Update on Hypertension and Adaptations for Treatment

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ABSTRACT

Hypertension (HTN) affects 46% of the US adult population and plays a major role in cardiovascular disease (CVD). Approximately, there were 90,098 deaths in 2017 primarily attributed to high blood pressure (BP). Recent guidelines recommend screening all adults for HTN. Management of elevated BP substantially reduces the risk of heart failure, stroke and myocardial infarction. Recommended lifestyle modifications include weight loss for overweight or obese patients, regular exercise, the dietary approach to stop hypertension (DASH) diet, reduced dietary sodium intake, and reduced alcohol intake. Most HTN patients will need at least 2 drugs to control BP. Current guidelines from the ACC and AHA state that a BP level goal of < 130/80mmHg for adults with confirmed HTN and with out additional markers of increased atherosclerotic cardiovascular disease (ASCVD) risk may be acceptable.

BACKGROUND

Hypertension (HTN) is one of the most important preventable contributors to disease and death in the U.S., resulting in myocardial infarction (MI), stroke, and renal failure if it is not detected early and treated appropriately.¹ Starting at a blood pressure of 115/75 mm Hg, every increase of 20 mm Hg in systolic blood pressure (SBP) and/or increase of 10 mm Hg in diastolic blood pressure (DBP) is associated with a doubling of the risk of death from stroke, heart disease, or other vascular disease.² HTN is largely managed with drug therapy, clinical pharmacists often participate in management, especially, to manage HTN along with risk factors. This book chapter will emphasize the new recommendations for BP management and will focus on the pharmacotherapy of HTN.

The prevalence of HTN in U.S. adults has continued to increase with age (Table 1). The American College of Cardiology and American Heart Association (ACC/AHA) 2017 blood pressure guidelines lowered the threshold for the diagnosis of HTN to 130/80 mm Hg, which led to a new HTN prevalence of 46% of U.S. adults. HTN is more prevalent in blacks in both men (59%) and women (56%) followed by white (47%) in men and 41% in women).³

OUTCOME STUDIES ON ANTI-HYPERTENSIVE THERAPY

SBP begins to rise steadily at about age 45 and continues throughout life. In contrast, DBP rises until about age 55, then decreases steadily.⁵ For every 2 mm increase in Systolic Blood Pressure (SBP),

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risk of fatal stroke increases by 7% and coronary heart disease by 5%, as suggested by a large observational study. SBP must be closely monitored throughout life and evaluating DBP alone will result in underestimation of cardiovascular (CV) risk.⁶

Thiazide-like diuretic and β -blockers

In 1991, *Systolic Hypertension in the Elderly Program (SHEP)* demonstrated the effect of antihypertensive therapy in older patients with elevated SBP significantly reduced the risk of stroke. 4736 patients were randomized to active treatment (n=2365) with chlorthalidone with the addition of atenolol based on blood pressure response, or to placebo (n=2371). The five-year incidence of total stroke was 5.2 per 100 participants with active (average BP= 143/68mmHg) treatment compared with placebo (average BP= 155/72mmHg) 8.2 per 100 participants (P=.0003).⁷ Relative risk reduction of nonfatal MI plus coronary death (0.73), major cardiovascular events (0.68) and death from all causes (0.87) in the patients who received antihypertensive therapy. *Medical Research Council (MRC)* study reported 19% reduction of cardiovascular events (p < 0.05) and 45% of strokes in patients who were randomized to propranolol or thiazide compared to placebo.⁷ Furthermore, *Swedish Trial in Old Patients with Hypertension (Stop-Hypertension)* have shown the 38% reduction in combined stroke and MI (p=0.003) with 45% reduction in stroke alone (p=0.008) in patients who were treated with β -blockers and one diuretic compared to placebo.⁹

Badve et al.'s.¹⁰ meta-analysis described that β -blockers lowers the risk of all-cause and cardiovascular mortality in patients with Chronic Kidney Disease (CKD) and systolic heart failure.¹¹ β -blockers are effective in broad range of CKD Patients who are post-MI. Abbott et al.¹¹ reported that the β -blockers lowered the risk of heart failure (HR 0.69, 95% CI 0.52-0.91, p=0.008) and cardiac death on dialysis patients from the US Renal Data System (USRDS).

Angiotensin-converting enzyme inhibition (ACEI) and Calcium channel blocker (CCB)

Heart Outcomes Prevention Evaluation (HOPE) study was stopped early because of convincing evidence of the benefit of ramipril treatment on the cardiovascular death, non-fatal MI and non-fatal stroke (14% vs. 17.8% on

TABLE 1.

ramipril and placebo, respectively; relative risk reduction 22%, p<0.001). This study reported a risk reduction of 32% for stroke, 20% for MI, 26% for cardiovascular death and 16% for all-cause mortality, as well as a reduction in the risk of several other endpoints including heart failure and revascularization procedures.¹²

In 1999, *Systolic Hypertension in the Europe (Syst-Eur)* investigated the effect of nitrendipine with the possible addition of enalapril and hydrochlorothiazide to reduce the cardiovascular complications in older patients with elevated SBP of 160-219 mmHg. The total rate of stroke was reduced by 42% (P=.003) and of nonfatal stroke by 44% (P=.007), as well as all cardiac endpoints, including sudden death (26%; P=.03). Nonfatal cardiac endpoints decreased by 33% (P=.03) and all fatal and nonfatal cardiovascular endpoints by 31% (P<.001). Cardiovascular mortality was slightly lower (27%) in the patients who received antihypertensive therapy (P=.07), but all-cause mortality was not significantly decreased (14%; P=.22).

The *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)* was designed to determine whether the occurrence of fatal coronary heart disease (CHD) or nonfatal MI is lower for high-risk hypertensive patients treated with NORVASC (CCB), lisinopril (ACEI), or doxazosin (β -adrenergic blocker), compared with chlorthalidone (diuretic treatment). At the initial visit, the proportion of participants at or below the BP goal (<140/90 mm Hg) was 26-28%; at five years, it was 68%, 66%, and 61% for the chlorthalidone, amlodipine, and lisinopril groups, respectively. No significant difference was observed between the relative risk (RR) of Fatal CHD and

nonfatal MI for amlodipine compared to chlorthalidone (RR=0.98; 95% CI 0.90-1.07) and between lisinopril and chlorthalidone (RR= 0.99, with a 95% CI 0.91-1.08).¹³ The Lisinopril group had a 15% higher risk for stroke. Based on these study results chlorthalidone was superior to lisinopril and doxazosin in preventing aggregate CV events, principally stroke, heart failure, angina, and coronary revascularization and no difference for stroke between the amlodipine and chlorthalidone groups. The three core messages for the ALLHAT antihypertensive trial are:

1. Diuretics should be the drug of choice for first step therapy of HTN.
2. For the patient who cannot take a diuretic (which should be an unusual circumstance), CCB's and ACEI's may be considered.

3. Most HTN patients require more than one drug. Diuretics should generally be part of the antihypertensive regimen. Lifestyle advice should also be provided.

The *Anglo - Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm - ASCOT-BPLA* evaluated whether CCB with or without an ACEI is more effective than an older regimen of β -blocker with or without a diuretic and whether it reduces coronary heart disease (CHD) events in hypertensive patients with relatively low cholesterol levels. The trial was discontinued early due to efficacy in the amlodipine/perindopril group and concerns regarding the patients in the atenolol/ bendroflumethiazide group. The reduction in the primary endpoint of nonfatal MI and fatal CHD was not significant in amlodipine/perindopril group (HR 0.90, 95% CI 0.79-1.02, $p = 0.1052$). However, several prespecified secondary endpoints were significantly lower

TABLE 2.

Best proven nonpharmacological interventions for the prevention and treatment of hypertension¹⁷

	NONPHARMACOLOGICAL INTERVENTION	GOAL	APPROXIMATE IMPACT ON SBP	
			HYPERTENSION	NORMOTENSION
WEIGHT LOSS	Weight/body fat	Best goal is ideal body weight but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg
HEALTHY DIET	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg	-3 mm Hg
REDUCED INTAKE OF DIETARY SODIUM	Dietary sodium	Optimal goal is <1500 mg/d but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg
ENHANCED INTAKE OF DIETARY POTASSIUM	Dietary potassium	Aim for 3500-5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg
PHYSICAL ACTIVITY	Aerobic	→ 90-150 min/wk → 65%-75% heart rate reserve	-5/8 MM HG	-2/4 mm Hg
	Dynamic resistance	→ 90-150 min/wk → 50%-80% 1 rep maximum → 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 MM HG	-2 mm Hg
	Isometric resistance	→ 4 × 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/wk → 8-10 wk	-5 MM HG	-4 mm Hg
MODERATION IN ALCOHOL INTAKE	Alcohol consumption	In individuals who drink alcohol, reduce alcohol to: → Men: ≤2 drinks daily → Women: ≤1 drink daily	-4 MM HG	-3 mm Hg

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in the amlodipine/perindopril group, including all-cause mortality (HR 0.89, 95% CI 0.81-0.99, $p = 0.025$), all coronary events (HR 0.87, 95% CI 0.79-0.96, $p = 0.007$), all cardiovascular events and procedures (HR 0.84, 95% CI 0.78-0.90, $p < 0.0001$), stroke (HR 0.77, 95% CI 0.66-0.89, $p = 0.0003$), and cardiovascular mortality (HR 0.76, 95% CI 0.65-0.90, $p = 0.001$).¹⁴

ANGIOTENSIN RECEPTOR BLOCKER (ARB)

The *Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)* Trial showed that amlodipine significantly reduced both systolic and diastolic BP compared with valsartan throughout the six-year duration of the trial. The amlodipine arm showed significantly fewer MIs than the valsartan arm ($P = 0.02$ and $HR = 1.19$; valsartan had 19% excess risk of MI). The rates of stroke were similar between the 2 arms ($P = 0.08$). There was a statistically significant decrease of stroke in the amlodipine arm in the first three months of the trial and a trend favoring amlodipine remained until the end of the trial (non-significant).¹⁵

The *Systolic Blood Pressure Intervention Trial (SPRINT)* compared the safety and efficacy of intensive lowering of SBP to <120 mm Hg versus routine management to <140 mm Hg and were followed-up for over 5 years. The trial was terminated early due to overwhelming evidence of benefit. The primary outcome, MI, acute coronary syndrome (ACS), stroke, congestive heart failure (CHF), or CV death, was significantly lowered in the intensive BP management arm compared with the routine management arm (5.2% vs. 6.8%, $HR 0.75$, 95% CI 0.64–0.89; $p < 0.0001$).¹⁶

PREVENTION

The most important way to prevent CV risk in hypertensive is to promote a healthy lifestyle throughout the life. All adults should consume a healthy diet with consumption of fruits, vegetables, whole grains, fish and low-fat dairy products with reduced intake of alcohol, trans fats, red meat, carbohydrates and sweetened beverages. Counseling and caloric restriction are recommended for achieving and maintaining weight loss in overweight and obese individuals.

TABLE 3.

Compelling indications for individual for BP management¹⁹

	DIURETIC	β-BLOCKER	ACEI	ARB	CCB	ALDOSTERONE ANTAGONIST
CHF	•	•	•	•		•
POST-MI		•	•			•
CAD-RISK	•	•	•			
DIABETES MELLITUS	•	•	•	•	•	
RENAL DISEASE				•	•	
RECURRENT STROKE PREVENTION	•		•			

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

The seventh report of the Joint National Committee (JNC VII) on prevention, detection, evaluation, and treatment of high BP reported that thiazide-like diuretics are effective and relatively safe for the management of uncomplicated HTN.¹⁸ HTN may exist in association with other conditions in which there are compelling indications for BP management (Table 3). Therapeutic decisions should be aimed at both the compelling indication and lowering BP. Diabetics and CKD patients will require more than two medications to achieve goal BP.

In 2014, JNC VIII guidelines for the management of HTN in adults announced that the initial anti-hypertensive treatment should include a thiazide diuretic, calcium channel blocker, ACEI, or angiotensin receptor blocker (ARB) in general non-black population where as in general black population the initial treatment should include a thiazide diuretic or calcium channel blocker, including those with diabetes. Blood pressure should be monitored, and the treatment regimen adjusted until the target blood pressure is reached. If the target BP is not achieved within one month after initiating therapy, increase the dosage of the initial medication or second medication should be added from the drug classes listed above (do not combine an ACEI with an ARB). A third drug should be added if necessary; Antihypertensive drugs from other classes can be used (e.g., beta blockers, aldosterone antagonists) if the target BP is not achieved using only the above drug classes listed.²⁰ Adults with CKD and hypertension should receive

an ACE inhibitor or ARB as initial or add-on therapy, based on moderate evidence that these medications improve kidney-related outcomes in these patients.

In addition to recent published guidelines recommending a total risk approach for reducing the risk of CV events, the recent British Hypertension Society (BHS)/ National Institute for Health and Care Excellence (NICE)^{22,23} guidelines for HTN is also changing the recommended choices of drug therapy based on recent clinical trials.

The essential effect of ACEIs on the angiotensin aldosterone system (RAAS) is to block the conversion of the relatively inactive angiotensin I (Ang I) to the active Ang II. Angiotensin II receptor blockers (ARBs) bind to the AT1

receptor with high affinity. All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACEIs and ARBs, the result is increased plasma renin activity (PRA). Studies have shown that antihypertensive agents that target the renin-angiotensin system prevent kidney decline better, even when achieving similar BP goals.²⁶ These results were found primarily in patients with proteinuria, whereas the benefit was less substantial for those without proteinuria. Based on these findings, guidelines recommend ACEIs or ARB therapy as first-line treatment for those with diabetes or those presenting with nondiabetic kidney disease, HTN, and proteinuria. Data indicate that ACEIs and ARBs are

equally effective in lowering BP and reducing proteinuria.²⁷ A recent meta-analysis suggests that ACEI therapy may provide superior benefit over ARB therapy for the treatment of HTN due to a 10% reduction in all-cause mortality.²⁸ These results were determined for patients with HTN and did not apply to patients with additional comorbidities such as CKD. Therefore, selection of one agent over another will depend on patient-specific factors such as potential for side effects and cost. Treatment with both an ACE inhibitor and an ARB is not recommended, as this combination has been shown to worsen kidney function. Combination

ACE inhibitor and ARB therapy did not reduce cardiovascular mortality or morbidity in comparison to monotherapy of an ACE inhibitor.^{27, 28}

The BP thresholds and recommendation treatment according to 2019 ACC/AHA prevention Guidelines as shown in Figure 1.²⁹ The patients with diabetes/ CKD are automatically classified in the high-risk category. For stage 2 hypertension 2 antihypertensive agents of different classes need to be consider for initiation of therapy and should be closely monitored.

Renal sympathetic denervation (RDN) is being actively investigated as a novel treatment modality for patients with HTN.

TABLE 4. Joint National Committee (JNC) VII vs VIII: Drug Therapy ¹⁹	
JNC VII	JNC VIII
RECOMMENDED → 5 classes to be considered as initial therapy → Thiazide-type diuretics as initial therapy for most patients without compelling indication for another class → Included a dual dose range of antihypertensive medications Specified antihypertensive medication classes for most patients without compelling indications such as diabetes, CKD, heart failure, myocardial infarction, stroke and high CVD risk.	RECOMMENDED → 4 specific medication classes to be considered as initial therapy → ACEI/ARB, CCB or Thiazide-type diuretic as initial therapy for most patients → Doses based on randomized clinical trial (RCT) evidence Specified medication classes based on evidence review for racial, CKD, and diabetic subgroups.

TABLE 5. BHS/NICE guidelines recommendations for combining antihypertensive drugs ^{24, 25}		
	AGE <55 YR AND NON-BLACK	AGE >55 YR OR BLACK
STEP 1	A (ACEI or ARB)	C (CCB) or D (Diuretic)
STEP 2	A	+ C or D
STEP 3	A	+ C or D
STEP 4 RESISTANT HYPERTENSION	Add either α-Blocker or loop diuretics/spironolactone or β-Blocker	
A: Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) C: Calcium channel blocker (CCB) D: Thiazide diuretic		
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Pivotal trials for renal denervation (RDN) for uncontrolled HTN using radiofrequency ablation in the main renal arteries showed that RDN was effective in lowering blood pressure (BP) of 15-20mm Hg.³⁰ Recent data, from meta-analysis, suggest that the BP lowering effect of RDN, even if smaller than initially anticipated, is similar to that observed with many currently approved antihypertensive drugs. Nevertheless, many questions remain about RDN, including its long-term safety and effectiveness, and how it might be integrated into the treatment for HTN.

To determine the appropriateness of pharmacological therapy after quantitative risk estimation in cases that are unclear, selective use of a coronary artery calcium (CAC) measurement can inform decision-making for cholesterol-lowering or antihypertensive medication use in intermediate-risk individuals. Coronary artery calcium (CAC) score is a direct measure of subclinical atherosclerosis.³¹

AUTHOR DISCLOSURES:

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FIGURE 1.

Blood Thresholds and Recommendations for Treatment and Follow-Up¹⁷

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