COMMENTARY

Levels of evidence and evidence of levels: Quo Vadis blood pressure?

Rajen Moodley

Specialist Physician/part-time lecturer, Department of Medicine, University of KwaZulu-Natal, Durban, South Africa

Address for correspondence:
Dr Rajen Moodley
PO Box 25434
Gateway
Durban
4321
South Africa

Email:
rjmoodley@mweb.co.za

ABSTRACT

There has historically been a series of guidelines for the diagnosis and management of elevated blood pressure. The recent publication by some members of the Joint National Committee (JNC 8), based only on randomised controlled trials, has generated much interest in view of newer levels for intervention and control. Clinicians and policymakers take their cue from these publications and hence there needs to be critical comment to promote rational prescribing. Comorbidities and "frailties" must dictate pharmaco-therapeutic choices to avoid risk in such patients. Conversely, we must guard against physician inertia also if guidelines seem to promote "relaxed" targets. This article seeks to cast some perspective on the current pronouncements.
SAHeart 2015;12:20-23

Since Lewington published his meta-analysis[1] indicating that hypertension is the most important cause of death globally, associations have endeavoured to scientifically update guidelines regarding thresholds and targets. Healthcare managers and clinicians must realise that the condition exacts a similar toll, regardless of income status.[2] The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) revised their guidelines following an interval of 6 years. Some members of the National Committee (JNC) in the United States published their eighth report in 2014. This occurred not without controversy as the initial organisers, the National Heart, Lung and Blood Institute (NHLBI) which outlined the processes, withdrew in June 2013.[3] It opted to partner with specific bodies to achieve this aim.[4] Eventually, the remainder of the committee pursued their initial goal of addressing 3 important questions amongst others – thresholds of blood pressure to intervene at, targets to achieve and to ascertain if there was robust enough evidence to dictate the preferred use of a specific agent in a particular clinical situation.

The JNC 8 Committee decided to study only randomised controlled trials (RCT) and well conducted meta-analyses thereof for their primary recommendations. These recommendations were given an "A" rating. Data with ratings below "A" were relegated. Some large scale RCTSs were excluded e.g. the ONTARGET study, as the trial did not specify hypertension as an admission criterion. Expert opinions were used only in situations in which there was no scientific data available from well controlled trials. The ESH/ESC, British Hypertension Society, National Institute of Clinical Excellence (NICE) and South African guidelines included more mega-trials in their processes.

Evidence suggesting improved compliance with single pill combinations has also influenced the drawing up of guidelines.[5] The JNC and ISH guidelines currently emphasise the superiority of single pill combinations in patients displaying systolic blood pressure levels in excess of 20mmHg over threshold values and diastolic values in excess of 10mmHg over threshold values. The South African guidelines recommend similar management. The need for 2 or more agents in stage 2 or 3 hypertension cannot be over emphasised.

Clinical guidelines have been determined by data based on sustained, elevated blood pressure levels in all studies to date. The concept of "variability" has not been a major feature. The Anglo-Scandinavian Cardiac Outcomes Trials (ASCOT) results has recently reminded us that increased variability, rather than mean achieved blood pressure, better predicted stroke and coronary heart disease outcomes.[6] This raises the new daunting aspect that intermittent hypertension may be more deleterious than sustained hypertension over a protracted period. If this concept is explored further in future trials it may well shape future guidelines.

Curiosities in clinical medicine do occur. After participants in the ACCORD[7] trial achieved a lower systolic blood pressure in the "intensive" group, (119mmHg) without any cardiovascular benefits, some organisations (notably the American Diabetic Association) suggested a return to a target of 140mmHg in such patients despite the knowledge that in another trial which achieved a similar "intensive" level (ADVANCE)[8] in patients, there was a demonstrable mortality benefit of 14%. Many doctors were confused for a period of time before guidelines were published.

The focus here will be on the JNC 8 recommendations. The first recommendation of initiating therapy in the over 60 years group at a threshold of 150mmHg systolic blood pressure and 90mmHg diastolic blood pressure was given an "A" recommendation. The guide is to achieve levels below this, with the advice being that if patients achieve levels less than 140mmHg (systolic) with no adverse events, then such a patient is to be maintained on treatment. The main evidence supporting this recommendation comes from the HYVET[9] and Syst-Eur[10] studies. Supporting evidence also comes from the JATOS[11] and VALISH[12] studies, in which there appeared to be no additional benefit of lowering the systolic blood pressure to less than 140mmHg in the over 60 years age group .

The panel, as expected, were greatly divided regarding this goal blood pressure in the over 60 years age group. The contention is that those large meta-analyses and other RCTs with smaller numbers, which guided previous recommendations, had not been considered. Field experience dictates that in high risk groups (Blacks, stroke patients, multiple risk factors) patients may be prejudiced if targets such as "less than 150mmHg" are recommended. The ESH/ESC and the NICE group recommend a level that is different: systolic of 140mmHg or less and diastolic of less than 90mmHg in high risk patients.

In the group below 60 years of age, the JNC 8 recommends that the threshold for intervention should be 140mmHg and 90mmHg (systolic and diastolic respectively) and that levels should be less than these figures. Here, diastolic blood pressure should come to the fore. Trials lending grade A evidence for such a recommendation include the ANBP[13] and HDFP[14] trials. The hitherto much quoted HOT[15] trial found no favour as the trial outcomes did not reach robust statistical significance.

Patients in the younger than 30 years age group are disadvantaged in terms of scientific guidelines, as no robust trials can guide management. For now most commentators will argue that similar recommendations, as in the case of the younger than 60 years age group, should apply. Fortunately, all major groups (JNC 8, NICE, ESH/ESC) seem to agree in principle that if one aims for a diastolic of less than 90mmHg, then the systolic blood pressure is bound to be controlled in this group.

The diabetic group of patients, because of high prevalence, was of major interest as a subgroup. The JNC 8 recommends that intervention should begin at threshold levels of 140mmHg systolic blood pressure and 90mmHg diastolic blood pressure, and targets are defined as "below 140mmHg" and below "90mmHg". The ACCORD trial group achieved a level of less than 140mmHg and both control and intervention groups had similar outcomes, apart from stroke reduction. The ADVANCE trial groups were not used as evidence as there were no pre-specified randomised blood pressure thresholds or targets. The large UKPDS[16] study did not add value to the JNC 8 paper as the study did not pre-specify that the systolic and diastolic blood pressure levels were to be critically looked at.

In patients with a reduced glomerular filtration rate of less than 60ml/min, or albuminuria of 30mg/g of creatinine, the advice is to initiate treatment at a threshold level of 140mmHg systolic and 90mmHg diastolic blood pressure. Further advice from JNC 8 is to "achieve levels of less than 140 and 90mmHg" respectively. Surprisingly, there appears to be no "grade A" evidence to support a target of less than 130mmHg systolic and 80mmHg diastolic respectively. Moreover, in the over 70 years age group with chronic kidney disease, no evidence exists at all for any goal blood pressure. Individualisation of therapy with due respect to comorbidities and frailty must guide the decision making. There is consensus though, in chronic kidney disease with proteinuria (>3g/day) and hypertension, to achieve a goal of 130/80mmHg. The MDRD study[17] supports this conclusion. The KDIGO guidelines do support these targets, but the diastolic target is set at a less stringent target of less than 90mmHg.

Debates on thresholds and targets are not the only focus of interested groups; indeed the selection of specific agents in certain clinical situations also remains a focus of interest. Criteria for specific agents need to be supported by robust data. In the non-black population; placebo comparator trials were not included in the JNC 8 analysis. As expected ace inhibitors (ACEI) and thiazide diuretics, when used as initial agents, tended to have favourable effects on heart failure outcomes. This did not preclude a decision to include angiotensin receptor blockers (ARB) or calcium channel blockers (CCB) as first line agents. The LIFE[18] study however held sway in relegating beta blockers from the choice as a first line drug.

It must be stressed that certain groups of anti-hypertensives, listed next, are not recommended as first line therapy. These include centrally acting drugs, aldosterone antagonists, imidazoline receptor antagonists, combined alpha-beta-blockers and central sympatholytic agents. There is no robust evidence to support their first line usage.

In Black subjects, the ALLHAT[19] trial, because of pre-specification of their analysis of subgroups at the outset, provides convincing data in this group. Thiazide type diuretics and calcium channel blockers are favoured as outcomes appear better.[20]

Fortunately all guidelines seem to accept that patients with chronic kidney disease, across the spectrum, should have as part of their initial therapy a renin angiotensin system blocker (ACEI or ARB). In terms of validity of data though, it must be stressed that currently the only endpoints showing statistical benefit though are renal ones and not cardiovascular. In our part of the world, we must specifically address the hypertensive Black patient with chronic kidney disease and proteinuria and discern whether CCB's or thiazide diuretics should remain the first choice. There are, according to the JNC 8 group, no RCTs addressing this point. Expert opinion (level of evidence ranked as "E") favours an ACEI or ARB as the preferred agent to preferentially lessen the progression of renal disease. In this respect, the superiority of ramipril for renal endpoints in the African-American study of Kidney diseases is supportive.[21]

Time frames for achieving the target are just as important as knowing the threshold or the target blood pressure. The JNC 8 guideline suggests a period of 4 weeks. Thereafter, the clinician should have some decision latitude in terms of further therapy. Allowance is made for either increasing the dose of the initial agent or adding in a second agent. Most national guidelines are in accordance with this concept. Expert opinion has guided this thinking. Individualisation of therapy and enforcement of lifestyle and drug therapy must be continued till targets are achieved.

Clinical trials largely exclude patients with comorbidities. In this respect, most experts agree that individualisation of therapy with senior advice in complex situations is indispensable.

Ambulatory blood pressure monitoring entered clinical practice about 2 decades ago. This recording must be done on a portable machine in the non-dominant arm. The usual duration is 24 hours. Intervals favoured are usually 15 minutes (diurnal) and 30 minutes (nocturnal), but these may vary from country to country. More important is that at least two thirds of all recordings must be available for analysis. Average systolic and diastolic levels in the time periods are the usual indices which guide therapy; most workers use the 10h00 to 20h00 period as the waking up or diurnal period and midnight to 06h00 as the nocturnal period.[22] In most humans, there is a "dip" or a step down of average levels by approximately 10% or more; loss of this "nocturnal dip" may be associated with sleep apnoea syndrome, chronic kidney disease and dysautonomia as common comorbidities. Twenty four hour values have been demonstrated to have a stronger relationship to morbidity and mortality than office blood pressure measurements.[23,24] This is applicable across all ages, both sexes and in treated and untreated patients.[25,26]

Home blood pressure readings also have a common feature in general practice. If correctly done on arm devices, it can add value as some work has been done to show that the prognostic significance may be as good as ABP levels. Generally, devices using the brachial artery cuff with 2 readings at different times of the day are measured; the initial day's reading may be discarded and an average obtained from a study of the remainder of the levels.[27] These may unravel the common problem of white coat hypertension (normal home and ambulatory readings and higher office readings) as well as masked hypertension (normal office readings with high home and ambulatory levels). As hypertension is a common disease with comorbidities, doctors must seek a higher opinion on initiation or change (step up, step down, stoppage) if treatment is planned.

Current guidelines may fall short of meeting all the tenets of the Institute of Medicine's (IOM) "Standards of trustworthiness",[28] but at the least, there has been increased transparency about conflicts and evidence of quality. We should all anticipate updates and revisions, another tenet of the IOM's Standard of trustworthiness. It must be emphasised though that most guidelines are reasonably consistent enough with respect to definitions, thresholds, targets and choice of first line therapy to assist the physician in updated decision making.

Conflict of interest: none declared.

REFERENCES

1. Lewington S, Clarke R, Qizilbash N, et al. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-1913.
2. Danaei G, Singh GM, Paciorek CJ, et al. The global cardiovascular risk transition: Association of 4 metabolic risk factors with national income, urbanisation and Western Diet in 1980 and 2008. Circulation 2013; 127(14):1493-502.
3. Gibbons GH, Harold JG, Jessup M, et al. The next step in developing clinical practice guidelines for prevention. J Am Coll Cardiol 2013;62915: 1399-1400.
4. Gibbons GH, Shurin SB, Mensah Galauer MS. Refocusing the agenda on cardiovascular guidelines: An announcement from the National Heart, Lung and Blood Institute. Circulation 2013;128(15):1713-1715.
5. Gupta AK, Arsgad S, Poulter NR. Compliance, safety and effectiveness of fixed dose combinations of antihypertensive agents: A meta-analysis. Hypertension 2010;55:399-407.
6. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.
7. Cushman WC, Evans GW, Byington RP, et al. ACCORD Study Group. Effects of intensive blood pressure control in type 2 Diabetes mellitus. N Eng J Med 2010;362(17):1575-1585.
8. ADVANCE Collaborative group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Eng J Med 2008; 358(24):2560-2572.
9. Beckett NS, Peters R, Fletcher AE, et al. HYVET Study Group of hypertension in patients 80 years of age or older. N Eng J Med 2008;358(18): 1887-1898.
10. Staessen JA, Fagard R, et al. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double blind comparison pf placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350(9080):757-764.
11. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients. (JATOS) Hypertensive Res 2008;31912)2115-2127.
12. Ogihara T, Saruta T, Rakugi H, et al. Valsartan in elderly isolated systolic group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: Valsartan in elderly isolated systolic hypertension study. Hypertension 2010;56(2):196-202.
13. Report by the management committee. The Australian therapeutic trial in mild hypertension. Lancet 1980;1(8181):1261-1267.
14. Hypertension detection and follow-up programme cooperative group. Five year findings of the hypertension detection and follow-up programme, 111: Reduction in stroke incidence among persons with high blood pressure. JAMA 1982;247(5):633-638.
15. Hansson L, Zanchetti A, Carruthers SG, et al. HOT Study Group. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351(9118):1755-1762.
16. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38 BMJ 1998;317(7160):703-713.
17. Klahr S, Levey AS, Beck GJ, et al. Modification of diet in renal disease study group. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. N Eng J Med 1994;330(13): 877-884.
18. Dahlof B, Devereux RB, Kjeldsen SE, et al. LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. Lancet 2002;359(9311):995-1003.
19. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid lowering treatment to prevent heart attack trial: Major outcomes in high risk hypertensive patients randomised to angiotensin converting enzyme inhibitor or calcium channel blocker vs. diuretic. JAMA 2002;288(23):2981-2997.
20. Seedat YK. Varying response to hypotensive agents in different racial groups: Black vs. white differences. J Hypertension 1989:7:515.
21. Effect of Ramipril vs. Amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomised clinical trial. J.A.M.A 2001; 285(21:2719).
22. Fagard R, Brguljan J, Thijs L, et al. Prediction of the actual awake and asleep blood pressure by various methods of 24 hour pressure analyses. J Hypertension 1996;14:557-583.
23. Staessen JA, Thijs L, Fagard R, et al. Prediction of cardiovascular risk using conventional against ambulatory blood pressure in older patients with systolic hypertension. Systolic hypertension in Europe trial investigators. JAMA 1999;282:535-546.
24. Clement DL, De Buyezere MS, De Bacquer DA, et al. Office vs. ambulatory blood pressure study investigators. Prognostic value of ABP recordings in patients with treated hypertension. N Eng J Med 2003;348: 2407-2415.
25. Sega R, Fachetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population; follow up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005;111:1777-1783.
26. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in the older patients in general practice. J Human hypertension 2005;19:801-807.
27. Mancia G, Fachetti R, Bombelli M, et al. Long term risk of mortality associated with selective and combined elevation in office, home and ambulatory blood pressure. Hypertension 2006; 47:846-853.
28. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. JAMA 2013;309(2):139-140.