



MANAGEMENT OF HYPERTENSION AMONG THE PATIENTS WITH DIABETES MELLITUS AND HEART DISEASES

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Abstract

Hypertension is one of the serious chronic disorder that can affect millions of people worldwide. Uncontrolled hypertension may progress toward other complications such as Left ventricular hypertrophy and other cardiovascular diseases (CVD). Hypertension is a common comorbidity with diabetes mellitus and heart diseases. Management of hypertension with different classes of antihypertensive drugs is a big challenge for health care providers. β -blockers, Diuretics, Angiotensin converting enzymes (ACE) inhibitors, Angiotensin Receptor blocker (ARB), calcium channel blockers are among the most commonly prescribed groups in the current era. It has been estimated that 10%-25% of the population are expected to be benefit from drug therapy against hypertension. Proper selection of Drug class and appropriate combination with other classes is necessary to overcome the problem. Pharmacological intervention with antihypertensive drugs require vigilant patient assessment as well as Therapeutic Drug Monitoring (TDM) to ensure the safety and efficacy of the drug to achieve the aims and goal of therapy and reduce the risk of further complications. Along with pharmacological agents, non-pharmacological interventions (lifestyle modification) are also important to achieve the target blood pressure in hypertensive patient's comorbid with heart diseases and diabetes mellitus. The main Focus of this review article is to investigate the proper management of different classes of anti-hypertensive drug in the presence of other body diseases and recent advancement and discoveries in this field as well.

Keywords: Hypertension, Management, Anti-hypertensive drugs, Coronary Diseases, Chronic Heart failure, Diabetes mellitus, non-pharmacological interventions

Introduction

Hypertension (HTN) or high blood pressure (B.P) is a chronic medical disorder in which pressure of the blood against the arteries wall is elevated. Arterial resistance or impedance to flow of blood is usually raised due to different known as well as unknown factors. Measuring of blood pressure involves two terms, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively, in the arterial system. When the left ventricle is most contracted, it will be termed as systolic pressure; likewise when the left ventricle is most relaxed prior to the next contraction, it will be called as diastolic pressure. Normal blood pressure is in range of 100–130 mmHg systolic and 60–90 mmHg diastolic. A person is said to be hypertensive if his/her blood pressure is persistently at or above 140/90 millimeters mercury (mmHg) for most of the adults [1].

Blood Pressure is generated when the heart pushes the blood into the blood vessels and arteries impede the blood flow. Ohm's Law can be applied as follows:

$$\begin{aligned} R &= \Delta P/F, \text{ MAP} = C.O \times SVR, \\ C.O &= SV \times HR \end{aligned}$$

MAP = mean arterial blood pressure, estimated by DBP + (SBP - DBP)/3, C.O = cardiac output, SVR = systemic vascular resistance, HR = heart rate, SV = stroke volume (dependent on pre-load, contractility, after-load).

On the basis of etiology hypertension are of two types. Primary Hypertension (Essential, Idiopathic) that usually accounts for 95% of all cases and is most probably occurs due to unknown cause. Secondary Hypertension accounts for less than 5% of cases and occur secondary to rectifiable causes such as Intrinsic renal disease, Reno-vascular disease, Mineralocorticoid excess, Sleep Breathing disorder, Pheochromocytoma, Glucocorticoid excess (Cushing's Syndrome), Coarctation of Aorta, Hyper/hypothyroidism. Classification of hypertension on the basis of systolic and diastolic blood pressure is present in the form of a table (Table 1) at the bottom of the article. It is estimated that about 1.2 billion people will be suffering from hypertension worldwide [3].

"Globally, the overall prevalence of raised blood pressure in adults aged 18 and over was around 22% in 2014 [4]. Across the WHO regions, the prevalence of raised blood pressure was highest in Africa, where it was 30% for both sexes combined

as well as for men and women separately [4]. The lowest prevalence of raised blood pressure was in the WHO Region of the Americas at 18% for both sexes. Men in this region had higher prevalence than women (21% for men and 16% for women). In all WHO regions, men have slightly higher prevalence of raised blood pressure than women [4]".

Most of the patients with primary hypertension will need two or more antihypertensive drugs preferably acting by different mechanism (Polypharmacy) to control their blood pressure [5, 6]. If the blood pressure is 20/10 mm Hg above the target blood pressure, drug therapy should be initiated with two anti-hypertensive drugs [5, 6]. According to an estimate about 40% of patient will not respond to regimen with two hypertensive drugs. These patients will have resistant hypertension and need a combination of three or more antihypertensive drugs. Proper combination of different available agents and vigilant monitoring of patient is the responsibility of health care providers to achieve the targets.

Poorly Controlled Hypertension may progress toward some serious complications that may prove fatal. High blood pressure was the greatest mediator to enhance the burden of cardiovascular diseases and accounts for approximately 42.1% of total burden [7]. Systemic hypertension is a major risk factor for cardiovascular and coronary events such as stroke [5, 6, 8], congestive heart failure (CHF) [5, 6, 9, 10] and peripheral arterial disease [5, 11]. Approximately 69% of patients with first myocardial infarction have hypertension [12], similarly 77% of patients with first stroke [12], 74% of patients with chronic heart failure, and 60% of patients with peripheral arterial disease [12, 13] are all associated with hypertension. Proper management of hypertension according to situation and severity is important to prevent the risk of any further complications. Controlling the hypertension with appropriate agents, reduces the incidence of all type of strokes by 38% in women, 34% in men, 36% in older persons, and by 34% in persons older than 80 years [14].

Pharmacological Management of Hypertension

Pharmacological management of hypertension will begin with different groups of antihypertensive drugs. Among individuals with age below 55 years Angiotensin converting enzymes (ACE) inhibitors or Angiotensin receptor blockers is usually preferred as a part of an initial regimen. If a patient didn't respond well then progress toward β -blockers and if the condition remains same, a combination of calcium channel blocker and ACE inhibitor or ARB

should be considered as mainstream agents to combat hypertension [15]. The combination of diuretics and β -blockers increased glucose intolerance and may induce diabetes [53, 55] similarly calcium channel blockers together with β -blockers cause AV bundle block and heart failure [25]. So these combinations should be avoided. In patients age above 55 years Calcium channel blockers and diuretics can tolerate well but in African Caribbean Calcium channel blockers together with ACE inhibitors or Angiotensin-II type 1 receptor blockers should be preferred as people in that region respond well to this combination [15]. Pulsatile release of drugs should be more effective in the case of hypertension as blood pressure fluctuates time to time so Chrono pharmacotherapy provides better management of hypertension [16]. During the office working hour's (stress hours) critical management of hypertension should be required to prevent any complication while rest hour's (at night) requires much less attention.

Management of Hypertension in Coronary Heart Disease

The Risk of fatal coronary diseases increases to double with the 20/10mmHg rise in blood pressure among the individuals aged between 40-90 years [17]. So by controlling blood pressure we can minimize the chances of fatal coronary events. Hypertension also accelerates progression and development of Atherosclerosis, thrombus formation due to endothelium dysfunction as well as turbulent blood flow. In the presence of CHD (coronary heart diseases), hypertension is managed by use of different groups of anti-hypertensive drugs alone as well as in combination together with non-pharmacological interventions (life style modifications). β -blockers should be used as first-line agent against hypertension among the individuals with coronary heart diseases unless it is contraindicated [18-20]. Cardioselective β 1-blocker (Bisoprolol, carvedilol) is generally preferred. β -blockers reduce the size of infarct, increase survival period, decrease the risk of recurrent of myocardial infarction and sudden death among the patients with both hypertension and myocardial infarction [21-23]. Hence β -blockers are the first choice to treat hypertension in coronary heart diseases.

Long-acting calcium channel blockers (CCBs), (amlodipine, nifedipine) can be added with β -blockers if BP remains elevated or angina continues. For long-term treatment with nifedipine extended-release preparation should be used. Immediate release may cause ventricular dysfunction,

channel blockers (diltiazem, verapamil) can be used as a substitute to β -blockers if β -blockers are contraindicated [24]. When β -blockers are used in combination with a non-dihydropyridine calcium channel blockers, there is an increased risk of AV block or severe bradycardia hence non-dihydropyridine agents should be avoided in patients with systolic Heart Failure [25].

Now a day's ACE (Angiotensin-converting Enzyme) inhibitors are also among the most commonly prescribed agents by the physicians after myocardial infarction. In EUROPA studies, 12,218 patients were accessed by giving treatment with an ACE (Angiotensin-converting Enzyme) inhibitor (perindopril) or placebo. Perindopril treated group had significantly less Myocardial infarction, cardiac arrest and death associated with cardiovascular events,[26]. Similarly, VALIANT study on Angiotensin type 1 receptor Blockers (ARB) shows ARB (Valsartan) was as effective as ACE inhibitor (Captopril) in reducing cardiovascular event after myocardial Infarction [27]. For long term use evaluation of Valsartan (VALUE), trials on 15,245 hypertensive patients, shows that ARB (Valsartan) was as effective as calcium channel blocker (Amlodipine) in preventing coronary event after Myocardial infarction [28]. So both of these groups that are associated with renin-angiotensin system inhibition gives a better outcome in patients with coronary heart diseases.

The ALLHAT trials on the use of Diuretics clearly show marked benefit in patients with coronary heart diseases [29]. Despite of their effectiveness in controlling BP and reducing the risk of cardiovascular event in different studies [30, 31] there are some studies that raise the question on use of diuretics as it is involved in contributing the metabolic effects of thiazide that enhance the risk of cardiovascular and coronary events [32]. Their use in acute myocardial infarction is usually not encouraged. Effective combination of antihypertensive agents is usually required to achieve sustain and long-term BP control [33]. Therefore, the best possible strategy to achieve the target is by using combination therapy. Non-pharmacological interventions (Lifestyle modification, Exercise, diet control) should be encouraged in all individuals with hypertension [33]. Exercise improves blood circulation, endothelium function, reduces BP and cardiac afterload by a variety of mechanisms, including reduced arterial stiffness [34]. Therefore non-pharmacological intervention should be encouraged among the patients with hypertension comorbid with coronary heart diseases.

Management of Hypertension in Chronic Heart Failures

Hypertension increases the risk of heart failure by 2-3 times [2]. Pharmacological intervention with antihypertensive drugs for the long duration of time reduces the risk of heart failure by 50% [35]. Renin-Angiotensin system blocker that includes Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blocker (ARB) should be used as first-line therapy against hypertension among patient with or without heart failure. Different trials show that ACE inhibitors reduces the risk of mortality in the patients with Left Ventricular dysfunction, decrease death by 1-4 patients at any stage of heart failure that arises after myocardial infarction [36-38].

ACE inhibitors that are used as the first-line agent against hypertension in heart failure may be replaced by ARB (valsartan) as different trials show that Valsartan cause remarkable reduction in Mortality and Morbidity [39, 40]. The combination of ACE inhibitors with ARB may markedly increase the adverse effects such as renal dysfunction and hyperkalemia. Thus, such combination should be avoided in the patients with heart failure.

Administration of β -blockers should be started immediately after diagnosis of systolic dysfunction. Carvedilol, and bisoprolol have been shown marked improvement in the survival of patients with heart failure. β -blockers (Pindolol) with intrinsic sympathomimetic effect should be avoided. Many patients with heart failure have other conditions for which β -blockers respond well such as prior to myocardial infarction, atrial fibrillation etc. Combination therapy with nitrates and hydralazine is very effective in prolonging the life of a patient with heart failure [41].

Among Diuretics loop diuretics (furosemide, bumetanide, torsemide) are most commonly used followed by Thiazide diuretics (hydrochlorothiazide, indapamide) which are less effective and produces more side effects among the patients with heart failure. Thiazide diuretics should be preferred in those patients who are at risk of development of heart failure. Patient with chronic heart failure have reduced cardiac output and on the other hand Diuretics may lower the venous return to the heart as a result of which there is a marked decrease in cardiac output which may be harmful (retention of salts in kidney, ischemic injuries). So the long term use of diuretics in a patient with heart failure should be avoided Calcium channel blockers should be contraindicated in the patient with chronic heart failure because they can worsen the situation in

heart failure and didn't reduce the risk of mortality in the patients. Treating with Amlodipine and felodipine neither improves nor worsen the survival of heart failure in patients [42, 43]. Therefore in the presence of other well tolerating agents use of calcium channel blocker is just wastage of money with no benefits. Potent vasodilators such as minoxidil should be avoided because it can promote sodium retention.

Management of Hypertension in Diabetes mellitus

Hypertension in most of the cases co-exists with diabetes mellitus. Chances of Diabetic patient to have hypertension are three to four times more than in non-diabetic individuals [44]. Uncontrolled hypertension in diabetic patients is the major factor that provokes cardiovascular events (Strokes, Myocardial infarction, Heart Failure) and account for 65% of death [45]. Diabetes together with Hypertension may promote some other complications such as nephropathy, retinopathy [44]. The target blood pressure to avoid any complication among diabetic patient is less than 130/80 mmHg according to Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the American Diabetes Association [6, 46]. Individuals whose systolic and diastolic blood pressure is in range of 130-139/80-89 mmHg should be treated with non-pharmacological interventions (lifestyle modification) and individuals whose blood pressure is above 140/90 mmHg should be treated with both pharmacological therapy as well as non-pharmacological interventions to achieve the goal blood pressure less than 130/80 mmHg [6, 46, 47]. Angiotensin-converting enzyme (ACE) Inhibitors should be recommended as a first-line agent against hypertension among diabetic patients. [46-48]. Such Inhibitors are the drug of choice as they inhibit the progression of diabetes-associated kidney diseases (nephropathy) [6, 46, 47]. A systemic review on the use of Angiotensin-converting enzyme (ACE) Inhibitors reveals that ACE inhibitors can significantly reduce the risk of all type of mortality in hypertensive patient's comorbid with diabetic-kidney diseases [49]. Therefore, ACE inhibitors must be included in the regimen of the diabetic patient unless it is contraindicated as in the case of hyperkalemia. Angiotensin-II type 1 receptors blockers (ARBs) also reduces the risk of complications that are associated with diabetes (e.g., nephropathy, kidney failure) [46]. ARBs are very efficacious in delaying these complications among patients with type 2 diabetes, hypertension, and macro albuminuria [46, 47, 50]. Therefore, ARBs are also among the preferred agents

against hypertension in diabetic patients who didn't respond to ACE inhibitors. Thiazide Diuretics (Indapamide, chlorthalidone) alone or in combination should be recommended as a second line agent in diabetic patients to treat hypertension. In case if the BP still remains above the target BP then diuretics should be combined with Calcium channel blockers or ACE inhibitors [6]. Chlorthalidone shows a marked reduction in cardiovascular and cerebrovascular events in the diabetic patients and ALLHAT study shows no significant difference in their efficiency compared with Lisinopril or Amlodipine [51, 52].

Thiazide Diuretics are less efficient in patients with renal dysfunction [46] and also they can produce metabolic alteration therefore prescriber should switch toward other classes of diuretics such as loop diuretics. Metabolic Alterations such as poor glycemic control, elevation in triglycerides and cholesterol are commonly associated side effects with diuretics when used in higher doses [53] but we can easily manage these side effects by controlling the dose of other drugs (insulin, lipid lowering agents) as the benefit provided by Diuretics in preventing cardiovascular events and heart failure is significantly more than their adverse effects. β -blockers should preferred in combination with other groups most probably with ACE inhibitors where they show the synergistic effect to lower uncontrolled BP with heart beat greater than 84/min in diabetic patients [54].

According to several reports, trials and reviews β -blockers are involved in worsening insulin sensitivity and promote glucose intolerance resulting in hyperglycemia [6, 53, 55]. But on the other hand their significance in preventing coronary events, post myocardial infarction mortality, other cardiovascular events and heart failure is more hence β -blockers should be the main component of antihypertensive regimen in patients with diabetes, coronary arteries diseases and various types of Angina [6, 47]. Carvedilol which have both β -blocker as well as α -blocker activity is less likely to produce hyperglycemia and worsen insulin sensitivity in diabetic patients. Therefore, carvedilol should be the most preferred agent among the β -blockers [55, 56]. Calcium channel blockers should be prescribed in the case of hypertension comorbid with diabetes, coronary heart diseases, myocardial infarction and other cardiovascular events. Comparative study of calcium channel blockers and ACE inhibitors shows a significant risk of fatal and non-fatal myocardial infarction in diabetic patients treated with calcium channel blockers [57]. Calcium channel blockers are

also associated with heart failure and are less effective as compared to ACE inhibitors and ARB in limiting the progression of nephropathy associated with diabetes [47]. Calcium channel blockers are only reserved for the patients who didn't respond well to a combination of two or more classes of antihypertensive drugs or patient develop tolerance against these drugs [47, 48]. In the former case, CCB should be added as a third agent to manage hypertension (polypharmacy).

Non-pharmacological interventions must be encouraged in patients with both Hypertension and Diabetes mellitus. These include reduction in alcohol consumption, implement of Dietary approach to stop hypertension (DASH), increase calcium (1250 mg daily), magnesium (500 mg daily) and potassium (4700 mg daily) intake, restriction of sodium to 2.4 g per day and lowering of cholesterol-rich diet and cessation of smoking [58]. Regular Exercise for 30-40 minutes not only improves blood circulation, reduce blood pressure [34] but also increase insulin sensitivity and reduce glucose intolerance [59].

In short hypertensive patient's comorbid with Coronary heart diseases, β -blockers should be the first choice followed by calcium channel blockers. ACE inhibitors and ARBs are also well tolerated among patients with Coronary Heart Diseases. Diuretics should be avoided as it may promote coronary heart diseases due to metabolic alteration. If hypertension coexists with diabetes, pharmacological therapy should be initiated with ACE inhibitors. If the patient didn't respond well to ACE inhibitors, ARB should be added to the regimen or substituted by thiazide or loop Diuretics. If still Blood pressure is beyond the goal limits, β -blockers in combination with ACE inhibitors should be used. Calcium channel blockers should be reserved for coronary heart diseases, diabetes, and hypertension if all exist at the same time. Lifestyle modification is mandatory in all patients in order to achieve target blood pressure in CHD and diabetes.

Conclusion

Different classes of antihypertensive drugs give a different outcome in patient's belonging to different races, ages and in the presence of comorbid diseases. African-American and patient aged above 55 years respond well to diuretics and Calcium channel blockers while young patients respond well to ACE inhibitors. β -blockers are well tolerated in heart diseases and ACE inhibitors respond well in diabetic patients. So proper choice of drug class and appropriate combination with other groups of antihypertensive drugs if required shows marked

benefit in reducing the other complications that are associated with hypertension such as cardiovascular events, coronary heart diseases, heart failure, retinopathy, nephropathy. During the selection of any kind of antihypertensive agent to initiate the therapy, different factors must be considered. These Factors include patient age, level of blood pressure, their standard of living, your aim to achieve target blood pressure, goal of therapy, and severity of vital organ damage due to blood pressure and risk of cardiovascular diseases. Blood pressure during working hours (stress hours) and rest hours should be monitored vigilantly in order to assess the patient response to a drug therapy that may help in selecting the proper regimen. Non-pharmacological intervention such as cessation of smoking, weight reducing, lowering alcohol intake, sodium restricted diet, peace living and daily exercise should be encouraged among all the patients. It's the responsibility of physicians and pharmacist to guide and educate the patient about hypertension properly so that he may able to take the right decision in case of any emergency. Different seminars, conferences, articles in printing media and programs in electronic media regarding prevention, detection, evaluation and treatment of hypertension should be arranged to increase awareness among public and to educate the community.

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Conflict of Interest

There exist no conflict of Interest.

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Table 1. Classification of Hypertension on the basis of Systolic/Diastolic Blood Pressure [2].

Stages of Hypertension	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	<80
Pre-hypertension	120–135	80-89
Hypertension	≥140	≥90
Stage 1 hypertension	140–159	90-99
Stage 2 hypertension	≥160	≥100