Hypertension in Elderly – Pathogenesis and Treatment
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Abstract
Hypertension is the leading cause of cardiovascular events in the elderly and its prevalence increases with age. Elderly patients have altered biological functions which coupled with multiple comorbidities presents a unique therapeutic challenge. Due to contrasting major society guidelines and data from large trials the optimum target blood pressure is less well defined in elderly. This confusion and the resulting dilemma between whom to label as hypertensive or normotensive may lead to delays in treatment. Hypertension in elderly has certain unique clinical situations like isolated systolic hypertension, “dippers”, orthostatic hypotension and pseudohypertension. The presence of multiple comorbidities like CAD, CVA, gout, cognitive decline and diabetes, their complications and management only further complicate the therapeutic challenge. The management of hypertension in the elderly has to be individualized based on various factors.

Key words: Hypertension, elderly hypertensive, blood pressure

Introduction
“Old age is like a plane flying through a storm. Once you’re aboard, there’s nothing you can do."

-Golda Meir

Hypertension (HTN) is a leading risk factor in the aged for cardio/cerebrovascular events, the prevalence of which increases with age. Pathophysiologically, it differs from HTN of the young (altered structure and function of conduit arteries vis-a-vis resistance vessels of the young). Older hypertensives have altered or downregulated biological functions, have multiple comorbidities warranting polypharmacy with attendant drug interactions. Elevated blood pressure (BP) is the most common cause of mortality over the globe, being responsible for about 13% of all deaths every year, accounting for about 57 million disability-adjusted life years.[1] The prevalence of elevated BP worldwide in 2008 was about 40%, being highest in the WHO African region (46%) and lowest in the Americas (35% in both sexes). The prevalence of uncontrolled HTN has increased by approximately 600 million compared to that in 1980.[2] The burden of HTN is rising globally due to the growth of the obese and aged population and is projected to affect around 70% of the global population by 2025.[3] HTN continues to be one of the most common easily identified and important risk factors for coronary artery disease (CAD), atrial fibrillation, cerebrovascular disease/accidents, heart failure, peripheral arterial disease, aortic diseases (dissection/aneurysm), and cognitive decline.[4,5] The burden of HTN is maximum in the developing world, where poor BP control has contributed to the growing epidemic of cardiovascular disease (CVD). Elevated BP continues to be responsible for 67% of cerebrovascular accidents (CVA) and 50% of CAD globally.

Definition
HTN is defined as an office BP of 140/90 mmHg or higher. However, epidemiologic data have shown a positive linear relationship between the risk of death due to CAD and CVA with systolic or diastolic BP (DBP) down to values as low as 115 or 75 mmHg, respectively.[6] The dilemma and confusion between defining HTN and normotension in elderly population may delay medication management until there is an irreversible compromise of vascular health by elevated BP values that were previously considered normal.
As a consequence of this data put together with the outcomes of landmark trials like Systolic Blood Pressure Intervention Trial (SPRINT), the ACC/AHA 2017 guidelines have recommended a cutoff 130/80 mmHg or higher to diagnose HTN. The SPRINT showed a significant benefit of lowering the BP even in patients >75 years of age, concluding that chronological age alone should not be a reason to deny treatment. Healthy people living independently should receive appropriate therapy for HTN. While most of the guidelines have defined elderly population as >60 years, the ESC 2018 guidelines define the elderly as those >65 years.

The ACC/AHA guidelines (2017) define HTN as systolic blood pressure (SBP) ≥130 mmHg and DBP ≥80 mmHg,[7] whereas the ESC 2018 guidelines define HTN as office SBP ≥140 mmHg and/or DBP ≥90 mmHg.[8] The ACC/AHA recommends out-of-office BP measurements to make a diagnosis of HTN and to initiate and titrate BP-lowering therapies (Class I). Table 1 shows the relationship for corresponding values between out-of-office BP and clinic measurements.

### Table 1: Corresponding values of SBP/DBP for clinic, ABPM: Home BP monitoring, Daytime, nighttime, and 24 h ABPM (ambulatory BP monitoring) measurements

| Clinic | HBPM | Daytime ABPM | Nighttime ABPM | 24 h ABPM |
|--------|------|--------------|----------------|-----------|
| 120/80 | 120/80 | 120/80       | 100/65         | 115/75    |
| 130/80 | 130/80 | 130/80       | 110/65         | 125/75    |
| 140/90 | 135/85 | 135/85       | 120/70         | 130/80    |
| 160/100| 145/90 | 145/90       | 140/85         | 145/90    |

ABPM indicates ambulatory blood pressure monitoring; BP: Blood pressure, DBP: Diastolic blood pressure, HBPM: Home blood pressure monitoring, SBP: Systolic blood pressure

### HTN in the Elderly

HTN tends to be more prevalent with rising age. There is a prevalence of HTN of ~60% in individuals >60 years and ~75% in those >75 years. Elderly populace can be further classified as old elderly (60–79 years) and very old (≥80 years) of age. The elderly HTN differs in pathophysiology when compared to midlife HTN. Between age 50 and 69, DBP is high in 50%. At age 70, only 10% have high DBP.

After 55 years of age, isolated systolic HTN (ISH) defined as an SBP >140 mmHg and DBP <90 mmHg predominates. In developed countries, an increase in SBP is linear with age; while in contrast, DBP rises until about 55 years of age, then falls progressively. Figure 1 illustrates the variation of systolic and diastolic pressures with age and gender.[9] As a consequence of the increased stiffness of the arterial wall in the central aorta and a brisker return of the reflected peripheral pulse wave, the pulse pressure widens leading to a rise in SBP [Figure 2]. ISH may represent an exaggeration of this age-dependent stiffening process, although SBP and pulse pressure do not rise with age in the absence of urbanization. ISH is found to occur with a greater preponderance in females and those with prehypertension and is usually found in conjunction with a greater incidence of heart failure with preserved ejection fraction. The major differences between midlife and systolic HTN are mentioned in Table 2.

In the past two decades, a multitude of controlled trials and observational studies has demonstrated the importance and utility of the pulse pressure as a major risk factor for CVD, which was demonstrated by a study of the Multiple Risk Factor Intervention Trial data. The study found that patients who had an SBP >160 mmHg and a DBP <80 mmHg constituted the highest risk group.[10] In the Framingham Heart Study, a combination of mean arterial pressure (MAP) (a measure of resistance) and pulse pressure (a hitherto mentioned measure

![Figure 1: Behavior of systolic and diastolic blood pressure with age and gender](image-url)
of vascular stiffness) used together yielded a better chance of predicting CVD collectively or CAD, CVA, and heart failure independently, rather than any individual BP component on its own.\[11\] Combining the pulse pressure with the MAP, the two major physiologic components of hydraulic load could be related to the clinical outcomes.\[2\] In individuals with ISH and a normal or low DBP (<70 mmHg), there is a body of evidence-backed data to support the existence of a diastolic J-curve of increased cardiovascular risk, this was seen in about one-third of treatment-naïve persons of at least 60 years of age in the National Health and Nutrition Examination Survey.\[12\] Widened pulse pressure and a low DBP were found with a greater prevalence in females, diabetics and those with advanced age.

There is a very real concern of an exaggerated nocturnal “dipping” of BP in elderly patients on antihypertensive therapy, a concern that only gains more mileage from the fact that most BP measurements at clinics are done during the daytime/waking hours. These nocturnal dippers have cerebral hypoperfusion during the dips and have been found to be at a greater risk for CV adverse events.

**Pathophysiology**

With advanced age, there is a fragmentation and degradation of elastin (forms as a nidus for calcification), increase in collagen content, and cross-linking of collagen and elastin by advanced glycation end products which leads to a stiffening of the aorta [Figure 3]. Pulse wave velocity (PWV) indicates vascular age and aortic stiffness (arteriosclerosis). Carotid to femoral PWV >10 m/s correlates with increased pulse pressure and poor outcomes. Brain and kidney are high flow, low resistance organs which are more likely to be affected by SBP. Aortic stiffness is not affected by BP lowering drugs which leads to the therapeutic challenges in the management of HTN in the elderly. There is a variable response to change in posture in the elderly as a consequence of autonomic dysregulation which leads to orthostatic hypotension (risk of falls/CVA) as well as orthostatic HTN, leading to the left ventricular hypertrophy (LVH), and an increased risk of CVA and CAD.\[13\]

**Comorbidities in the Elderly**

Gout is 3 times more common in the elderly hypertensives and thiazide diuretics worsen it. Arthritis, common in the elderly, causes a chronic inflammatory burden. Nonsteroidal anti-inflammatory drug use leads to arterial stiffness and a consequent rise in BP. Pseudohypertension is due to non-compressible vessels due to arteriosclerosis.

**Treatment**

Choice of antihypertensive drugs for elderly patients should take into account that the beneficial clinical trials were based on either a diuretic\[14,15\] or calcium channel blocker (CCB)\[6\] as initial therapy. Angiotensin receptor blockers (ARBs) are more effective in stroke prevention compared to beta-blockers (losartan intervention for endpoint trial).\[16\] Furthermore, the increased potential for bradycardia and exacerbation of obstructive pulmonary disease has to be kept in mind with using a beta-blocker, and hence, beta-blockers are best reserved for used in patients with compelling cardiac indications (e.g., CAD and LV dysfunction). In elderly hypertensive patients, intensive
BP control (SBP <140 mmHg) leads to a decreased rate of major CV adverse events including mortality as evidenced by data from a 2017 meta-analysis of four major trials. There were limited data on adverse events, but an increased risk of renal failure was suggested with intensive therapy. The authors concluded that when an intensive BP lowering regimen is considered a careful balance of CV benefit versus potential risks including that of falls and renal failure is essential.\cite{17}

It is prudent to initiate drug therapy using a single drug in lowest possible dose with uptitration. Issues of polypharmacy, non-adherence, and drug interactions are of concern in average elderly hypertensive patients, most of whom use around six drugs. HTN in the elderly is salt sensitive and is more prone to diuretic-related side effects. The various physiological changes that take place with aging affect the pharmacokinetics of BP lowering drugs [Table 3]. Unrelated to the class of drug used, it is important to monitor the patient carefully for adverse reactions [Table 4] that may affect the quality of life [Figure 4]. The risk of hyponatremia in the elderly is significant and is found to be much more common in women than men matched for age among the elderly [Figure 5].\cite{18}

BP lowering drug therapies reduce rather than eliminate the risks, not to mention the potential adverse drug effects/interactions and high costs of many antihypertensive medications. A multitude of experimental and observational studies has shown that there exists a string relationship between BP and nutrition. Due to these, there has been a recent renewal of interest in non-pharmacological approaches to prevent and treat HTN. The importance of weight loss and dietary sodium restriction in the treatment of HTN in middle-aged patients has been proven in clinical trials. Such non-pharmacological interventions are also central to the management of HTN in older individuals. In the Trial of Nonpharmacologic Interventions in the Elderly, sodium restriction alone as well as in combination with weight reduction was better than in those assigned to usual care in terms of rates of withdrawal of antihypertensive therapy (93% vs. 87%, respectively) and led the authors to conclude that sodium restriction and weight reduction constituted a safe, effective, and feasible non-pharmacological BP lowering therapy in elderly population with HTN.\cite{19}

There is irrefutable proof from many placebo-controlled trials that any antihypertensive regimen reduces CV events in elderly patients with HTN, and this benefit is seen even in frail older individuals where BP lowering is associated with a reduction in mortality risk. In most trials, the mean age of the population was 70–76 years with the exception of the HTN in the Very Elderly Trial (HYVET). In the HYVET trial, all patients were ≥80 years.\cite{20} The SPRINT found that in those >75 years of age, an intensive treatment goal of an SBP <120 mmHg was more

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**Table 3:** Physiologic changes with aging potentially affecting the pharmacokinetics of antihypertensive drugs

| Process | Physiological change | Result | Drugs affected |
|---------|----------------------|--------|---------------|
| Absorption | ↓ Gastric acid production, ↓ Gastric emptying time, ↓ GI motility, GI blood flow, and absorptive surface | ↓ Tablet dissolution and ↓ solubility of basic drugs, ↓ Absorption for acidic drugs, ↓ Opportunity for drug absorption | BB/central α agonists, ACEIs, Propranolol |
| Distribution | ↓ Total body mass, ↑ proportion of body fat, ↓ Proportion of body water, ↓ Plasma albumin, disease-related increased α1 acid glycoprotein, and altered relative tissue perfusion | ↑ Vd of highly lipid-soluble drugs, ↓ Vd of hydrophilic drugs, Changed percent if free drug Vd and measured levels of bound drugs | Propranolol, Diltiazem, Labetalol, Verapamil |
| Metabolism | ↓ Liver mass, liver blood flow, and hepatic metabolic capacity | Accumulation of metabolized drugs | Propranolol, Diltiazem, Labetalol, Verapamil |
| Excretion | ↓ Glomerular filtration, renal tubular function, and renal blood flow | Accumulation of cleared drugs | ACEI, Atenolol, Sotalol, Nadolol |

ACEI: Angiotensin-converting enzyme inhibitor, GI: Gastrointestinal, Vd: Volume of distribution
effective when compared to those between 50 and 75 years of age.[21] However, many older patients are more likely to be less healthy that those enrolled in HYVET or SPRINT.

The presence of comorbid conditions such as CAD with or without heart failure, past CVA, cognitive dysfunction, and other chronic conditions affects optimal decisions for best outcomes. Treatment of ISH had myriad benefits which included fewer coronary events, strokes, HF events, and deaths. However, the intensity of BP lowering must be weighed against the increased risk of hypotension, which can precipitate falls and ischemic events.[22] Orthostatic hypotension may be asymptomatic until increased medication is given to achieve lower goals. Risk of falls and serious fractures may occur with intensive treatment of more frail elderly.

The 2017 ACC/AHA guidelines have placed renewed emphasis on home and ambulatory BP recordings for clinical decision-making which is in line with the data from IDACO International Database which laid emphasis on home and ambulatory BP recording as routine for elderly individuals, especially to detect masked and white coat HTN as well as to identify extreme dippers.[24]

The guideline recommendation of the ACC/AHA is to an SBP goal of <130 mmHg for non-institutionalized ambulatory adults ≥65 years of age with an average SBP of ≥130 mmHg (Class I).[7]

On the contrary, the 2018 ESC guidelines recommend BP lowering with drugs and lifestyle intervention in fit older patients (>65 years but not >80 years) when SBP is in the range of 140–159 mmHg, provided that treatment is well tolerated (Class I). The BP targets for individuals <65 years are recommended to be 120–129 mmHg and in older patients (≥65 years), it is recommended to target a BP range of 130–139 mmHg.[8]

**Pseudohypertension**

A condition results as a consequence of the failure of densely sclerotic arteries to collapse during BP cuff inflation, leading to false high values, which can be confirmed by intra-arterial BP measurement. It has been reported to have an incidence of 1.75–70% of the elderly. The Osler maneuver has been recommended to identify this condition but with doubtful efficacy.

**Orthostatic Hypotension**

A reduction in SBP of at least 20 mm Hg or DBP of at least 10 mmHg within 3 min of quiet standing, or, a similar decline

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**Table 4: Adverse effects of antihypertensive therapy in the elderly**

| Drug class                        | Adverse effect                                                      |
|-----------------------------------|---------------------------------------------------------------------|
| Thiazide and loop diuretics       | Hypokalemia, hyponatremia, hypomagnesemia, volume depletion hypotension, renal impairment, hyperuricemia, gout, hyperglycemia |
| Potassium sparing diuretics       | Hyperkalemia, hypotension                                           |
| Beta-blockers                     | Sinus bradycardia, fatigue, AV nodal heart block, bronchospasm, intermittent claudication, confusion, aggravation of acute heart failure, hyperglycemia |
| Alpha-beta adrenergic blockers    | Hypotension, hseart block, sinus bradycardia, bronchospasm          |
| Alpha-1 adrenergic antagonists    | Orthostatic hypotension                                             |
| ACEIs                             | Cough, hyperkalemia (with eGFR <50 ml/min), angioneurotic edema, rash, altered taste sensation, renal impairment |
| Central-acting drugs              | Sedation, constipation, dry mouth                                   |
| CCB                              |                                                                     |
| Non-di hydropyridines             | Rash, exacerbation of GERD, sinus bradycardia, heart block, heart failure, constipation (verapamil), gingival hyperplasia |
| Di hydropyridines                 | Peripheral edema, heart failure, tachycardia, aggravation of angina (short-acting agents) |
| Direct vasodilators               | Tachycardia, fluid retention, angina pectoris                      |

AV: Atrioventricular, ACEI: Angiotensin-converting enzyme inhibitor, GERD: Gastroesophageal reflux disease
during head-up tilt testing at 60° is defined as orthostatic hypotension. The clinical presentation may be in an asymptomatic individual, where it is detected during a routine physical examination or it may be diagnosed in a patient who presents for the evaluation of giddiness, light-headedness, frequent falls, or syncope. The orthostatic drop in BP may be chronic as in diabetics or in those with pure autonomic failure. The clinical dilemma and therapeutic challenge are to control the BP in such patients with orthostatic hypotension and concomitant supine HTN. The supine hypertensive person is at risk of serious consequences, such as LVH and CVAs. In addition to orthostatic hypotension, the incidence of postprandial hypotension is also very common among elderly population.

Table 5: Effects of intensive BP lowering in elderly individuals

| Beneficial effects | Drawbacks |
|--------------------|-----------|
| ~29% reduction in MACE | Patients use an increased number of antihypertensive medications |
| ~33% reduction in CV mortality | Possible increase in renal failure |
| ~37% reduction in heart failure | Possible increase in serious adverse events |

CV: Cardiovascular

Diabetes and HTN

HTN in persons with diabetes needs to be controlled to prevent micro- and macrovascular complications of the same; the predicted goals for such treatment had been <130/80 mmHg for office pressures. However, the results of the ACCORD trial combined with several large prospective surveys support a goal of about 135/85 mmHg for office pressures. The value of ACEIs and ARBs may be additive to BP reduction for diabetics for the prevention of renal disease and reduction of microalbuminuria or proteinuria. Some authors have suggested that diabetic hypertensives are relatively resistant to antihypertensive drug treatment, but the data from ACCORD indicate that currently available drugs in combination at appropriate doses can achieve treatment goals well below 140 mmHg systolic pressure.

Stroke/CVAs

Elevated BP per se is an important risk factor, leading to stroke/CVAs. Even after the development of stroke, appropriate antihypertensive therapy plays a central role in secondary prophylaxis. A combination of an ACEI and diuretic has been reported to be effective for preventing a second stroke. Intervisit BP variability has been found to contribute to an increased risk of recurrent strokes.

Cognitive Impairment

HTN in the elderly has been associated with an increased risk of dementia and various other forms of cognitive impairment. Cognitive decline has been linked to signs of cerebral microvascular pathology on imaging. Antihypertensive therapy does not appear to significantly increase the likelihood of dementia or cognitive impairment. In the ONTARGET comparing an ACEI with an ARB, there was no difference between the two with regard to rates of cognitive impairment during the study. Among the ACEIs, those that cross the blood–brain barrier (captopril, lisinopril, ramipril, perindopril, fosinopril, and trandolapril) may be more effective in preventing cognitive decline than those that do not.

Conclusion

HTN is a modern-day curse on the chronicle of human history. It is present with an alarming rate of prevalence among elderly
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populace and accounts to a considerable rate of morbidity and mortality. Due to the effects of aging on the arterial wall, HTN in the elderly is characterized by an elevated systolic and pulse pressure with low DBP.

Definition of optimal BP goals in the elderly continues to be highly individualized and ultimately rests more on flexible targets based on prudent clinical judgment rather than targets set in stone. The pros and cons of BP lowering in the elderly are summarized in Table 5.

There is an ongoing trial, the ESH-CHL-SHOT (optimal BP and cholesterol targets for preventing recurrent strokes in hypertensives) which may shed some light regarding optimal targets for BP lowering in the elderly.[33]

It is important to keep in mind that in the very elderly population, too much becomes too bad as a low BP leads to a higher mortality, especially in those having multiple drugs as part of their BP lowering armory. BP lowering therapies in the elderly generally have a favorable risk/benefit ratio with treatment to an SBP <150 mmHg. The SPRINT suggested that even in individuals >75 years, a lower SBP target could provide benefits, however, this trial notably excluded more frail individuals. In elderly individuals, we thus have to balance the benefits of BP lowering with the risks of renal injury, orthostatic HTN, and consequent falls and CVAs. Non-pharmacological therapies such as salt and weight reduction also play a major role in control of BP and may even enable the withdrawal of antihypertensive therapy in this population.

Thus, the management of HTN in the elderly is not a “one size fits all” approach but must rather be individualized based on various factors including but not limited to the age, comorbidities, and frailty of the individual.

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