Recent advances in the management of hypertension

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ABSTRACT

يعتبر فرط التوتر الشرياني مرض منتشر على مستوى العالم. يؤدي هذا المرض إلى اعتلال الصحة والوفاة. إن أسباب حدوث فرط التوتر الشرياني، والعوامل الوراثية، والمضاعفات متفق عليها عالمياً، إلا أنه يوجد اختلاف في طريقة معالجته. نستعرض في هذا المقال الدلائل والمستجدات في علاج فرط التوتر الشرياني، والتي تحتوي على عقاقير جديدة. كما سيتم اقتراح أسلوب علاجي حديث حتى يتم الاتفاق على طريقة العلاج.

Hypertension is a worldwide prevalent disease that leads to considerable morbidity and mortality. While its underlying basis of genetics and pathology as well as its complications are universally agreed upon, management of hypertension remains to be controversial. In this article, we will present clear evidence of the recent advances in the management of hypertension that include newer therapeutic agents replacing old strategies. Moreover, a suggested approach that is evidence based is provided to help in establishing agreement in line of therapy.

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Hypertension is a worldwide prevalent disorder, and current evidence suggests further increase in the prevalence of hypertension in the coming generations.[1] The etiology of hypertension is either due to known causes (secondary), or it may be due to obscure reasons and hence the name essential hypertension. Recent research is looking at those who are distend to develop hypertension by identifying the genetic abnormalities responsible for the development of hypertension as well as their response to certain therapy.[2-5] High blood pressure is a recognized strong risk factor for many catastrophic health events related to cardiovascular, cerebrovascular, retinal, renal, and peripheral vascular disease. Consequently; hypertension was found to be the leading cause of death worldwide.[6] The lack of symptoms as a result of hypertension may lead to delay in the proper management of hypertension until complications ensue. Therefore, keeping normotensive state is healthcare priority to prevent morbidity and mortality related to hypertension.

Definitions of hypertension. The current agreement for hypertension from the European Society of Hypertension (ESH), European Society of Cardiology (ESC), and the World Health Organization-International Society of Hypertension (WHO-ISH) as well as British hypertensive society (BHS) and the American Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identify an individual with hypertension if the systolic blood pressure (SBP) is ≥140 mm Hg and or the diastolic blood pressure (DBP) is ≥90 mm Hg.[7-10] However, some slight difference among authorities as to what is considered normal blood pressure, as well as grading of hypertension, nonetheless, our concern here is the definition of hypertension. Moreover, there is an agreement on the definition of isolated systolic hypertension when the SBP is ≥140 mm Hg and the DBP is normal.

Treatment goals and target BP. There is mounting evidence resulting from many clinical trials

demonstrating that the reduction of blood pressure in patients with hypertension is associated with a reduced risk of cardiovascular events and death.[11-17] Ideally, the target reduction of BP should maintain a normotensive state at all times. However, several trials have looked at the optimal treatment of hypertensive patients to either prevent or at least halt the progression of target organ damage secondary to hypertension with variable outcomes. Recent study, African American Study of Kidney Disease and Hypertension (AASK), conducted on population of African American hypertensive patients with chronic kidney disease, showed no significant benefit of the lower blood pressure goal in the primary analysis of all patients during the trial phase or after 5 years of extended follow-up. However, upon subgroup analysis, there was a possible long-term benefit of initial assignment to the lower BP goal in patients with baseline proteinuria of 300 mg/day.[18] In the Hypertension Optimal Treatment (HOT) trial patients were randomly assigned to target diastolic blood pressures (DBP) of 90, 85, and 80 mm Hg. The group randomly assigned to a target DBP of 80 mm Hg had a significantly lower relative risk for cardiovascular death and major cardiovascular events compared to the group randomly assigned to a target DBP of 90 mm Hg.[19] Furthermore, high risk patients such as diabetics, and patients with chronic kidney disease may require lower target blood pressure for optimal control. The Hypertension Detection and Follow-up Program (HDFP) randomly assigned diabetic patients to intensive care (tight blood pressure control) versus usual care. The data from this trial were analyzed and found statistically significant reduction in the cardiovascular mortality and morbidity among patients with tight BP control.[20] The United Kingdom Prospective Diabetes Study (UKPDS) randomly assigned patients to a "tight" blood pressure control group or a "less tight" control group. In the tight control group, there were substantial reductions in risk for any diabetes end point, deaths related to diabetes, and stroke.[21] The current guidelines from ESC, ESH, and JNC 7 advise target blood pressure control of less than 140/90 for most patients and less than 130/80 for diabetic patients and patients with chronic kidney disease. Despite these guidelines and recommendations, blood pressure remains far from control in clinical practice and is confirmed by epidemiological trials in developed or developing countries.[22-28]

Lifestyle modifications. Animal studies noted significant increases in blood pressure accompanying weight gain from overfeeding.[29,30] Numerous clinical studies in humans examined the relationship of weight loss to blood pressure change. A meta-analysis of 25 studies concluded that a one-kg loss of body weight was associated with an approximate one mm Hg drop in systolic blood pressure. Furthermore, this blood pressure reduction was accomplished without the necessity of attaining normal weight status.[31,32] Moreover, the Trial of Hypertension Prevention (TOHP) found a 2-kg loss in weight over a 6-month period resulted in a decline of 3.7 mm Hg in systolic and 2.7 mm Hg in diastolic blood pressure. In addition, a 42% decline in the incidence of hypertension was noted in the same sample.[33,34] Another analysis of 8 clinical trials on blood pressure reduction was conducted for the effects of weight on blood pressure and concluded that weight gain was associated with increased blood pressure whereas weight loss resulted in reduced blood pressure.[35,36] Clearly, obesity and overweight are directly related to the development of hypertension. Consequently, JNC 7 advocates that 10 kg weight reduction will result in 5-10 mm Hg blood pressure reduction. Other important lifestyle modifications are well established in reducing blood pressure in the form of salt reduction in diet, adopting dietary approach to stop hypertension (DASH), as well as regular physical activity, and stress relieving measures. **Table 1** summarizes the recommendation of JNC 7 for lifestyle modifications.

Drug therapy. Clinical trials confirmed what we see in clinical practice; blood pressure can be difficult to control. For instance; in North America, Europe, and Australia, it has been shown that in as many as 50% to 75% of people being treated for hypertension target blood pressure levels are not achieved.[37,38] There are several factors contributing to failure of achieving target blood pressure in the majority of treated patients. These may include an incorrect diagnosis of secondary forms of hypertension, inadequate anti-hypertensive therapy, associated factors or diseases, such as the use of non-steroidal anti-inflammatory drugs, non-compliance with antihypertensive drug regimens, or physicians' inertia in prescribing proper therapy.[39-43] Moreover, each hypertensive patient should be individualized prior to initiation of certain drug regimen. Certainly, the presence of compelling indications or contraindications

Table 1 - Lifestyle modifications: American Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[8]

Modification	Systolic BP reduction range
Weight reduction of 10 kg	5-10 mm Hg
Adopt DASH eating plan[49,50]	8-14 mm Hg
Dietary sodium reduction	2-8 mm Hg
Physical activity	4-9 mm Hg
Moderation of alcohol	4-4 mm Hg

DASH - dietary approaches to stop hypertension eating plan

Table 2 - Compelling indications, cautions, contraindications.

Recommended drugs	Compelling Indications	Cautions	Compelling contra-Indications
ACE-I	Heart failure, EF <40%, Post-MI, CAD, DM, Stroke	Renal impairment PVD	Pregnancy RAS
ARBs	ACE-I intolerance LVH	Renal impairment, PVD	Pregnancy RAS
Diuretic	Elderly, ISH, stroke, heart failure	DM	Gout
CCB	Elderly, ISH, Angina	Heart failure	Heart block
Alpha-blocker	Benign prostatic hypertrophy	Postural hypotension heart failure	Urinary incontinence
Beta-blocker	MI, Angina, heart failure	PVD, DM, COPD heart failure	Asthma, heart block, pulmonary edema

ACE-I - angiotensin converting enzyme inhibitor; ARBs - angiotensin receptor blockers;
CCB - calcium channel blocker; EF - ejection fraction; MI - myocardial infarction;
CAD - coronary artery disease; DM - diabetes mellitus; PVD - peripheral vascular disease;
RAS - renal artery stenosis; ISH - isolated systolic hypertension; LVH - left ventricular hypertrophy;
COPD - chronic obstructive pulmonary disease.

Table 3 - Compelling Indication JNC 7.[8]

Compelling Indication	Recommended Drugs					
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT
Heart failure	+		+	+		+
Post-myocardial infarction		+	+			+
High coronary disease risk	+	+	+		+	
Diabetes	+	+	+	+	+	
Chronic kidney disease			+	+		
Recurrent stroke	+		+			

ACEI - angiotensin converting enzyme inhibitor;
ARB - angiotensin receptor blocker; Aldo ANT - aldosterone antagonist;
BB - beta blocker; CCB = calcium channel blocker.
JNC - The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

may be helpful in choosing initial therapy (**Table 2 & 3**). However, most patients require more than one drug to control the blood pressure. The use of 2 or more complementary agents may improve response rates because more than one physiologic pathway is interrupted. Additionally, the use of multidrug therapy may reduce side effects by using lower dosages; hence increasing compliance. The renin-angiotensin system (RAS) is a major regulator of blood pressure and vascular response to injury. There is increasing and current evidence that RAS inhibition may provide end-organ protection independent of BP lowering. Two drug classes directly target angiotensin II through complementary mechanisms. Angiotensin-converting enzyme (ACE) inhibitors block the conversion of angiotensin I to the active peptide angiotensin II and increase the availability of bradykinin. Angiotensin receptor blockers (ARBs) selectively antagonize angiotensin II at AT 1 receptors and may also increase activation of the AT 2 receptor and modulate the effects of angiotensin II breakdown products. Hypertension can be broadly classified as renin responsive or non-renin responsive and is therefore best treated initially with one of 2 categories of antihypertensive drug; those that inhibit the renin-angiotensin system: ACE-I or ARBs in high renin patients. We do not recommend routine measurement of serum renin to identify those who are renin responsive, however, those who are younger than 55 years and caucasians tend to have higher renin concentrations, while people aged 55 years or older or the black population (of African descent) tend to have lower renin, and therefore their initial therapy would be either calcium channel blocker and/or diuretic drug regimen. The drug used should ideally be effective for 24 hours when taken as a single daily dose. An interval of at least 4 weeks should be allowed to observe the full response, unless it is necessary to lower blood pressure more urgently.[44] Interestingly, it has been shown that combining ACE inhibitors and ARBs (if no contraindication) to provide more extensive RAS inhibition may provide greater antihypertensive efficacy and end-organ protection than use of either class alone.[45] Among women with hypertension without cardiovascular (CV) end organ damage, a 2-drug-class regimen of a calcium channel blocker plus a diuretic was associated with a higher risk of CV mortality versus a beta-blocker plus a diuretic. Risks were similar for an ACE inhibitors plus a diuretic and a beta-blocker plus a diuretic.[46] It is worth to emphasize the limitations of clinical trials; first, selecting high risk elderly patients

subsequently; younger or low risk patients are not represented. Second, the short duration (4-5 years) of the trials means the extra 20-30 years are not studied. Third, multiple combined primary end points are set in the design of the trial, thus; single end point, as a beneficial effect, cannot be concluded. Finally, by definition, the design of meta-analysis studies is post-hoc analysis. The metabolic derangement associated with the use of beta blockers compared to ACE-I or ARBs (particularly, increasing incidence of diabetes) made these drugs unappealing initial therapy for hypertension. We think in countries with high prevalence of diabetes mellitus and hypertension such as Saudi Arabia, we should move on to newer drugs with less side effects and proven efficacy in controlling hypertension.[47-48]

In summary, life style modifications are an important initial step in the management of hypertension. The initial drug therapy in the absence of compelling indications and contraindications should include ACE-I or ARBs in younger non-black patients. Rational choice of drugs facilitated by understanding their effects, but systematic trial and error may still be necessary. A primary goal in treating hypertension should be to reach a patient's target BP, but initial selection of drugs based on hypertension morbidity trial results and other compelling indications should be given priority.

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