

## HYPERTENSION AND CARDIOVASCULAR DISEASE

# Management of Hypertension in Patients with Cardiovascular Disease

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## ABSTRACT

Systemic hypertension (HTN) is the most common risk factor for cardiovascular disease (CVD) in the world. Management of HTN in established CVD requires an integrated approach that is built on the foundation of pathophysiology and tailored to the major patient subsets – stable ischemic heart disease (SIHD), acute coronary syndromes (ACS) and heart failure (HF). This review expands on these concepts by establishing the link between hypertension and the CVD subsets, discussing goals and targets in each situation, and finally looking at what the current guidelines recommend regarding the choice of pharmacotherapy.

**Keywords:** Acute coronary syndrome, Heart failure, Hypertension, Stable ischemic heart disease.

**How to cite this article:** Venugopal K, Ahmad ZS. Management of Hypertension in Patients with Cardiovascular Disease. *Hypertens J* 2016;2(1):10-15

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

Hypertension (HTN) is the most common risk factor for cardiovascular disease (CVD) in the world, particularly so in South Asia as reported by the Global Burden of Disease Study.<sup>1</sup> The INTERHEART study across 52 countries demonstrated that nine risk factors were responsible for the development of acute myocardial infarction (MI) all over the world.<sup>2</sup> The most important and frequent risk factor identified among these was systemic HTN. It has been shown that reduction in blood pressure (BP) would result in significant reduction in the occurrence of coronary artery disease (CAD), stroke, and renal failure. Recent guidelines have modified the targets for BP lowering in elderly patients. Management of HTN in patients with cardiovascular problems, from primary and secondary prevention measures to control of BP in specific clinical situations such as stable ischemic heart disease, acute coronary syndromes (ACS), and heart failure (HF), needs to be critically assessed with respect to targets of BP, specific pharmacotherapy in different

situations and maintaining optimal tissue perfusion especially in the coronary and cerebral circulation.

## Prevalence of Hypertension in India

A meta-analysis of prevalence, awareness, and control of HTN in India published in 2014 showed an overall prevalence of 33% in urban and 25% in rural population. Only 25.3% of the rural population and 42% of urban population are aware of HTN and 25.1% of rural and 37.6% urban population are getting treatment. Control of BP was seen in 10.7% of rural Indians and 20.2% of urban Indians.<sup>3</sup> As nearly 18% of the world population is from India, this would translate into vast numbers of potentially treatable patients who would benefit by prevention of premature CAD, stroke, and renal disease. It is estimated that HTN is directly responsible for 57% of all stroke deaths and 24% of coronary deaths in India.<sup>4</sup>

## Secondary Prevention in Patients with Hypertension and Coronary Artery Disease

It is now clearly recognized that the lowering of BP is more important in long-term prognosis than the class of drugs used. The independent risk factors of CVD risk other than HTN are diabetes mellitus (DM), dyslipidemia, smoking, obesity, and chronic kidney disease (CKD). Presence of other concomitant risk factors greatly increases the risk of cardiovascular morbidity and mortality. Control of other risk factors is equally important when managing patients with HTN and established CVD. Recent lipid guidelines advocate the use of only statins in the four high-risk groups and the use of other lipid-lowering drugs has not been shown to reduce CVD risk.<sup>5</sup> Control of diabetes in a patient with established CAD and HTN is important in secondary prevention strategies. Smoking in hypertensive patients carry higher mortality than nonsmokers and the HTN is severe in smokers compared with nonsmokers. Weight reduction, regular physical activity, and salt restriction are other important strategies in secondary prevention in hypertensive patients with CAD. Chronic kidney disease and peripheral arterial disease (PAD) are important considerations in the treatment of patients with HTN and CAD.

Drug therapy for secondary prevention in hypertensive patients with CAD has been mainly focused around

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angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and beta-blockers (BBs). Beta-blockers are drugs of choice in patients with CAD and angina and with left ventricular (LV) dysfunction. Angiotensin-converting enzyme inhibitors are indicated in all patients after an MI. The HOPE trial<sup>6</sup> and EUROPA trial<sup>7</sup> demonstrated the cardioprotective effects of ACEIs. Angiotensin receptor blockers are currently indicated in a situation where ACEIs cannot be given. It is to be noted that the combination of ACEIs and ARBs did not give an additional benefit and are not currently recommended together. Calcium channel blockers (CCBs), though effective antihypertensive and antianginal agents, are not routinely recommended in secondary prophylaxis due to lack of data showing effectiveness. They can be considered in situations wherein BBs cannot be used as in severe bronchospastic disease.

### Hypertension in Established Cardiovascular Disease

Management of HTN in established CVD is discussed under the following situations:

- Hypertension in a patient with stable ischemic heart disease (SIHD);
- Hypertension in a patient with ACS;
- Hypertension in a patient with HF.

### Hypertension Management in Patients with SIHD

#### *The link*

The relationship between HTN and SIHD can be considered under the following aspects:

- Increase in myocardial oxygen demand: Episodes of surges in HTN could lead to an increase in myocardial oxygen demand and anginal episodes.
- Acceleration of atherosclerosis: Hypertension is well known to accelerate the atherosclerotic process and produce newer lesions and worsen angina.
- Left ventricular hypertrophy: Left ventricular hypertrophy, as a result of longstanding HTN, can worsen angina due to increase in the myocardial oxygen demand and can also lead to sudden cardiac death.
- Aortic dissection: Hypertension is the most important cause of aortic dissection in older patients and frequently coexists in the setting of atherosclerotic aortic disease and obstructive CAD.

### Aims of Treatment

The aims of treatment in hypertensive patients with chronic stable angina are relief of anginal symptoms, reduction of ischemic episodes and prevention of death,

MI, and stroke. The current target for BP control is <140/90 mm Hg, though lower targets of <130/80 mm Hg have been considered in the past. The role of specific drug groups is discussed as follows:

- Beta-blockers: The pharmacological properties of negative inotropism and chronotropism of BBs make them the ideal drugs for patients with HTN and angina. Cardioselective BBs without intrinsic sympathomimetic action are the agents that are being used now for this purpose. Sinoatrial blocks, atrioventricular (AV) blocks, and severe bronchospastic disease are major contraindications for their use. Peripheral arterial disease was considered a relative contraindication for their use, but a meta-analysis showed that there was no worsening of claudication. The ACC/AHA practice guidelines on PAD 2005<sup>8</sup> recommend the use of BBs in this situation. The newer generation drugs such as nebivolol and bisoprolol may be more appropriate in view of their selective actions and vasodilator properties.
- Calcium channel blockers: Currently, CCBs are prescribed in HTN with stable angina when BBs are contraindicated or not tolerated. They can be combined with BBs if the symptoms are not controlled with BBs or if the BP is remaining elevated. Dihydropyridine agents are preferably combined with BBs to avoid excess bradycardia. In patients with LV dysfunction, nondihydropyridine CCBs (verapamil and diltiazem) should not be used.
- ACEIs/ARBs: ACEIs are indicated in all CAD patients with stable angina and DM, LV dysfunction, or CKD if there are no contraindications. The current role for ARBs is in the same indications as ACEIs but when ACEIs are not tolerated. There is no clinical situation in CAD where ARBs have been found superior to ACEIs.
- Diuretics and nitrates: The ALLHAT trial demonstrated that diuretics can reduce cardiovascular events in hypertensive patients.<sup>9</sup> Their role would mainly be supportive to BBs and ACEIs in hypertensive patients with CAD. Nitrates (long-acting) are useful in situations of angina when BBs or CCBs fail to control symptoms or are contraindicated.

### ACC/AHA/ASH Recommendations 2015

Patients with HTN and chronic stable angina/SIHD can be treated with a regimen on the basis of the following recommendations<sup>10</sup>:

- Beta-blockers (prior MI), ACEI/ARB (prior MI, LV dysfunction, DM, CKD) and a thiazide diuretic (control of HTN), class 1 A level of evidence (LOE) A.

- The same combination of drugs in the absence of above indications becomes class 11a (if there is no LV dysfunction) in SIHD.
- Nondihydropyridine CCBs can be used if BBs are not tolerated or contraindicated, class 11a LOE B.
- For control of angina or HTN, a nonhydropyridine CCB can be added to BB, ACEIs/ARBs/thiazide such as diuretic class 11a LOE B.
- The target BP is <140/90 mm Hg (class 1 LOE A) but a lower target of <130/80 mm Hg may be considered in patients with stroke, carotid artery disease, peripheral artery disease, and abdominal aortic aneurysm.

### Hypertension and Acute Coronary Syndromes

#### *The link*

The relationship between systemic HTN and ACS can be considered from the following perspectives:

- Hypertension as a risk factor for ACS: Apart from being an established factor for CAD, accelerated HTN can be a trigger for plaque rupture and hence precipitate an ACS.
- ACS leading to surge in BP: A high BP in a patient with ACS may be related to pre-existing HTN or due to sympathetic activation and anxiety.
- Hypertension and bleeding risk: Uncontrolled HTN increases the risk of bleeding in a patient with ACS who is being treated with antiplatelet agents, anticoagulants, and/or thrombolytic agents. Further, access sites for coronary interventions may be a source of bleeding too. Traditionally, a BP of >180/110 mm Hg has been considered to be a relative contraindication for thrombolytic therapy in ST-elevation myocardial infarction (STEMI) due to a higher risk for intracerebral hemorrhage.<sup>11</sup> Such situations usually warrant a reduction in BP (commonly with nitroglycerine infusion) before administration of the thrombolytic agent. In addition, transient lowering of BP may often accompany thrombolytic therapy with streptokinase.
- Hypertension and mechanical complications of STEMI: Systemic HTN is a risk factor for free wall rupture. On the contrary, patients with pre-existing HTN are less likely to develop interventricular septal rupture.
- Drug treatment: The initiation and titration of BBs, ACEIs, and nitrates in ACS patients is closely linked to the patient's BP.
- Aortic dissection: A hypertensive patient with aortic dissection may present with an ACS, especially with an inferior wall MI, due to right coronary artery involvement by the proximal aortic dissection flap.

### Blood Pressure Goal in ACS

The therapeutic BP goal has not been established in ACS. A high BP increases myocardial oxygen demand. On the contrary, an excessively low diastolic BP may impair coronary perfusion. Thus, the BP management in ACS must incorporate this "demand-supply" relationship. Further, there can be a marked fluctuation in BP in the initial phase of an acute MI. Blood pressure should therefore be lowered slowly and gradually, with care taken to avoid a diastolic BP of <60 mm Hg. Generally, a BP of <140/90 mm Hg is acceptable in a post-ACS patient who is hemodynamically stable. A BP goal of <130/80 mm Hg at predischarge is a reasonable goal.

### Drug Therapy of Hypertension in ACS

A brief approach to the use of specific drugs in the setting of ACS is given below, based on the ACC/AHA/ASH recommendations 2015:

- Nitroglycerin: Nitroglycerin is an extremely useful and commonly prescribed drug for the management of high BP in ACS patients, especially in the setting of pulmonary edema or ongoing angina. However, it should be cautiously used in inferior wall MI and is contraindicated in right ventricular MI. Patients at an increased risk of hypotension include the elderly, individuals who are volume depleted, or those have used sildenafil within 24 hours or tadalafil within 48 hours.<sup>12</sup> Nitrate tolerance is a problem that can occur within 24 hours of infusion.
- Beta-blockers: They are particularly useful in the ACS because of reduction in BP, heart rate, and, therefore, myocardial oxygen demand. Unless contraindicated, they should be started in all ACS patients within 24 hours of onset of the index event. Cardioselective (beta 1) BBs without intrinsic sympathomimetic activity such as metoprolol and bisoprolol are generally preferred. Carvedilol has an additional alpha 1 blocking effect that helps lower the BP; however, its beta 2 antagonism makes it unfavorable in patients with reactive airway disease.<sup>13</sup> Intravenous agents such as esmolol may be considered in case of severe HTN with ongoing ischemia or tachyarrhythmia.
- Calcium channel blockers: The nondihydropyridine CCBs (verapamil and diltiazem) may be given if BBs are contraindicated due to reactive airway disease. However, they are contraindicated in ACS with left ventricular dysfunction. Dihydropyridine CCBs effectively lower the BP in the setting of ACS and are recommended if BP is not controlled with BBs and ACEIs. They have a specific role in the management of vasospastic angina too.

- ACEIs and ARBs: These drugs have an established role in ACS, regardless of the presence of systemic HTN. ACEIs are preferred as first-line agents, with ARBs being recommended as effective replacements in case of intolerance to ACEIs. The combination of these two classes of drugs is not recommended.
- Aldosterone antagonists: Eplerenone and spironolactone are extremely useful drugs in ACS with HF and diabetes. However, they are contraindicated in renal dysfunction (creatinine >2.5 mg/dl in males and >2.0 mg/dl in females) and hyperkalemia (serum potassium >5 meq/l), due to risk of hyperkalemia, especially if creatinine clearance is <50 ml/min and along with ACEI/ARB therapy.<sup>14</sup>
- Diuretics: They are not primarily chosen for BP control in ACS. Loop diuretics are often preferred in ACS patients with HF and pulmonary venous congestion, especially if there is renal dysfunction. However, particular attention must be given to the avoidance of hypokalemia, which can be particularly proarrhythmic in the setting of ACS.<sup>15</sup>

## Hypertension and Heart Failure

### The link

The interactions between these two major cardiovascular disorders can be viewed from the following angles:

- Hypertension as a risk factor for HF: Systemic HTN is one of the major risk factors for HF, both in systolic HF and in HF with preserved ejection fraction. Acute HF with pulmonary edema can occur in accelerated HTN.
- Shared pathophysiology: Both these disorders share common pathophysiological pathways, including activation of the renin-angiotensin system, heightened sympathetic tone, elevated endothelin levels, reduced nitric oxide (NO) levels, and endothelial dysfunction.
- Shared environmental influence: A high salt intake can increase the BP and also lead to worsening of pre-existing HF. Therefore, dietary salt restriction is an integral component of treatment of these conditions.
- Relation to atrial fibrillation (AF): Both HTN and HF are well-established risk factors for AF, being components of the well-established CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system.
- Relation to renal disease: Uncontrolled or resistant systemic HTN may be a result of or by itself be a reason for renal dysfunction. Similarly, both acute and chronic HF can lead to cardiorenal syndromes.
- Common pharmacotherapeutic options: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, BBs, and diuretics are established drugs for the treatment of both these conditions.

## Goal Blood Pressure in Heart Failure

In HF with reduced ejection fraction, the goal BP may be the “lowest reasonable” value that is not associated with symptoms of hypotension and/or evidence of hypoperfusion (e.g., prerenal azotemia). The achievement of the standard BP goal in the general population should not hinder the uptitration of HF medications to the guideline-directed doses, as these drugs have favorable survival benefits in HF that are independent of their BP-lowering effects. Generally, the goal BP is <140/90 mm Hg. However, consideration may be given to lowering it to <130/80 mm Hg. In the octogenarians, a BP <130/65 mm Hg should be avoided and special care must be taken to avoid orthostatic hypotension.

## Drug Therapy in Hypertension and Heart Failure

Specific issues pertaining to drug therapy of HTN in HF and vice versa are discussed as follows, based on the ACC/AHA/ASH recommendations 2015:

- Beta-blockers: The three major BBs that have proven benefit in HF are carvedilol, extended-release metoprolol, and bisoprolol.<sup>16,17</sup> The additional alpha receptor blocking effect of carvedilol might theoretically provide an advantage in HTN. Nebivolol, with its NO donating property, might also be useful.<sup>18</sup> Co-administration of BBs with digoxin and amiodarone is common in the setting of HF, especially in patients with atrial fibrillation. In such patients, in addition to heart rate, the electrocardiogram should be monitored for possible additive effects on the AV node.
- ACEIs and ARBs: In HF, the commonly used ACEIs are enalapril, ramipril, lisinopril, and trandolapril, and the major ARBs are losartan, valsartan, and candesartan.<sup>19,20</sup> Combination of these two classes of drugs is discouraged due to higher incidence of adverse effects. Cardiorenal syndrome, with elevation of serum creatinine, may be an impediment to the use of these drugs in optimal doses. Among the ARBs used in the treatment of HTN, telmisartan has been noted to have a specific drug interaction with two drugs that are commonly prescribed in HF—digoxin and warfarin; the blood levels of these drugs may rise when coadministered with telmisartan.<sup>21</sup>
- Diuretics: Even though diuretics have not been found to improve survival in HF, their role is undeniable in controlling symptoms of HF and in reducing hospitalization rates. Chlorthalidone and hydrochlorothiazide, the major diuretics used in HTN, do not have an established role in HF. The coadministration of these drugs along with loop diuretics may be considered as part of “sequential nephron blockade” in patients with resistant HTN and/or HF with diuretic

resistance. However, a higher incidence of electrolyte abnormalities should be anticipated.

- Calcium channel blockers: Verapamil and diltiazem are contraindicated in patients with systolic dysfunction. However, the dihydropyridine CCBs may be safely used in the treatment of HTN in HF patients. The renal safety and electrolyte neutrality are particularly helpful in patients with advanced HF. However, a small increase in heart rate may be anticipated.
- Aldosterone receptor antagonists: Spironolactone is a well-established component of the therapeutic armamentarium in systolic HF. In addition, it has been tested in diastolic HF and in resistant HTN.
- Drugs to avoid: Drugs to avoid in patients with HTN and HF with reduced ejection fraction are nondihydropyridine CCBs (such as verapamil and diltiazem), clonidine, moxonidine, and hydralazine without a nitrate. Nonsteroidal anti-inflammatory drugs should also be used with caution in this group, due to their effects on BP, volume status, and renal function.

## CONCLUSION

The 2014 eighth Joint National Committee (JNC 8), while recommending a target BP for the general population of <140/90 mm Hg (for age <60 years) and <150/90 mm Hg (for age >60 years), does not make any specific recommendation for patients with established CVD. The 2015 scientific statement from the AHA/ACC/ASH makes the following recommendations for target BP in patients with CAD: <140/90 mm Hg (weak recommendation), <130/90 mm Hg for some patients with CVD, such as those with MI or stroke (very weak recommendation), and <150/90 mm Hg for those over 80 years of age (weak recommendation). The SPRINT trial<sup>22</sup> that has been published recently has shown that an intense BP control to targets <120/80 mm Hg compared with standard BP reduction <140/90 mm Hg reduced primary end points of MI, ACS, stroke, HF, hospitalization, or death from CVD but at a higher serious adverse events of hypotension, syncope, electrolyte imbalance, acute kidney injury, or renal failure. It appears as if the last word is yet to be written on target BP goals.

There remains no doubt regarding the fact that systemic HTN is a common and major risk factor for CVD and treating high BP is important in both primary and secondary prevention strategies. However, controversy still exists regarding the optimal target BP that balances the benefits and the risks, especially in specific patient subsets such as CAD, HF, stroke, and the elderly.

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