

Putting Evidence Based JNC 8 Guideline into Primary Care Practice

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Introduction

The global hypertension prevalence is estimated to increase from 40% to 50% in the year 2025, with a significant upsurge in future morbidity and mortality due to heart disease and strokes [1-3]. In the Kingdom of Bahrain, hypertension control has been achieved in only 1 out of 6 treated patients [4], which suggests that there is a major shortcoming either in clinician inertia or failure to take appropriate action to drive blood pressures ("BPs") down to guideline-recommended levels [5].

We suggest that clinicians and the Ministry of Health ought to select one of the current guidelines and follow its recommendations. The Joint National Committee for Hypertension Detection and Management updated the JNC 8 guideline (2013), which if followed correctly, will achieve enhanced patient management and improve outcome indicators [6]. The JNC 8 panel has a different, focused and more simplified treatment approach than other expert panels, with a single BP recommendation (140/90 mm Hg) for both the

pharmacologic treatment threshold and treatment goal for patients between the ages of 18 to 60 years old with/without diabetes ("DM") or chronic kidney disease ("CKD") [7] (Table 1) [8]. Furthermore, the JNC 8 relies solely on critical assessment of randomized controlled trials and reduces the number of first-line drugs from five to four [9-12].

Nonetheless, guidelines are not a substitute for clinical judgment, and clinicians must consider each patient's circumstances and clinical condition when making decisions about medical care [7].

Objectives

To initiate antihypertensive pharmacologic therapy at specific BP thresholds and to a specified BP goal improves health outcomes.

To start various antihypertensive drugs or drug classes differ in their comparative benefits and harms on specific health outcomes.

Recommendation	Strength of Recommendation
In patients age \geq 60 years, initiate pharmacologic treatment at systolic BP \geq 150 mm Hg or Diastolic BP \geq 90 mm Hg and treat to a goal systolic BP $<$ 150 mm Hg and diastolic BP $<$ 90 mm Hg Corollary recommendation: If treatment results in lower achieved systolic BP (for example, $<$ 140 mm Hg) that is well tolerated, treatment does not need to be relaxed.	Grade A Expert opinion
In patients age $<$ 60 years, initiate pharmacologic treatment at systolic BP $>$ 90 mm Hg or Diastolic BP $<$ 90 mm Hg	Grade A for ages 30-59 years Expert opinion for ages 18-29 years
In the general population age $<$ 60 years, initiate pharmacologic treatment at systolic BP $>$ 140 mm Hg or Diastolic BP $<$ 140 mm Hg	Expert Opinion
In Patients with CKD age \geq 18 years, initiate pharmacologic treatment at systolic BP \geq 140 mm Hg or Diastolic BP \geq 90 mm Hg and treat to a goal systolic BP $<$ 140 mm Hg and diastolic BP $<$ 90 mm Hg	Expert Opinion
In patients age 18 years and older with diabetes, initiate pharmacologic treatment at systolic BP \geq 140 mm Hg or Diastolic BP \geq 90 mm Hg and systolic BP $<$ 140 mm Hg and diastolic BP $<$ 90 mm Hg	Expert Opinion
In nonblack patients, with or without diabetes, initial treatment should include any of the following: a thiazide diuretic, calcium channel blocker, ACE inhibitor or ARB	Grade B
In balck patients with or without diabetes, initial treatment should include a thiazide diuretic or calcium channel blocker	Grade B for general black population Grade C for black patients with diabetes
In patients with CKD, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. This applies to all patients with Hypertension and CKD regardless of race or diabetic status	Grade B
If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6. Continue to assess BP and adjust treatment by adding and titrating an additional first line drug or drug from other classes until goal BP is reached. Do not combine ACE inhibitor and ARBs. Consult a hypertension specialist if needed.	Expert Opinion

Table 1: JNC 8 recommendations for pharmacologic treatment of hypertension in adults [8].

Case Presentations

Case 1: Hypertension in an old age patient ≥ 60 years

A 68 years old male Bahraini presented with systolic uncontrolled hypertension (which ranged between = 160 - 200) for the past three years, in spite of continues compliance of angiotensin-converting enzyme inhibitor ("ACEI") on the maximum dose.

The patient's son inquired about the specific BP threshold to initiate antihypertensive pharmacologic therapy and specific level BP goal needed to be reached by the father. (Table 2). The JNC 8 recommendation for the management of hypertension patients aged 60 years and older confirms beginning treatment for BP with 150 mm Hg systolic or 90 mm Hg diastolic or greater, and keep treating until the BP falls below those thresholds (strong recommendation- Grade A) [13-14]. However, if the patient tolerates a lower BP (e.g. ≤ 140 mm Hg systolic), then it is recommended not to adjust treatment to raise BP closer to 150 mm Hg (expert opinion- Grade E). Setting a goal systolic blood pressure ("SBP") of ≤ 140 mm Hg; in this age group provides no additional benefit in comparison with a higher SBP goals of 140 to 160 mm Hg or 140 to 149 mm Hg [15-16].

If a patient does not respond to ACEI, the alternative drug preferences specific for geriatric are calcium channel blocker ("CCB") and thiazide-type diuretics. The thiazide diuretics which include, chlorthalidone and indapamide; it does not include loop or potassium-sparing diuretics.

The patient was very well controlled on thiazide diuretics and CCB tablet.

Hypertensive Guidelines	JNC 7 2003	JNC 8 2013	NICE 2011	CHEP 2013	ESH/ESC 2013	ASH/ISH 2013
BP (mmHg) Goal						
Age<60 years	< 140/90 for all ages (except CKD or DM)	< 140/90			< 140/90	
Age ≥ 60 years		< 150/90			< 150/90	
Age<80 years		< 140/90	< 140/90			< 140/90
Age ≥ 80 years		< 150/90	< 150/90			< 150/90
Diabetes	<130/80	< 140/90	<130-140/80	<130/80	< 140/85	< 140/90
CKD	<130/80	< 140/90	<130-140/80-90	<140/90	< 130/90	< 140/90
Initial drug preference						
General nonblack population	Thiazide diuretic ACEI inhibitor/ARB CCB Beta blocker	ACEI /ARB CCB	ACEI/ARB in age <55 years CCB in age ≤ 55 years	Thiazide diuretic ACEI /ARB in age <60 years CCB in age ≤ 60 years	Thiazide diuretic ACEI /ARB CCB Beta blocker	Thiazide diuretic ACEI /ARB CCB
Black population	No preference for any subpopulation	Thiazide diuretic CCB	CCB	No preference	No preference	Thiazide diuretic CCB
DM		Thiazide diuretic ACEI /ARB CCB	ACEI /ARB	Thiazide diuretic ACEI /ARB CCB	Thiazide diuretic ACEI /ARB CCB Beta blocker	Thiazide diuretic ACEI /ARB CCB
CKD		ACEI /ARB	ACEI /ARB	ACEI /ARB	ACEI /ARB	ACEI /ARB

Table 2: Comparisons of many hypertensive guidelines' goals and the initial drug therapy [8].

Case 2: Hypertension in a young age patient < 65 years.

A 38 years old female Bahraini presented with uncontrolled diastolic hypertension (which ranged between = 100 - 120) for the past 6 months. She was on Hydralazine 25 mg and Tenormin 100 mg, despite patient following strict life style modification. She was a symptomatic and questioning the benefits of her long-life treatment.

In the general population younger than 60 years old, JNC 8 recommends initiation of pharmacologic treatment, if diastolic blood pressure ("DBP") remains at 90 mm Hg or above (strong recommendation – Grade A) [17-18]. The guideline's goal is to lower

the DBP lower than 90 mm Hg, which in turn reduces cerebrovascular events, heart failure and overall mortality [19].

The panel did not recommend β -blockers for the initial treatment of hypertension due to a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction or stroke when compared to the use of an ARB [20].

There were no randomized controlled trials ("RCTs") of good or fair quality focusing on the following drug classes: dual α_1 - + β -blocking agents (e.g. Carvedilol); vasodilating β -blockers (e.g. Nebivolol); central α_2 -adrenergic agonists (e.g. Clonidine); direct vasodilators (eg.

Hydralazine); aldosterone receptor antagonists (e.g. Spironolactone), adrenergic neuronal depleting agents (e.g. Reserpine), and loop diuretics (e.g. Furosemide). The drugs of choice in younger age group are one of the followings: use of either ARB or ACEI and/or calcium channel blocker and/or medium potency diuretic (Figure 1). The patient was very well controlled on Indapamide diuretics and ACE inhibitor tablet [21].

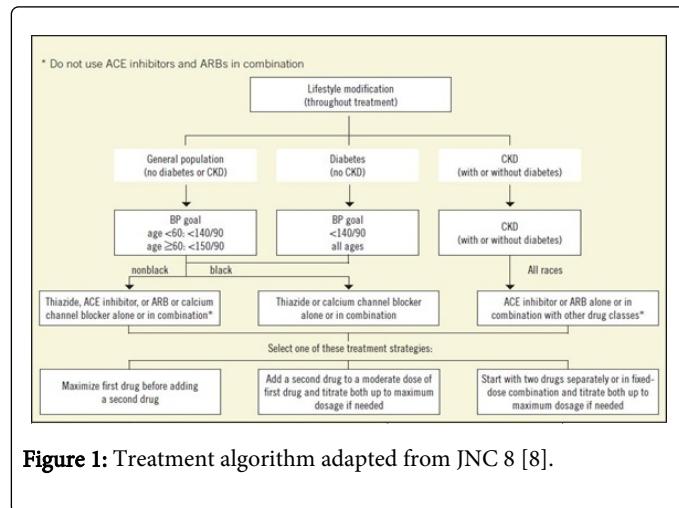


Figure 1: Treatment algorithm adapted from JNC 8 [8].

Case 3: Hypertension in a black patient

A 52 years old Ethiopian black male presented with uncontrolled resistant hypertension for the past 5 years. He was on calcium channel blocker with thiazide diuretic prescribed from his country and strict life style modification. He was enquiring about the maximum dose.

For black patients, initial therapy should be a thiazide diuretic or calcium channel blocker. Thiazide diuretics were more effective in black patients for improving cerebrovascular, heart failure and combined cardiovascular outcomes. Additionally, a calcium channel blocker reduced rate of stroke to a greater degree than an ACE inhibitor in black population (moderate recommendation – Grade B) [22].

In non-black patients with hypertension, the initial treatment can be selected from the 4 drug classes recommended by the panel {a thiazide diuretic, calcium channel blocker ("CCB"), angiotensin-converting enzyme ("ACE") inhibitor or angiotensin receptor blocker ("ARB")} which effects on overall mortality, cardiovascular, cerebrovascular, and kidney outcomes, with one exception; heart failure. Therefore, our personal preference is that to initiate a thiazide-

type diuretic is more effective than a CCB; but the panel did not reach this conclusion in its recommendation [22]. The patient has responded well to maximum drug dose (Table 3) strategy C (combined diuretic + calcium channel blocker) (Table 4) with.

Antihypertensive Medication	Initial daily Dose, mg	Target Dose in RCTs Reviewed, mg	No. of Doses per Day
ACE Inhibitors			
Captopril	50	150-200	2
Enalapril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candesartan	4	Feb-32	1
Losartan	50	100	1-2
Valsartan	40-80	16-320	1
Irbesartan	75	300	1
B-Blocker			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium channel blocker			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100 ^a	1-2
Indapamide	1.25	1.25-2.5	1

Table 3: Evidence-based dosing for antihypertensive drugs [8].

Strategy	Description	Details
A	Start one drug, Titrate to maximum dose, and then add a second drug	If a goal drug is not achieved with the initial drug, titrate the dose of initial drug up to the maximum recommended dose to achieve goal BP If a goal drug is not achieved with the use of one drug despite titration to maximum recommended dose, add a second drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB) and titrate up to the maximum recommended dose of the second drug to achieve goal BP If goal BP is not achieved with 2 drugs, select a 3rd drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the 3rd drug up to the maximum recommended dose to achieve goal BP
B	Start one drug and then add a second drug before achieving maximum dose of initial drug	Start with one drug then add a second drug before achieving the maximum recommended doses of the initial drug, then titrate both drugs up to the maximum recommended doses of both to achieve goal BP. If goal BP is not achieved with 2

		drugs, select a 3rd drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the 3rd drug upto the maximum recommended dose to achieve goal BP
C	Begin with 2 drugs with the same time, either as to separate pills or as a single pill combination	Initiate therapy with 2 drugs simultaneously, either as to separate drugs or as a single pill combination. Some committee members recommended starting therapy with >2 drugs when SBP is >160 mm Hg and/or DBP is >100 mm Hg, or if SBP is >20 mm Hg above goal and/or DBP is >10 mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the 3rd drug upto the maximum recommended dose.

Table 4: Strategies to dose of anti-hypertensive medication [8].

Case 4: Hypertension in a chronic kidney disease (CKD) patient

A 55 years old Bahraini female presented with hypertensive for the past 10 years and recent micro-albuminuria. The BP was very well controlled on calcium channel blocker ("CCB"); the patient queried about micro-albuminuria treatment and the recommended dose.

In patients with CKD, initial or add-on therapy should be an ACE inhibitor or ARB, regardless of race or diabetes status (moderate recommendation- Grade B) since it improves kidney outcomes for patients with CKD. This recommendation applies to CKD patients with or without proteinuria, as studies using ACEIs or ARBs presented evidence of improved kidney outcomes in both groups - the patient's BP and proteinuria were very well controlled on ACEI + CCB [23] (Tables 4 and 5).

Case 5: Hypertension in a diabetic patient

A 45 years old Bahraini female presented with hypertensive for the past 10 years and recent diabetes mellitus. She asked about her treatment of ARB and the recommended dose.

In the general non-black population, together with those with diabetes, primary antihypertensive treatment should include any one from the 4 anti-hypertensive class {thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB)} (moderate recommendation – Grade B) [16].

In the general black population, together with those with diabetes, early antihypertensive treatment should include a thiazide-type diuretic or CCB (weak recommendation – Grade C) [22].

The patient was advised to continue on her maximum dose of her ARB, she was doing well (Tables 4 and 5).

Case 6: Hypertension patient on thiazide treatment

A 50 years old foreigner patient with controlled hypertensive on thiazide-type diuretic was told previously that his BP was uncontrolled (systolic blood pressure ranged between 135 - 140; while diastolic blood pressure ranged between 85 - 90).

JNC 7 favors thiazide diuretics as a first-line treatment in utmost patients, while JNC 8 places thiazide diuretics as an equivalent with the other 3 classes. Thiazides have an advantage over the other antihypertensive drug classes, only in prevention of heart failure; this is an inadequate motive for the panel to hold the favored status of thiazides. Similarly, all other recent guidelines do not give approval of thiazides over other first-line drugs. The patient continues on the same treatment and ensures the aforementioned BP goals are sustained [24–27].

Case 7: Hypertensive with compelling indication

A 58 years old Bahraini male presented with uncontrolled hypertension, diabetes, hyperlipidemia, moderate obesity and hyperuracemia for 10 years duration, on ARB; Thiazide; Oral Hypoglycaemic; Statin and Zyloric.

Primary care physicians should regularly assess BP, encourage evidence-based lifestyle modification, adherence interventions, and then adjust treatment until goal BP is attained and maintained. In most cases, adjusting treatment means intensifying therapy by increasing the drug dose or by adding additional drugs to the regimen.

JNC 7 recommends specific drug types for "compelling indications", including coronary heart disease, stroke, left ventricular dysfunction, heart failure, diabetes, gout and chronic kidney disease ("CKD") [6]. JNC 8 recommends specific drug classes for patients based on only four subtypes namely: age, race, diabetes, and CKD. These subtypes were the only ones with evidence randomized controlled trials studies [7]. Other recent guidelines incorporate these three subpopulations with age as a determinant of drug selection [9,12].

Most current guidelines approve of ACE inhibitors or ARBs for patients with diabetes and CKD, and thiazides or calcium channel blockers for black patients [7,9,12]. British and ASH/ISH guidelines prefer thiazides or calcium channel blockers as initial therapy for patients over ages of 55 or 60 years, respectively [9,12]. Both older age and black race are linked to low plasma renin levels, rendering drugs that inhibit the renin-angiotensin-aldosterone system ("RAAS") less effective if used solely (Table 5).

Hypertensive Co Morbidity	Antihypertensive Agents
Diabetes	ACE or ARB Blocker + Diuretics + CCB + Beta Blocker
Left Ventricular Hypertrophy	Central Active Agonist + ACEI + CCB

Congestive Heart Failure	Systolic Dysfunction	ACE I or ARB + Diuretic + carvediolol (Beta Blocker)
	Diastolic Dysfunction	CCB
Coronary Artery Risk Factors or Myocardial Infarction	Beta Blocker + ACEI	
Angina Pectoris	Beta Blocker + CCB (not Nifedipine)	
Atrial Tachycardia or Fibrillation	Beta Blocker + Non Hydropyridine CCB	
Benign Prostatic Hyperplasia	Alpha Antagonist - Avoid Diuretic	
Dyslipaemia	Alpha Antagonist + Diuretic + Beta-blocker	
Renal Disease	ACEI + Diuretic	
Pregnancy	Methyl Dopa + Hydralazine + Labetolol - avoid ACEI	
Obesity	Diuretic	
Gout	Avoid Thiazide Diuretic	
Osteoporosis	Thiazide Diuretic	
Obstructive Pulmonary Disease	Avoid Beta Blocker	
Peri-Operative Hypertensive	Avoid Beta Blocker	
Edema	Avoid Calcium Channel Blocker	
Peripheral Vascular Disease	CCB + Beta Blocker	
Peptic Ulcer Disease	Avoid CCB	
Essential Tremor	Non Cardio Selective Beta Blocker	
Neurological Disorder	Essential Tremor	Non Cardio Selective Beta Blocker
	Migraine	Non Cardio Selective Beta Blocker + Non Dihydropyridine CCB
	Depression	Avoid Beta Blocker
	Substance Abuse	Labetolol + combined Alpha Beta Blocker + CCB+ Nitrate

Table 5: Hypertensive drugs with compelling indication [8].

Case 8: Hypertension with combined Renin Aldosterone Angiotensin Blockage System (RAAS) treatment

A 68 years old Bahraini male with hypertension with multiple comorbid diseases (diabetes and CKD) on combined RAAS treatment (ACEI and ARB) and other multiple drugs, with frequent episodic symptomatic attacks of hypotension, enquired about the cause of hypotension attacks.

Neither JNC 7 nor JNC 8 addresses the combined use of drugs that block the RAAS, especially in patients with CKD [28,29]. There were three published randomized controlled trials that pointed out the threats of the Hypotension, acute renal failure and hyperkalemia [30-32]. The danger increases with the use of RAAS combined with a direct renin inhibitor such as aliskiren [30,31].

Conclusion

JNC 8 is a simpler guideline than other recent guidelines, with a single BP recommendation (140/90 mm Hg) for both the pharmacologic treatment threshold and treatment goal for patients between the ages of 18 and 60 years and patients with diabetes or

CKD. JNC 8 also reduces the number of first-line drugs from five to four while recommending specific drug preferences for only three subpopulations: black patients, patients with diabetes, and patients with CKD.

The JNC 8 guideline is very helpful for primary care clinicians to better manage patients with hypertension. Primary care physicians can easily apply the evidence based JNC 8 guideline into their practice, however, the guideline is not a substitute for clinical judgment, and decisions about care must be carefully individualized.

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