Update in Hypertension: The Seventh Joint National Committee Report and Beyond

Mahmoud A. Moawad,* Walid Hassant

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII) had new key messages that need to be highlighted for practicing physicians. More than two years has elapsed since its publication and several important trials and meta-analyses were published during this period. Most of these publications supported and reinforced the JNC-VII recommendations, but others did not fully agree. Thus, some questions have arisen that need to be addressed in future research. This review will discuss what is new in JNC-VII and post-JNC-VII evidence that supports or disputes the recommendations. In addition, the results of other significant trials will be addressed. Finally, we outline the clinical "bottom line" and emphasize the practical application of this evidence.

*From the King Faisal Specialist Hospital & Research Centre,
*Department of Medicine, †King Faisal Heart Institute, Riyadh,
Saudi Arabia*

Correspondence:

*Mahmoud A. Moawad, MD,
MPH*

*Head, Internal Medicine Section
King Faisal Hospital
& Research Centre
Department of Medicine, MBC 46
P.O. Box 3354 Riyadh 11211,
Saudi Arabia
Tel: 966-464-7272
moawad@kfshrc.edu.sa*

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The weighted percentages for the 1999-2000 US National Health and Nutrition Examination Surveys (US NHANES) showed a slight improvement in patient awareness of hypertension (68% to 70%), an increase in treatment (54% to 59%), and an increase in control of blood pressure to <140/90 mm Hg (27% to 34%) in adults with hypertension aged 18 to 74 years old as compared with the 1991-1994 surveys.¹ These results, which show that less than 60% of hypertension patients are being treated and only one in three of those are adequately controlled, indicate that a lot of work is still needed, even in a developed country with huge health care resources and expenditures such as the USA.

What is new in JNC-VII?

The JNC-VII¹ has several "key" messages, which include:

- The risk of cardiovascular diseases (CVD), beginning at 115/75 mm Hg, doubles with each 20/10 mm Hg increment.
- A systolic blood pressure (SBP) of 120-139 mm Hg and a diastolic blood pressure (DBP) 80-89 mm Hg is now termed "pre-hypertension".
- Hypertension is now classified into two stages: stage 1: 140-159/90-99 mm Hg, and stage 2: >160/100 mm Hg.
- For patients at stage 2, consider starting therapy with two medications at once (Table 1).

Other messages included in the JNC-VII recommendations that were also in the JNC-VI recommendations are that in persons >50 years old, SBP is a much more important a CVD risk factor than DBP, thiazide-type diuretics are the drug of first-choice for uncomplicated hypertension, most patients will need ≥2 drugs, and patient motivation is necessary.

Table 1. Classification of blood pressure for adults 18 years of age and older in the recommendations of the Sixth and Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI and JNC VII).

JNC-VI (1997)	Blood pressure (mm Hg)	JNC-VII (2003)
Optimal	<120 & <80	Normal
Normal	120-130 & 80-85	Pre-hypertension
High-normal	130-139 & 85-89	
Hypertension		
Stage 1	140-159 or 90-99	Stage 1
Stage 2	160-179 or 100-109	Stage 2 (≥160 or ≥100)
Stage 3	>180 or >110	

Three new CV risk factors were added in the JNC-VII recommendations. These were obesity (BMI ≥ 30), physical inactivity, and microalbuminuria or an estimated GFR <60 mL/min. Other risk factors included in previous JNC recommendations included hypertension, cigarette smoking, dyslipidemia, diabetes mellitus, age (>55 years for men, >65 years for women) and a family history of premature cardiovascular disease (men <55 years or women 65 years).

The compelling indications for certain drugs (Table 2) included three new categories: chronic kidney disease, secondary prevention of cerebrovascular disease, and high coronary artery disease (CAD) risk. The other three indications remained unchanged but with the additional indications of some drug classes. For heart failure, beta-adrenergic blockers (β-blockers), angiotensin receptor blockers (ARBs) and aldosterone antagonists (AAs) were added to diuretics and angiotensin-converting enzyme inhibitors (ACE-inhibitors). For diabetes mellitus, thiazide diuretics, β-blockers, ARBs and calcium channel

blockers (CCBs) were added to ACE-inhibitors. For high CAD-risk patients (a new category replacing isolated systolic hypertension [ISH] in the elderly in a previous report) β-blockers and ACE-inhibitors were added to what was recommended previously for ISH (thiazides and CCBs).

Post JNC-VII Evidence

The results of most studies published since the publication of the JNC-VII support the recommendations for lifestyle modifications and blood pressure control, the use of low-dose diuretics as first-line therapy, lower-dose combination treatment vs. single drug, and diuretic-based therapy in older patients with ISH and diabetes. The results of some studies, however, dispute the recommendation that ACE-inhibitors and ARBs be used in elderly patients with hypertension.

Evidence in agreement with JNC-VII recommendations

Lifestyle modification and blood pressure control

The effect of established lifestyle recommendations (ELR) for BP reduction were examined in a six-month, randomized clinical trial of patients with SBP of 120-159 mm Hg and DBP of 80-95 mm Hg who were not on antihypertensive medications.² The three-arm study included a group assigned to ELR, including weight loss, sodium reduction, increased physical activity, and limited alcohol intake, a group assigned to ELR plus a diet rich in fruits, vegetables, whole grains, low fat dairy products, refined carbohydrates and low sodium (DASH diet³). The third group was a comparison group that received advice only. The first two groups had a greater reduction in SBP and DBP than did the advice only group. The two behavioral intervention groups did not differ

Table 2. JNC-VII: Compelling indications for anti-hypertensive drugs recommended in the Seventh Report of the Joint National Committee.

Condition	Recommended anti-hypertensive drugs					
	TD	β - B	ACE-I	ARB	CCB	AA
Heart failure	+	+	+	+		+
Post-MI		+	+			+
High CAD risk	+	+	+		+	
Diabetes	+	+	+	+	+	
Chronic kidney disease			+	+		
Cerebrovascular accident - secondary prevention	+		+			

significantly in BP reduction. Compared with the baseline hypertension prevalence of 38%, the prevalence at 6 months was 26% in the advice only group; 17% in the ELR group ($P=0.01$ vs. advice only); and 12% in the ELR plus DASH ($P<0.001$ vs. advice only). The number needed to treat (NNT) was 8 for the ELR group and 4 for the ELR + diet group compared with advice only.

Conclusion: Individuals with less than optimal BP, including stage 1 hypertension, can make multiple lifestyle changes that lower BP to reduce their cardiovascular disease risk. The DASH diet led to an additional decrease in hypertension prevalence compared to ELR alone although the mean between-groups difference in blood pressure was not significant ($P=0.12$).

Low-dose diuretics as first-line therapy

A meta-analysis of RCTs comparing low-dose thiazide diuretics (12.5 to 25 mg/d) with placebo, ACE-inhibitors, CCBs, ARBs, and β -blockers or α -blockers yielded 42 RCTs (192 478 patients) with a mean follow-up of 3 to 4 years. The outcomes included coronary heart disease (CHD), congestive heart failure (CHF), stroke, cardiovascular disease (CVD) events, CVD mortality, and total mortality. Low-dose diuretics reduced the risks for all CVD outcomes more than placebo and were equal to, or better than, other antihypertensive agents for all outcomes. There was a trend for a lower relative risk with low-dose diuretics compared to all other classes (with the exception of ARBs) (Table 3).

Conclusion: The only class that was truly comparable to low-dose thiazide diuretics were the ARBs.⁵ There was no statistically significant difference between these two classes.

Single- vs lower-dose combination treatment

A systematic review of randomized, double-blinded, placebo-controlled trials that examined changes in BP in relation to a specified, fixed dose of any thiazide, β -blocker, ACE-I, ARB, or CCB, found 354 trials (39 879 patients).⁶ All five drug categories gave a similar BP reduction. The mean placebo-adjusted reduction was 9.1 mm Hg (95% CI, 8.8 to 9.3 mm Hg) for SBP and 5.5 mm Hg (95% CI, 5.4 to 5.7 mm Hg) for the "usual maintenance dose" and 7.1 mm Hg (95%CI, 6.8 to 7.5 mm Hg) for SBP and 4.4 mm Hg (95%CI, 4.2 to 4.6 mm Hg) for DBP at a half-standard dose. Fifty trials tested the effect of two drugs separately and in combination. Two drugs used in combination resulted in an additive placebo-

Table 3. Relative risks for CVD outcomes for low-dose diuretics vs. other agents that achieved statistical significance in a network meta-analysis.⁴

Low dose diuretic vs.	Relative risk (95%CI)
β -blockers for CVD events	0.89 (0.80 to 0.98)
ACE-inhibitors for CHF	0.88 (0.80 to 0.96)
ACE-inhibitors for stroke	0.86 (0.77 to 0.97)
CCBs for CHF	0.74 (0.67 to 0.81)
β -blockers for CHF	0.51 (0.43 to 0.60)
β -blockers for CVD events	0.84 (0.75 to 0.93)

adjusted reduction in mean BP of 14.6 mm Hg for SBP and 8.6 mm Hg for DBP. Adverse effects of thiazides, β -blockers and CCBs were dose-related. Single drugs caused adverse effects in 5.2% (95%CI, 3.6 to 6.6) of participants and two drugs used in combination caused adverse effects in 7.5% (95%CI, 5.8% to 9.3%).

Conclusion: The five main categories of drugs gave similar reductions in BP. When drugs are used in combination, the BP reductions are additive, but the adverse effects are less than additive.

Diuretic-based therapy in older patients with ISH and diabetes

Low-dose thiazide diuretics are considered the drug of choice for ISH in the elderly by both JNC-VI in 1997 and JNC-VII in 2003. They are considered one of the drugs that can be used for diabetic patients as well, but the metabolic adverse effects of diuretics have been always a concern, particularly in diabetic patients.^{8,9}

A 10-year extended follow-up of the Systolic Hypertension in the Elderly Program (SHEP) patients showed that diabetes developed in 13% in the stepped-care (chlorothalidone-based) group compared to 8.7% in the placebo group ($P<0.001$).⁸ Patients who developed diabetes during follow-up had higher mortality rates than did those who did not develop diabetes in the placebo group (47% vs. 40%, hazard ratio 1.3, 95%CI 1.1 to 1.7), but not in the stepped-care group (39% vs. 40%, hazard ratio 1.2, 95% CI 0.9 to 1.4). A similar pattern was seen for CV mortality. Patients who had diabetes at baseline, or who developed diabetes during follow-up and received stepped care had lower all-cause (44% vs. 52%, hazard ratio 0.8, CI 0.7 to 0.95) and CV (20% vs. 29%, hazard ratio 0.7, CI 0.5 to 0.8) mortality rates than those who received placebo. The uncontrolled nature of the extended follow-up period

is the most important limitation of this study.

Conclusion: Patients on long-term diuretic-based therapy develop diabetes more than those on placebo. However, treating these patients with diuretic-based regimen resulted in mortality rates comparable to those who did not develop diabetes.

Evidence that disputes the JNC-VII recommendations

ACE-inhibitors and ARB for elderly patients with hypertension

The use of ACE-inhibitors and ARBs were examined in two studies addressing the treatment of elderly patients with hypertension.^{10,11} Since the predominant form in this population is ISH, the drugs of first choice should be thiazide diuretics followed by long-acting CCBs as per JNC-VI and JNC-VII. These two trials, despite limitations, suggest a possible role for these two classes in the elderly hypertensive patient.

Outcomes in patients aged 65 to 84 years old with hypertension were studied in 6083 subjects with SBP > 160 mm Hg or an average DBP of > 90 mm Hg (if the SBP was at least 140 mm Hg).¹⁰ The second Australian National Blood Pressure Study (ANBPS-2) was a prospective, randomized, open-label study with blinded assessment of end points (PROBE). Patients received health care at 1594 family practices and the median follow-up was 4.1 years. By the end of the study, BP had decreased to a similar extent in both groups (- 26/12 mm Hg). The cardiovascular events or death from any cause was 56.1 per 1000 patient-years in the ACE-inhibitor group and 59.8 per 1000 patient-years in the diuretics group (hazard ratio 0.89, 95% CI 0.79 to 1.00) ($P=0.05$). Among male subjects, the hazard ratio was 0.83 (95% CI 0.7 to 0.97; $P=0.02$); among female subjects, the hazard ratio was 1.00 (95% CI 0.83 to 1.21; $P=0.98$). Despite allocating patients to one of the treatment arms at the beginning of the study, the choice of the specific agent and the dose was made by the family practitioner.

Some of the limitations of the study include the presence of some significant differences in the baseline risks between both groups. Also, the ANBPS-2 population was 95% white as compared to the ALLHAT population with less than 50% whites. If ACE-inhibitors have more positive effects in whites than non-whites, independent of BP lowering effects, this could affect the interpretation of the

ANBPS-2 results. Moreover, both ANBPS-2 and ALLHAT were large trials where small differences can be found to be statistically significant, despite being insignificant clinically.

A predefined subgroup analysis of elderly patients aged 70 to 89 years old with ISH (SBP >160 mm Hg and DBP <90 mm Hg) were randomized to candesartan or placebo in a double-blind fashion in another trial.¹² Patients who did not achieve the BP goal first doubled their dose (candesartan or placebo), and then added open-label antihypertensive therapy (mostly thiazide diuretics) as needed to control blood pressure. Patients were followed for an average of 3.6 years. Fatal/non-fatal strokes in the candesartan group were 7.2/1000 patient-years and 12.5/1000 patient-years in the control group, yielding a relative risk of 0.58 (0.33 to 1.00, $P=0.05$), which is an impressive relative risk reduction of 42%.

Conclusion: The use of ACE-inhibitors and ARBs in elderly patients (most of whom have ISH) has proven beneficial. These two classes may be considered in treating these patients in addition to thiazide diuretics and CCBs.

Other significant evidence

Candesartan mortality and hospital admissions in chronic heart failure (CHARM trial)

The CHARM trial was a 3-component, international, multicenter, randomized, placebo-controlled trial that was blinded at all levels.¹³ The question was whether the use of the ARB candesartan reduces death and hospital admissions. The investigators enrolled 7601 patients with symptomatic CHF (NYHA II to IV) in 1 of 3 component trials. CHARM-added involved patients with left ventricular ejection fraction (LVEF) <40% who were being treated with an ACE-inhibitor. CHARM-alternative involved similar patients who were intolerant to ACE-inhibitors. CHARM-preserved involved patients with LVEF >40 %. CHARM-overall¹⁴ involved all patients. The median follow-up was 37.7 months. The trial showed that candesartan reduced mortality (particularly cardiovascular) and hospital admissions for worsening heart failure. Patients with reduced LVEF with or without baseline ACE-inhibitor treatment showed the most benefit. The NNT were 46 for CHARM-overall, 21 for CHARM-added, 11 for CHARM-alternative. There was borderline significance for CHARM-preserved.

Calcium antagonist-based vs traditional therapy for hypertension and CAD

In a randomized, multicenter, international, open-label, blinded end-point study of 22 576 hypertensive with CAD patients aged 50 years or older, patients were randomized to verapamil sustained-release (trandolapril added if needed) and atenolol (hydrochlorothiazide added if needed) to achieve BP control according to JNC-VI recommendations. After an average of 2.7 years follow-up per patient, there was no statistically significant difference in death, non-fatal MI or stroke.¹⁵

Perindopril and cardiovascular outcome in patients with stable coronary artery disease (EUROPA)

In the EUROPA trial, 12 218 patients with stable coronary artery disease (64% had prior MI) were randomly assigned to perindopril 8 mg or matching placebo. The mean follow up was 4.2 years, and the primary endpoint was cardiovascular death, MI or cardiac arrest. Eight percent of perindopril patients experienced a primary endpoint as compared to 10% for the placebo group. This 20% relative risk reduction and 2% absolute risk reduction means that 50 patients needed to be treated with perindopril for 4 years to prevent one major cardiovascular event.¹⁶

Antihypertensive drug therapy and the risk of development of diabetes

Since 1999, there have been 11 prospective, randomized, clinical trials comprising over 106 000 patients with or at high risk of CV disease treated with standard CV therapies. The vast majority of patients were >60 years old. More than 88 000 of these patients did not have diabetes at enrollment. Treatment groups containing either agents blocking the effects of angiotensin-II (ACE-inhibitors or ARBs) and/or CCBs had fewer patients who developed diabetes than treatment groups containing diuretics and/or β -blockers. The difference in 9 out of these 11 trials reached statistical significance.¹⁷

The clinical "bottom line"

In summary, the following recommendations can be drawn from the available evidence to date:

- Aim for tight control because an increase in CVD risk starts above 115/75 mm Hg and doubles with each 20/10 mm Hg increase after age 50 years.
- In the pre-hypertension stage (120-139/80-89 mm Hg) both patients and physicians should be aware that a disease process has already started that can be halted or even reversed with lifestyle modifications.

- Stage 2 hypertension ($\geq 160/100$ mm Hg): For the first time, starting therapy with two drugs from the outset is recommended. This again underscores the need for tight control, which is often difficult to achieve with a single drug.
- A patient-centered strategy should be adopted that includes education, two-way communication, and BP-self-monitoring to achieve the target level so as to maximize patient motivation.
- New cardiovascular risk factors are obesity (BMI >30 kg/m²), physical inactivity, microalbuminuria or GFR <60 mL/min.
- Compelling indications for certain drugs (Table 2) are based on the strongest and most consistent evidence in all reports. Not following these indications requires explanation or justification.
- Lifestyle modifications (including the DASH diet) should underlie hypertension and pre-hypertension management.
- The use of low-dose diuretics as first-line therapy has stood the test of time since they are better or at least equal to all other classes. Moreover, they have the lowest cost.
- Lower-dose combinations are better than a single drug. Tight control is difficult with a single drug. Lower-dose combinations give additive control, but less than additive side effects.
- ACE-inhibitors and ARBs might have a role for elderly patients with ISH and a high CV risk. More trials are needed.
- Candesartan for chronic heart failure provides the most benefit for patients with LVEF $<40\%$, with or without an ACE-inhibitor.
- A calcium antagonist-based regimen in CAD (slow-release verapamil and trandolapril) were comparable to atenolol/thiazide in CAD patients with hypertension.
- The addition of perindopril for stable CAD in patients with hypertension showed a moderate reduction in major CV events.
- There is mounting evidence that chance of developing diabetes is reduced with ACE-inhibitors, ARBs, and CCBs compared to BBs and diuretics. It seems prudent at this point to consider your patient's profile before prescribing for obese patients, patients with a sedentary lifestyle, and patients with a family history of diabetes.

The physician who applies these recommendations will be incorporating the most recent evidence into his or her clinical practice.

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