART FAILURE

Our patient, the 62-year-old man, is discharged from the hospital on metoprolol succinate 50 mg per day, lisinopril 40 mg per day, chlorthalidone 25 mg per day, sublingual nitroglycerin when necessary, and aspirin 81 mg per day, and a statin. His blood pressure on discharge is 128/76 mm Hg and he is hemodynamically stable, with no evidence of left ventricular decompensation. He is followed up every 3 months and is doing well.

Three years later he is admitted to the hospital with progressive dyspnea on exertion (now 10 yards), bilateral ankle edema, an elevated jugular venous pressure, and bibasilar pulmonary crackles. His blood pressure is 162/88 mm Hg, heart rate 86 beats per minute, sinus rhythm; he has a third heart sound and a 2/6 ejection systolic murmur. Serum electrolyte concentrations are normal. The chest radiograph shows moderate cardiomegaly and moderate-to-severe pulmonary venous congestion. An echocardiogram shows increased left ventricular and left atrial lumen diameters, mild mitral regurgitation, mild aortic valve calcification, and an ejection fraction of 32%.

What Is the Appropriate Antihypertensive Drug Regimen for This Patient? What Is the Blood Pressure Goal?

The therapeutic goals in patients presenting with heart failure are to reverse hemodynamic abnormalities, relieve symptoms, and initiate treatments that will decrease disease progression and improve survival. Most of the agents shown in clinical trials to improve survival in heart failure with reduced ejection fraction are also antihypertensive drugs, which makes management easier. On the other hand, the same drugs have largely been disappointing in the long-term management of heart failure with preserved ejection fraction, but are still prescribed for blood pressure control.

Diuretics. Diuretics are used both as antihypertensive drugs and to reverse volume overload and associated symptoms. Thiazide or thiazide-type diuretics should be used for blood pressure control and to reverse volume overload and associated symptoms in NYHA Class I and II heart failure. In severe heart failure (NYHA Class III and IV), or in patients with severe renal impairment (glomerular filtration rate <30 mL/min), loop diuretics should be used for volume control, but these are less effective than thiazide or thiazide-type diuretics in lowering blood pressure.

ACE Inhibitors and ARBs. ACE inhibitors and ARBs reduce ventricular remodeling, improve ischemic preconditioning, reverse angiotensin II-induced vasoconstriction, prevent the depletion of high-energy phosphate stores, enhance nitric oxide release through prevention of bradykinin breakdown, and reduce blood coagulability through the endothelial release of tissue plasminogen activator. ACE inhibitors have been shown in many trials to be beneficial in patients with left ventricular dysfunction of ischemic origin.[14,17,25,29] Both Val-HeFT,[30] and the CHARM program[31] reported a significant benefit with the use of valsartan and candesartan, respectively.

Beta-blockers. The role of beta-blockers in the management of patients with heart failure is well established. MERIT-HF[32] (metoprolol), the COPERNICUS trial[33] (carvedilol), CIBIS-II[34] (bisoprolol), and a study in the elderly, SENIORS,[35] with nebivolol, have all shown reduced mortality in patients with heart failure.

Aldosterone Receptor Antagonists. Aldosterone promotes myocardial fibrosis. The RALES (spironolactone) and EPHESIS (eplerenone) trials, previously referred to,[27,28] have both shown significant reduction in mortality and heart failure hospitalization in severe hypertension (NYHA Class III and IV). More recently the EMPHASIS-HF trial[36] of eplerenone in heart failure with reduced ejection fraction, but with mild symptoms (NYHA Class II), reported a 37% reduction in cardiovascular death or heart failure hospitalization. Because these agents are also major players in antihypertensive treatment, their use in hypertension and heart failure is particularly compelling.

Nitrates and Hydralazine. The African-American Heart Failure Trial (A-heFT)[37] showed that a combination of isosorbide dinitrate and hydralazine provided additional benefit over conventional therapy in black patients with advanced heart failure (NYHA Class III or IV).

Blood Pressure Goal in Heart Failure

Because there are no definitive data for optimal blood pressure targets in patients with hypertension and heart failure, the 2015 Statement[2-5] made the conservative recommendation that the target should be <140/90 mm Hg, but it was also suggested that consideration could be given to lowering the blood pressure even further, to <130/80 mm Hg. Once again the Statement gave expression to the idea that where there are no definitive studies to guide us; therapy should be tailored to the particular individual.

Therefore, according to the 2015 Statement, our patient should be treated as follows:

Drug therapy should include a beta-blocker (carvedilol, metoprolol succinate, bisoprolol, or nebivolol), an ACE inhibitor (or ARB, candesartan or valsartan), and an aldosterone receptor antagonist (spironolactone or eplerenone). A thiazide or thiazide-like (chlorthalidone) diuretic can be used for blood pressure and volume control; however, because our patient is NYHA Class III, a loop diuretic (furosemide) is indicated.

After 3 days in the hospital, our patient is discharged on carvedilol (3.125 mg twice a day [bid], increasing to 6.25, 12.5, and 25 mg bid at 2 weekly intervals, if tolerated), lisinopril 40 mg/d, spironolactone 25 mg/d, furosemide 20 mg bid, aspirin 81 mg/d, and a statin. He is no longer fluid overloaded, his blood pressure is 128/76 mm Hg, heart rate is 68 beats per minute, sinus rhythm, and he can walk 200 yards with no dyspnea or angina. Follow-up visits at 3 and 6 months show no decline in exercise tolerance and no signs of cardiac decompensation. A therapeutic victory.

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