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 RCTs 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 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) 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 and Syst-Eur studies. Supporting evidence also comes from the JATOS and VALISH 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 diastolic blood pressure, 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 150/80mmHg. The UKPDS study 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 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.

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