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Review Article

Blood Pressure Goals in Patients with Coronary Artery Disease

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Abstract

Hypertension is implicated as an independent and strong risk factor, for the occurrence of coronary artery disease (CAD), stroke and renal failure that leads to significant morbidity and mortality throughout the world. Several epidemiological studies show a consistent relationship between high blood pressure (BP) and the risk of CAD. In this review, the BP goals in hypertensives with CAD are discussed. BP targets in accordance to recent guidelines are reviewed and the therapeutic strategies for the management of various presentations of CAD are highlighted. There is a controversy about the lower target range of BP in CAD patients. Some studies support the "J curve" hypothesis, whereas the recent SPRINT trial refutes it. Furthermore, lower BP targets are associated with prescription of multiple drugs, posing a problem of both cost and compliance for patients. Management includes treatment of hypertension along with targeting other comorbidities such as dyslipidemia, obesity, diabetes mellitus, and smoking.

Key words: Hypertension, coronary artery disease, J curve, blood pressure targets

Introduction

Hypertension is implicated as an independent and strong risk factor that leads to significant morbidity and mortality throughout the world. Several observational studies so far, have shown a log-linear and continuous association with the level of blood pressure (BP) and vascular events down to 115/75 mmHg in patients without any baseline major illness.[1] It is noted that there is a 40–50% decrease in death from coronary artery disease (CAD) with every 10 mmHg decrease in systolic blood pressure (SBP).[1]

Hence, in clinical practice, whether BP goals should be guided by this evidence is a question to ponder. Lower BP targets cause adverse events and also escalate treatment costs. However, recent evidence from non-randomized trials in patients with vascular disease, have shown a J-curve association between BP and outcomes.[2] A recent meta-analysis provided evidence that intense BP lowering (SBP <130 mmHg) in high risk patients, reduced cardiovascular (CV) events, although at the risk of causing hypotension.[2]

The recent European Society of Cardiology (ESC) 2018 hypertension guidelines has classified BP into the following categories.[3]

Category	SBP/DBP mmHg
Optimal	<120/<80
Normal	120–129/80–84
High normal	130–139/85–89
Grade 1 hypertension	140–159/90–99
Grade 2 hypertension	160–179/100–109
Grade 3 hypertension	>180/>110
Isolated systolic hypertension	>140/<90

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Treatment Thresholds

High normal BP: Pharmacological treatment has to be considered if the CV risk is very high, like the presence of any established CV disease, especially CAD.

Grade 1 hypertension (with low risk): These patients have no evidence of target organ damage and therefore antihypertensives are initiated, only after a trial of lifestyle modification.

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Similarly, in older patients (>65 years, not >80 years) antihypertensives and lifestyle modification is recommended in fit older patients who can tolerate the treatment.

Targeting How Much Lower is Better?

"J curve" hypothesis

A non-linear relationship exists, between the level of BP and most CV adverse events, with increased risk noted at low BPs. This is termed the "J curve" relationship.[4] Myocardial perfusion occurs mainly during diastole; hence. diastolic blood pressure (DBP) is considered as the coronary perfusion pressure. The coronary flow is autoregulatory [Figure 1], such that any decrease in the perfusion pressure leads to vasodilation in the coronary vessels that in turn maintains a constant coronary flow. However, the capacity for this autoregulatory response is limited. It is noted that, after a point of maximal vasodilation, any further decrease in coronary perfusion pressure will only result in a further reduction in coronary flow. Therefore, reducing DBP below the autoregulatory limit can compromise coronary flow and lead to adverse coronary events.[5]

The presence of structural CAD influences the pressure-flow inter-relation in the coronary vasculature, causing a decreased tolerance to DBP. The "J curve" relationship is still a controversy. There are some studies which support this hypothesis and some

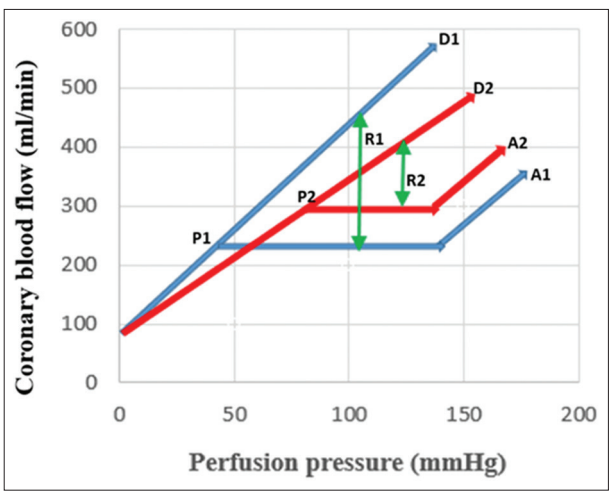

Figure 1: The coronary autoregulation. The coronary flow remains constant because of autoregulation in coronary circulation. With decrease in DBP the coronary vascular bed dilates, so as to maintain constant flow. However, this autoregulatory capacity is limited. P1 marks the lower autoregulatory limit. D1 shows the pressure-flow inter-relation seen with maximal vasodilatation. R1 demonstrates the coronary flow reserve. A2, P 2, and R2 reflect the values in the presence of hypertension or left ventricular (LV) hypertrophy. In these scenarios, there is a shift in the lower autoregulatory limit to the right (P1→P2), thereby making the myocardium vulnerable to drastic dips in diastolic pressure. The coronary flow reserve is also less in patients with hypertensive/hypertrophied hearts (Modified from Rosendorff C).[4]

which argue against it. In the TNT trial, it was noted that a very low arterial pressures (<110–120/<60–70 mmHg) portended a high risk of adverse events.[4] J-curve between DBP and CV outcomes was also noted in CAD subgroup of Cruickshank *et al.* and also in the subgroup analyses from INVEST, ONTARGET, Framingham Heart Study, and ACCORD.[6-10] A meta-analysis by Bangalore *et al.*[2] showed similar outcomes. Similar outcome was also noted in patients who presented with acute coronary syndrome (ACS) in PROVE-IT TIMI 22 trial.[11] The nadir BP here was 136/85 mmHg, while in INVEST trial the nadir systolic BP was ~119 mmHg. On the whole, these analyses noted that the risk of CV events increased at lower systolic pressures (<110 mmHg). The coronary perfusion is driven by the diastolic pressure. Hence, a low DBP in presence of CAD can cause ischemia. Evidence in support comes from the analysis of the TNT trial, where high incidence of angina was noted in patients with lower diastolic pressures.[4] In the INVEST trial, patients were revascularized experienced high event rates at low DBP, compared to those without revascularization.[7] Recently data from the Atherosclerosis in Communities study cohort analyzed by Mc Evoy *et al.* also noted that, low diastolic pressure (<60 mmHg) was associated with sub-clinical myocardial damage and increased CV events.[12] Similar J curve effect was also noted in the data analysis of the Prospective Observational Longitudinal Registry of Patients With Stable CAD (CLARIFY) registry.[13] Hence, studies noted that systolic of <120 mmHg and diastolic of <70 mmHg was associated with poor CV outcomes. However, in the SPRINT trial, treating to a lower target (systolic of <120 mmHg vs. <140 mmHg) in older (≥75 years) patients and also in high-risk hypertensives, reduced the overall CV risk, death, and readmissions for heart failure (HF).[14]

Based on these findings, the current ESC 2018 hypertension guidelines have given the following BP targets [Table 1].

Management of Hypertension in Stable Ischemic Heart Disease (SIHD)[3,15]

The BP goals and therapeutic strategies in hypertensive patients with SIHD are shown in Table 1 and in Figure 2.

Beta-blockers

Beta-blockers are initiated for patients with hypertension and angina. They decrease the heart rate; increase the diastolic filling time and thereby the coronary blood flow. They decrease the oxygen demand of the ischemic myocardium and relieve angina. Metoprolol or bisoprolol, which are cardio selective Beta-1 blockers without intrinsic sympathomimetic activity are recommended.[3,15,16]

RAS blockers

ACE inhibitors are preferred in patients with stable angina. Any associated comorbidities such as hypertension, lower LV ejection fraction ≤40%, diabetes mellitus, and chronic kidney disease further justify their use in them.[3,15] The role of ACEI in

hypertension and angina has been studied in various trials such as HOPE with ramipril, EUROPA with perindopril, and SAVE with captopril.[17-19] Angiotensin receptor blockers (ARB's) are used in patients who do not tolerate ACE inhibitors. In the VALUE trial, there were no differences in CV events, in hypertensives who received valsartan versus amlodipine. Similar observations were noted, in VALIANT trial where patients received valsartan versus captopril.[20,21]

Table 1: BP targets for all and in patients with SIHD[3]

ESC 2018 BP targets	
Recommendations	COR, LOE
Initial objective is to decrease BP to <140/90 mmHg in all and if well tolerated, to achieve a BP of ≤130/80 mmHg	I, A
The target systolic range is 120–129 mmHg for patients who are <65 years	I, A
The target systolic range is 130–139 mmHg for patients who are ≥65 years	I, A
The target systolic range is 130–139 mmHg for patients who are very elderly (>80 years), if tolerated	I, A
To target diastolic pressure of <80 mmHg, and not <70 mmHg (irrespective of the patient's risk level and presence of comorbidities)	I, A
BP goals and therapeutic strategies in patients with hypertension and SIHD	
Recommendations	COR, LOE
Beta-blockers and RAS blockers are the drugs of choice in hypertensives with a prior history of myocardial infarction	I, A
Beta-blockers and/or CCBs are the drugs of choice in hypertensives with angina	I, A

COR: Class of recommendation, LOE: Level of evidence, RAS: Renin Angiotensin System, CCBs: Calcium channel blockers

Calcium channel blockers (CCB's)

Non-dihydropyridine CCBs, such as verapamil, are initiated in hypertensives with stable angina.[3,15] In the INVEST trial (Verapamil vs. Atenolol), there was no difference in CV end points.[7] In the CAMELOT trial amlodipine or enalapril was compared with a placebo. It was noted that the amlodipine arm had less adverse CV events compared to the other two.[22] The ALLHAT trial had three groups, one received a thiazide-type diuretic, the other an ACE inhibitor, while the other used a long-acting dihydropyridine CCB. The trial noted no statistically significant outcome differences among the three groups.[23]

Non-dihydropyridine CCBs are initiated for relief of angina, in the presence of contraindication to the use of beta-blockers. They are not initiated in HF and also along with beta-blockers, as their synergistic effects they can cause profound bradyarrhythmias.[3,15]

Diuretics

The Veterans Administration studies, Survey of Health Experiences of Patients, and Medical Research Council trials

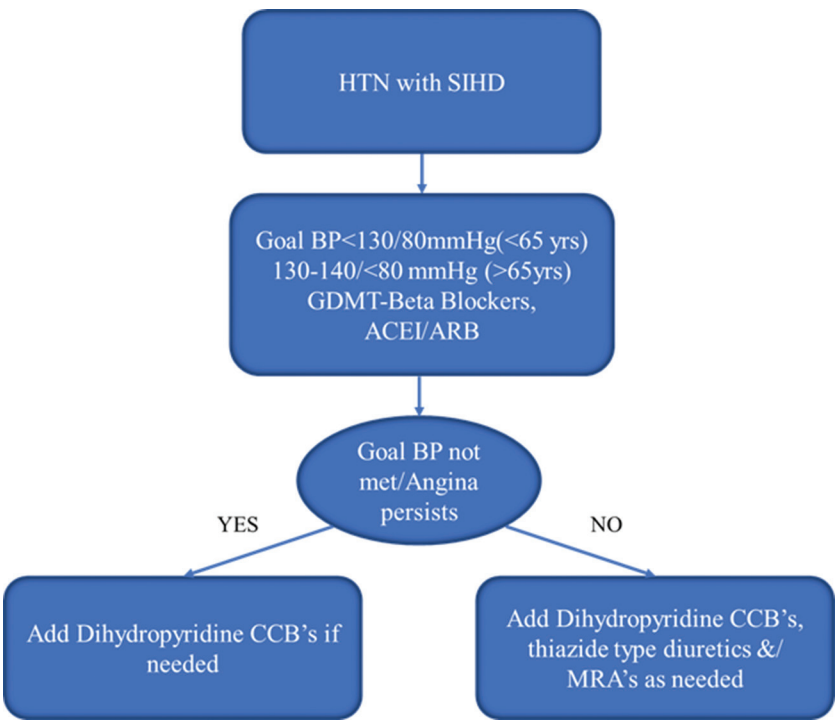

Figure 2: Treatment options in patients with hypertension and SIHD. SIHD: Stable ischemic heart disease, GDMT: Guideline directed medical therapy, ACEI/ARB: Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, CCBs: Calcium channel blockers, MRA: Mineralocorticoid receptor antagonists

which used thiazides showed reduced CV events.[24-26] Similarly, chlorthalidone therapy showed benefit in hypertensives in the ALLHAT trial.[23] Furthermore, the HYVET trial with indapamide showed decreased CV events.[3,15,27]

Management of Hypertension with ACS

The recent ESC 2018 guideline does not address the treatment of hypertension in ACS. According to 2015 ACC/AHA guidelines, in hemodynamically stable ACS patients, the BP is decreased to <140/90 mmHg (Class IIa, C). During discharge, a target of <130/80 mmHg is advised (Class IIb, C). The BP should be lowered slowly and also decrease in diastolic pressure to <60 mmHg should be avoided, as this can compromise coronary perfusion and thereby worsen ischemia.[3,15]

There are no trials that address the treatment of hypertension in the presence of ACS. Drugs that have a role in risk reduction, independent of lowering BP, are preferred.[15] These are beta-blockers, ACE inhibitors (or ARBs), and MRA's [Table 2]. They should be titrated to maximum doses, before other drugs without established evidence are initiated.

Table 2: Therapeutic strategies in patients with ACS

Class of drug	COR, LOE	Recommendation[15,28]
B-blockers	I, A	In hemodynamically stable patients, a short-acting β1-selective agent without intrinsic sympathomimetic activity such as metoprolol tartrate or bisoprolol are initiated in the first 24 h
Nitrates	I, C	To decrease the blood pressure and any pulmonary congestion or to relieve ongoing ischemia
Calcium channel blockers	IIa, B	Non-dihydropyridine CCB such as verapamil or diltiazem are indicated in the presence of ongoing ischemia, in those who are intolerant to beta-blockers Furthermore, along with beta-blockers and ACE inhibitors, in patients who have uncontrolled angina or hypertension
ACE inhibitors	ACEI-I, A	ACE inhibitor or ARB should be added in the presence of anterior wall MI and Persistent hypertension Presence of LV dysfunction or heart failure Presence of diabetes mellitus
ARB	ARB-I, B	
ACEI	IIa, A	In non-diabetic patients who present with ACS and preserved LV ejection fraction.
Aldosterone antagonists	I, A	After MI, along with beta-blockers and ACE inhibitors if there is associated: LV dysfunction Heart failure Diabetes mellitus
Loop diuretics	I, B	In patients with ACS who present in NYHA class III or IV

COR: Class of recommendation, NYHA: New York Heart Association, LOE: Level of evidence

Nitrates

They play an important role in relieving angina, pulmonary edema, or acute hypertension in ACS.[15,28] GISSI-3 and International Study of Infarct Survival (ISIS)-4 trials found no mortality benefit with nitrates.[29,30] Nitrates are contraindicated in hypotension and in presence of right ventricular ischemia. Initial treatment is with sublingual or intravenous nitroglycerin, followed by switch over to longer-acting formulation, if needed.[15,28]

Beta-blockers

These drugs decrease: (1) Myocardial oxygen demand, (2) infarct size, (3) sudden cardiac deaths due to anti-arrhythmic effects. Beta 1 selective agents – metoprolol or bisoprolol are preferred. Carvedilol (β1/β2/α1 adrenergic receptor blocker) is a potent BP-lowering agent and is preferred in ACS with severe hypertension.[15,28,31]

RAS blockers

ACE inhibitors play an important role in ACS.[32] They prevent: (1) Infarct expansion and (2) LV remodeling and dilatation. They also decrease the incidence of arrhythmias, admissions for HF, and cardiac rupture.[15,28,31] The GISSI-3, ISIS-4, and Chinese Cardiac Study-1 trials have demonstrated a clear benefit with early initiation of ACE inhibitors.[29,30,33] ARBs can be used as alternatives for ACE inhibitor-intolerant patients, as noted in the VALIANT trial, with valsartan.[21]

CCB's

Dihydropyridine CCB's decrease BP and may relieve ischemia. Non-dihydropyridine CCB such as verapamil or diltiazem are indicated in the presence of ongoing ischemia, in patients with intolerance to beta-blockers.[15,28]

Mineralocorticoid Receptor Antagonists

In the EPHESUS trial (eplerenone vs. placebo) after myocardial infarction (MI), eplerenone reduced CV mortality and sudden cardiac death.[34] The role of spironolactone in ACS is not known, but it has shown significant mortality benefit in patients with HF in the RALES trial.[35]

Diuretics

In ACS, loop diuretics are initiated in patients with pulmonary edema or HF (New York Heart Association [NYHA] class III or IV). Thiazide diuretics are useful for long-term control of BP.[15,28]

Management of Hypertension and Ischemic HF

Hypertension is implicated as an important risk factor in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The treatment of hypertension reduces the risk of incident HF by around

50%.[36] Several trials have shown that control of BP, delays the development of HF and also prolongs life. Optimization of BP is very important in these patients. Drugs that improve outcomes in patients with HFrEF, generally also lower BP. These drugs are also safe in HFpEF. The target SBP is <130 mmHg. Sodium restriction is important in managing both hypertension and LV dysfunction. The preferred drugs are:

RAS blockers

ACE inhibitors have shown benefit in ischemic heart disease and LV dysfunction.[6,19,37] The AIRE trial supports, ACE inhibition in hypertensives with LV dysfunction after MI.[38] Among ARB's valsartan and candesartan have shown benefit in the Val-Heft and CHARM program, respectively.[39,40]

Beta-blockers

They have emerged as an important group of drugs in the management of HF. Several trials such as MERIT-HF with metoprolol, COPERNICUS with carvedilol, cardiac insufficiency bisoprolol study-II with bisoprolol, and SENIORS with nebivolol have demonstrated decreased mortality in HF.[41-44]

Mineralocorticoid Receptor Antagonists

The RALES and EPHESUS trials have shown the benefit of spironolactone and eplerenone respectively in patients with CAD.[34,35] The subgroup analysis of EMPHASIS trial, demonstrated that hypertensives with chronic HF in NYHA Class II, had a greater improvement in relative risk with eplerenone than normotensives.[45]

Diuretics

Thiazide diuretics prevent HF in hypertensives. They are initiated in patients with mild HF for control of BP. In severe HF, loop diuretics such as furosemide and torsemide are indicated to relieve volume overload.[15,46]

Nitrates and Hydralazine

In HF patients (NYHA Class III or IV), with persistent symptoms and uncontrolled BP, a combination of hydralazine and isosorbide is recommended. The A-heFT trial showed that this combination provided an added benefit in African Americans.[15,46,47]

Thus, ACEI's (or ARB's), beta-blockers, or MRA's (or a combination) are recommended as first-line drugs. A thiazide diuretic is added when hypertension persists despite treatment. Amlodipine or hydralazine is recommended to further reduce BP to optimal levels.

Conclusions

Although we are treating hypertension since several decades, the optimal treatment targets have undergone several revisions, since the JNC-7 guidelines published in 2003. The present evidence shows that intense BP control (≤130/80 mmHg) in patients with CAD reduces MI, HF, and stroke. However, this benefit is noted at the expense of increased risk for hypotension. Randomized trials are needed in these patients to further prove the efficacy and safety of such aggressive treatment. Intensive BP reduction goals should weigh the risk of need for multiple medications versus compromise of compliance. It is prudent to focus on choosing targets that are based on patient's risk profile and their tolerance to antihypertensive medications.

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