

Hypertension-A review

Hypertension is a common clinical condition evaluated in primary care by any doctor in day to day practice. It therefore forms an important aspect of patient evaluation as hypertension leads to myocardial infarction, stroke, renal failure, and death. Yet there is no generally accepted definition of hypertension. This was evaluated by hypertension specialists and three approaches were published based on measured blood pressure, subclinical disease and clinical phenotypes.¹

Hypertension is defined by the American Society of Hypertension (ASH) Writing Group 2 as updated.³

Hypertension is a progressive cardio-vascular syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before blood pressure elevation is sustained; therefore hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature and other organs and lead to premature morbidity and death.

The above definition does not establish any blood pressure threshold or a target blood pressure for the management of hypertension in clinical practice. Both of these are elusive if one searches medical history for the answer. Most recent reviews like JNC 8 collected evidence leading to the conclusion that for hypertensive patients >60 years a BP target of <150/90 and for those younger than 60 years a BP target of <140/90.⁴ ACCORD Trial also did not support lowering blood pressure below 135-140 mm Hg in Diabetic patients.⁵ However Sprint trial revealed that lower the blood pressure better in terms of CV outcome.⁶

Epidemiologic data generally support a continuous incremental risk of cardio-vascular disease, stroke and renal disease across levels of both systolic and diastolic blood pressure.

Although early definition of hypertension focussed on diastolic blood pressure it is now recognised that systolic blood pressure is a more powerful predictor of coronary artery disease than diastolic blood pressure particularly among older individual.^{7,8} But according to Framingham Heart Study before age 50 years

diastolic blood pressure is a stronger predictor of coronary artery disease. However with increasing age there is a transition from diastolic blood pressure to systolic blood pressure as the dominant predictor of coronary artery disease. Wide pulse pressure is predictive of coronary artery disease. So at age >60 years coronary artery disease is more closely related to systolic blood pressure and risk factor increases with wide pulse pressure.^{9 10} In a meta-analysis of 61 studies that included almost one million adults BP was related to fatal Coronary Artery Disease over the BP range of 115/75 to 185/115 mm of Hg for all ages.¹¹ Overall, each increase in systolic BP of 20 mm Hg or each 10 mm Hg increase in diastolic BP doubles the risk of a fatal coronary event.

Effect of treatment on blood pressure:

The risk of cardio-vascular disease in the patient with hypertension has been shown to be greatly and rapidly reduced with effective anti-hypertensive therapy.¹¹ Surprisingly in elderly population of >85 years a significant association of lower blood pressure was detected with lower stroke deaths and heart failure but not with lower rate of myocardial infarction.¹²

Summary of BP goals:

BP Goal(mm Hg)	Condition	Level of evidence
< 150/90	Age: >80 years	IIa/B
<140/90	CAD	I/A
	ACS	IIa/C
	HF	IIa/B
<130/80	CAD-	IIb/C
	Post-MI, Stroke, TIA, Carotid artery Disease, PAD, AAA	IIb/C
<130/80	chronic renal insufficiency & albuminuria	NKF guideline
<140/80	Diabetic patients- lower BP in young if tolerates	ADA guideline

Several studies like HOPE, SAVE, EUROPA have shown benefit of ACE inhibitors on Cardio-vascular outcomes in individuals. There is no definite outcome from treatment of individuals for prevention of hypertension in TROPHY study.¹³ ACCORD study did not demonstrate benefit with reduction of blood pressure <120 in terms of composite event of heart attack, stroke, or cardiovascular death but significantly reduced the incidence of stroke.¹⁴

Cardio-vascular Risk Factors:

In addition to Hypertension there are other modifiable risk factors which have multiplicative effect on cardio-vascular disease risk. These are smoking, dyslipidaemia, diabetes mellitus, obesity, renal insufficiency and peripheral artery disease. There are non-modifiable risk factors are age, sex, race, family history.

Anti-hypertensive in specific circumstance:

Obesity:

Obesity is considered a major risk factor for poor BP control in hypertensive patients.¹⁵ Mechanism of obesity related hypertension are numerous: activation of sympathetic nervous system, sodium retention, Renin –angiotensin-aldosterone system activation, insulin resistance, and altered vascular function.¹⁶ Investigators have found a beneficial effect of ACE Inhibitors in this group of patients as well as reduce the incidence of diabetes by virtue of increasing insulin sensitivity.¹⁷ This is in sharp contrast to thiazide diuretics which are associated with increased risk of diabetes and should be avoided in this group.¹⁸ Beta blockers are beneficial in obese hypertensive by reducing renin secretion and cardiac output both of which are elevated.¹⁹ But the enthusiasm beta blocker use is dampened by the finding of negative stroke outcome compared with placebo and other anti-hypertensive classes. ²⁰

Peripheral vascular disease (PAD):

PAD is associated with similar involvement of other vascular beds like coronary. So treatment of PAD is associated with significant reduction of MI, Stroke Heart Failure and death. There is no specific recommendation for any drug. Beta blockers are effective agents (level of evidence A). ACE inhibitors or ARB is reasonable in symptomatic (level of evidence B) or asymptomatic

patients (level of evidence C). BP goal is <140/90 for non-diabetic and <130/80 for diabetics and kidney patients.²¹

Chronic kidney Disease (CKD):

In patients of CKD cardio-vascular death is more likely than progression to end-stage renal disease and is the leading cause of death.²² ACE inhibitors, or ARB are considered as anti-hypertensives of choice. Only concern with this treatment is potassium which should be kept under observation.

Coronary (Artery Disease CAD):

Hypertension in the setting of CAD is quite common. Pathophysiologic mechanism involves overactive sympathetic nervous system, and RAAS activity and deficiency of vasodilation by nitric oxide and prostacyclin and changes in natriuretic peptides. There is increased expression of growth factors and inflammatory cytokines. There is increased vascular stiffness and endothelial dysfunction.²³ These factors interact with genetics, demographic and environmental factors to cause hypertension in the setting of CAD. In addition, vasoactive adipocytokines contribute to vasoconstriction, endothelial dysfunction, inflammation and increased oxidative stress contributing to hypertension and cardio-vascular disease.^{24,25}

As mentioned before a blood pressure target of 140/90 is reasonable in hemodynamically stable ACS a target of 130/80 should be achieved at the time of discharge. However caution is advocated in lowering the diastolic blood pressure below 60 which may affect coronary perfusion and affect ischemia. In all cases blood pressure should be lowered very slowly.

Combination anti-hypertensive drug therapy can achieve and sustain long term BP control. There is no evidence to support initiating therapy with any one drug class over another for primary prevention of CAD. But in contrast, for secondary prevention underlying comorbidity guides the optimal drug therapy. Class effect has been demonstrated in case of thiazide and thiazide type diuretics, ACE inhibitors and ARB which have high degree of homogeneity in both their mechanisms of action and side-effects. But there are major heterogeneous differences in the class of drugs like beta blocker and calcium channel blockers. Most recent trials have shown beneficial effect of combining renin-angiotensin blocking agents with thiazide diuretics or with calcium

channel blockers in prevention of cardio-vascular events but prohibited combining ARB with ACE inhibitors.

Beta blockers – Carvedilol, Metoprolol, Bisoprolol and Nebivolol are preferred in the setting of heart failure to improve outcome.²⁶ Beta blockers are preferred in the setting of CAD-angina, myocardial infarction and LV dysfunction. In ACS short acting beta1 selective blockers without intrinsic sympathomimetic activity like Metoprolol tartrate or bisoprolol are preferred. It is a heterogeneous class of anti-hypertensive with varying effect on resistance vessels and on cardiac conduction and contractility.

ACE inhibitors are effective in reducing initial CAD events and recommended after Myocardial infarction especially anterior infarction and left ventricular dysfunction or heart failure. They prevent and improve both heart failure and progression of CKD. ^{27,28,29} With thiazide diuretic they reduce the incidence of stroke.³⁰ ACE inhibitors might not be necessary as routine therapy in low risk patients of CAD with preserved LV function especially those who have received intensive treatment with revascularisation and lipid lowering agents.

ARBs reduce the incidence and severity of CAD events, the progression of renal disease in type2 diabetes mellitus and cerebro-vascular events. They are alternative to ACE inhibitors if not tolerated.

Aldosterone antagonists added to other anti-hypertensives have mortality benefit in patients with chronic and advanced heart failure. It also, when added, to other anti-hypertensives help in difficult to treat hypertension.^{31,32,33} It should be avoided in patients with elevated creatinine and potassium level.

Calcium channel blockers are alternatives to beta blockers in the treatment of angina but not in prevention of heart failure compared to ACE inhibitors. They are not useful in acute coronary syndrome setting.

Direct renin inhibitors aliskiren lowers blood pressure but have no other beneficial effect in cardio-vascular disease.³⁴

Nitrates long acting or calcium channel blockers can be prescribed if beta blockers are contraindicated in stable angina. All the three can be combined in angina treatment. It is the cornerstone of therapy in hypertensive with acute coronary syndrome (ACS) for relief of ischemic symptoms and pulmonary congestion with moderate effect in lowering blood pressure. However nitrates

are contraindicated in right ventricular infarction and used with caution in inferior wall infarction.

Heart Failure:

Drugs used to improve outcomes in patients with heart failure are ACE inhibitors or ARB, Beta blockers (carvedilol, metoprolol succinate, bisoprolol, nebivolol) and aldosterone receptor antagonists. In heart failure patients with hypertension and preserved ejection fraction control of systolic and diastolic pressure is important with ventricular rate control in presence of atrial fibrillation and relief of pulmonary congestion and peripheral oedema. Drugs helpful in heart failure with preserved ejection fraction are beta blockers, ACE inhibitors/ARB or calcium channel blockers. It is important to avoid in patients with reduced ejection fraction the drugs like verapamil, diltiazem, clonidine moxonidine and hydralazine without nitrates and NSAID. Although blood pressure target is 140/90 lowering further to 130/ 80 is considered and done slowly. However lowering diastolic blood pressure <60 is likely to affect coronary perfusion and is detrimental. People >80 years should be checked for postural changes and standing systolic blood pressure <130 and a diastolic blood pressure <65 should be avoided.

Conclusion:

Hypertension is a common problem faced by medical professionals in day-to-day practice. When decided to treat the hypertension in an individual choice of the pharmacological agent is tailor made to the individual patient condition and tolerability. There is no fixed choice of medication or algorithm for all patients. Above is a general guideline for drug treatment of hypertension. In addition to the drug treatment there are other non-drug modalities of treatment. Aim of treatment is to keep blood pressure under control to halt organ damage.

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