CAN WE STAY ON TARGET?
A REVIEW OF HYPERTENSION TREATMENT IN THE ELDERLY

Abstract
Hypertension is a leading cause of mortality. The prevalence is reported to be between 40 and 80 percent in those aged over 80 years. There has historically been a lack of consensus concerning the identification and treatment of hypertension in the elderly, making this a research priority. Recent studies and guidelines focusing on the treatment of hypertension in elderly patients have demonstrated the benefit of treatment, but suggest higher targets. However, a comprehensive assessment of each patient’s comorbidities, frailty, risk of falls, and cognition is crucial. Each of these variables has the potential to impact therapy, targets, and follow-up requirements.

Case
A 71-year-old woman presents to clinic for an initial evaluation of recent falls with minor trauma. Her medical history includes atrial fibrillation, dyslipidemia, and osteoporosis. The nurse tells you her blood pressure is 177/99. The patient asks, “Is that high?”

Introduction
Estimates for the future suggest that people aged over 65 years will exceed 20% of the population in the next 30 years. Hypertension is a modifiable risk factor for morbidity and mortality in the elderly, being the single greatest contributor to the development of stroke, myocardial infarction, and atrial fibrillation. The treatment of hypertension is decidedly more complex in the elderly, due to differences in the pathophysiology of hypertension with aging and the accumulation of end organ disease. Although many trials have scrutinized various aspects of treatment, historically there has been no clear consensus regarding targets and treatments in older patients. This has contributed to the diminished rates of treatment in the elderly, compared to the general population. Both over-treatment and under-treatment can result in harm, presenting a unique clinical challenge. This article reviews current literature and suggests an approach to hypertension treatment in elderly patients.

Management of Hypertension in the Elderly
Hypertension is most often identified by the absolute blood pressure (BP) values. However, hypertension might be more aptly described pathologically as the BP that increases morbidity and mortality. In recent guidelines, a pharmacotherapy target for patients aged 80 years and over with isolated systolic hypertension has been defined as a systolic BP greater than 150 mmHg, which is higher than the standard targets.
for other patients. In older patients, it is unlikely that one single age-based target is appropriate. This does not reflect a deficiency in clinical acumen, but the heterogeneity within older populations. Regarding treatment of hypertension in the elderly, evidence interpretation suffers from a lack of standard terminology, varying levels of evidence, lack of clear targets, non-representative samples in trials, and conflicting recommendations. There are little data available on the treatment of mild hypertension in elderly patients. As noted by Zanchetti and colleagues, no trials have included patients with an initial systolic BP less than 160 mmHg; and no placebo-controlled trials have achieved an average systolic BP <140 mmHg. Despite these concerns there is evidence to support the treatment of hypertension in older patients.

**Current Evidence and Benefits of Treatment**

Many earlier studies compared placebo and active therapy in elderly patients. The Systolic Hypertension in Europe Trial (Syst-EUR) looked at active treatment with nitrendipine +/- hydrochlorothiazide (HCTZ) and enalapril. This study established that there was a distinct benefit to the active treatment of hypertension, which resulted in a reduction of all cardiovascular events by 31% (P < 0.001) and all stroke types by 42% (P = 0.003). The Systolic Hypertension in the Elderly Program (SHEP) demonstrated a reduction in the incidence of all types of stroke when treated with chlorthalidone +/- atenolol or reserpine, versus placebo, to maintain systolic BP at a target of less than 160 mmHg or >20 mmHg decrease. In this study, total stroke incidence was reduced by one-third when participants were treated to a target of 160 mmHg (decreased by 33% or RRR 0.67; 95%CI 0.51–0.89), and lowered still when below 150 mmHg (decreased by 38% or RRR 0.62; 95%CI 0.47–0.82), with less reduction below 140 mmHg (decreased by 22% or RRR 0.78; 95%CI 0.57–1.07). The STOP-Hypertension and MRC trials also demonstrated a reduction in stroke and cardiovascular events.

Extending SHEP by up to 14 years post-trial, there was still a clear benefit to being in the initial active treatment group (chlorthalidone), demonstrating an adjusted relative risk of 0.86 (95%CI 0.76–0.98, P < 0.026) for reduced cardiovascular death. However, in contrast with other studies, a continued benefit for stroke was not noted in this trial (P = 0.26).

The Hypertension in the Very Elderly Trial (HYVET) included non-frail participants aged between 80 and 105 years being treated with indapamide and perindopril, versus placebo. Target BP (<150/80 mmHg) was achieved in approximately 50% of patients. The trial lasted approximately two years and was terminated early due to the clinically significant benefit in the treatment versus placebo group. Their main findings are discussed in Table 1.

Medications were well tolerated in the treatment group, with little orthostatic hypotension and few adverse drug-related events reported. However, the population studied was healthier than the average for the age group; mild hypertensive patients (those with systolic BP between 140 and 160 mmHg) were not included; and there was a relatively short follow-up time.

The HYVET extension trial, an open-label study, took the entire placebo group and placed them on indapamide and perindopril, if needed, to reach targets. By the end of one year, there was no difference in stroke or congestive heart failure (CHF) mortality between the former placebo group and the active treatment group. However, there was a significant difference between the continued therapy group and the previous placebo group in all-cause (HR 0.48; 95%CI 0.26–0.87, P = 0.02) and cardiovascular mortality (HR 0.19; 95%CI 0.04–0.87, P = 0.03), favouring the initial active treatment group. This suggests that early active therapy can have an immediate benefit to morbidity and long-term reduction in mortality. This is congruent with data from SHEP and Syst-Eur, which demonstrated that a longer therapy course was associated with improved outcomes.

In the older population, the impact of antihypertensive therapy on cognition must also be considered. Reducing the incidence of dementia by treating vascular risk factors has been a prominent focus of research. However, the results of antihypertensive therapy in the prevention of incident dementia have been mixed. Wysocki and others observed that, in nursing home patients, the initiation of antihypertensives was beneficial to patients at high risk of developing dementia. They found that, in the patients with a clinical dementia rating scale (CDR) of 0.5 (very mild) at baseline, there was a statistically significant decline in the Mini-Mental State Examination (MMSE) in the hypertensive patients versus “non-hypertensive” (that is, controlled hypertensive) patients (decrease in MMSE of 0.78 a year, compared to an increase in the MMSE of 0.76 a year; P = 0.006). This difference was not identified in patients with CDR 0 or CDR 1, suggesting that perhaps the benefit in treating hypertension was in those patients at highest risk of dementia and not in those with low risk or who already had dementia. However, many other larger studies of antihypertensives in the elderly (for example, HYVET, Medical Research Council [MRC, SHEP, and the Study on Cognition and Prognosis in the Elderly [SCOPE]) have described a lack of effect on incident dementia or a non-significant trend towards improvement. SCOPE found that cognition was preserved between the two groups (losartan versus placebo or open-label antihypertensive therapy), even with considerable reductions in BP in the treatment group. This is likely due to the short duration, small sample size and study design, and the fact that the study’s primary outcomes were not focused on cognitive outcomes.

The above findings are contrasted by the Syst-Eur extension trial,
Table 1. Included Studies by Age Range, Drugs Used, and Major Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age Range</th>
<th>Drug Used</th>
<th>Major Trial Outcomes</th>
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| MRC 1992              | 65-74     | Atenolol or HCTZ/Amiloride vs. Placebo | Active treatment resulted in:  
1. Active treatment (either β-blocker or diuretic) caused a 25% (P = 0.04) reduction in stroke, 19% reduction in coronary events and 17% (P = 0.03) reduction in all cardiovascular events.  
2. Diuretics had significant reduction compared with placebo for stroke (31%, P = 0.04), coronary events (44%, P = 0.0009) and cardiovascular events (44%, P = 0.0005).  
3. β-Blocker alone did not show this significance. |
| SYST-EUR 19979-11      | ≥60       | Nitrendipine +/- Enalapril or HCTZ vs. Placebo | Active treatment reduced total stroke by:  
1. SBP <160 mm Hg = 33% RR 0.67 (95% CI 0.51–0.89)  
2. SBP <150 mm Hg = 38% RR 0.62 (95% CI 0.47–0.82)  
3. SBP <140 mm Hg = 22% RR 0.78 (95% CI 0.57–1.07)  
4. Overall <160 mm Hg with ≥20mmHg decrease from baseline = 33% RR 0.67 (95% CI 0.51–0.84) |
| SHEP 200010-12         | ≥60       | Chlorthalidone +/- Atenolol vs. Reserpine vs. Placebo | Active treatment reduced total stroke by:  
1. Fatal or Non Fatal Stroke –reduced by 30% (P = 0.06)  
2. All Cause Mortality –reduced by 21% (P = 0.02)  
3. All cardiac endpoints by 26% (P = 0.03), non-fatal cardiac outcomes 33% (P = 0.03), Fatal cardiac outcomes by 31% (P <0.001). No significant change in all cause mortality (-14%, P = 0.22) |
| ALLHAT 200213          | ≥55       | Lisinopril vs. Chlorthalidone vs. Amlodipine | 1. Combined fatal coronary disease or non-fatal myocardial infarction (MI): no difference between groups, compared with chlorthalidone, lisinopril was 11.5% at 6 years, RR 0.98 (95% CI 0.9–1.07) and amlodipine was 11.3% at 6 years, RR 0.99 (95% CI 0.91–1.08).  
2. All cause mortality: no difference between groups.  
3. Higher rate of heart failure with amlodipine (10.2% vs. 7.7%, RR 1.38, 95% CI 1.25–1.52) vs. chlorthalidone.  
4. Higher rate of combined cerebrovascular disease (33.3% vs. 30.9%, RR 1.1, 95% CI 1.05–1.16) and heart failure (8.7% vs. 7.7%, RR 1.19, 95% CI 1.07–1.31) with lisinopril vs. chlorthalidone. |
| SCOPE 200314           | 70-89     | Candesartan | Candesartan therapy reduced  
1. First major cardiovascular event by 10.9% (95% CI –6.0–25), P = 0.19.  
2. Non-fatal stroke by 27.8% (95% CI 1.3–47.2), P = 0.04  
3. All stroke by 23.6% (95% CI -0.7–42.1), P = 0.056  
4. MMSE dropped 28.5 to 28.0 vs. 28.5–27.9 in the control group (P = 0.2) |
| HYVET 200815           | 80-105    | Indapamide +/- Perindopril | Active treatment reduced:  
1. Fatal or Non Fatal Stroke –reduced by 30% (P = 0.06)  
2. All Cause Mortality –reduced by 21% (P = 0.02)  
3. Cardiovascular Mortality –reduced by 23% (P = 0.06)  
4. Congestive Heart Failure –reduced by 64% (P <0.001) |
| INVEST Substudy 201016 | ≥50       | Verapamil vs. Atenolol | 1. Increasing age was associated with a wide pulse pressure (P < 0.001)  
2. Patients >80 years old had higher rates of the primary endpoint of all cause death, non-fatal MI or non-fatal stroke, 23.6% (P < 0.001).  
3. Adjusted HR for this primary endpoint display a J-shaped curve for the age groups with treatment. The SBP HR nadir increased with increasing age. |
| VALVET 201117          | >70       | Valsartan/HCTZ vs. Valsartan or HCTZ | 1. Median time to blood pressure meeting target (<140/90) was shorter in the combination group at 4 weeks vs. HCTZ 8 weeks (P < 0.05) or valsartan 12 weeks (P < 0.0001) |
| LIFE 201218            | 55-80     | Atenolol vs. Losartan | 1. Blood pressures were similar in both groups  
2. Losartan was superior to atenolol in patients greater than 67 years old in regards to the composite endpoint of cardiovascular death, non-fatal stroke, or non-fatal MI, HR 0.79 (95% CI 0.69 to 0.91, P = 0.001).  
3. In the ≥67 years old group the composite endpoint of cardiovascular death, non fatal stroke and MI was found 38.4%/1000 patient years for atenolol and 30.2%/1000 patient years for losartan (P = 0.001). |
| COPE 201219            | ≥65 (vs. <65) | Benidipine +/- β-blocker, ARB or Thiazide Diuretic | 1. Achieved blood pressure was similar in all three therapy groups.  
2. Primary cardiovascular outcome was higher in the ≥65 group (12.7 vs. 8.3 per 1000 person years, P = 0.023)  
3. The rates of all fatal and non-fatal cardiovascular outcomes were not significantly different among the three therapy groups.  
4. Higher hazard ratios were observed in the benidipine-β-blocker vs. benidipine-ARB group for new-onset diabetes (HR 2.47, 95% CI 1.03–5.91, P 0.043) and in the benidipine-β-blocker vs. benidipine-thiazide group for all stroke (HR 2.74, 95% CI 1.08 to 6.96, P = 0.022). |

SBP = systolic blood pressure. RR = relative risk. HR = Hazard ratio.
which demonstrated the most robust effect: a 55% reduction in the risk of dementia ($P < 0.001$) in patients on long-term antihypertensive therapy.20,22 Some promising data in the area come from a recent study of cognitive change by Gottesman and others, whose data suggest that midlife hypertension is independently associated with a decline in cognitive performance over a period of 20 years.23 This correlation with increasing BP leading to worsening cognitive performance was observed mainly in the Caucasian population.23 Patients who received treatment for hypertension in mid-life had less decline in cognition, whereas the same was not observed in older patients who were started on treatment for hypertension later in life.23 This suggests that treatment of hypertension may have the most significant benefit in regards to dementia prevention when initiated in early adulthood, versus later in life.23 This strengthens the argument that hypertension is a risk factor for dementia. Overall, more information is needed to elucidate the role and timing of antihypertensive therapy in preventing dementia.

It is still prudent to examine whether antihypertensives for other indications will impact cognition in older patients. This is a multifactorial assessment; patients with cognitive impairment are also more likely to be frail and to have an increased risk for falls. A recent systematic review by Beishon and colleagues24 included 24 papers focusing on the treatment of hypertension in dementia patients. Unfortunately, this study was unable to conclude either in support of or opposing treatment of hypertension in this population.24 Another recent review scrutinized observational studies of hypertension treatment in patients with dementia and found that they received the same treatment as patients who did not have dementia, despite the increased risk of adverse events.25 Ultimately, hypertension is a vascular risk factor and contributes to dementia risk. Early treatment in adulthood may be helpful in prevention, but treatment following dementia diagnosis is less clear. Any decision to treat patients with known cognitive impairment should be made carefully and should include close follow-up to assess for underreported adverse effects.

**Recommended Agents**

When selecting antihypertensive therapy in elderly patients, there are a few key studies to consider. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, atenolol was compared to losartan and a composite endpoint of cardio- or cerebrovascular outcomes was measured.26 Despite similar reductions in BP, there was a relative risk reduction of 13% ($P = 0.021$) in the composite endpoint and a 25% ($P = 0.001$) relative risk reduction in stroke in the losartan group.26,27 COPE, compared benidipine with diuretic, angiotensin receptor blocker (ARB) or ß-blocker.28 This trial demonstrated that all three combinations were similar in reducing BP and cardiovascular risk in older patients. In the group of benidipine with ß-blocker, stroke risk (ß-blocker versus diuretic; HR 2.74, 95%CI, 1.08–6.96; $P = 0.022$) and new-onset diabetes risk (ß-blocker vs. ARB, HR 2.47; 95%CI 1.03–5.91; $P = 0.043$) were elevated. Consequently, these results, along with additional data, have resulted in the recommendation that ß-blockers are not recommended as first-line treatment when considering antihypertensive therapy in the elderly, unless otherwise indicated.28 The combination of thiazide and ARB was further studied in the ValVET trial.29 In this trial patients were assigned to ARB, diuretic, or ARB/diuretic combo. Patients whose BP was >140/90 at any of the assessment dates were up-titrated to combination therapy.23 At Week 4 the BP reduction was greater with the combination therapy than with ARB/diuretic alone ($–17.3 \text{ mmHg vs. } –8.6 \text{ mmHg}; P < 0.001$), demonstrating that combination therapy is effective in patients aged over 70 years.23 Moreover, combination therapy required a shorter time to achieve BP control (4 weeks combination vs. 8 weeks diuretic, $P < 0.05$; and 12 weeks ARB, $P < 0.001$).29 This may be beneficial if a patient has severe hypertension and, in this study, the combination therapy was not associated with more adverse outcomes than monotherapy.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) demonstrated that, when compared with chlorthalidone, lisinopril and amldopine had a similar effect in reducing mortality related to coronary artery and cerebrovascular disease (CVD) (amlodipine RR 0.98; 95%CI 0.90–1.07 and lisinopril RR 0.99; 95%CI 0.91–1.08).30 However, when compared to chlorthalidone, amldopine had more CHF (RR 1.38; 95%CI 1.25–1.52), and when compared to chlorthalidone, lisinopril had more CVD (RR 1.15; 95%CI 1.02–1.30) and CHF (RR 1.19; 95%CI 1.07–1.31). HYVET demonstrated that

**Key Points**

1. Treatment of hypertension reduces the risk of morbidity and mortality in the elderly.
2. There is no single blood pressure (BP) target for the elderly.
3. Recommendations that differ for patients over 80 years:
   - Treatment should not be initiated until systolic BP ≥160 mmHg (if no evidence of diabetes or target organ damage).
   - The aim of treatment is a systolic BP <150 mmHg.
   - Frail patients may warrant a higher target.
4. Initiation of adequate lifestyle modifications is useful and safe.
5. Initial therapy should include a thiazide diuretic, CCB, or ARB/ACE, unless there is a compelling indication for other agents.
6. Excessive lowering of BP should be avoided.
7. Combination therapy is safe.
8. Close clinical follow-up and monitoring for complications is essential.
indapamide as a diuretic with a long-acting ace inhibitor (perindopril) was beneficial. A summary of the agents used in major trials that included older participants is outlined in Table 1. Overall, therapy must be individualized depending on the patient’s comorbidities (for example, diabetes or coronary disease), because the presence or absence of these may identify a class of drug that should or should not be used.¹ When focusing on isolated systolic hypertension, recommended therapy includes treatment with a diuretic, long-acting calcium channel blocker, or an angiotensin receptor blocker.¹ Further therapy for other indications are outlined in CHEP (Table 3).

Targets
Any discussion of hypertension focuses on the idea of a “target” BP. Part of the problem is the definition of “elderly.” These subgroups are not a simple age range, but groups separated by overall health status. A recent study by Odden and colleagues focused on the correlation between hypertension-associated mortality and the relation to different walking speeds (a surrogate marker of frailty).³³ Higher systolic BP was associated with an increased risk of mortality in faster walkers aged 65 years and over (adjusted HR of 1.35; 95%CI 1.03–1.77), but not with slower walkers nor those who did not complete the walk test.³³ This suggests that older adults who are not frail would benefit from treatment of hypertension, with respect to mortality.³³ However, frail older adults may not obtain the same benefits and may be at an increased risk of harm from therapy.³³ This supports the argument that age alone is insufficient to determine clinically relevant BP targets in the elderly, and a frailty assessment should accompany any decision to initiate antihypertensives.³³ Excessive lowering of BP in the elderly is also associated with adverse outcomes.¹ During HYVET, a non-significant decrease in the rate of fractures was seen in treatment arm versus placebo.¹⁶ However, Butt and colleagues found a 43% increased risk of incident hip fracture, with an incident risk ratio of 1.43 (95%CI 1.19–1.72) in the first 45 days post-treatment initiation (ACE inhibitors and β-blockers).²⁴ Overall, a proclivity towards slower and longer-acting antihypertensives is preferable. Thus, caution and frequent monitoring of BP and symptoms is important to ensure adequate BP and to avoid potential overtreatment or postural BP changes.¹
A sub-study of the International Verapamil SR-Tradolapril Study (INVEST) that focused on “very old hypertensive” patients exhibited a J-shaped curve for the adjusted hazard ratio and systolic/diastolic BP. This information indicates there is a point at which both too high and too low BP can be associated with increased mortality. The nadir BP for patients aged over 80 years was 140/70, while younger patients (aged under 60 years) tolerated a much lower nadir of 110/75.¹¹,¹² This suggests that, although there is an upper limit to BP, a lower limit must also be considered. Many trials have focused on achieving standard targets. The Japanese trial to assess optimal systolic BP in elderly hypertensive patients (JATOS) attempted to study this issue by comparing strict (<140 mmHg) and non-strict (140–160 mmHg) anti-hypertensive therapy in the elderly.³⁵ Despite significantly lower BP in the strict treatment group (135.9/74.8 versus 145.6/78.1), no reduction in the incidence of cardiovascular disease or renal failure was observed. Therefore, one unified target in the elderly is impractical—one case should be treated individually.

Current Consensus and Guidelines
There are two key documents that act as the guidelines for antihypertensive therapy in the elderly. The American College of Cardiology Foundation (ACCF) consensus document¹ supports a measured approach to antihypertensive therapy. They recommend the initiation of therapy in patients aged between 65 and 79 years, with a goal BP of less than 140/90 (based on expert opinion; Table 2).¹ A lower BP target is likely beneficial when there is concomitant end organ disease.¹ However, it should be reinforced that there is no clear-cut target for BP control and the over-zealous lowering of BP may contribute to worse outcomes. Given the available data, a higher BP (if tolerated) in older patients is suggested, particularly in frail older adults. The Canadian Hypertension Education Program (CHEP) provides a review of hypertension diagnosis and management in a wide range of patients and has been updated to include a focus on the elderly.³ (https://www.hypertension.ca/en/professional/chep/therapy/hypertension-without-compelling-indications). One of the main changes is that in patients aged over 80 years, the overall systolic BP target should be less than 150 mmHg, and treatment should not be initiated until 160 mmHg for those without diabetes or target organ damage.³ It is suggested that combination therapy can also be beneficial.³ This document clearly states that the available trials are typically performed in a healthier older population and that treatment in the frailer older population must be undertaken with caution.³ Appropriately medications for hypertensive patients and indications for specific therapy are reviewed by CHEP explicitly (Table 3).³ (https://www.hypertension.ca/en/professional/chep/therapy/hypertension-with-compelling-indications).

Table 2. ACCF Recommended Targets for Antihypertensive Therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Systolic BP Target</th>
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<tr>
<td>&lt;79 years</td>
<td>Aim &lt;140 mmHg</td>
</tr>
<tr>
<td>≥80 years</td>
<td>Aim &lt;150 mmHg</td>
</tr>
</tbody>
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ACCF =BP = blood pressure.

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AGARDE and BURBACK

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Summary

Treatment of hypertension in elderly patients is complex and warrants a case-by-case assessment of all clinical data to aid in making an informed decision. The goal of therapy is to reduce the risk of fatal and debilitating disease without causing complications such as hypotension, falls, fractures, worsening cognition, or mortality. Complications are best avoided by slow titration and closely monitored therapy (including monitoring for falls, near falls, and postural hypotension).

Case Conclusion

This particular reading of the patient’s BP is elevated; however, a full examination plus repeat BP measurements is required to confirm the diagnosis. Given her recent falls, she would require orthostatic BP measurements as well as neurologic and cardiac assessments to ensure there is no other etiology. Depending on these results, we would have to discuss options for therapy with her and arrange close clinical follow-up. The simple question, “Is my blood pressure too high?” is a multi-faceted question that requires a careful and measured approach to ensure safe treatment.

References


