

Possible challenges posed by new 2017 ACC/AHA guidelines for management of hypertension in diverse populations

Introduction

Although hypertension is a disease of unknown etiology, it is associated with multiple risk factors such as obesity, diabetes, alcoholism and increased consumption of salt. The exact physiological limits of blood pressures to make a diagnosis of hypertension are still undefined, despite several attempts by the American Heart Association, American College of Cardiology and International College of Cardiology. It is well accepted that out of all the non-communicable disease (NCD), high blood pressure is second most common problem after obesity.^{1,2} The Five City Study in India, revealed that hypertension was commonest in South and West India compared to North and east India.² Of all the above risk factors of hypertension, obesity, physical inactivity appear to be most common, followed by increased intake of salt, alcoholism and family history in most of the studies.²

The normal physiological limits of many clinical and behavioral risk factors such as body weight, blood pressures, waist/hip ratio, moderate alcohol intake, moderate exercise training as well as prayer and meditation are not known. Therefore, the exact physiological limits of these marker need further research.

It is well known that the magnitude of reductions in total and cardiovascular mortality can be increased if other risk factors are also decreased along with decline in blood pressure among patients with hypertension.¹⁻³ The risk of mortality after low-density lipoprotein (LDL) cholesterol lowering depend on the baseline LDL-cholesterol level as well as on presence of other risk factors such as hypertension and type 2 diabetes mellitus.³ There is some evidence that it is oxidized cholesterol which is atherogenic, whereas native cholesterol may not be absolutely unhealthy. However, a recent meta-analysis involving 34 randomized clinical trials, including 270 288 subjects, revealed that more intensive lowering of LDL cholesterol by statin therapy was associated with a marked decline in total mortality with higher baseline concentrations of LDL cholesterol (rate ratio, 0.91 for each 40-mg/dL increase in baseline level). The relationship was absent when the baseline LDL-C level was less than 100 mg/dL. Cardiovascular mortality also revealed a similar relationship which means that the greatest benefit from reduction of LDL cholesterol can occur for patients with baseline LDL cholesterol concentration of 100 mg/dL or greater.³

The global burden of hypertension and systolic blood pressure [SBP] which were 110 to 115mm Hg, were reported for the years 1990 to 2015 in the GBD study.⁴ Further analysis revealed that SBP of at least 110 mm Hg could be a strong predictor of chronic kidney outcomes as well as coronary artery disease [CAD], stroke, and heart failure.⁴ Despite our understanding about the role of diet in hypertension, the burden of systolic BP of 110 mmHg is considered high, which should be treated by drug therapy.⁵⁻⁸ Since obesity is the commonest risk factor of hypertension, the global obesity epidemic

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RB Singh,¹ Sergey Chibisov,² Omar Al-bawareed tha,² Maria Abramova,² Mikhael L Blagonravov,² Anuj Maheshwari,³ Narsingh Verma,⁴ Viliam Mojto⁵

¹Halberg Hospital and Research Institute, India

²People,s Friendship University of Russia, Russia

³King George's Medical University, India

⁴Babu Banarasi Das University, India

⁵Comenius University, Slovakia

Correspondence: Sergey Shastun, MD, Division of Chronomedicine, People,s Friendship University of Russia, Moscow, Russia, Tel +79264712428, Email kalcna@mail.ru
Ram B Singh, Halberg Hospital and Research Institute, Civil Lines, Moradabad, India, Tel +91 9997794102, Email rbs@tsimtsoum.net

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or a modest increase in body mass index above 23 Kg/m² may cause central obesity and further increase systolic BP in some populations such as South Asians.² There were 8.69 million subjects, from 154 countries. It is assessed that, the rate of systolic BP of at least 110 to 115mm Hg, has increased from 73 119 to 81 373 per 100 000 subjects. Systolic BP of 140mm Hg or greater increased from 17 307 to 20 526 per 100 000 subjects. The rate of annual deaths in association with systolic BP of at least 110 to 115mm Hg is higher from 135.6 to 145.2 per 100 000 subjects, and for systolic BP of 140mm Hg or higher increased from 97.9 to 106.3 per 100 000 subjects according to new estimates.⁴ Therefore, it appears that during the last 25 years, there is worldwide marked increase in estimated deaths with systolic BP levels of at least 110 to 115mm Hg and of 140mm Hg or higher. According to European guidelines, it is possible to stratify all the patients with hypertension into four categories (Table 1).

Table 1 Categories of high blood pressure as per earlier guidelines

High-normal blood pressure (130-139 systolic or 85-89 mmHg diastolic),
Grade 1 hypertension (140-159 systolic or 90-99 diastolic mmHg),
Grade 2 hypertension (160-179 systolic or 100-109 mmHg diastolic),
Grade 3 hypertension (>180 systolic or >110 mmHg diastolic).

Hypertension has been the focus of multiple guidelines for clinical management beginning from the first Joint National Committee in 1977. In 2014, the ICC-ICN Expert Group published Sofia declaration for prevention of CVDs and type 2 diabetes mellitus as a scientific statement of the International College of Cardiology and International College of Nutrition.¹ In the same year, the National Heart, Lung,

and Blood Institute focused on a few key treatment questions, commissioned a writing group, which used only data from randomized clinical trials (RCTs) to inform their recommendations.⁹ All these agencies gave due consideration to management of high blood pressure, because hypertension is a modifiable risk factor of CVDs. Some of the treatment goals for subgroups were relaxed by the writing group as there was little evidence of benefit. These recommendations were; relaxation in treatment of patients aged 60 years or older and subjects with kidney disease or diabetes who are at increased risk of further complications.⁹⁻¹¹ These conservative guidelines were criticized and finally rejected by major professional societies as well as by other writing group who wrote original guidelines.¹¹

Possible challenges posed by the new 2017 ACC/AHA consensus guideline on high blood pressure

There is an addition of interesting new findings from recent randomized, controlled trials, with focus on high blood pressure, the American College of Cardiology and the American Heart Association (ACC/AHA) have now produced the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.¹²⁻¹⁵ There is a summary; Clinical Guidelines Synopsis published recently in JAMA.¹⁴ Compared to 2014 guideline, the scope of this guideline appears to be quite extensive, due to the inclusion of multiple aspects such as diagnostic workup and evaluation, definition and limits of high BPs, strategies for lifestyle management for prevention and for treatment. The thresholds for BP treatment and initial pharmacotherapy, and about methods; home BP or ambulatory BP measurement in the long-term monitoring are also part of the guidelines.¹⁴ New recommendations include many substantial changes on newer aspects of blood pressure variations in the management of high BP.¹⁴ The majority of the recommendations give is a consistent advice for a more aggressive approach for early diagnosis and treatment, consistent with growing evidence from epidemiological studies and drug trials. The interesting points are how health professionals will translate these guidelines into clinical management of high BP. The purpose is to more effectively treat high BP at population as well as individual levels because the new treatment limits are further lowered.

In some patients, other cardiovascular risk factors as well as end organ damage/disease that may be present, have to be duly addressed in the decisions for treatment of hypertension for which a full risk-assessment algorithm is included in the guidelines. Diet and lifestyle advice for reducing BPs are as important as drug therapy.^{3,16-18} Recommending salt intake of approximately 5-6 g per day, in contrast to a typical intake of 9-12g per day, may be useful to some patients,¹⁰ although the BP response to salt restriction should be assessed on an individualized basis, since in some patients, salt reduction can actually increase blood pressure, as shown by Franz Halberg as well as others.¹⁹⁻²³ Conventional (non-chronobiologic) studies indicate that, on average, a decrease in salt intake to 5 g per day can cause reduction in systolic BP of about 1-2mmHg in subjects with normotension and 4-5 mmHg in patients with high BP. Since the optimal body mass index (BMI) is not known, it is recommended to reduce BMIs below 25 kg/m². Reduction of waist circumferences to less than 102 cm in men and 88 cm in women in Caucasians may be fine but for Asians, it is too much, who need advice for lower levels. A weight loss of about

5 kg may reduce 4 mm Hg of systolic BP, aerobic endurance physical training can reduce systolic BP by 7 mmHg, independently of any decrease in body weight.^{10,16-18} Exercise also benefits brain function by increasing brain derived neurotrophic factor and neuronal growth factor. Exercise training particularly in the morning also has beneficial effects on HRV, VEGF and HDL, which protect against atherosclerosis and neuronal degeneration.¹⁷ The major recommendations of Guideline title 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults are given below^{12,13} which have also been critically evaluated by other experts.^{14,15} In the diagnosis of hypertension, BPs should be categorized as given in Table 2. Other recommendations include out-of-office BP measurements for confirmation of the diagnosis of high BP as well as for change in drug therapy for reducing BP in conjunction with telehealth counseling or clinical interventions.^{12,13}

Table 2 Categories of high blood pressures according to new guidelines

Normal (<120/80 mm Hg),	High (120-129/>80 mm Hg),
Stage 1 hypertension (130-139/80-89 mm Hg), or	
Stage 2 hypertension (≥140/90 mm Hg) (strong recommendation; moderate-quality evidence).	

Management of high blood pressure

Initiating therapy should be initiated with non-drug interventions that are effective in lowering BP are recommended for people with elevated BP or hypertension because it has high quality evidence hence there is strong recommendation. Hristova et al.¹ advise to take 400g/day of fruits (200g/day) and vegetables (150g/day) and nuts (20-50g/day) and another 400g/ day of whole grains, in conjunction with 30-100g vegetable oil, preferably a blend of oils containing olive oil (50%) + rape seed oil (30%) + rice bran oil (11%) + flax seed oil (9%) to achieve adequate monounsaturated fatty acids, omega-3 fatty acids and polyphenolics as well as other antioxidants.¹ Patients with clinical CVD as well as those with an estimated 10-year atherosclerotic CVD (ASCVD) risk of 10% or higher need drug therapy. A systolic BP of 130 mm Hg or higher or a diastolic BP of 80 mm Hg or greater should be treated by drug therapy with expert opinion for diastolic BP. Those patients without history of CVD and an ASCVD risk of less than 10%, drug therapy for reducing BP is advised. However, those patients having systolic BP of 140mm Hg or greater or a diastolic BP of 90mm Hg or greater, there is a strong recommendation for drug therapy although it has low-quality evidence. A target BP of less than 130/80mm Hg is advised strongly, for patients with CVD or ASCVD event risk of 10% or higher, although the quality of evidence is moderate for systolic BP. There may be a need for expert opinion on drug therapy for diastolic BP. In low-risk subjects, there is weak recommendation of moderate-quality evidence for BP target of 130/80mm Hg. Expert opinion may be desirable for drug therapy for diastolic BP. Pharmacotherapy as first line should include; thiazide diuretics, calcium channel blockers (CCBs), and angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) with strong recommendation and high-quality evidence. Patients can begin treatment with 2 first line drugs of different groups, in stage 2 hypertension and an average BP of more than 20/10mm Hg above.

The clinical problem and challenges of high blood pressure

Hypertension is a leading risk factor for mortality and disability and it is estimated that 874 million adults worldwide have an SBP of 140mm Hg or higher.^{12,13} Hypertension is second only to cigarette smoking, as a preventable cause of death with its association of CVDs; stroke (cerebrovascular accident [CVA]), heart failure, and chronic kidney disease (CKD).¹⁶ The complications are likely to increase due to given demographic trends and the increasing prevalence of hypertension with increasing age; 79% of men and 85% of women >75 years old have hypertension.^{12,13} This guideline was developed by; The ACC/AHA Task Force on Clinical Practice Guidelines which selected a writing committee that was notable for its inclusion of people with a breadth of backgrounds, wide scope of practice, and freedom from conflicts of interest. The guideline provides a comprehensive overview of the diagnosis and therapy of hypertension with 106 graded recommendations divided into 47 modular knowledge chunks with 8 recommendations of clinical covered in this JAMA Clinical Guidelines Synopsis. This guideline recommends classifying BP into 4 categories as given in Table 2. These categories of BP are made for facilitation of making decisions for clinical and public health objectives. They also indicate data on observation for suggesting an extent or severity of risk of CVD as BP increases from normal to elevated to hypertension stages 1 and 2.^{12,13}

This guideline recommends routine use of out-of-office BP measurements (home or ambulatory BP monitoring) in the diagnosis and treatment of hypertension, although it is known that 24hour ambulatory BP is an independent risk factor for future CVDs. This recommendation reflects the differences between office and home BP values with focus on masked hypertension and white-coat hypertension and acknowledges that the tighter BP goals recommended in this guideline may require closer BP monitoring. The evidence for this recommendation was reviewed in one of the commissioned systematic reviews.¹⁷ Compared with usual care, patients using home BP monitoring had a greater reduction in office S systolic BP at 6 months vs office-measured BP (4.9 [95% CI, 1.3-8.6] mm Hg). This result did not persist at 12 months. There was also no evidence of clinical benefit. Non-pharmacologic interventions are strongly supported in the guideline for their primary and complementary effect in lowering BP. These interventions include weight loss in patients who are overweight or obese; a heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet; sodium reduction; potassium supplementation; increased physical activity; and moderation of alcohol consumption.¹⁸ Most of these interventions have been shown in randomized trials to reduce systolic BP by 5 to 10mm Hg. Weight loss has been shown to decrease BP by about 1mm Hg per 1kg of weight loss.^{12,13} Taking of the DASH diet yielded an 11-mm Hg decrease in SBP.¹⁸

Drug therapy is recommended for patients with or at high risk of CVD at BP levels of 130/80 mm Hg or higher. Drug therapy is also recommended for patients without and at low risk of CVD at 140/90 mm Hg or higher. The guideline recommends using an ASCVD risk score indicating the estimated 10-year risk of myocardial infarction, CVA, or CAD death, of 10%. In other recent hypertension guidelines, such risk stratification has been used which could help translate group-level evidence from trials to individual patients.¹⁹ For individuals with or at high risk of CVD, the lower systolic threshold is well supported by data from a patient-level meta-analysis.²⁰ Drug therapy in patients

without and at low risk of CVD at BPs $\geq 140/90$ is unchanged from the JNC 7 and JNC 8 recommendations because the evidence for this recommendation is strong but mostly indirect. A meta-analysis of patients without CVD and with BP levels of 140/90 to 159/99mm Hg who were randomly assigned to an antihypertensive vs a control (placebo in 95%; less intensive regimen in 5%) BP-lowering regimen show interesting findings.²¹ The odds ratios for events over the 5 years in this study were 0.72 (95% CI, 0.55-0.94) for stroke, 0.75 (95% CI, 0.57-0.98) for cardiovascular death, and 0.78 (95% CI, 0.67-0.92) for overall mortality. The BP difference in this study between treatment and control groups was only 3.6/2.4mm Hg and 96% of the patients had diabetes mellitus and the benefits in CVDs were only non-significant.

In another systematic review commissioned for this guideline,¹⁷ included trials that compared an systolic BP target of less than 130mm Hg with any higher target, patients benefited in terms of major cardiovascular events (relative risk [RR], 0.84; 95% CI, 0.73-0.99) and stroke (RR, 0.82; 95% CI, 0.70-0.96) but not myocardial infarction (RR, 0.85; 95% CI, 0.73-1.00) or all-cause mortality (RR, 0.92; 95% CI, 0.79-1.06). Similar to the data on initiating therapy, very little information from clinical trials is available to guide recommendations about treating DBP and low risk patients. The choice of initial pharmacologic therapy for hypertension were based on another commissioned systematic review.¹⁷ This meta-analysis examined trials that compared any 2 of the antihypertensive classes: thiazides, ACEIs, ARBs, CCBs, and β -blockers. A total of 152 379 patients were included in this meta-analysis, with an average of 3.5 years of follow-up and the results showed that in terms of all-cause mortality, all classes were similar. Thiazides showed added benefits on secondary end points; CVA, cardiovascular events, and heart failure. Recommendation was for thiazide diuretics, CCBs, ACE inhibitors, or ARBs as first-line agents depending upon comorbidities; CAD, heart failure, CKD, acute stroke, and hypertensive emergency, among others. The use of 2 first-line agents of different classes for patients with stage 2 hypertension remains unchanged since JNC 7. These therapies are based on expert opinion based on studies using fixed-dose combinations that show greater BP lowering and better adherence to therapy with fixed-dose combinations.^{12,13}

The JNC 7 categorized stage 1 hypertension as a BP of 140-159/90-99mm Hg and recommended 140/90mm Hg as the threshold for initiation of antihypertensive drug therapy in the general adult population and 130/80mm Hg or higher for patients with diabetes or CKD. The JNC 8, published in 2014, recommended that for people aged 60 years or older, pharmacologic therapy should be initiated at a BP of 150/90mm Hg or higher and treated to a goal of less than that number. In the ACCORD trial, there was an increase in serious adverse events attributable to BP medications (3.3% vs 1.27%; $P < .001$).²² In the SPRINT trial, there were increases in hypotension (2.4% vs 1.4%; $P < .001$) and syncope (2.3% vs 1.7%; $P = .05$), despite no overall increase in adverse events.²³ The potential harms associated with the adoption of this guideline are the adverse effects of medications and tight BP and the costs of overuse of medication and home BP monitors, if the treatment thresholds and targets are shown to be overly aggressive. In view of the high attributable risk of heart disease and stroke due to high BP, from the public health point of view, the benefits of tighter control of BP appear to be greater. Randomized trials as well as observational and modeling studies support the idea that lower treatment thresholds and targets are beneficial in higher-risk patients, since progressively greater absolute risk reductions occur as

baseline risk increases.^{17,24} Many studies indicate that lowest levels in BP can improve outcome in most patients, including elderly above 75 years. Therefore, the balance of the cost of medication, adverse effects and potential benefits of BP control as well as polypharmacy should be evaluated for each subject. Shared decision making between patients and their clinicians is required to arrive at an optimal treatment plan for each patient. There is little high-quality evidence in the literature about some patient populations; most notably the frail elderly who also need similar targets of BPs.²⁴ There is a need to have team based approach with, electronic medical record, and population health approaches to BP control.

However, these guidelines are not final because they are based on the findings that one treatment is better than other, without an absolute risk reduction. Home BP, self-measurements as a supplement to clinic BP are unable to quantify the night time/asleep BP and pattern of 24-h BP levels, hence there could be wrong classification up to 50% of all evaluated subjects. In subjects who are likely to have a blunted dipping or nighttime BP decline, ABPM should be a priority because there may be an increased risk of CVD. These subjects are elderly, may have obesity or overweight and secondary or resistant hypertension, and those diagnosed with CKD, sleep disorders, metabolic syndrome, and type 2 diabetes. ABPM could be a new gold standard for assessment of accurate risk due to high BP and diagnose true hypertension as well as consequent tissue/organ, maternal/fetal, and CVD risk, for suitable therapy of hypertension.²⁵⁻²⁷

Joint recommendations from various international agencies such as the International Society for Chronobiology (ISC), American Association of Medical Chronobiology and Chronotherapeutics (AAMCC), Spanish Society of Applied Chronobiology, Chronotherapy, and Vascular Risk (SECAC), Spanish Society of Atherosclerosis (SEA), and Romanian Society of Internal Medicine (RSIM) also support the idea that 24 h BP assessment by ABPM is gold standard in the assessment of risk of high BPs.²⁵ However, there is a need to design drug trials with adequate number of patients with adequate power for clinical end points. Since lower BP is associated with better outcomes, future trials should refine knowledge regarding the balance between harms and benefits of BP treatment, particularly among patients with stage 1 hypertension by assessment of risk via 24 hour ABPM.²⁸

Some experts believe that it is more worrisome because many experts are critical at the new guidelines for making too many individuals in the United States “sick” or labeling them with a disease.²⁹ After the cholesterol guideline appeared, similar opinions were expressed that the “new guideline” turned billions of people into candidates for statins.³⁰ Now, drug industry would be delighted, because too many people will be defined as hypertensive because of a new lower threshold for diagnosis and treatment of hypertension. Therefore, ABPM appears to be gold standard because many subjects diagnosed to be hypertensive by following new guidelines, may be actually normotensives on assessment with ABPM.^{28,31} Indian Society of Chronomedicine and Lebanon Society of Chronomedicine as well as Russian Society of Chronobiology and Chronomedicine emphasize on taking 7-day ABPM for the diagnosis of hypertension before any drug therapy is given to these patients.³¹ Previous research has demonstrated that magnetic forces and storms in the space can influence biorhythms and blood pressures which need to be given due consideration while drugs are administered for reducing blood

pressures.³²⁻³⁵ People taking alcohol regularly also need special attention in measuring BPs and administering drug therapy because therapy varies according to alcohol intake.³⁶

In brief, multifaceted interventions in few trials, that include out-of-office BP measurements are critical to understand and it is not clear that these measurements considered in the decisions for management will prove truly beneficial. The assessment of threshold for BP treatment to individual cardiovascular risk is attractive, which should be assessed by ABPM by a 24 h BP record, preferably 7 day record, taken half hourly, because it could concentrate efforts on patients who will obtain the most benefit. It is also possible that the greater complexity of applying guidelines based on ASCVD risk could undermine the expected benefit. Support with electronic health record which calculates and trends individual ASCVD risk, may reduce the burden in clinical practice but needs further research.

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Conflict of interest

Conflict of interest has not been declared by the authors.

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