Management of the Spectrum of Essential Hypertension: A 2013 Perspective

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Abstract

Management of hypertension: The association of hypertension with cardiovascular and renal disease is continuous and independent of other risk factors. Despite the increase in awareness and treatment of hypertension in the past decade, less than 50% of adults in the U.S have adequate blood pressure control. Every 10% increase in the treatment of patients with hypertension could prevent an additional 14,000 deaths. This article reviews the latest evidence guiding current hypertension management.

The main classes of drugs used to treat hypertension are diuretics (thiazides, loop and aldosterone antagonists), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers. Alpha-adrenergic blockers and direct renin inhibitors are used infrequently and are mostly used as the 4th or 5th added agent.

No consensus has been established on initial drug choice. In patients with compelling indications, such as ischemic heart disease, diabetes, chronic kidney disease and stroke, some classes have shown greater benefits. Widely accepted is that blood pressure reduction is the most important determinant in lowering cardiovascular risk when there is no indication for a particular class of drugs. Hypertensive patients with central and peripheral vascular disease, chronic kidney disease and diabetes should have a lower target blood pressure.

In patients with mild primary hypertension undergoing monotherapy, with inadequate blood pressure control, sequential monotherapy may be attempted prior to adding another drug. Combination therapy should be considered from the onset in individuals with blood pressures that exceed 20/10 mmHg above the set target range.

The combination of angiotensin converting enzyme inhibitor plus a calcium channel blocker has been proven to be superior to other combinations. Considering the impact that adequate treatment can make in preventing deaths, the challenge is to improve access to care of patients with hypertension.

Introduction

Despite the increase in awareness and treatment of hypertension in the past 10 years, less than 50% of adults in the U.S have adequate Blood Pressure (BP) control [1,2]. The age-adjusted prevalence of hypertension among adults in the U.S is estimated to be 28.6%, which translates to over 50 million people affected by the disease [2]. The population aged 60 and over has an even higher prevalence of 66.7%. Prediction models show that every 10% increase in the treatment of patients with hypertension, among the adult population, could prevent an additional 14,000 deaths [3].

Classification

The current classification of Blood Pressure (BP), as defined by the Seventh Report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), is based on the average of three seated BP readings on at least three separate occasions at least one week apart [4]. In the last JNC report the prehypertension category was added, highlighting the increased risk of progression to hypertension in this group (Table 1). The association of blood pressure with cardiovascular (CV) and renal disease is continuous and independent of other risk factors [5-7]. Patients with a BP in the range of 130-139/80-89 mmHg have two times the risk of developing hypertension than those below this range [8]. Over 5 years the CV risk increases in a direct relationship with increasing Systolic Blood Pressure (SBP) [8].

Obtaining accurate BP values

Blood pressure should ideally be measured in a controlled, standardized fashion. Home measurements performed by the patient, 3 times a week, at different times of the day provide a more comprehensive method than spot measurements at a clinic visit. The patient should be instructed to utilize a calibrated, automated, upper arm cuff BP monitor, taking measurements while seated (for at least

BP classification	SBP* mmHg	DBP* mmHg	Initial drug therapy	
			without compelling indication	with compelling indications
Normal	<120	and <80	No antihypertensive drug indicated	Drugs for compelling indications
Pre Hypertension	120-139	or 80-89		
Stage 1 Hypertension	140-159	or 90-99	Consider ACEi/ARB, CCB, Thiazide-type or combination.	Drug(s) for compelling indications. Other antihypertensive drugs: diuretics, ACEI/ARB, CCB, BB, aldosterone antagonist, alpha-blockers, direct renin inhibitor.
Stage 2 Hypertension	≥ 160	or ≥ 100	Two-drug combination ACEi/ARB+CCB** or Thiazide-type diuretic	

BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ACEi: Angiotensin Converting Enzyme inhibitor; BB: Beta-Blocker; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker.
*BP range based in patients with no cardiovascular risk factors or cardiovascular risk equivalents.
**The ACCOMPLISH trial showed that ACEi combined with a CCB was superior to ACEI and thiazide in non-obese patients.

Table 1: Classification of blood pressure.

5 min) and perform measurements 3 times, 2 minutes apart. Discard the first recording and take the average of the last two recordings as the BP for that time. Alterations in BP medications should be based on the average of the many recordings [9]. Never focus treatment on the highest or lowest recording. The average monthly value is the major consideration for medication adjustment.

Non- pharmacological therapy

Lifestyle Modifications should be recommended to all individuals for both prevention and as an integral part of hypertension management. Table 2 lists non-pharmacologic therapies that can have an adjunctive impact on BP control [4]. Even a few mmHg decreases in BP can improve both morbidity and mortality. Studies have demonstrated a significant reduction in SBP with weight loss, moderation in alcohol consumption, adoption of DASH diet (Dietary Approaches to Stop Hypertension) [10], low sodium intake (aim for less than 1500 mg/day, but learn to accept 2000 mg/day) and aerobic physical activity (150 minutes of moderate intensity activity/week) [11,12]. The DASH diet is based on an eating plan rich in fruits, vegetables, low-fat or non-fat dairy, whole grains, high fiber, with limited sugar-sweetened foods and beverages, red meat and added fats. Adoption of these measures reduces cardiovascular mortality alone and improves response to drug therapy. Achieving the desired sodium (Na+) restriction should decrease the SBP/diastolic(D) BP by about 3-4/2-3 mmHg [4,10]. Important to note that a Na+ intake of >4 g/day reduces the anti-proteinuric effect of the renin-angiotensin-aldosterone system (RAAS) blockade by up to 50% [13]. The mechanism of an increased Na+ intake on proteinuria is thought to be related to increased oxidant stress (partially) and an increase in the BP (partially) [14,15].

Pharmacological therapy efficacy

The effectiveness of antihypertensive agents is similar in lowering BP across different classes. Overall, adequate control is obtained in up to 50% of patients, with response rates to each class varying from patient to patient [16,17]. One of the significant beneficial effects of anti-hypertensive treatment is on decreasing the incidence of cardiovascular (CV) complications, especially in those with moderate to severe hypertension (DBP 105-114 mmHg) [18]. It is estimated there can be a 20% CV benefit with lowering BP in this cohort. In contrast, the CV benefit from treatment in the mild to moderate hypertensive group is estimated to be 2% (from 17 trials involving approximately 48,000 patients) [19]. Patients who are over 60 years of age have an increased CV risk from BP elevation as compared to those with a similar BP who are less than this age. Therefore, treatment of BP in the elderly should be as aggressive as in younger individuals in an attempt to decrease complications [20].

The single most important determinant of reduction in cardiovascular risk is the amount of blood pressure reduction, as shown by several meta-analyses, including the American Heart Association (AHA) and the European Society of Hypertension (ESH) [11,16,21]. The BP goal in uncomplicated primary hypertension should be less than 140/90 [4]. Hypertensive patients with chronic kidney disease (with microalbuminuria or overt proteinuria) and/or diabetes (with microalbuminuria or overt proteinuria) should have a target blood pressure 120-130/70-80 mmHg [22]. This lower target should also be pursued in patients with known Coronary Artery Disease (CAD), or with CAD risk equivalents, such as carotid artery disease (carotid bruit, abnormal carotid ultrasound or angiography), peripheral arterial disease, abdominal aortic aneurysm or a 10-year Framingham risk score ≥ 10% [11]. This score, derived from the Framingham Heart Study, is used to estimate the 10-year risk of developing a heart attack in individuals aged 20 and older who do not have heart disease or diabetes. Variables include: age, gender, total cholesterol, HDL cholesterol, smoking status, SBP and current use of antihypertensives [23,24].

Choice of therapy

The main classes of drugs used to treat hypertension are diuretics (Thiazides, loop and aldosterone antagonists), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor Blockers (ARB), Calcium Channel Blockers (CCB), Beta-Blockers (BB) and alpha-adrenergic blockers. The alpha-adrenergic blockers and direct renin inhibitors are often 4th or 5th tier agents, added when less than optimal control is achieved with other medications.

Modification	Approximate SBP reduction
Weight reduction	5-20 mmHg/10 kg weight loss
DASH diet	8-14 mmHg
Dietary sodium ≥ 2 grams	2-8 mmHg
Physical activity (aerobic)	4-9 mmHg
Reduction in alcohol consumption	2-4 mmHg

Table 2: Lifestyle Modifications

Initial monotherapy-general concepts

Single drug therapy in mild primary hypertension is effective in most patients. However, combination therapy may be required in patients with SBP in excess of 20 mmHg and DBP above 10 mmHg of the target range. For these patients combination therapy is indicated from the onset. Predictable differences in how each patient will respond to a given drug class have been observed. For example, African Americans often respond better to thiazide or CCB monotherapy as compared to ACEI or a BB. Caucasians have better response rates to BB and ACEI and less to thiazides [25].

No consensus has been established on initial drug choice for every patient, and the most common therapeutic approach is trial and error. It is widely accepted that the amount of blood pressure reduction is the most important determinant in reduction of CV risk when there is no indication for a particular class of drugs [11,17,26]. Meta-analyses of all studies indicate that BP reduction is the major determinant of decreasing CV risk, not the choice of anti-hypertensive agent(s). In the following trials (ALLHAT, CAPPP, NORDIL, UKPDS, Stop Hypertension-2, CAMELOT) there was no difference in hard CV outcomes with different anti-hypertensive therapies [27-31].

In patients with compelling indications such as Ischemic Heart Disease (IHD), Chronic Kidney Disease (CKD) or stroke (CVA), some classes have shown greater benefits (Table 3). Patients with prior MI or heart failure have better outcomes with ACEI [11].
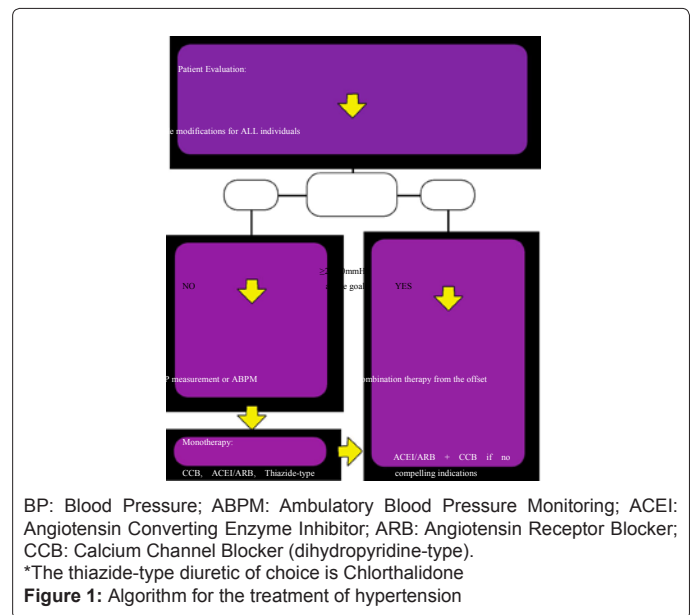
The optimal dosing across drug classes should start at half standard

Compelling indication	Drug class indicated
Heart failure (EF ≤ 40%)	ACE inhibitor/ARB, BB, aldosterone antagonist, diuretic
Ischemic heart disease	BB, ACE inhibitor, aldosterone antagonist (post MI)
Diabetes with proteinuria	ACE inhibitor/ARB
Chronic kidney disease	ACE inhibitor/ARB
Cerebrovascular disease	Thiazide, ACE inhibitor

Table 3: Drug choice based on Disease: Compelling indications.

doses. Increasing to a full standard or double the standard dose resulted in a small decrease in blood pressure values with a significant increase in both metabolic and symptomatic side effects [16,32]. Thiazide diuretics, CCB and BB were the main classes observed to have significant increase in adverse effects with higher doses. ACEI and ARB had a lower rate of side effects and no dose dependence was observed [16]. Therefore, dose titration up to a single step is generally recommended, the next step being adding another drug class at half the standard recommended maintenance dose.

Monotherapy guidelines

BP: Blood Pressure; ABPM: Ambulatory Blood Pressure Monitoring; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker (dihydropyridine-type).
*The thiazide-type diuretic of choice is Chlorthalidone
Figure 1: Algorithm for the treatment of hypertension

The 2011 NICE guidelines recommends, if there is no indication for a specific class of drugs, CCB or ACEI/ARB as first line therapy [9]. ACEI/ ARB for individuals under the age of 55 and CCB for individuals aged 55 and older or African Americans of any age. Table 4 shows, in order, the NICE recommendations of a CCB, ACEI or ARB, thiazide-type diuretic, BB, alpha-adrenergic blocker being added in sequential order to achieve the target BP.

Diuretics

A thiazide-type diuretic is indicated if a CCB is not tolerated (lower extremity edema) or if there is evidence of heart failure (given EF>40%) or at high risk of developing heart failure. The drug of choice for this class is chlorthalidone.

Lessons learned from large-scale anti-hypertensive trials guide current day treatment. For example, the ALLHAT study (involved over 41,000 patients) demonstrated benefit with lower rates of heart failure and better blood pressure control with chlorthalidone as compared to CCB and ACEI in patients with at least one coronary risk factor (with similar primary outcomes across all classes of agents) [27].

When compared to hydrochlorothiazide (HCTZ), chlorthalidone is 1.5 to 2 times as potent and has a longer duration of action (24-72 hours vs. 6-12 hours) [33,34]. The recommended starting dose is 12.5mg daily, titrated up to 25 mg daily. Concerns with the use of chlorthalidone are the metabolic adverse effects, namely hypokalemia, glucose intolerance and hyperuricemia (the same exists for HCTZ). Hypokalemia occurred in up to 8% of treated patients within the first 1-2 weeks [35]. When a mean BP baseline of 146/84 was noted in the ALLHAT trial, combination therapy was required in 30% of patients at one year and 40% at four years. As already stated, the choice of anti-hypertensive agent does not predict outcomes. At years one and two of treatment with chlorthalidone the mean SBP decrease was 3.7 mmHg. In contrast, HCTZ led to a 2.8 mmHg SBP lowering in the same time frame [27].

In both the ALLHAT and SHEP trials, low dose chlorthalidone (12.5-25 mg/day) was more efficacious than HCTZ in reducing all CV events for up to 5 years, including Congestive Heart Failure (CHF). This finding was independent of the attained BP [27,36]. A recent

observational cohort study of over 10,000 individuals compared primary and safety outcomes in patients treated with chlorthalidone versus HCTZ [37]. CV events or death were similar between the two groups with a higher incidence of electrolyte abnormalities with chlorthalidone, particularly hypokalemia. Both groups were matched to sex, year of treatment initiation, and propensity score. It is important to mention that no adjustment was made to the difference in potency between each drug. Doses of 12.5 mg, 25 mg and 50 mg oral daily (HCTZ and chlorthalidone) were compared as being equipotent.

Predictors of lack of BP control in the ALLHAT study (in descending order) [27]:

- Older age
- Obesity
- Female
- Initial SBP
- Chronic kidney disease
- Left ventricular hypertrophy
- Black race

Angiotensin Converting Enzyme Inhibitors (ACEI)

ACEI are the drug of choice for individuals younger than 55 and with no compelling indications for other drug class (NICE guidelines) [9]. ACEI are also considered standard of care in patients with heart failure and systolic dysfunction (EF ≤ 40%), post myocardial infarction, proteinuric CKD and diabetes [11,38,39]. It is important to reiterate the importance of obtaining a lower blood pressure goal in this group of patients, ≤ 130/80 mmHg [4,40].

Angiotensin Receptor Blockers (ARB)

Generally, similar indications as compared to ACEI. They are appropriate in patients with CV disease who are intolerant to ACE inhibitors (cough being the major side effect from ACEI that leads to stopping this agent). ARB have shown to reduce incidence of cerebrovascular events, kidney disease and Ischemic Heart Disease (IHD) events [41]. The ONTARGET study compared telmisartan (ARB) and ramipril (ACEI) head-to-head and in combination in patients with vascular disease (known CAD or CAD equivalent) or diabetes with end-organ damage. Telmisartan was equivalent to ramipril in reducing primary outcomes with less angioedema. The combination arm had more adverse events without an increase in benefit [42].

Calcium channel blockers (CCB)

CCB are first line therapy in individuals over the age of 55 or in African American patients of any age (NICE guidelines) [9]. CCB confer similar BP lowering properties with distinct actions on cardiac contractility and conduction. The dihydropyridines are long-acting agents, the most common drugs being amlodipine and nifedipine. The non-dihydropyridine class possesses additional chronotropic effects and can be used for rate control in atrial fibrillation and angina pectoris. Non-dihydropyridines are contra-indicated in patients with heart failure with left ventricular systolic dysfunction [43].

Beta-Blockers (BB)

Beta-Blockers are considered standard of care post Myocardial Infarction (MI), in left ventricular dysfunction with or without symptoms of heart failure and in patients with angina pectoris [17]. Cardiovascular protection has not been demonstrated in patients without symptomatic CAD, no history of MI or without heart failure [44]. In patients over 60 and no risk factors, an increase in CV risk was observed, particularly stroke [45].

Aldosterone antagonists

Spironolactone and eplerenone reduce blood pressure and confer cardioprotective effect in patients with heart failure (ejection fraction ≤ 40%) when combined with an anti-heart failure regimen (BB, ACE inhibitor and diuretic) [46]. No major study has analyzed CV outcomes in those treated for hypertension without left ventricular dysfunction.

Alpha- adrenergic blockers

There is no indication for monotherapy of primary hypertension with alpha-blockers. The ALLHAT trial showed an increased risk of heart failure and rate of CV events when compared to chlorthalidone alone in patients with hypertension [27].

Direct renin inhibitors

Aliskiren was the first oral direct rennin inhibitor to become available. It has shown BP lowering effect comparable to other classes [47]. Patients intolerant to ACEI/ARB may benefit from Aliskiren, especially if anti-proteinuric effect is desired. It should not be used in pregnancy or in combination with ACEI or ARB (see Combination Therapy section).

Combination therapy

Combination therapy should be considered from the beginning in individuals with blood pressures that exceed 20/10mmHg above set target range. In patients with mild primary hypertension undergoing monotherapy, with inadequate blood pressure control, stepwise monotherapy may be attempted prior to adding another drug. Up to 50% of individuals are likely to have adequate blood pressure control with the stepwise monotherapy approach [48,49]. Combination treatment can follow if there is a failure of stepwise monotherapy.

Several large trials have helped guide an evidence-based approach to treatment. The ACCOMPLISH trial (emphasizing combination therapy) noted when the mean baseline BP was 145/80 or greater in patients at high risk for a CV event, benazepril in combination with amlodipine produced better end results as compared to a combination of benazepril with HCTZ [50]. Significant reductions in the primary composite endpoint of fatal or non-fatal CV event and secondary endpoint of CV death, non-fatal MI or stroke were noted. Lower rates of adverse events were documented in the benazepril-amlodipine combination, and benefits were independent of the achieved BP lowering [50]. If there is no compelling indication for a particular drug class, the combination of ACEI and a dihydropyridine CCB should be used instead of a combination of ACEI and thiazide, particularly in the non-obese individual [50,51].

Other trials have supported combination therapy to achieve various endpoints. The ACCORD trial in type 2 diabetics showed a lower incidence of strokes with intensive treatment to lower the BP, but there was no difference in coronary events [52]. The HOPE trial addressed the timing of combination anti-hypertensive therapy [53]. ACEI before sleep reduced the incidence of combined CV death, MI and stroke. Bedtime dosing of at least one anti-hypertensive agent should be tried when the BP does not fall by at least 10% during sleep

(non-dipping) [53]. Non-dipping is a stronger predictor of adverse CV outcomes and evening dosing of at least one anti-hypertensive drug that is not a diuretic can restore dipping. VALUE, ASCOT and the BPLA trials noted better outcomes with amlodipine as compared to valsartan or atenolol, but differences were no longer significant when adjusted for differences in attained BP [54,55].

In addition to a decrease in the incidence of CV events, a decrease in the development of CKD was also noted with combination therapy [56]. In this particular study, benazepril 20mg (starting dose) daily was the ACEI utilized in combination with either amlodipine 5mg daily (starting dose) or HCTZ 12.5mg daily. Individuals with compelling indications for a BB utilized a combination of CCB or thiazide. Alpha-blockers can be added to combination therapy in patients with symptomatic benign prostatic hyperplasia. A recent study found that a three-drug combination of ARB, CCB and HCTZ was more effective in achieving BP control when compared to a two-drug combination of the given classes (ARB/CCB, ARB/HCTZ, CCB/HCTZ). The regimen was well tolerated and effective in both elderly (≥ 65) and non-elderly (<65) groups [57].

The role for oral direct renin inhibitors (aliskiren) is yet to be determined. It has been shown to lower BP comparably to other drug classes and to reduce proteinuria when used in combination with losartan. The AVOID trial assessed this combination in patients with hypertension, type 2 diabetes and albuminuria [58]. The combination therapy was associated with 20% greater reduction in the albumin-to-creatinine ratio as compared to losartan alone, independent of BP reduction. Clinical benefits of this reduction were not measured in this study. A higher rate of adverse events such as hyperkalemia, hypotension and non-fatal stroke were observed in the ALTITUDE trial (ACEI or ARB in combination with aliskiren) [59].

Isolated Systolic Hypertension (ISH)

ISH is defined as SBP ≥ 140 mmHg with a DBP<90 mmHg, and this scenario is invariably noted in the elderly. Goals of therapy, as documented in the following trials (SHEP, Syst-EVR, MRC, HYVET) are a SBP <140 mmHg and no side effects from the medications employed [20,36,60,61]. Another target of treatment if the initial SBP is ≥ 180 mmHg is a reduction to <160 mmHg. Aim for a SBP that is 20 mmHg below the initial SBP of 160-180 mmHg. The HYVET study provided evidence that treatment of hypertension in patients greater than 80 years of age or older with indapamide (sustained release), with or without perindopril, is beneficial [20].

Resistant hypertension

The definition is that the BP remains above target goal in spite of 3 concurrent anti-hypertensive agents of different classes at optimal doses, one drug being a diuretic. By this definition, 12.8% of treated hypertensive patients have resistant hypertension from NHANES data [62]. In the ASCOT study, 49% were diagnosed as having resistant hypertension during a median follow up of 4.8 years [63]. 25-28% of all patients in the accomplish trial remained with uncontrolled BP after a follow up of 3 years [50]. An elevated heart rate, especially after BB therapy, suggests a possible heightened sympathetic tone. New interventional advances in the treatment of resistant hypertension are based on the supposition that the nerves leading in and out of the kidney play a central role in Sympathetic Nervous System (SNS) hyperactivation. Percutaneous transluminal ablation of the renal nerves, also known as Renal Denervation (RDN), is a developing novel therapeutic option for the treatment of resistant hypertension. Radio frequency ablation (RDN) reduces the drive of the SNS, which

is central to BP regulation. By denervation of the renal sympathetic nerves encircling the renal arteries, achieved by a proprietary generator and flexible catheter introduced into each renal artery, the output of the sympathetic nerves located outside the renal artery walls can be modulated [64]. Two RDN trials in Europe and Australia demonstrated the drop in SBP and DBP as charted below in a cohort with a baseline BP 178/97mmHg, while on an average of 5.2 anti-hypertensive agents [65,66].

Fall in SBP/DBP (mmHg) after Treatment with RDN

1 month 20/7

3 months 24/8

6 months 32/12

Glucose, fasting insulin levels and C-peptide levels fell co-incident with the drop in BP. Another observation was that sleep apnea improved after RDN [66]. There is now an ongoing multi-center RDN trial in the United States (the Symplicity HTN-3 Trial).

Conclusion

Considerable improvements in awareness, detection and treatment of hypertension have been made in the past decade. New techniques and genetics advance the field and provide us with new tools to treat and detect individuals at risk. Despite these advancements, the management of hypertension continues to be challenging with only half of the affected population having adequate BP control. Considering the impact that adequate treatment can make in preventing deaths, there is a constant challenge to improve care of patients with hypertension.

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