Management of Hypertension in Coronary Artery Disease
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Abstract
Hypertension (HTN) is a major modifiable independent risk factor for coronary artery disease (CAD) for all age, race, and sex groups. HTN initiates and accelerates the development of atherosclerosis. Sustained elevation of blood pressure (BP) can precipitate acute coronary events by destabilizing vascular lesions. The cardiovascular risks attributed to uncontrolled HTN can be reduced by optimal BP control. Varying therapeutic goals for BP control and availability of numerous antihypertensives make the management of HTN in patients with CAD controversial. This article examines the pathophysiological mechanisms that link HTN with CAD and discusses the available treatment options and therapeutic goals that are consistent with recently published American College of Cardiology/American Heart Association guidelines for the prevention, detection, evaluation, and management of high BP in adults published in 2017.

Key words: Coronary artery disease, guidelines, Hypertension, therapeutic goals

Introduction
Epidemiological studies have shown significant association of hypertension (HTN) with coronary artery disease (CAD). HTN has been shown to be a significant modifiable independent risk factor for the development and progression of CAD, heart failure (HF), chronic kidney disease, and stroke. HTN not only plays a major role in the initiation of atherosclerosis leading to CAD but also persistently elevated levels lead to rapid progression of the disease along with destabilization of vascular lesions, precipitating acute coronary events, and HF.[1] Various studies have shown that HTN conferred a greater adjusted relative risk of acute myocardial infarction (MI) than diabetes mellitus with national level surveys conducted in different countries in North America, Asia, and Africa indicating that HTN, on the one hand, has a high prevalence and, on the other hand, a low awareness among the patient group leading to poor control.[23] These cardiovascular (CV) risks attributable to HTN can be decreased significantly with optimal blood pressure (BP) control. The present article examines and discusses appropriate systolic BP (SBP) and diastolic BP (DBP) targets in patients with established CAD, the optimal choice of antihypertensive agents and evaluation of their efficacy in secondary prevention of CAD among patients with stable ischemic heart disease (SIHD) and acute coronary syndrome (ACS).

Epidemiology of HTN and CAD in India
BP control remains an important strategy for reducing CV disease (CVD) mortality. The prospective urban rural epidemiology (PURE) study evaluated HTN awareness, treatment and control in 17 countries at various stages of economic development.[4] Among the 142,042 participants, 40.8% had HTN and 46.5% were aware of the diagnosis. Among those who were aware of the diagnosis, the majority (87.5% of those who were aware) were receiving pharmacological treatments, but only 32.5% of those receiving treatment were controlled. The percentages of those aware were 49.0% in high-income countries (HICs), 52.5% in upper middle-income countries (UMICs), 43.6% in lower middle-income countries (LMICs), and 40.8% in lower income...
Mechanisms of HTN and CAD

Several pathophysiological mechanisms contribute to BP elevation and subsequent target organ damage, including CAD.\(^1\) These mechanisms include as follows:

1. Activation of sympathetic nervous system
2. Activation of the renin-angiotensin-aldosterone system
3. Inhibition of the cardiac natriuretic peptide system
4. Deficiencies in the release or activity of vasodilators such as nitric oxide and prostacyclin

5. Increased expression of inflammatory cytokines and growth factors in the arterial tree resulting in increased vascular stiffness and endothelial dysfunction.

The complex interaction of these neurohumoral pathways with genetic, demographic, and environmental factors (such as increased psychosocial stress and excessive dietary intake of sodium along with inadequate intake of potassium and calcium) determines the development of HTN and related CAD.

Concomitant metabolic disorders such as diabetes mellitus, insulin resistance, and obesity also lead to the production of vasoactive cytokines that promote inflammation, endothelial dysfunction, and increased oxidative stress in the blood vessels, contributing to an increase in both BP and CVD risk.

New Definition of HTN

The recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for prevention, detection, evaluation, and management of high BP in adults (2017) categorized BP into four levels on the basis of average BP measured in a health-care setting (office pressures).\(^9\)

1. Normal
2. Elevated
3. Stage 1 HTN
4. Stage 2 HTN.

Categories of BP in adults [Table 1].

This new categorization differs from that recommended in the JNC 7 report, with Stage 1 HTN now being defined as an SBP of 130–139 or a DBP of 80–89 mmHg, and Stage 2 HTN corresponding to Stages 1 and 2 in the JNC 7 report.\(^10\)

The recent ESC/EHS guidelines for HTN 2018 have categorized HTN into the following categories:

1. Normal
2. High normal
3. Grade 1 HTN
4. Grade 2 HTN
5. Grade 3 HTN [Table 2].

BP Threshold and Goals for Patients With HTN and CAD

Numerous randomized control trials (RCTs) in HTN associated with CAD have yielded conflicting results regarding the optimal BP targets. In summary, these trials have demonstrated that reduction of SBP to 130 mmHg may not provide additional benefits.
Management of hypertension in CAD

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Table 2: Parametric analysis of BP

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>And</td>
</tr>
<tr>
<td>Normal</td>
<td>120–129</td>
<td>And/or</td>
</tr>
<tr>
<td>High normal</td>
<td>130–139</td>
<td>And/or</td>
</tr>
<tr>
<td>Grade 1 HTN</td>
<td>140–159</td>
<td>And/or</td>
</tr>
<tr>
<td>Grade 2 HTN</td>
<td>160–179</td>
<td>And/or</td>
</tr>
<tr>
<td>Grade 3 HTN</td>
<td>≥180</td>
<td>And/or</td>
</tr>
</tbody>
</table>

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, HTN: Hypertension

The yet to be published ESC/EHS guidelines for HTN 2018 recommend initiation of BP-lowering medication for patients with Grade 1 HTN in high or very high-risk patients with CV disease and in Grade 2 and 3 HTN at any level of CV risk. It is also recommended to initiate BP-lowering medications in patients with high-normal SBP (130–140 mmHg) in patients with very high-risk patients with established CV disease. [14]

Non-Pharmacological Management

Studies have shown that various lifestyle behaviors such as unhealthy diet, physical inactivity, and smoking, promote the development of CAD. Therefore, modifications in lifestyle with adoption of healthy behaviors are equally important in the management of HTN and CAD.

These include correction of unhealthy dietary patterns, excessive consumption of alcohol, and physical inactivity which along with pharmacological therapy form an important complementary approach in the management of high BP, thereby significantly reducing CVD risk in the population.

Recent ACC/AHA guidelines 2017 recommend the following non-pharmacological measures for the management of HTN.

1. Weight loss is recommended to reduce BP in adults with elevated BP or HTN who are overweight or obese (COR 1, LOE A).
2. A heart-healthy diet, such as the (dietary approaches to stop hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or HTN (COR 1, LOE A).
3. Sodium reduction is recommended for adults with elevated BP or HTN (COR 1, LOE A).
4. Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or HTN unless contraindicated by the presence of CKD or the use of drugs that reduce potassium excretion (COR 1, LOE A).
5. Increased physical activity with a structured exercise program is recommended for adults with elevated BP or HTN (COR 1, LOE A).
6. Adult men and women with elevated BP or HTN who currently consume alcohol should be advised to drink no >2 and 1 standard drinks per day, respectively (COR 1, LOE A).

Pharmacological Management

Epidemiological studies have shown that elevated levels of BP in CAD cause significant morbidity and mortality in the population and that treating HTN based on specific thresholds and to certain goals result in improvement of CV outcomes resulting in significant positive impact on public health.

Management of HTN in Patients with SIHD

The management of HTN in patients with chronic SIHD is directed toward the prevention of death, MI, and stroke along with reduction in the frequency and duration of myocardial ischemia, leading to symptomatic improvement. Numerous RCTs have demonstrated the benefits of antihypertensive drug therapy in reducing the risk of ischemic heart disease.

Pharmacological strategies for the prevention of CV events in these patients include beta-blockers, angiotensin-converting...
enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), thiazide and thiazide-like diuretics, and calcium channel blockers (CCBs).

The recommendations for the management of HTN in patients with SIHD without HF are as follows: [Table 3].

**Basis of Evidence for the Current Recommendations**

1. In the SPRINT trial, aggressive treatment in patients with increased CV risk (including MI and ACS) with reduction of SBP to <130/80 mmHg has been shown to reduce CVD complications by 25% and all-cause mortality by 27%.\[13\]

2. In HOPE study, after 5 years of randomized therapy in high-CVD-risk patients with normal ejection or without HF, ramipril produced a 22% reduction in MI, stroke, or CVD in high-risk patients compared with placebo.\[15\] In EUROPA trial, after 4.2 years of therapy in patients with SIHD, perindopril reduced CVD death, MI, or cardiac arrest by 20% compared with placebo.\[16\]

3. Beta-blockers are effective in preventing angina pectoris, improving exercise time until the onset of angina pectoris and reducing exercise-induced ST-segment depression. Beta-blockers have a compelling indication for the treatment of SIHD which result in these drugs to be recommended as a first-line therapy in management of HTN when it occurs in these patients. Beta-blockers used to treat SIHDs that are also effective in HTN management include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol. Atenolol is not considered as effective as other antihypertensive drugs in the treatment of HTN.\[9\]

4. Dihydropyridine CCBs have similar efficacy as drugs that decrease BP levels and relieve angina when these are added to beta-blockers in patients with HTN and persisting angina despite beta-blocker therapy.\[9\] The ALLHAT study showed that the primary prevention of CV events with amlodipine was equivalent to that produced by the diuretic, chlorthalidone or the ACEI, and lisinopril.\[17\]

5. Various randomized controlled trials and meta-analysis have demonstrated that the use of beta-blockers after MI reduced all-cause mortality by 23%. This established efficacy of beta-blockers for treating HTN and SIHD provides reasonable evidence for continuation of beta-blockers beyond 3 years after MI.\[9\]

6. Beta-blockers and CCBs are effective antihypertensive and antianginal agents. CCBs including both dihydropyridine and non-dihydropyridine agents can be used separately or together with beta-blockers beginning 3 years after MI in patients with CAD who have both HTN and angina.\[9\]

**Management of HTN in Patients with ACS**

HTN is one of the major modifiable risk factors for CAD, but the impact of HTN on ACS outcomes has not been well documented due to the limited number of studies available on specific BP targets in patients with either STEMI or NSTEMI/UA (Non-ST-elevation MI/unstable angina).

In patients with ACS, therapeutic BP targets have not been established. Current guidelines recommend a BP target of <140/90 mmHg which applies more to secondary prevention than HTN management during acute phase of MI.\[14\] Thus, initially, it is prudent to focus on pain control and clinical stabilization, before BP levels are specifically targeted.

The BP should be lowered gradually with emphasis to avoid decrease in DBP to <70 mmHg, which may reduce coronary perfusion, thereby worsening ischemia.

Due to the lack of specific trials to assess lowering of BP in patients with ACS, it becomes necessary to select the antihypertensives that have established efficacy in CV risk reduction for patients with ACS independent of their BP-lowering effects. These drugs include beta-blockers, ACEI, ARBs, and, in selected patients, aldosterone antagonists [Table 4].

**Beta-blockers**

β-Blockers form a cornerstone of ACS treatment due to their ability to reduce myocardial oxygen demand by decreasing heart rate and BP. β-blockers demonstrate a reduction in

| Table 3: Recommendations for the treatment of HTN in patients with SIHD |
|------------------------|------------------|-------------------------|
| COR | LOE | Recommendations |
| I | SBP: B-R | In adults with SIHD and HTN, a BP target of <130/80 mmHg is recommended. |
| | DBP: C-EO | |
| IIa | SBP: B-R | Adults with SIHD and HTN (BP≥130/80 mmHg) should be treated with medications (e.g., GDMT beta-blockers, ACEIs, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control HTN. |
| | DBP: C-EO | |
| III | B-NR | In adults with SIHD with angina and persistent uncontrolled HTN, the addition of dihydropyridine CCBs to GDMT beta-blockers is recommended. |
| IIIa | B-NR | In adults who have had an MI or ACS, it is reasonable to continue GDMT beta-blockers beyond 3 years as long-term therapy for HTN. |
| IIb | C-EO | Beta-blockers and/or CCBs might be considered to control HTN in patients with CAD (without HFrEF) who had an MI more than 3 years ago and have angina. |

GDMT: Guideline-directed medical therapy, HFrEF: Heart failure with reduced ejection fraction, MI: Myocardial infarction, COR: Class of recommendation, LOE: Level of evidence, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, HTN: Hypertension, SIHD: Stable ischemic heart disease, BP: Blood pressure, ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCBs: Calcium channel blockers
in patients with STEMI, due to established long-term efficacy of post-discharge β-blocker administration in various studies, these drugs are routinely prescribed at the time of discharge.

**CCBs**

CCBs have not been found to be useful in the setting of acute STEMI with studies documenting increase in mortality with the use of rapid-release form of nifedipine in post-MI settings.\(^1\) Numerous RCTs have also noted that non-dihydropyridine agents such as diltiazem and verapamil lack clinical efficacy in early MI setting and are not recommended for routine use in patients with STEMI. Few RCTs suggested efficacy for CCBs in non-ST-elevation ACS patients and since these trials were performed >30 years ago before the practice of routine beta-blocker therapy, the use of CCBs in these patients is limited. Thus, CCBs are not indicated for routine use in patients with UA or NSTE-MI.\(^1\)

The AHA/ACC guidelines (2015) for the management of UA and NSTE-MI suggest that, in patients with persisting or recurring ischemia with contraindications to β-blockers, non-dihydropyridine CCBs (verapamil or diltiazem) may be used as an effective alternative in the presence of normal LV function or the absence of other contraindications.\(^1\) The use of verapamil or diltiazem in patients who have LV dysfunction should be avoided, and they should not be used together with β-blockers in these patients to avoid acute cardiac decompensation.

**ACEI**

ACEIs are indicated for most patients with ACS and are a recommended option for BP management in both STEMI and NSTEMI/UA. In STEMI, ACEIs decrease infarct size and prevent LV remodeling and dilatation, thereby improving CV outcomes. The GISSI-3 and ISIS-4 trials demonstrated a benefit from early administration of ACEI, with significant reductions in mortality of 0.8% and 0.5% seen as early as within 30-day post-MI.\(^1\) A meta-analysis from the ACEI MI Collaborative Group included approximately 100,000 patients with recent onset MI found that patients treated with ACEIs had a 7% lower mortality rate at 30 days. The benefits of ACEIs were pronounced among individuals with LV dysfunction and when continued long term. Significant reduction in mortality rates by 20%–25% in long-term trials evaluating ACEIs in these high-risk subgroups has been observed.\(^1\)

**ARBs**

ARBs are a useful alternative to ACEI in patients with contraindication or intolerance to an ACEI.\(^1\) The VALIANT trial randomized patients after acute MI with LV dysfunction or HF within 10 days to valsartan, captopril, or both.\(^19\) After 2 years of follow-up, the efficacy of valsartan was found to be equal as captopril for reducing CV events in these high-risk patients. However, the group which received both valsartan and captopril had increased rate of adverse events with no improvement in survival.

Recent studies have shown that in hypertensive patients with compelling indications (in both ACS and SHHD), there is no difference in efficacy between ARBs and ACEIs with regard to the surrogate end point of BP and the outcomes of all-cause mortality, CV mortality, MI, HF, stroke, and end-stage renal disease with overall rates of withdrawal adverse events significantly lower with ARBs than with ACEIs. In view of similar efficacy and fewer adverse events with ARBs and the risk-to-benefit analysis in aggregate indicating that ARBs in the current era reduce CV events, including the risk of MI, as effectively as but more safely than ACEIs, the ARBs might be preferred over ACEIs for the above indications.\(^19\)

**Diuretics**

Thiazide and thiazide-type diuretics have a role largely in the long-term control of HTN. In patients with ACS, diuretics are used primarily in patients with the left ventricular dysfunction, resulting in increased filling pressures, pulmonary venous congestion, or HF. Loop diuretics are considered more effective than thiazide and thiazide-type diuretics and preferred in ACS patients with HF (NYHA Class III or IV).\(^1\)
Conclusion
Systemic HTN remains an important modifiable risk factor for CAD involved in both progressions of atherosclerosis and precipitation of acute coronary events, leading to increased CV morbidity and mortality. The pathophysiological linkage between CAD and uncontrolled HTN and the clinical implications of HTN on CAD have been described in various guidelines with considerable debate existing regarding the specific thresholds for treatment initiation and optimal therapeutic goals beneficial in reducing CV events. Recently published guidelines recommend treatment initiation at BP levels ≥130/80 mmHg to a therapeutic BP goal to 130/80 mmHg in patients with HTN and SIHD with a target BP of <140/90 mmHg in patients with HTN and ACS. However, cautious observation is necessary while reducing the DBP <80 mmHg due to adverse events attributed to the J curve phenomenon, leading to coronary hypoperfusion and increased CV events. These specific targets can be achieved by effective single or sequential combination drug therapy, which includes beta-blockers, ACEIs, or ARBs, irrespective of LV function with CCBs used as an alternative to beta-blockers or an addition to standard therapy. The aim is to achieve and maintain target BP goal resulting in reduced morbidity and mortality associated with both CAD and HTN. It is expected that ESC/EHS guidelines for HTN to be published in 2018 might offer more insight regarding the management of HTN in CAD patients.

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