REVIEW ON CURRENT TRENDS IN THE MANAGEMENT OF HYPERTENSION

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Synopsis

Cardiovascular diseases have been cited as the leading causes of death in the industrialized world. This trend is slowly shifting to the low and middle income countries. In Kenya, for instance, the prevalence of hypertension among adults is almost reaching 50 %. This disease is asymptomatic and most of the patients are diagnosed during routine checkups at clinics. Even though the Ministry of Health has developed guidelines on the management of hypertension, local studies have revealed that most of the patients are inadequately managed. A number of challenges to the management have been identified. For instance, patient assessment as to who should or should not receive therapy, drug selection and the management of complications. This article reviews the current trends in the management of hypertension, with an emphasis on the diagnoses, assessment of the patient and drug selection.

Key Words: Hypertension, Management, Assessment, Drug selection

1.1 Introduction

Hypertension (HTN) may be defined as a cardiovascular disease characterized by elevated blood pressure (BP) above arbitrary values considered "normal" for people of similar racial and environmental background. The World Health Organization (WHO) defines HTN as a persistent increase of systemic blood pressure above 140mmHg systolic or 90mmHg diastolic, or both[1,2]. The American Heart Association (AHA) defines HTN as BP greater than 140/90 mmHg[2].

HTN is a common problem in the industrialized world. Worldwide, there are about one billion adults with hypertension and this figure is expected to rise by half, by the year 2025[2]. It affects about 30% of the black population aged 18 years and over. There is no acute clinical presentation of HTN and the disease is usually referred to as a "silent killer." Most patients are diagnosed as routine checkups during clinic visits. Local studies have revealed there is a high prevalence of the disease, but patients are being treated inadequately [3] despite the availability of treatment guidelines [4].

The systolic blood pressure (SBP) represents the peak of the blood pressure when the ventricles are contracting, whereas the diastolic blood pressure (DBP) represents the trough of the blood pressure curve and reflects the minimal pressure in the vasculature at the end of ventricular diastole (when the ventricles are filling with blood) [5]. Evidence from Framingham studies indicates that systolic pressure is the most important determinant of cardiovascular risk, coronary, heart and myocardial diseases[6].

Classification of HTN (Table 1) is based on the average of two or more BP readings taken on three different clinic visits according to the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) released in 2003[1].

Table 1: Classification of Adult Blood Pressure [1]

Definition	Diastolic BP(mmHg)	Systolic BP(mmHg)
Normal	<85	100-120
High Normal ₹	85-89	121-140
Borderline ₹	90-94	141-160

Mild [ɾ]	95-104	161-180	
Moderate [ɾ]	105-114	>180	
Isolated Systolic HTN	<90	≥140	
Severe	>114		
Malignant*	>140		

[ɾ] High normal HTN may also be termed prehypertensive stage while patients with borderline and mild HTN can be said to have stage 1 hypertension. Patients with SBP ≥140 and DBP ≥100 are said to have stage 2 hypertension.

*Malignant hypertension is characterized by systolic BP > 200 and Diastolic BP > 130mmHg. It is usually accompanied by severe retinopathy, renal failure and a rapidly deteriorating clinical course. Symptoms such as headache and visual disturbances are common.

Some patients are known to suffer from isolated systolic hypertension (ISH) which is characterized by systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure less than 90mmHg. The prevalence of ISH increases with age and is higher in blacks and women. The prevalence of ISH over the age of 70 years (both in men and women) is 13%-20 %.[5]

Primary and secondary HTN are the two main types of HTN classified according to aetiology. Essential or primary hypertension accounts for approximately 95% of the cases, whereas secondary hypertension accounts for about 5% of patients. There is no known cause of primary hypertension[1] unlike in secondary hypertension where there is usually a secondary cause [7] as shown in Table 2 below[8].

Table 2: Causes of Secondary Hypertension

Cause	Comments
Renal diseases (Commonest cause)	•Renoparenchymal disease (accounts for ¾ of renal causes) •Examples: glomerulonephritis, chronic pyelonephritis •Renovascular disease (accounting for 25 % of renal causes) •Frequently atheromatous renovascular disease
Endocrine	•Primary hyperaldosteronism •Cushing's syndrome •Phaeochromocytoma •Conn's syndrome •Acromegally •Hyperthyroidism •Hyperparathyroidism
Drugs	•Adrenocorticosteroids •Alcohol •Anorexics(e.g. phenylpropanolamine) •Phenothiazines •Cyclosporine •Licorice

Drugs	•Monoamine oxidase Inhibitors •Non-Steroidal Anti-inflammatory •Oral Contraceptives(OCs)- "the pill" •Oral decongestants (e.g. Pseudoephedrine) •Tricyclic antidepressants

1.2 Pharmacotherapy of Hypertension

Management of hypertension usually involves assessment, non-pharmacological and pharmacological therapy [9].

The USA Joint National Committee Guidelines (JNC) 2003 recommends that for assessment, at least three different measurements on both arms on at least two separate health care visits (except those with very high blood pressure readings especially in end organ dysfunction)[1]. Assessment also involves taking a complete patient's history, physical examination and evaluating for secondary causes of hypertension through basic investigations such as urea, electrolytes, creatinine, cholesterol, glucose, electrocardiogram, urine analysis (for protein or blood) and specific investigations (if a secondary cause is suspected), for example renal ultrasound, renal arteriography, urinary free cortisol, renin, aldosterone, and glomerular filtration rate[1,10] . It is also important to check for target organ damage such as renal, eye, heart and brain, and to rule out associated conditions for example diabetes mellitus, pregnancy or thyrotoxicosis because this will determine the first line agent for the management of hypertension[9].

Patients who have been assessed and a diagnosis of hypertension made should be managed appropriately. For most patients, the blood pressure target should be aimed at <140/85, but 130/80 in patients with diabetes (<125/75 if proteinuria). Blood pressure should be reduced gradually because a rapid reduction can be fatal, especially in the context of stroke[10]. . For stage 1 hypertension, non-pharmacologic therapy (Table 3) and lifestyle advice are recommended, after which reassessment of blood pressure is done in about three to six months prior to prescribing drugs. After an assessment of the patient, if blood pressure has not reduced, then it is better to begin pharmacologic therapy. [9, 11]

Table 3: Non Pharmacologic Management of Hypertension

- Diet- low fat, low salt
- Regular aerobic exercises
- Weight reduction
- Stress relief
- ↓ alcohol
- Quit smoking
- ↓Exacerbating factors e.g. pain
- Control other factors leading to arteriosclerosis

Key ↓ -Reduce

1.3 Principles of Drug Selection

All patients with malignant hypertension or sustained pressure >160/100mmHg should be treated pharmacologically. For those with BP >140/90, the decision to give the medication depends on the risk of coronary events, presence of diabetes or end-organ damage[12]. Treatment can be initiated with a single agent of proven benefit, for example, thiazides or β-blockers. Calcium channel blockers (CCB), angiotensin receptor blockers (ARBs) and Angiotensin Converting enzyme inhibitors (ACE-Is) are less well studied, but seem effective[8].

If one drug fails, then it is recommended to switch to another. The most appropriate first line treatment depends on age, sex, race and concomitant illnesses. In thyrotoxicosis, for instance, beta blockers may blunt palpitations associated with elevated levels of thyroid hormones while in diabetes mellitus, ACE-I or ARB may retard progression of nephropathy. [13]

Thiazide or beta blockers are often used as first line agents in patients with non-compelling indications. It is important to note that thiazide diuretics may precipitate hyperglycaemia or hypeuricaemia in susceptible individuals [14]. On the other hand, non-selective beta blockers should be avoided in diabetic patients because they tend to mask hypoglycaemic reactions. Even for the cardioselective agents such as atenolol,bisoprolol and metoprolol, the cardioselectivity is lost with increasing dose.

For hypertensive patients presenting with left ventricular dysfunction, the most appropriate first line agent are ACE-Is which have been shown to slow down maladaptive remodeling of the injured ventricle. In pregnancy, methyldopa or labetalol may be the first line, as their use is not known to be harmful to the foetus.[10]

If monotherapy proves unsuccessful, then it is suggested that a logical combination therapy be initiated. For instance, ACE-I plus diuretic (thiazide), beta blocker plus diuretic or CCB plus beta blocker. Resistant hypertension is mainly due to non-adherence, but sometimes may be due to underlying secondary cause or genuine refractory hypertension requiring multiple combination therapy. Most drugs take 4-8 weeks to produce maximal effect. Efficacy cannot be based on a single clinic blood pressure measurement.[7,15]

Loop diuretics (for example, frusemide) have a hypotensive effect but are not generally used for hypertension especially due to their shorter duration of action, but they are very useful in relieving pulmonary oedema[7]. Aldosterone antagonists (for example, spironolactone) diuretics are not effective antihypertensives alone except in hyperaldosteronism. They are usually used together with thiazides[16].

ACE-Is are very effective and are considered first line therapy in treatment of hypertension. ACE inhibitors, in general, are effective antihypertensive agents, but they differ with respect to potency, pharmacokinetics properties and duration of action. Fosinopril, for instance, differs with other ACEIs in that it is eliminated through the hepatobiliary and renal route implying that it can be used in treatment of HTN in patient with impaired kidney or liver function, and also in elderly patients. [14, 17]

CCBs may also be used as first line agents. However, verapamil and diltiazem can cause sinus tachycardia, heart block or worsen already existing conduction defects. Short acting CCBs should be avoided as they cause large variations in BP and reflex tachycardia.

Table 4 below shows the choices of the antihypertensive agents for different patients, while Table 5 displays the major classes of antihypertensive agents.

Table 4: Hypertension Treatment Guidelines and Blood Pressure Targets for Patients*

Patient Assessment		**Target BP (mmHg)**	**Initial Drug Choices**
JNC 7(2003)			
No compelling indication	Stage 1 HTN (140-159/90-99)	$\leq$ 140/90	Thiazide diuretic (for most patients), ACEI, ARB, BB,CCB or combination
	Stage 2 HTN (> 160/ > 100)	$\leq$ 140/90	2-drug combination for most patients: Thiazide diuretic plus (+) ACEI/ARB/CCB
Compelling indication	Diabetes mellitus	$\leq$ 130/80	1st – ACEI or ARB 2nd – Thiazide diuretic 3rd – BB or CCB
AHA (2007)			
Primary Prevention	Framingham risk score < 10%	$\leq$ 140/90	ACEI (or ARB), CCB, thiazide diuretic or combination if needed
	Framingham risk	$\leq$ 130/80	ACEI (or ARB), CCB, thiazide diuretic or

	score > 10%		combination if needed
High CAD risk	Diabetes mellitus	≤ 130/80	1st – ACEI or ARB 2nd – Thiazide diuretic 3rd – BB or CCB
ACEI – Angiotensin Converting Enzyme Inhibitor; AHA – American Heart Association; ARB – Angiotensin Receptor Blocker; BB – Beta Blocker; BP – Blood Pressure; CAD – Coronary Artery Disease; CCB – Calcium Channel Blocker; HTN – Hypertension; JNC 7 - Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure.			

*Source: Hypertension: Clinical Practice Updates, American College for Clinical Pharmacists

Table 5: Classes of Antihypertensive Agents, with Examples of Drugs

Alpha blockers	ACE-i	ARB	β-Blockers		CCB	CAA	Diuretics		Vasodilators
Doxazocin	Captopril	Irbesartan	**Non selective**	Nandolol	Diltiazem	Clonidine	**Thiazide**	HCTZ	Hydralazine
Phenoxybenzamine	Enalapril	Losartan		Oxprenol	Isradipine	Methyldopa		Bendrofluazide	Minoxidil
phentolamine	Fosinopril	Telmisartan		Pindolol	Nicardipine	Moxonidine		Furosemide	
Prazocin	Lisinopril	Valsartan		Propranolol	Nifedipine	Reserpine	**Loop**	Bumetanide	
	Ramipril			Sotalol	Nimodipine			Torsemide	
				Timolol	Verapamil				
							K+ Spairing	Spironolactone	
								Amiloride	
			Cardioselective	Atenolol					
				Bisoprolol					
				Metoprolol					
			α1, B-blockers	Carvedilol					
				Labetalol					
			ISA	Acebutolol					
				Oxprenolol					
				Pindolol					

CAA: Centrally acting antiadrenergics, HCTZ: hydrochlorothiazide, ISA: Intrinsic sympathomimetic activity, K+ potassium.

1.4 Hypertensive Crisis

This is malignant or accelerated hypertension that has BP equal to or greater than systolic 180mmHg or diastolic of 110mmHg. There are usually no known symptoms, but patients may report headaches (22% of cases), altered level of consciousness, and breathlessness due to heart failure, visual failure due to retinopathy or general malaise due to nephropathy. Evidence of this acute or ongoing end-organ damage constitutes a hypertensive emergency while the absence of such complications is known as hypertensive urgency. [18]

The goal for the management of hypertensive crises is prompt, but gradual reduction of blood pressure.A reduction of diastolic pressure to 100 or 110 mm Hg over the course of several minutes to several hours may be acceptable. End-organ ischemia or infarction can occur when pressure is reduced too rapidly. Sudden drop in BP causes poor cerebral autoregulation and so increases the risk of stroke. [8]

Although there is no specific drug for the management of hypertensive crises, it may be desirable to initiate furosemide plus hydralazine intravenously (IV) every 15minutes till the desired effect is achieved. The total

dose maybe repeated IV or intramuscularly after 6 hours of 0.25-10µg/kg/minute sodium nitroprusside IV infusion. Alternatively, one may give nifedipine 20mg orally repeated after one hour till the target BP is achieved. Sublingual nifedipine should not be used as it can cause uncontrolled drop in blood pressure. [8] Once BP is controlled, monotherapy may be considered for continuation of therapy. [19]

1.5 Major Side Effects of Selected Antihypertensive Agents

The main adverse effects of thiazide diuretics are metabolic effects such as hyperlipidaemia, hyperuricaemia, impaired glucose tolerance and hypokalemia. Thiazide diuretics may also cause neonatal thrombocytopenia, postural hypotension and impotence.

Beta blockers may cause bradycardia, "cold peripheries," fatigue, and bronchospasm. They may also precipitate heart failure and asthma. They inhibit the usual hypoglycemic response in diabetics and may also cause intrauterine growth restriction. [5]

ACE inhibitors are well tolerated at low doses. However, they may cause skin rash and taste disturbances. Chronic dry cough is common with captopril. ACE-I may cause renal failure and hyperkalemia, just like ARBs, due to aldosterone antagonism and this primarily seen in patients with renal disease or diabetes mellitus. They are contraindicated in pregnancy, aortic and renal artery stenosis. [8]

Patients who are slow acetylators are more prone to developing systemic lupus erythematosus (SLE) when given hydralazine, but this is reversible upon discontinuation of drug. Hydralazine may also cause drug fever, hepatitis, vascular headache and peripheral neuropathy. [16]

CCBs cause reflex stimulation of sympathetic nervous system. They may cause headache, flushing and ankle oedema. CCB may also cause fatigue and gum hyperplasia. Verapamil is associated with a higher degree of constipation and profound negative inotropic effect compared with other calcium channel blockers. [20]

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