

Management of hypertension: Current state of the art and challenges

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Abstract

Hypertension is a major modifiable cardiovascular risk factor. Hypertension is also recognized as the most

important risk factor for global disease burden. It is well established that a sustained reduction in blood pressure by drugs reduces the incidence of cardiovascular morbidity and mortality. In recent years, studies and new guidelines published for the management of hypertension. Awareness, treatment and control of hypertension are very poor, despite the new guidelines. We highlighted the management of hypertension in the light of current literature.

Key words: Hypertension; Therapy; Blood pressure; Cardiovascular risk factor

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Core tip: Hypertension is a major modifiable cardiovascular risk factor. It is well established that a sustained reduction in blood pressure by drugs reduces the incidence of cardiovascular morbidity and mortality. There are several types of drugs that can be used in the management of hypertension. But, the ideal treatment strategy remains uncertain for such a common and treatable disease. In recent years, studies and new guidelines were published addressing management of hypertension. Despite new guidelines, awareness, treatment and control of hypertension are very poor. We highlighted the management of hypertension in the light of current literature.

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INTRODUCTION

Hypertension, a major contributor to cardiovascular

complications and premature death, is a modifiable cardiovascular risk factor^[1]. Several studies have demonstrated that high blood pressure (BP) has a strong positive association with cardiovascular morbidity and mortality^[2,3]. Hypertension is remarkably common across the world and its prevalence is strongly influenced by age and lifestyle factors^[4,5]. Management of hypertension is especially important as hypertension is well recognized as the most important risk factor for global disease burden.

It is well established that treatment of hypertension reduces the risk of cardiovascular morbidity and mortality^[6,7]. In contrast, untreated or poorly controlled hypertension is associated with permanent morbidity and mortality. The ultimate goal of antihypertensive therapy is the reduction of cardiovascular morbidity and mortality. There are several types of drugs that can be used in the management of hypertension. Yet, the ideal treatment strategy remains uncertain for such a common and treatable condition. There are new evidences regarding the management of hypertension. More recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) published joint hypertension guidelines in 2013^[8]. The panel members who were appointed to the Eighth Joint National Committee (JNC) also published the 2014 JNC report^[9]. While these were in agreement on many points with previous guidelines, there were some important differences. This review highlights the management of hypertension in the light of current literature.

NON-PHARMACOLOGICAL THERAPY

Lifestyle changes

All guidelines recommend that the management of hypertension should start with life style modification^[8-10]. Several lifestyle interventions have been shown to reduce BP^[11,12]. Beside reducing high BP, these strategies are beneficial in managing most of the other cardiovascular risk factors^[13]. Lifestyle changes recommended by the current guidelines include several interventions and combination of all these interventions. This has not changed as compared to previous guidelines (Table 1). It is generally believed that BP lowering effect of lifestyle modification is equivalent to drug monotherapy and can also delay drug therapy in patients with stage 1 hypertension.

Renal nerve denervation

The sympathetic nervous system seems to play an important role in resistant hypertension^[14]. Two clinical trials (Symplicity HTN 1 and Symplicity HTN 2) have shown the efficacy of renal sympathetic denervation with a post-procedure decline of 27/17 mmHg at 12 mo and 32/12 mmHg at 6 mo, respectively, with few minor adverse events^[15,16]. Most recently, results of Symplicity HTN-3 (Renal Denervation in Patients with Uncontrolled Hypertension) trial showed no further reduction in office or ambulatory BP after 1-year follow up^[17]. It seems

Table 1 Recommended lifestyle modifications for the management of hypertension

Weight loss (in obese or overweight patients)
Salt reduction
Regular exercise
Moderation of alcohol consumption
Smoking cessation
Increased consumption of vegetables, fruits and low-fat dairy products

that renal denervation is safe but has no superior BP lowering effects compared with adjustment of drug treatment^[18]. In contrast, another more recent study, The Renal Denervation for Hypertension trial, showed that renal denervation plus standardized stepped-care antihypertensive therapy decreases BP more than the same standardized stepped-care antihypertensive therapy alone at 6 mo in patients with well-defined resistant hypertension^[19]. So far, conflicting BP lowering effects of renal denervation have been reported. Thus, further studies are needed to reinforce renal denervation as a treatment modality for hypertension.

PHARMACOLOGICAL THERAPY

Despite the non-pharmacological intervention, if BP is still above target, drug therapy should be initiated. There are five major classes of antihypertensive drugs: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers and β -blockers. In general, these drugs rarely have serious side effects when appropriately initiated and adequately monitored. We will not focus on the safety profile of these drugs, as it is beyond the scope of this review. According to current ESH/ESC hypertension guideline, grade 1 hypertensive patients with low/moderate cardiovascular risk can initially be treated with monotherapy^[8]. On the other hand, JNC-8 panel based their recommendation based on the age of the patients. They recommended initiating therapy to lower BP at systolic BP \geq 150 mmHg and diastolic BP \geq 90 mmHg for patients aged \geq 60 years, and systolic BP \geq 140 mmHg and diastolic BP \geq 90 mmHg for patients aged $<$ 60 years^[9].

MONOTHERAPY

After a long waiting time, recently JNC-8 report (recommendations from only randomized controlled trials) was published. In the same line with 2013 ESH/ESC and National Institute for Health and Clinical Excellence (NICE) hypertension guideline, JNC-8 no longer recommends only thiazide-type diuretics as the initial therapy in most patients. As initial therapy, a thiazide-type diuretic, calcium channel blocker, ACE inhibitor and ARB can be started for uncomplicated hypertension^[9]. The 2014 JNC report dismissed β -blockers as first-line therapy. Along the same line, the NICE clinical guideline did not recommend the first-

line use of diuretics and β -blockers^[20]. Nevertheless, the 2013 ESH/ESC hypertension guidelines kept all 5 major classes of drugs in their recommendations as first-line regimens because of their opinions that the main benefits of antihypertensive therapy are due to lowering BP *per se* and largely independent of the drugs employed^[8].

BP control seems to be more important than a specific agent used to achieve that control. In a recent meta-analysis of 18 trials of 23215 Asian patients, a 10 mmHg reduction in systolic BP was associated with a 39.5% reduction in composite cardiovascular endpoints, and a 30% reduction in stroke, regardless of drug class^[21]. Similarly, in a more recent meta-analysis of trials comparing the renin angiotensin aldosterone system (RAS) inhibitors vs other antihypertensive drugs as first-line therapy in patients with primary hypertension, all-cause mortality was similar between these drugs^[22]. Still, the choice of drugs may be influenced by other factors as age, ethnicity/race, and other clinical characteristics. Trials in special patient groups (patients with diabetes, coronary artery disease, chronic kidney disease and proteinuria) have proposed that a specific drug group or combinations of certain drugs might be superior to others^[8-10]. Thus, patients with special conditions should be considered to start with an appropriate drug based on their comorbidities (Table 2). We think that most hypertensive patients have comorbidities and initiating antihypertensive therapy generally requires compelling indications to select a specific drug group. Otherwise, in absence of comorbidity, it appears that the mere control of BP is more important than the class of antihypertensive drug being used.

RAS BLOCKERS

Based on a large body of evidence, RAS blockers have been used to decrease the incidence of end-organ damage and cardiovascular mortality^[23-25]. ACE inhibitors and ARBs can be considered first-line therapy in the management of hypertension, particularly in patients with diabetes mellitus. However, more recent studies showed that ACE inhibitors and ARBs do not have similar effects on cardiovascular outcomes and total mortality.

A meta-analysis of 20 clinical trials involving 158998 patients examined the effect of ACE inhibitors and ARBs in patients with hypertension^[26]. ACE inhibitors significantly reduced all-cause mortality (HR = 0.90; 95%CI: 0.84-0.97; $P = 0.04$) whereas ARBs did not (HR = 0.99; 95%CI: 0.94-1.04; $P = 0.683$). In a meta-analysis evaluating the effects of ACE inhibitors and ARBs on all-cause mortality, cardiovascular events and deaths in patients with diabetes mellitus, ACE inhibitors reduced all-cause mortality (RR = 0.87; 95%CI: 0.78-0.98), cardiovascular mortality (RR = 0.83; 95%CI: 0.70-0.99), and major cardiovascular events (RR = 0.86; 95%CI: 0.77-0.95), whereas ARBs

Table 2 Drugs to be preferred in patients with special conditions

Comorbidity	First-line therapy
Ischemic heart disease	β -blocker (unless contraindicated) Long-acting calcium channel blocker ACE inhibitors (ARBs if ACE inhibitors not tolerated)
Heart failure	ACE inhibitors (ARBs if ACE inhibitors not tolerated) β -blockers Aldosterone antagonists
Diabetes	ACE inhibitors (ARBs if ACE inhibitors not tolerated) β -blockers Calcium channel blockers
Chronic kidney disease	ACE inhibitors or ARBs Loop diuretics rather than a thiazide diuretic (or combination)
Stroke	Diuretic + ACE inhibitors
Asymptomatic organ damage	
Left ventricular hypertrophy	ACE inhibitors, ARBs, Calcium channel blockers
Proteinuria	ACE inhibitors, ARBs

ACE: Angiotensin converting enzyme; ARBs: Angiotensin II receptor blockers.

had no benefits on these outcomes^[27]. In another meta-analysis that included nine randomized controlled trials, no difference was found in total mortality or cardiovascular outcomes for ARBs as compared with ACE inhibitors^[28]. According to these evidences, we can conclude that while ACE inhibitors can be used as a first-line therapy, ARBs are preferred for patients who have adverse reactions to ACE inhibitors although there is no agreement among the guidelines.

DIURETICS

Thiazide and thiazide like diuretics (*e.g.*, indapamide, chlorthalidone) remain essential in the management of hypertension. The JNC-7 recommended that thiazide diuretics should be the preferred drugs in most hypertensive patients, either alone or combined with other classes of drugs^[10]. Although it is well known that thiazide-type diuretics are effective in reducing BP and preventing cardiovascular disease in hypertensive subjects, it is not clear whether all drugs in this class are equally safe and effective. Recently, the choice of diuretics has emerged as a controversial issue with some evidence favoring the long-acting agent, chlorthalidone, in preference to hydrochlorothiazide. A recent retrospective observational cohort analysis from the Multiple Risk Factor Intervention Trial data set compared the effects of chlorthalidone vs hydrochlorothiazide on cardiovascular event rates^[29]. Chlorthalidone treatment was associated with significantly fewer cardiovascular events; lower systolic BP, potassium, and total and low-density lipoprotein cholesterol levels; and significantly higher uric acid levels compared with hydrochlorothiazide.

A large observational study with up to five years of follow up reported head-to-head comparative data

on the effects of newly prescribed chlorthalidone vs hydrochlorothiazide on cardiovascular and safety outcomes in elderly patients^[30]. Chlorthalidone was not associated with fewer adverse cardiovascular events or deaths than hydrochlorothiazide in elderly patients; however, it was associated with a greater incidence of electrolyte abnormalities, particularly hypokalemia.

In a recent meta-analysis of 14 trials comparing head to head thiazide-like and thiazide-type diuretics, systolic BP reduction was greater with chlorthalidone and indapamide without more adverse effects^[31]. These data suggest using chlorthalidone as preferred thiazide type diuretic for the management of hypertension. On the other hand, hydrochlorothiazide has a dose related BP-lowering effect and greater effect on systolic BP than diastolic BP, thus lowering pulse pressure more than other antihypertensive drugs^[32]. We believe that it is too early to reach a final conclusion, as there are no randomized trials that directly compare cardiovascular outcomes in hypertensive patients treated with thiazide-type diuretics vs thiazide-like diuretics.

Mineralocorticoid receptors have been shown to play important roles in the pathogenesis of hypertension and hypertension-related cardiovascular outcomes^[33-35]. Recent studies have implicated that aldosterone excess as an important pathophysiologic factor in a large fraction of patients with resistant hypertension^[36]. Spironolactone can be tried in patients with resistant hypertension requiring three or more drugs to achieve BP control unless contraindicated^[20]. Eplerenone may be used as an alternative in patients who experience hormonally related side effects with spironolactone.

We conclude that diuretics remain as leading agents in the management of hypertension. Based on the available data, thiazide-like diuretics (such as chlorthalidone, 12.5 to 25 mg/d) may be preferred to thiazide type diuretics. Moreover, when BP cannot be controlled with other drugs, combining thiazide-like diuretics with ACE inhibitors or ARBs are usually very effective. Combining diuretics with aldosterone antagonists may also be worthwhile in special patient population.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers have potent BP-lowering effects and have been the most widely used antihypertensive drugs. Several studies have showed that calcium channel blockers had efficacy not only in lowering BP but also in reducing cardiovascular morbidity and mortality in patients with hypertension^[37]. In a recent meta-analysis of 31 randomized controlled trials, calcium channel blockers reduced stroke more than either placebo (OR = 0.68; 95%CI: 0.61-0.75) or β -blockers (OR = 0.79; 95%CI: 0.72-0.87), but was not different from ACE inhibitors and diuretics^[38]. Another Cochrane meta-analysis of randomized trials comparing first-line calcium channel blockers with other antihypertensive classes did not find difference among

calcium channel blockers, ACE inhibitors or ARBs in terms of all-cause mortality, however, it provided evidence supporting the use of calcium channel blockers over β -blockers in terms of total cardiovascular events, stroke and cardiovascular mortality^[39]. Calcium channel blockers are broadly classified into two groups as dihydropyridine and non-dihydropyridine groups. Non-dihydropyridine calcium channel blockers are more negatively chronotropic and inotropic than the dihydropyridine subclasses, and are generally not recommended to use as first-line therapy in the management of hypertension. The NICE guidelines recommend particularly calcium channel blockers as first-line therapy in hypertensive patients aged over 55 years^[20]. We conclude that calcium channel blockers may be used as initial first-line therapy particularly in hypertensive patients without compelling co-morbidities or as a component of combination therapy.

β -BLOCKERS

Whether β -blockers should be placed as first-line therapy in the management of hypertension is probably the most controversial issue among major guidelines. Some do not recommend β -blockers as first-line therapy for hypertension^[9,20]. But, the 2013 ESH/ESC guidelines continued to recommend β -blockers as one of the first-line anti-hypertensive drugs^[8]. On the other hand, the 2014 NICE hypertension guidelines put β -blockers as step 4 drugs. β -blockers can be used as additional therapy to further lower BP, but they may have a special benefit in preventing recurrent coronary artery disease^[7].

The class of β -blockers is heterogeneous, and all the drugs in this class may not be the same^[40]. Atenolol, metoprolol, carvedilol and nebivolol have different properties in terms of efficacy and side effects. But a recent meta-analysis comparing atenolol and non-atenolol β -blockers found that β -blockers had similar effect on cardiovascular end points in hypertensive patients without compelling indications^[41]. Only, in the elderly (> 60 years), atenolol was inferior to the other drugs in reducing stroke. We conclude that while β -blockers remain the standard of care for patients with coronary artery disease, particularly after acute myocardial infarction^[42], their role in the management of hypertension without coronary artery disease remains controversial.

COMBINATION THERAPY

Combination therapy may have benefit patients through multiple and potentially complementary pharmacologic mechanisms of action. Thus, combining drugs with different classes may be more effective than titrating dose of a single agent. Initiating treatment with a drug combination rather than a single agent is increasingly utilized as a therapeutic strategy. According to the current guidelines, a large majority of patients

require simultaneous administration of two or more antihypertensive drugs to reach the target BP^[8-10]. Specifically in patients with stage 2 hypertension, it appears that early combination therapy may lower BP to targets sooner.

Choice of combination therapy

A diuretic, β -blocker, calcium channel blocker and ACE inhibitors (or ARBs) can be combined in the management of hypertension. Amongst the various combinations of antihypertensive drugs, it is generally considered that combining an ACE inhibitor or ARB with a diuretic produces fully additive BP reduction^[43]. Combination of antihypertensive agents as initial therapy in stage 2 hypertension can lead to markedly improved BP control in patients as compared with mono-therapeutic regimens^[10,44].

Recently, it was noted that the addition of an ACE inhibitor or ARB to a dihydropyridine calcium-channel blocker is increasingly being used^[45]. The only trial (ACCOMPLISH) comparing ACE inhibitor-calcium channel blocker combination and ACE inhibitor-diuretic combination found significant superiority of ACE inhibitor-calcium channel blocker over diuretic combination^[46]. This combination may also reduce the incidence and severity of edema caused by calcium channel blocker. The combination of ACE inhibitor (or ARB) in addition to diuretic or calcium channel blocker may be used as initial combination therapy. But, it appears that calcium channel blockers are better than diuretics as a component in combination therapy.

Combination of RAS blockers

Currently, the combination of an ACE inhibitor and ARB is not recommended^[9]. Recent studies showed that combination therapy did not prove to be superior to the use of an ACE inhibitor or ARB alone in reducing the primary or secondary outcomes. Previously, in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, a randomized study of combination therapy vs monotherapy in persons at increased cardiovascular risk, no cardiovascular or renal benefits were observed with combination therapy^[47,48]. In a recent randomized, controlled study, combination therapy with ACE inhibitors and ARBs provided no benefit to major primary and secondary outcomes in patients with diabetic nephropathy^[49]. Furthermore, patients receiving combination therapy had an excess occurrence of hyperkalemia and acute kidney injury. The addition of direct renin inhibitor, aliskiren, to standard therapy with ACE inhibitors or ARBs in patients with type 2 diabetes did not reduce cardiovascular or renal outcomes as compared with placebo. On the contrary, the combination therapy resulted in an increased number of adverse events^[50].

CONCLUSION

In conclusion, based on the available data, the amount

of BP reduction rather than the choice of antihypertensive drug are the major determinant of reduction in cardiovascular risk in patients with hypertension. But, some hypertensive patients may have compelling indication for a specific antihypertensive drug, which may offer particular benefit independent of BP control. Successful treatment requires identification and reversal of lifestyle factors contributing to treatment resistance; diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective combination regimens. Combination therapy may be necessary in the majority of the patients with hypertension, and current guidelines recommend routine initiation of a combination in patients with stage 2 hypertension. ACE inhibitors, ARBs and diuretics including aldosterone antagonists can result in clinically significant alterations of serum electrolytes and kidney function. Thus, after the initiation of these agents, a chemistry profile should be obtained.

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