

REVIEW ARTICLE

Hypertension in the Old and Very Old: Current Concepts

Saumitra Ray

ABSTRACT

Old age is defined variably in medical parlour. Blood pressure (BP) increases with age as a continuous variable. Hypertension is the single most attributable risk factor for death worldwide and accounts for considerable morbidity. Control of BP reverses this process. However, when to treat the elderly and how, is sometimes a confusing area. Due to high rates of comorbidities and drug adverse effects, often the elderly are undertreated. But, it should be made clear that the benefit of treatment of BP in the elderly is very high and if treatment is provided with reasonable standard of care, the benefit far outweighs the risk.

Keywords: Elderly, Guidelines, Hypertension.

How to cite this article: Ray S. Hypertension in the Old and Very Old: Current Concepts. *Hypertens J* 2015;1(2):100-105.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

The subject under review demands defining the terms hypertension, old and very old and then the perspective of hypertension in old and very old.

After decades if not centuries of confusion and controversy, systemic hypertension in adults is now clearly defined as a sustained blood pressure (BP) of 140/90 mm Hg or above. And that is irrespective of other comorbidities.

Defining old age is not that easy. It has got many perspectives and ramifications. But for the present review, 60 years and above is considered as old age and 80 years for defining very old age.

High BP is an important public health concern because it is highly prevalent and the single most important contributing risk factor for adult mortality. Hypertension is the most important reversible risk factor for stroke, heart failure, chronic kidney disease, cognitive impairment and also contributes significantly to ischemic heart disease. Long ago, Framingham Heart Study showed a progressive increase in risk associated with increasing

BP above 115/75 mm Hg. And the excess risk is, at least partly, reversible with control of BP. However, the optimal systolic BP to reduce these adverse outcomes is unclear, and the benefit of reducing systolic BP well below 140 mm Hg has not been proven by clinical trials until very recently.

Broadly, all adults with hypertension need to be treated on some basic common premises. But unfortunately the outlook for hypertension in the elderly from definition to management are thought of as different entity by common people, general physicians and most unfortunately, by certain guidelines as well. It is true that pathophysiological background is slightly different from young hypertensives to elderly hypertensives. It is also true that certain drugs act differently in efficacy and side effects between young and old people. But that does not mean that the fundamental truths of hypertension and its management should be grossly different between the groups keeping the margin for individual variations. Also, whatever be the minor differences are there, they are like a spectrum with advancing age, and not abrupt at the age of 60 or 80 years.

Most of the major hypertensive trials included patients up to age 75 or 80 years and for that matter, the average age of patients in most trials are around 60 to 65 years. So, all the conclusions drawn from these, and the benefits of hypertension treatment shown by the various regimes, are equally applicable to older and younger patients.

This review attempts to settle down the confusions regarding management of hypertension in the elderly.

EXTENT OF THE PROBLEM

Hypertension is a common problem in old age reaching a prevalence as high as 60 to 80%. A related issue is the risk of developing hypertension over time in an elderly person who is normotensive.

This issue was addressed in two reports from the Framingham Heart Study:

One study examined the rate of new onset hypertension over a 4-year period among individuals who initially had optimal (less than 120/80 mm Hg), normal (120 to 129/80 to 84 mm Hg), or high-normal (130 to 139/85 to 89 mm Hg) BP. There was a progressive increase in the frequency of development of hypertension in patients over age 65 years

Professor

Department of Cardiology, Vivekananda Institute of Medical Sciences, Kolkata, West Bengal, India

Corresponding Author: Saumitra Ray, Professor 99/5/C Ballygunge Place, Kolkata, West Bengal, India, Phone: 00919830022317, e-mail: drsaumitra@yahoo.co.in

(16, 26 and 50 in the optimal, normal, and high-normal groups, respectively). In younger individuals the rates of progression were lower.

The second report estimated that individuals aged 55 to 65 years who do not have hypertension have a 90% lifetime risk of developing stage 1 hypertension (blood pressure 140 to 159/90 to 99 mm Hg) and a 40% lifetime risk of developing stage 2 hypertension (blood pressure $\geq 160/\geq 100$ mm Hg).

Hypertension is associated with considerable morbidity and an increased risk of cardiovascular disease (CVD), stroke, decreased quality of life, and mortality in the elderly. This is because older patients are less likely to achieve BP control once treated. Several reasons are attributed to this including resistant hypertension, adherence patterns to treatment regimens, more frequent adverse events with drug treatment, different blood pressure goals, lengthy and complex hypertension guidelines, etc.¹

Interestingly, both the prevalence and severity of hypertension are greater in elderly women than in elderly men and it is more difficult to achieve BP control in elderly women compared to men. These differences have been attributed to inadequate treatment intensity, inappropriate drug choices, lack of compliance, treatment resistance because of biological factors, or to other factors (e.g. central obesity).

PATHOPHYSIOLOGY OF HYPERTENSION IN THE ELDERLY

Arterial aging (e.g. arteriosclerosis) leads to consequences of isolated systolic hypertension (ISH), diastolic heart failure, and small vessel disease in the brain and other organs. Isolated systolic hypertension, defined as systolic BP (SBP) greater than or equal to 140 mm Hg with diastolic BP (DBP) less than 90 mm Hg, accounts for 87% of hypertension cases in older adults; and elevated SBP is more strongly associated with cardiovascular (CV) risk than DBP in the elderly.¹

Several factors have been associated with the increased BP in the elderly patients including increased vascular stiffness, decreased elastin content in the vessel wall, increased endothelial dysfunction, increased salt sensitivity, increased sympathetic activity, comorbid conditions, chronic kidney disease, obesity and white-coat effect.

CURRENT GUIDELINES AND THE CRITICAL ANALYSIS

At the beginning, it is worth to scrutinize the most recent guidelines on hypertension by the international societies. (Table 1).

Table 1: Recommendation to initiate pharmacotherapy in the elderly

	JNC 8	ASH/ISH	NICE 2011	ESC 2013	ACCF/AHA 2011
Age	>60 years	>80 years	>80 years	>80 years	>65 years
SBP mm Hg	150	150	160	160	140
DBP mm Hg	90	90	100	90	90

It is noteworthy that whereas in the European, British and even some American recommendations raise the threshold for pharmacotherapy in the very old, the JNC 8 raises this threshold for anybody above the age 60 years. (It should be noted that eighth joint national committee (JNC 8) committee actually dissolved and the recommendation was made by some committee members as a joint statement).²⁻⁵

Most guidelines published from the US tend to raise the target of SBP in people above 60 or 65 years of age to 150 mm Hg. The reason forwarded is the lack of strong evidence of benefit of further lowering the SBP to and below 140 mm Hg. The European guidelines, on one hand, set the target of SBP even higher (160 mm Hg) and on the other hand, raise the age of liberalization to 80 years. This creates real confusion for the treatment target for people between 60 and 80 years of age. The magnitude of the problem is enormous if it is remembered that in that age group prevalence of hypertension is almost 70% and isolated systolic hypertension represents almost 90% of hypertension.

But reality tells a different story. In most major international hypertension trials, elderly people are adequately represented. For example, in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT), there were 6471 patients of age group 55 to 64 years and 8784 patients of age 65 and above. The mean age was 66.9 years. In the Anglo-Scandinavian Cardiac Outcomes Trial– Blood Pressure Lowering Arm (ASCOT-BPLA) trial, the inclusion age was 40 to 79 years and the mean age was 63 years. Other major trials like Valsartan antihypertensive long-term use evaluation trial (VALUE), International verapamil SR-Trandolapril study (INVEST), avoiding cardiovascular events in combination therapy in patients living with systolic hypertension trial (ACCOMPLISH), all achieved SBP below 140 mm Hg in age group above 65 years and showed benefit of treatment. Thus, whatever conclusion these trials produce, they are equally applicable to people above 60 years and below 60 years, and even up to 79 years.

The very issue of safety and efficacy of SBP reduction in the very old people 80 years and above has been

specifically addressed in the HYVET trial.⁶ Here, 3845 patients of age 80 to 105 years were recruited from Europe, China, Australasia and Tunisia. Systolic blood pressure 160 mm Hg or above was the entry criterion and target was 150 mm Hg. Active arm used sustained release indapamide with or without perindopril against the control arm on placebo. The median follow-up was 1.8 years. The active arm achieved 15 mm Hg/6.1 mm Hg lower sitting BP compared to placebo arm. This accrued a 30% reduction of all strokes, 39% reduction of fatal strokes, 21% reduction of all cause mortality, 23% reduction of CV mortality and 64% reduction of heart failure. All the values were statistically significant. Even, the serious adverse events were reduced significantly in the treatment arm. Though the target SBP was 150 mm Hg, the mean achieved SBP in the active arm was 144 mm Hg.

Table 2 elaborates the mean achieved SBP in the major hypertension trials in the elderly and the mean age of patients. It clearly shows that many large trials attained mean SBP below 140 mm Hg in a mean age of population above 60 years and delivered considerable health benefit.

The concern of J curve is often highlighted as the reason for under treatment in the elderly. J curve concept entails that if BP falls too much, then coronary perfusion may decrease producing adverse cardiac events. This should be more of a concern with DBP as coronary filling usually occurs during the ventricular diastole. As shown in the ACC/AHA 2011 expert consensus document on the hypertension in the elderly, optimum DBP is between 60 and 90 mm Hg and optimum SBP is 120 to 140 mm Hg; and this is true for elderly hypertensives as well as the younger ones.²

It might be predicted that a J curve would have a more devastating effect on elderly individuals, with a nadir at higher pressures, because of the greater likelihood of their having coronary artery disease (CAD) and a lower coronary reserve. Very few studies have addressed this question, but those that have addressed it have produced reasonably reassuring results. An INVEST substudy¹⁵⁸

showed a J-shaped relationship between DBP and the primary outcome (all-cause death, nonfatal MI, or nonfatal stroke) but with a nadir of 75 mm Hg. As isolated systolic hypertension is a common entity in the elderly, it is sometimes noticed that overzealous treatment to reduce SBP to target brings down the diastolic pressure below 60 or even 50 mm Hg. Careful clinical judgment is required to fine tune the drug dosing in such situations.

The associated comorbidities in the elderly including postural hypotension, dementia, obstructive airway disease, etc. are often cited as the reasons for setting the target higher for SBP. Though the incidences of these comorbidities are higher in the elderly age group, they are no way age specific and antihypertensive treatment has to be individualized depending on the tolerance, socioeconomic status, attitude toward health and disease and so many other factors of a particular patient. It is not rational to raise the threshold for treatment for everybody above a certain age. And it is well known that biological age of a person matters more than his chronological age.

Of the four recent trials which specifically looked into the issue of benefit of treatment in the elderly hypertensive and specifically targeting the SBP, Hypertension in the very elderly trial (HYVET) and Felodipine event reduction study (FEVER) showed significant benefit in the treatment arm, whereas Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS) and valsartan in elderly isolated systolic hypertension (VALISH) did not find any benefit with treatment. The last two trials were grossly underpowered with very low event rate as exemplified by the low death rate in comparison to the total number of patients (17 of 4418 in 2 years in JATOS, 54 of 3260 in 2.8 years in VALISH; in contrast to 431 of 3845 in 2.1 years in HYVET and 263 of 9711 in 3.3 years in FEVER).

To sum up, broadly the current recommendations for the older population are as follows:

- In older patients with hypertension drug treatment is recommended when systolic BP is ≥ 160 mm Hg; there is solid evidence to recommend reducing SBP to between 150 and 140 mm Hg .
- In fit older patients aged <80 years, drug treatment may also be considered when systolic BP is in the 140 to 159 mm Hg range with a target systolic BP < 140 mm Hg provided that antihypertensive treatment is well tolerated.
- In individuals aged >80 years, with an initial SBP ≥ 160 mm Hg, it is recommend to reduce systolic BP to between 150 and 140 mm Hg provided they are in good physical and mental conditions.
- In frail older patients, it is recommended to leave decisions on antihypertensive therapy to the treating

Table 2: Major trials of elderly hypertension and the mean SBP attained

<i>Trial</i>	<i>Mean age (years)</i>	<i>Mean achieved SBP (mm Hg)</i>
ACCOMPLISH	68.4	131
Convince	65.6	136
INVEST	66.0	136
<i>Allhat</i>	66.9	138
Life	66.2	143
SHEP	71.6	146
Sys eur	70.2	151
MRC elderly	68.2	153
STOP 2	69.5	152
VALUE	67.2	137



physician, based on monitoring of the clinical effects of treatment and adapted to individual tolerability.

- Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian.

PHARMACOLOGICAL AGENTS SUITABLE FOR THE ELDERLY HYPERTENSIVE

Lifestyle modifications including aerobic exercise, dietary salt restriction, limiting alcohol consumption, and body weight optimization have been shown to reduce BP in elderly patients with hypertension and should be recommended to all elderly hypertensive patients.

Guidelines slightly vary regarding the recommended first line pharmacotherapy for the elderly. In the ASH/ISH Guidelines, for non-black people over the age of 60 years, the initial drug recommended is a calcium channel blocker (CCB) or a thiazide diuretic. For stage 2 hypertension the second drug added is an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). However, no such special recommendation is made by the ESC 2013 or JNC 8 Guidelines.

As for the types of antihypertensives, efficacy of diuretics has been established [European working party on high blood pressure in the elderly (EWPHE), Swedish trial in old patients with hypertension (STOP-Hypertension), MRC II, SHEP]. Efficacy of CCB, particularly of long acting dihydropyridine, has been demonstrated [Syst-Eur, SystChina, Shanghai trial of nifedipine in the elderly (STONE), National intervention cooperative study in elderly hypertensives study group (NICS-EH)].¹¹ In the very elderly subjects (aged 80 and over), benefits of antihypertensive has been established by HYVET study using sustained release indapamide with or without perindopril.⁶

The systolic hypertension in the elderly program (SHEP) trial randomized patients of 60 years or above with ISH to chlorthalidone or placebo. Target SBP for the active treatment group was below 160 mm Hg and/or decrease from baseline of ≥ 20 mm Hg. Atenolol could be added, if required, in the active treatment group. Mean follow-up was 4.5 years. At 5 years, BP was 143/68 vs 155/72 mm Hg in the active treatment and placebo groups, respectively with a 36% reduction in the primary endpoint of fatal or nonfatal stroke ($p = 0.0003$) in the active treatment arm. In a subanalysis by age category (60–69 years, 70–79 years, 80 years or older), the stroke rates were lower in the active treatment group in all groups. A post hoc analysis showed SBP < 150 mm Hg experienced a 38% reduction in stroke incidence compared

to those with SBP ≥ 150 mm Hg, while those with SBP < 140 mm Hg had a 22% risk reduction prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension.¹²

In the STOP-Hypertension-2 trial, 6,614 patients were randomized to one of three arms: conventional treatment (beta-blockers and/or diuretics), CCB, or ACE inhibitor. At 2 months, if BP was not in target ($< 160/95$ mm Hg), medications from other treatment arms could be added. Baseline BP was 194/98 mm Hg in all three groups. After a mean follow-up of 60.3 months, BP reduction was similar among the groups. There was no significant difference in risk of the primary composite endpoint of fatal stroke, fatal myocardial infarction (MI), and other fatal CVD among the three groups.¹³

As beta adrenergic receptors in the vascular system decrease with increasing age, the effectiveness of the beta blockers as anti-hypertensive agents decrease proportionately. Vasodilating beta blocker nebivolol showed beneficial effects in elderly people with heart failure in the SENIOR trial. As atenolol is the main target for criticism against the beta blockers and there is little chance of an off patent drug to have further trials, its difficult to embark strongly in favor of the molecule. However, it should be kept in mind that a short acting drug like atenolol should have been used twice daily instead of once daily dose as given in most clinical trials. Of the newer beta blockers, carvedilol is also a twice daily drug and as it is rather nonselective, it may not be suitable for reactive airway disease patients. Heart rate reduction is also inadequate at lower doses. Long acting metoprolol and bisoprolol are selective and safer drugs for airway disease and they also cause significant negative chronotropic effect and are good antiarrhythmic as well. So, if beta blocker is chosen, careful consideration is to be given to tailor made the particular agent for the patient. Direct vasodilators like calcium channel blockers or alpha adrenergic blockers (though not recommended as first line agents) and diuretics are very effective. However, postural hypotension needs to be carefully assessed while treating elderly people with these agents. Angiotensin converting enzyme inhibitor and ARB are effective but bilateral atherosclerotic renal artery stenosis needs to be kept in mind. Special issues like glaucoma and prostatic hypertrophy may dictate the choice of antihypertensive in the elderly population.

Recently, three meta-analyses reviewed this subject extensively.⁸⁻¹⁰

The meta-analysis by Law et al included 147 randomized trials involving 464,000 patients have shown that all classes of BP-lowering drugs have similar effects in reducing events and stroke for a given reduction in BP.

With the exception of the extraprotective effect of beta blockers given shortly after a MI and the minor additional effect of calcium channel blockers in preventing stroke, all the classes of BP lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in BP according to this study. The proportional reduction in CVD events was the same or similar regardless of pretreatment BP and the presence or absence of existing CVD.

Another recent meta-analysis included 18 clinical studies and examined 55,569 hypertensive patients and 59,285 controls. The study compared all commonly used antihypertensive therapies with each other (baseline BP 157/86 mm Hg; BP reduction to less than 140/80 mm Hg) and found that a similar BP reduction resulted in equivalent risk reduction for the substances compared. The study concluded that reducing BP to a level of 150/80 mm Hg is associated with large benefit in stroke, CV and all-cause mortality as well as heart failure risk in elderly individuals. Different antihypertensive regimens with equal BP reduction have similar effects on CV outcomes. Systolic BP rather than DBP reduction is significantly related to lower CV risk in this population.⁹

A third prospective meta-analysis comparing younger and older hypertensives (>65 years) treated with different antihypertensive drugs substantiated previous results and found similar drug-class efficacy in younger and older patients. This included 31 trials, with 190 606 participants. The meta-analyses showed no clear difference between age groups in the effects of lowering BP or any difference between the effects of the drug classes on major CV events (all $p > 0.24$). Neither was there any significant interaction between age and treatment when age was fitted as a continuous variable (all $p > 0.09$). The meta-regressions also showed no difference in effects between the two age groups for the outcome of major CV events ($<65 > 65$; $p = 0.38$).¹⁰

RECENT DEVELOPMENT

Meanwhile, a landmark study finds Intensive BP management may incur further benefit as compared to present day target of BP.

In the Systolic Blood Pressure Intervention Trial (SPRINT) released on 11th September 2015 by the National Institutes of Health, researchers recruited over 9,300 patients aged 50 years or more (with no upper limit) with SBP ≥ 130 mm Hg and belonging to high risk category due to CVD, chronic kidney disease, 10-year Framingham CVD risk score $\geq 15\%$, or age ≥ 75 years; in about 100 sites across the US and Puerto Rico from 2010 to 2013. The subjects were randomized into two groups with two different target levels of SBP. The standard group received drugs to achieve a target SBP of less than

140 mm Hg and on an average they required two drugs. The intensive treatment arm received, on an average three drugs, to achieve a target SBP of less than 120 mm Hg. Primary outcomes were MI, acute coronary syndrome, heart failure, stroke or CV death.

The results were heavily in favor of intensive BP control which produced 30% more reduction of MI, heart failure or stroke and almost 25% reduction of CV death compared to 140 mm Hg SBP target. The clinical guidelines recommend a SBP of less than 140 mm Hg for healthy adults and 130 mm Hg for adults with kidney disease or diabetes.

The results were so emphatic that the trial was terminated prematurely and made public 'to quickly communicating the results to help inform patient care and the future development of evidence-based clinical guidelines', as said by Gary H Gibbons, MD, director of the National Heart, Lung, and Blood Institute, the primary sponsor of SPRINT.

How these results may be relevant to the elderly. This trial targeted three prespecified subgroups: chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73 m), history of CVD, and 75 years of age or older. At the end, of the 9361 participants, 2636 were ≥ 75 years of age. Though the subgroup analysis is not complete, it may be assumed with reasonable certainty, that when more than 25% of patients are more than 75 years old, the results would have the same trend in this subgroup as well. And of course, majority of people would have been in 60 to 75 years age group as 50 years was the cut off age.¹⁴

CONCLUSION

The treatment of hypertension in the elderly is equally, if not more, rewarding to reduce morbidity and mortality compared to younger people. Because of increased prevalence of comorbidities and increased incidence of adverse events there is a general trepidation among the physicians to treat elderly hypertensives. The guidelines, though well meaning, encourage this mind set by advocating rather confusing thresholds, targets and drugs for treatment. It should be clarified that 140/90 mmHg threshold and target for BP management can safely be adopted for all adults irrespective of the age. The choice of drugs is also largely the same as for younger people. The usual precautions of monitoring drug safety and efficacy needs to be applied, may be more stringently to the elderly population to keep the risk benefit ratio of treatment to a minimum. Even lower targets of BP may be recommended in future as can be foreseen by recent trial results.



REFERENCES

1. Denker MG, Cohen DL. What is an appropriate blood pressure goal for the elderly: review of recent studies and practical recommendations. *Clin Interv Aging* 2013;8(8):1505-1517.
2. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF Task Force ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2011;123(21):2434-2506.
3. Mancia G, Fagard R, Narkiewicz K, et al. ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) *Eur Heart J* 2013;34(28): 2159-2219.
4. Weber MA, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014 Jan;32(1):3-15.
5. James PA, et al. 2014 Evidence based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8). *JAMA* 2013 Dec 18.
6. Beckett NS, Peters R, Fletcher AE, et al. HYVET Study Group Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358(18):1887-1898.
7. Treatment of hypertension in patients with coronary artery disease a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *Hypertension* 2015;65.
8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009 May 19;338:b1665.
9. Briasoulis A, Agarwal V, Tousoulis D, Stefanadis C. Effects of antihypertensive treatment in patients over 65 years of age: a meta-analysis of randomised controlled studies. *Heart* 2014;100(4):317-323.
10. Turnbull F, Neal B, Ninomiya T, et al. Blood pressure lowering treatment trialists' collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008;336(7653):1121-1123.
11. Peters R, Beckett N, McCormack T, Fagard R, Fletcher A, Bulpitt C. Treating hypertension in the very elderly-benefits, risks, and future directions, a focus on the hypertension in the very elderly trial. *Eur Heart J* 2014 Jul;35(26):1712-1718.
12. Final results of the systolic hypertension in the elderly program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265(24):3255-3264.
13. Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354(9192):1751-1756.
14. NHLBI Press Release: Landmark NIH study shows intensive blood pressure management may save lives. Embargoed for Release: September 11, 2015,10:30AM EDT.