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Review Article

Therapeutic Principles in Hypertension Management in Patients with Congestive Heart Failure and Coronary Artery Disease

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Abstract

Systemic hypertension (HTN) is the most common known risk factor for the development of cardiovascular disorders. Epidemiological studies have revealed strong association between elevated arterial blood pressure (BP) and the development of coronary artery disease (CAD), stroke, renal failure, aortic dissection, peripheral arterial disease, and heart failure. There is enough evidence to suggest that lowering BP has a significant impact on mortality and morbidity. Of all cardiovascular disorders, CAD and heart failure contribute to majority of deaths. Management guidelines are well established for heart failure with reduced ejection fraction, but less well established for HTN with preserved systolic function. Prevention, early detection, and control of HTN are of paramount importance. Antihypertensive drugs along with the management of comorbid conditions and adhering to lifestyle measures are considered the backbone of primary and secondary prevention strategies.

Key words: Coronary artery disease, heart failure, hypertension

Introduction

Systemic hypertension (HTN) is the most common identifiable risk factor for the development of cardiovascular diseases (CVD). Epidemiological studies have shown strong association between elevated arterial blood pressure (BP) and the development of coronary artery disease (CAD), stroke cerebrovascular accident, renal failure, aortic dissection, peripheral arterial disease (PAD), and heart failure (HF).^[1] There is enough evidence to suggest that lowering BP has a significant impact on morbidity and mortality.^[2] Out of all CV disorders, CAD and HF contribute to the majority of deaths. Thus, prevention, early detection, and control of HTN are of paramount importance. HTN is aptly classified as Stage A HF because of their strong association. Treatment of HTN in patients with HF must take into consideration the type of HF that is present: HF with reduced ejection fraction (HFrEF), in which systolic function is impaired; or HF with preserved ejection fraction (HFpEF), in which diastolic function is impaired but systolic function is preserved. Management guidelines are well established for HFrEF, but less certain for HFpEF. HF patients are nearly evenly divided

between those with reduced left ventricular (LV) systolic function and those with preserved LV systolic function. Elderly hypertensives are more prone to HF. Any increase in BP above 120 mmHg systolic or 85 mmHg diastolic is associated with increased risk of developing CAD and eliminating this risk factor is a major concern of primary prevention.^[3] Long-standing BP elevations promote endothelial injury, resulting in impaired nitric oxide (vasodilator) release and increased release of inflammatory mediators that promote the development of atherosclerosis and vascular occlusion. Uncontrolled HTN is also responsible for the occurrence of acute coronary events in patients with chronic stable angina.

Management of Hypertension in HF

Management of Hypertension in HF is Discussed Under the Following Situations

Management of HTN in patients at risk of HF

Control of both systolic and diastolic HTN reduces the risk of developing HF by 50%. Initial therapy should include a

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combination of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and calcium channel blocker (CCB), or diuretic.^[4] If the target BP is not achieved, escalate to triple-drug combination comprising ACEI or ARB, CCB, and diuretic. If BP remains above target, add either mineralocorticoid antagonist or a beta-blocker or an alpha-blocker.

Management of hypertension in patients with reduced EF

HFrEF has been well studied, but little is known about the benefits of treating coexisting HTN because BP usually normalizes or decreases as cardiac function declines. BP target is <130/80 mmHg in these patients. The target can be lower than this as long as there is no vital organ hypoperfusion because these drugs have favorable mortality benefits in HF that is independent of their BP-lowering effects. In the very elderly, special care must be taken to avoid orthostatic hypotension. During every out-patient visit, one should seek symptoms and signs of orthostatic hypotension in the elderly. The goals of antihypertensive therapy in the setting of HFrEF are to reduce both preload to diminish congestive symptoms using diuretics and afterload to improve cardiac output using particularly antagonists of the renin-angiotensin-aldosterone system (RAAS). Heightened sympathetic activity is the hallmark of HF, beta-blockers (BB) would counter this. HFrEF should be treated, if BP permits, with ACEI or ARB, BB, diuretics, and aldosterone antagonists. In addition to mortality benefit, many patients will experience considerable improvement in their EF. To maximize clinical improvement, whenever possible, titrate the dose to attain the target doses of these drugs that were used in the clinical trials.

ACEI are considered first-line drugs in the management of hypertension in the presence of HFrEF.^[5] Weekly up-titration of doses, if possible, is recommended. Monitoring of renal function, serum potassium, organ perfusion, and BP is mandatory while escalating the dose. Substitute ARBs in patients who are not tolerating ACEI.^[6] Combining ACEI and ARB should be avoided as it is fraught with serious adverse events. In PARADIGM-HF trial, the combination of ARB and angiotensin receptor-neprilysin inhibitors (ARNI) proved superior to ACEI therapy for HF. Presently, only limited data is available for the treatment of hypertension with ARNI.

Beta-blockers including carvedilol, metoprolol succinate, bisoprolol, and nebivolol have been shown to improve overall survival in patients with mild to advanced HF.^[7-9] Beta-blockers are considered first-line drugs along with ACEI or ARBs due to their favorable effects on survival and disease progression. Administration of BB should be started as soon as possible after the diagnosis of systolic dysfunction and up-titrated to the maximum dose while monitoring hemodynamics.

Mineralocorticoid receptor antagonists prevent myocardial fibrosis and LV remodeling which are attributed to hyperaldosteronism. Antagonizing negative effects of aldosterone can improve the survival of patients. Studies have shown, spironolactone (RALES) and eplerenone (EPHESUS), decrease both systolic and diastolic arterial pressures compared with placebo and can be of additional benefit in the management

of HTN not responding to first-line drugs in these HF populations.^[10,11] Monitoring of serum potassium and renal function is mandatory, especially when these drugs are combined with ACEI or ARBs or in the presence of renal dysfunction.

Hydralazine/nitrates are useful as add-on therapy when hypertension is not under control despite other drugs or when RAAS inhibitors are contraindicated because of intolerance, hyperkalemia, or renal failure. Although diuretics are the mainstay of therapy for acutely decompensated HF or volume overloaded state, none of the randomized clinical trials have shown mortality benefits in HF in the absence of congestion.

Loop diuretics are preferred in HFrEF and renal failure. Diuretics not only reduce congestion but also reduce BP. In hypertensive patients, diuretics may decrease systolic and diastolic BP (DBP) by as much as 15.8 mmHg and 8.2 mmHg, respectively.

Recent guidelines suggest initiation of therapy with ACEI or ARB, BB, and diuretic. Mineralocorticoid receptor antagonist is added if target BP is not reached. Long-acting dihydropyridine CCBs, amlodipine and felodipine, are useful in ACEI intolerance, renal dysfunction or when BP remains high despite other first-line drugs. CCBs have neutral effect on cardiac events and mortality.

Management of hypertension in patients with HFpEF

The optimal therapy of HFpEF is uncertain. In most of the cases, management of comorbid conditions helps relieve symptoms. HTN and LV hypertrophy (LVH) are frequently present and regression of LVH may improve diastolic dysfunction as well as symptoms. Most of the anti-hypertensive drugs promote regression of LVH with ARBs, ACEI, and CCBs causing more LVH regression than BB or diuretics.^[12-14] The same BP threshold and target for drug treatment of HFrEF are applicable to HFpEF. No single agent has been identified as being effective in improving CV outcomes in these patients Table 1.

Summary and Recommendations

1. Hypertension is the most prevalent modifiable risk factor for the development of HF
2. Treatment of hypertension in patients with HF must take into account the type of HF that is present
3. In general, patients with HFrEF should be treated, if possible, with ACEI or ARB, a beta-blocker, and a diuretic
4. A mineralocorticoid receptor antagonist is added if BP is not adequately controlled
5. The optimal therapy of hypertension in patients with HFpEF is uncertain; most antihypertensive agents can reduce LVH and relieve symptoms.

Management of Hypertension in CAD

Long-standing uncontrolled BP accelerates endothelial injury, resulting in impaired vasodilator (e.g., nitric oxide) release and increased release of inflammatory mediators that promote the development of atherosclerosis and vascular occlusion. Oxygen

Table 1: Therapeutic strategies in hypertensive patients with heart failure

Recommendations	Class	Level
In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is $\geq 140/90$ mmHg	IIa	B
In patients with HFrEF, BP-lowering treatment comprises an ACEI or ARB, a beta-blocker, a diuretic and/or MRA if required	I	A
Dihydropyridine CCBs may be added if BP control is not achieved	IIb	C
In patients with HFpEF, BP treatment threshold, and target values should be the same as for HFrEF	IIa	B
Because no specific drug has proven its superiority in HFpEF, all major agents can be used		
In all patients with LVH It is recommended to treat with an RAAS blocker in combination with a CCB or diuretic Systolic BP should be lowered to a range of 120–130 mmHg	IIa	B

BP: Blood pressure, HFrEF: Heart failure with reduced ejection fraction, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonist, CCB: Calcium channel blocker, HFpEF: Heart failure with preserved ejection fraction, LVH: Left ventricular hypertrophy, RAAS: Renin-angiotensin-aldosterone system

Table 2: Therapeutic strategies in hypertensive patients with CAD

Recommendations	Class	Level
To target SBP to ≤ 130 mmHg if tolerated, but not <120 mmHg	I	A
In older patients (aged ≥ 65 years), to target to an SBP range of 130–140 mmHg	I	A
To target DBP to <80 mmHg, but not <70 mmHg	I	C
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAAS blockers are recommended as part of treatment.	I	A
In patients with symptomatic angina, beta-blockers and/or CCBs are recommended	I	A

SBP: Systolic blood pressure, CAD: Coronary artery disease, DBP: Diastolic blood pressure, RAAS: Renin-angiotensin-aldosterone system, CCB: Calcium channel blocker

demand can increase because of increased afterload and LVH in patients with uncontrolled hypertension. Therefore, patients with elevated BP are more likely to develop manifestations of CAD (angina, and myocardial infarction [MI]) and are at higher mortality risk following an event.^[15] The INTERHEART study showed that 50% of the population-attributable risk of a MI can be accounted for by the lipids, with hypertension accounting for 25%. There is compelling evidence to show the beneficial effect of lowering of high BP on reducing the risk of MI. A recent meta-analysis of randomized controlled trials of antihypertensive therapy revealed that for every 10 mmHg reduction in systolic BP (SBP), CAD risk was reduced by 17%.

Younger subjects with hypertension (i.e., aged <50 years) often have an increased DBP, whereas older subjects usually have increased SBP.^[16,17] Accordingly, in younger individuals, DBP is more closely associated with CAD development, whereas SBP is more predictive in those aged 60 years or older. In elderly people, pulse pressure becomes a strong predictor of CAD risk. Importantly, the risk of CAD-related fatal events doubles for every 20 mmHg increase in SBP or 10 mmHg increase in DBP between a BP range of 115/75 and 185/115 mmHg. A target BP of approximately $<130/80$ mmHg in patients with CAD appears safe and can be recommended, however, achieving a BP $<120/80$ mmHg is not recommended.

Primary Prevention of CAD in Patients With Hypertension

Effective antihypertensive therapy substantially reduces all CV adverse outcomes. Therefore, sustained BP control is the primary goal. The optimal goal for reducing the risk of CAD development is not known. The current target for BP control is $<140/90$, though lower target $<130/80$ mmHg may be considered in high-risk population.

Management of HTN in Established CAD is Discussed Under the Following Situations

Management of hypertension in stable angina

The immediate aim of antihypertensive treatment in patients with symptomatic CAD is preventing acute coronary syndrome (ACS) and death. In addition to BP control, management of concomitant risk factors such as smoking, diabetes, lipid abnormalities, and weight substantially improves outcomes.

A BP goal $<140/90$ mmHg is currently recommended in patients with stable angina, or, optionally, $<130/80$ mmHg in selected patients, including those with the previous stroke or transient ischemic attack, CAD, PAD, or abdominal aortic aneurysm. These guidelines are published before the completion of systolic blood pressure intervention trial (SPRINT), but as only about 20% of patients enrolled in SPRINT had clinical or subclinical CVD, it may be premature to extrapolate the SPRINT findings to those with stable angina or the broader ischemic heart disease (IHD) population. As discussed previously, excessive lowering of DBP, in particular, may reduce coronary perfusion, thus increasing myocardial ischemia and coronary events. In the hypertension optimal treatment trial, in which patients were randomly assigned to three different DBP goals (≤ 90 mmHg, ≤ 85 mmHg, or ≤ 80 mmHg), a J-curve relationship was noted between DBP and the cardiac events in the subgroup of 3080 patients with IHD at baseline, whereas no such relationship was observed in the much larger subgroup without IHD at baseline.^[18]

BB, including metoprolol succinate and bisoprolol, are generally considered first-line agents in patients with symptomatic CAD and hypertension. These drugs relieve angina as well as control BP.^[19,20]

ACEIs are considered first-line therapy in all pts with stable angina and hypertension, unless contraindications exist. In the heart outcomes prevention evaluation trial, treatment with

Table 3: Pharmacologic treatments for hypertension in patients with CAD

Drug/class	Stable angina	Acute coronary syndrome	Heart failure due to CAD
ACEI or ARB	1 (prior MI, LV dysfunction, diabetes, or proteinuric CKD)	1 (prior MI, LV dysfunction, diabetes, proteinuric CKD)	1
Diuretic (chlorthalidone preferred)	1	1 (chlorthalidone preferred)	1
Beta-blocker	1	1 (esmolol IV, metoprolol tartrate or bisoprolol orally)	1 (carvedilol, metoprolol succinate, bisoprolol)
Non-DHP CCB (verapamil, and diltiazem)	2	2 (without LV systolic dysfunction)	contraindicated
DHP CCB	2	2	Uncontrolled BP
Nitrates	1	2 (IV NTG for control of BP)	2
Aldosterone antagonist	2	2	1
Hydralazine/isosorbide dinitrate	-	-	2 (limited data are available in heart failure due to CAD)

1=First-line drug, 2=Second-line drug. CAD: Coronary artery disease, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MI: Myocardial infarction, LV: Left ventricular, CKD: Chronic kidney disease, DHP: Dihydropyridine, CCB: Calcium channel blocker, BP: Blood pressure, IV: Intravenous

ramipril was associated with around 20% risk reduction in the primary outcome (MI, stroke, or death as a result of CV causes) among 80% of patients with baseline CAD. Similarly, in the European Trial on Reduction of Cardiac Events with Perindopril in Stable CAD (EUROPA),^[21] the addition of perindopril to the BB therapy significantly reduced the risk of CV events and death, without any greater risk of adverse events, among patients with low-risk stable CAD. ARBs can be used in patients who are intolerant of ACEIs.

When contraindications to the use of BB exist, nondihydropyridine (verapamil and diltiazem) or long acting dihydropyridine (e.g., amlodipine, felodipine, or long-acting nifedipine), CCBs are appropriate alternatives for angina and HTN. Studies of CCBs have similar efficacy to BB on controlling angina and reducing major adverse events, including death. Nevertheless, CCBs generally are recommended as second-line therapy, either as an alternative for patients unable to tolerate a BB or as adjunctive therapy when BP remains elevated or when angina persists despite BB use.

Aldosterone antagonists should be prescribed for post-MI patients and patients with LV dysfunction without significant renal dysfunction (serum creatinine ≥ 2.5 mg/dl in men and ≥ 2.0 mg/dl in women) or hyperkalemia (serum potassium ≥ 5.0 mEq/L).

Management of hypertension in ACS

Hypertension is common in patients with ACS, affecting two-thirds of patients with ST-elevation myocardial infarction (STEMI) and between 70% and 80% of patients with non-STEMI. Uncontrolled BP can precipitate an ACS by triggering plaque rupture. Hypertension management in these patients can be challenging for the following reasons. First, the relationship between BP and outcome is complex, particularly in the first few hours following ACS. Second, BP may be spuriously elevated because of discomfort and restlessness. The initial focus should

be on stabilizing the patient condition rather than hypertension. Finally, there are no outcome trials which assessed the impact of BP control in ACS. Incidence of hemorrhagic stroke is a major concern in patients with ACS who receive antiplatelet drugs, anticoagulants, and thrombolytic therapy. However, several studies have also observed that low BP, particularly SBP < 90 mmHg is much more strongly associated with risk of death than having HTN or elevated SBP.^[22,23]

The goals of therapy in patients with ACS and hypertension are to safely control BP, balance myocardial 2 supply and demand, and prevent acute coronary events, and death.^[24] The anti-hypertensive agents with the most compelling evidence for use in patients with hypertension and ACS include IV nitrates and oral administration of beta-blockers, ACEI or ARBs, and aldosterone antagonists. Intravenous BB and ACEI should be avoided. Cardioselective BB should be initiated within 24 h of symptoms onset. The most recent ACC/AHA/ASH guidelines recommend continuing BB therapy for at least 3 years. These agents reduce infarct size and the occurrence of both sudden cardiac death and subsequent re-infarction. However, the maximum benefit is seen in the 1st year.^[25]

Long-acting dihydropyridine CCBs have not been studied in AMI. Nevertheless, these agents are frequently used as add-on therapy in patients with an AMI when HTN is not adequately controlled by BBs, ACEIs/ARBs, and diuretics.^[26,27] Short-acting nifedipine should be avoided in CAD patients.

An ACEI in combination with beta-blockers is reasonable in most patients with ACS, including any patient with hypertension, as well as in those with normal BP, if the patient has LVEF 40% or less, DM, or CKD. Evidence for the use of ACEI in NSTEMI or UA is largely extrapolated from the studies carried out in the STEMI population. Importantly, ACEI should be used cautiously in the acute phase of an MI, especially in those with low SBP (< 120 mmHg) at presentation, in whom critical hypertension or acute kidney injury may be precipitated.

Aldosterone antagonists, which decrease ventricular remodeling and fibrosis, are appropriate in patients with AMI complicated by LV systolic dysfunction or HF (EPHESUS, and RALES). The role of new drug ARNI is not studied in the management of hypertension in ACS Tables 2 and 3.

Summary and Recommendations

1. Recent meta-analyses suggest that all major BP-lowering drug classes have a similar impact in primary prevention of CAD events and stroke and that the critical issue is smooth BP lowering, independent of drug class
2. Lowering of BP is known to benefit patients with CAD but to what extent BP should be lowered is not clear
3. In primary and secondary prevention of CAD in patients with arterial hypertension, BP lowering to at least <140/90 mmHg is critical
4. Care should be taken in lowering BP smoothly because sudden rapid fall is detrimental in patients with significant occlusive CAD
5. Nevertheless, it seems reasonable to recommend the use of an ACEI, usually with a thiazide diuretic, or an ACEI with CCB, as first-line drugs in the primary prevention of CAD in patients with hypertension
6. Treatment choices for the patient with hypertension and established CAD are more straight forward. Beta-blockers are effective in the management of hypertension, angina, and ACS
7. If both BBs and CCBs are required for angina and hypertension control, then a long-acting dihydropyridine along with BBs should be used.

Conclusions

Systemic arterial hypertension is the most prevalent major risk factor contributing to CV disorders such as CAD, HF, stroke, renal failure, PAD, and dissection of aorta. Ever-increasing morbidity and mortality due to CV disorders is unequivocally linked to the rising incidence of HF and CAD. There is abundant evidence to suggest that control of elevated arterial pressures results in a reduction in the incidence of CAD and HF. Antihypertensive therapy, management of comorbid conditions, and lifestyle measures are considered cornerstones of primary and secondary prevention strategies.^[28] In primary and secondary prevention of CAD in patients with arterial hypertension, BP lowering to at least 140/90 mmHg is critical. Caution should be exercised while lowering BP as sudden changes in BP may precipitate acute coronary events with attendant morbidity and mortality. Beta-blockers, RAAS inhibitors and diuretics are considered first-line of therapy of hypertension in the presence of CAD and HF. Newer agents such as valsartan/sacubitril, now indicated for HF, may represent potent therapies to reduce the progression from hypertension to HF.

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