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Management of Hypertension in Older People

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WIN and TEO: Management of Hypertension in Older People: Systolic hypertension above >160 mmHg is associated with cardiac, renal and cerebrovascular complications. In older people, treating hypertension offers cardiovascular benefits. Reduced salt intake and weight loss for obese older people improves blood pressure without any risk of adverse drug reactions. Blood pressure reduction is more important than the type of antihypertensive for cardiovascular risk reduction. The recommended drugs to start an older patient with isolated systolic hypertension are thiazides, calcium-channel blockers or angiotensin II receptor blocker. Studies were performed on relatively fit older patients, so benefits may not be generalisable to frail elderly. Alpha-blockers and beta-blockers are not recommended for first line therapy of hypertension but may be considered if there are other indications for their use. (J HK Coll Cardiol 2017;25:1-8)

Drugs, elderly, hypertension, medication

Introduction

Older people are less likely to receive treatment for hypertension. Hypertension is also more difficult to control with age, particularly in women.1,2 In United States, although increasing awareness among patients and physicians may have improved treatment and control between 1988 to 2008, it was still disproportionately less for those age 60 years and over.3 These high rates of hypertension and inadequate treatment and control for older people was also found in low and middle income countries.4

The prevalence of hypertension increases with age. There is also a step-wise increase in risk of major cardiovascular events with each hypertension stage. For patients age 80 years and older, the Framingham Heart Study found a 9.5% risk with normal blood pressure to 19.8%, 20.3% and 24.7% in pre-hypertension, Stage 1 and Stage 2 hypertension respectively.1 Therefore, further study was required to assess whether hypertension treatment in older people attenuated this risk.
The potential benefit of treating hypertension in older people was identified since the 1980s. Coope and Warrender found reduced stroke risk when hypertensive patients between 60 to 79 years old were treated, mostly with atenolol and bendrofluazide. The European Working Party on High Blood Pressure in the Elderly trial (EWPHE) identified reduced cardiac mortality and a trend towards improved stroke mortality when treating those above 60 years with hydrochlorothiazide and triamterene.

When EWPHE subgroup analysis was performed, although participants 70 years and older had similar improved outcomes as those between 60 to 69 years, there appeared little benefit for patients over 80 years old.

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) further extended the evidence for treatment to 84 years. Participants aged 70 to 84 from primary health care who received treatment with beta-blockers and diuretics had reduced stroke, myocardial infarction, cardiovascular death, stroke mortality and all-cause mortality.

The Hypertension in Very Elderly Trial (HYVET) then specifically reviewed people aged 80 years and older. Treatment with indapamide and perindopril as required reduced strokes and stroke mortality, cardiac failure, cardiovascular mortality and all-cause mortality.

These studies offer cumulative evidence that age alone is not an appropriate reason to withhold treatment. Management considerations for treating hypertension are discussed subsequently based on studies specifically of older people.

**Hypertension Guidelines: The Need To Individualise Treatment**

Table 1 summarises the recommendations from three major recent guidelines on hypertension treatment for older people (NICE, ESH/ESC, JNC8). There are subtle differences between them, reflecting uncertainty in some aspects of management. All studies performed also enrolled ambulatory older people with isolated systolic hypertension so these recommendations may not be generalisable to frail older people or those with multiple medical conditions.

There is consensus that systolic blood pressure above 160 mmHg should be treated to a target of below 150 mmHg. The Systolic Blood Pressure Intervention Trial (SPRINT) challenges this as patients 75 years and older had lower rates of major cardiovascular events and all-cause mortality with intensive (<120 mmHg) rather than standard (<140 mmHg) treatment. A meta-analysis of studies on blood pressure targets may help clarify this issue. Whether benefits of intensive treatment without adverse events can be replicated outside trial settings with close supervision is uncertain.

While awaiting a consensus after the SPRINT trial, the guideline recommendations remain clear. Treatment is appropriate above systolic blood pressure of 150/90. The intensive or standard target should be individualised to tolerability of antihypertensive treatment and the general health of the patient i.e. fitter, independent older patients may benefit more from the intensive approach.

NICE guidelines additionally gives targets for ambulatory or home blood pressure monitoring of 135/85 for under 80 years and 145/85 for above 80 years. For practical purposes, we would advocate for clinic blood pressure targets, with ambulatory or home blood pressure monitoring only if there was a concern regarding white coat hypertension.

**Non-pharmacological Therapy: Reduced Salt Intake and Weight Loss (If Obese)**

A small trial of 47 people 60 to 78 years old found reduced salt intake resulted in blood pressure lowering for both normotensive and hypertensive subjects, similar to a thiazide treatment effect. The findings were replicated in the Trial of Non-pharmacologic Interventions in the Elderly (TONE). When participants aged 60 to 80 years old reduced sodium intake or lost weight (if they were obese), there was improvement in blood pressure control compared to usual care. However, there was no reduction in cardiovascular events.

As reduced salt intake and weight loss for obese older people improves blood pressure without any risk
<table>
<thead>
<tr>
<th>Table 1. Summary of guideline recommendations specific for older patients</th>
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<tbody>
<tr>
<td><strong>NICE 2011</strong></td>
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<td><strong>When to Treat</strong></td>
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<td><strong>Blood Pressure Goals</strong></td>
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<tr>
<td><strong>Hypertension management when adverse reaction present e.g. orthostatic hypotension or falls</strong></td>
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<tr>
<td><strong>Cardiovascular Comorbidities</strong></td>
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<td><strong>Cerebrovascular Comorbidities</strong></td>
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</tbody>
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(continued on page 3)
### Table 1. Summary of guideline recommendations specific for older patients (cont’d)

<table>
<thead>
<tr>
<th>Renal Comorbidities</th>
<th>NICE 2011</th>
<th>ESH/ESC 2013</th>
<th>JNC8 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Comorbidities</td>
<td>No specific recommendations</td>
<td>No specific recommendations</td>
<td>No evidence to support RAAS inhibition if older than 75 years - thiazide-type diuretic or CCB may be considered.</td>
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<tr>
<td>Diabetic Comorbidities</td>
<td>No specific recommendations</td>
<td>Consider HBA1c target of 7.5 to 8.0% in 'fragile elderly' patients with a longer duration of diabetes, more comorbidities and at high risk of complications.</td>
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<tr>
<td>Non-pharmacological</td>
<td>No specific recommendations</td>
<td>No specific recommendations</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>Age over 55 years: Step 1: Calcium channel blockerIf intolerance from oedema, evidence of heart failure or high risk of heart failure, thiazide diuretic. Thiazide like diuretic (Chlorthalidone, Indapamide) preferred over conventional thiazide diuretic (Bendroflumethiazide, hydrochlorothiazide). Beta-blockers not preferred initial therapy for hypertension 'but may be considered in younger people'. 'Diuretics and calcium antagonists may be preferred in isolated systolic hypertension'. Initial antihypertensive treatment should include thiazide type diuretic, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker.</td>
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</tr>
</tbody>
</table>

NICE - National Institute for Health and Clinical Excellence; JNC8 - Eight Joint National Committee; ESH - European Society of Hypertension; ESC - European Society of Cardiology; SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure; ABPM - Ambulatory Blood Pressure Monitoring; HBPM - Home Blood Pressure Monitoring; TIA - Transient Ischaemic Attack.
of adverse drug reactions, this is recommended for hypertensive older people.

**Pharmacological Therapy**

When comparing classes of antihypertensive agents, none have stood out as superior over others in terms of cardiovascular outcomes. The International Verapamil-Trandolapril Study (INVEST) randomised patients 50 years and over to calcium antagonist (Verapamil) or non-calcium antagonist strategy (Atenolol) with trandolapril and hydrochlorothiazide as required to achieve blood pressure targets. There was no difference between groups for blood pressure reduction, myocardial infarction, stroke, mortality or treatment related adverse events.16

The STOP-Hypertension-2 trial randomised 70 to 84 years old to beta-blockers and diuretics (active treatment in STOP-Hypertension trial), ACE Inhibitors or calcium channel blockers.17 All three groups had similar reductions in systolic blood pressure, cardiovascular events and rate of treatment related adverse events. This suggests blood pressure reduction is more important than type of antihypertensive used.18

However, the three classes with most evidence-base for hypertension treatment of older people are thiazide-type diuretics, calcium channel blockers and angiotensin II receptor blockers.

**Thiazide-Type Diuretic**

The Medical Research Council (MRC) trial compared outcomes for patients aged 65 to 74 years randomised to placebo or active treatment with either atenolol or diuretic (hydrochlorothiazide and amiloride combined). Active treatment reduced strokes and cardiovascular events but was more significant with diuretics.19

Participants aged 60 and older were randomised to treatment with chlorthalidone and atenolol or placebo in the Systolic Hypertension in the Elderly Program (SHEP). Active treatment for almost five years reduced strokes, major cardiovascular events and all-cause mortality.20 Non-insulin dependent diabetics also had twice the absolute risk reduction in major cardiovascular events with chlorthalidone compared to non-diabetics in SHEP.21

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reinforced the benefits of thiazide diuretics. Patients 55 years and above were randomised to receive chlorthalidone, amlodipine or lisinopril. There was no difference between groups in terms of coronary heart disease or all-cause mortality. However, amlodipine had a higher rate of heart failure and lisinopril a higher rate of combined cardiovascular disease, stroke and heart failure compared to chlorthalidone.22

The HYVET trial mentioned earlier demonstrated benefits of indapamide-based diuretic treatment for hypertensive patients 80 years and over.9 Even with factoring in frailty using the frailty index, there was no interaction between treatment effect and frailty, as both frail and fitter subjects seemed to benefit with treatment.23

At the conclusion of HYVET trial, an open label active treatment extension was performed for a year, with both groups given indapamide (and perindopril if required). The treatment group had reduced cardiovascular and total mortality but no difference in stroke and cardiovascular events, suggesting older patients benefit from early initiation in addition to long term treatment.24

**Calcium-Channel Blockers (CCBs)**

The Systolic Hypertension in Europe Trial (Syst-Eur) randomized patients 60 years and older to nitrendipine (with enalapril and hydrochlorothiazide if required) or placebo. Treatment was associated with reduced stroke rates, all cardiac endpoints and all cardiovascular endpoints with a trend to reduced cardiovascular mortality.25

This study was replicated in Systolic Hypertension in China Trial (Syst-China), except captopril was added instead of enalapril to nitrendipine-based treatment. Despite the smaller sample size, there were larger-scale benefits with reduced strokes, stroke mortality, cardiovascular endpoints, cardiovascular mortality and all-cause mortality.26

As there were concerns regarding CCB treatment with diabetes, post-hoc analyses were performed comparing outcomes in diabetic and non-diabetic
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patients. For Syst-Eur, reduction in all cardiovascular events, cardiovascular mortality and total mortality was more significant in diabetics.\textsuperscript{27} In Syst-China, diabetics had two to three-fold risk for all endpoints in the placebo group but nitrendipine-based treatment reduced this excess risk to a non-significant level.\textsuperscript{28}

The Felodipine Event Reduction (FEVER) trial compared risk of stroke and cardiovascular events in Chinese patients between 50 to 79 years with hydrochlorothiazide monotherapy and addition of felodipine or placebo. Additional felodipine reduced blood pressure by 4/2 mmHg, with reduced in stroke rate, cardiovascular events, heart failure and all-cause mortality.\textsuperscript{29} Subgroup analysis of FEVER confirmed benefits of felodipine in uncomplicated hypertensives, Grade 1 hypertensives and older patients.\textsuperscript{30} The blood pressure reduction achieved is unlikely to be clinically significant to cause such beneficial effects, supporting use of calcium-channel blockers for older people regardless of hypertension severity.

Angiotensin II Receptor Blockers (ARBs)

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared cardiac outcomes in patients age 50 and older randomized to valsartan or amlodipine. There were larger reductions in blood pressure especially earlier in the trial with amlodipine but no differences in myocardial infarction, stroke and all-cause mortality.\textsuperscript{31} In VALUE, additional antihypertensive agents were added if required. When analysis was limited to those receiving monotherapy only, there were lower rates of cardiac failure and new-onset diabetes with valsartan.\textsuperscript{32} The reduction in cardiac failure with valsartan was more apparent with a longer duration of monotherapy, suggesting a true treatment effect.

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study compared outcomes in patients aged 55 to 80 years randomised to losartan or atenolol-based therapy. Despite no differences in extent of blood pressure reduction, the losartan group had lower risk of myocardial infarction, stroke or death and less frequent episodes of new-onset diabetes.\textsuperscript{33} This suggests losartan may confer benefits beyond blood pressure reduction.

The Study on Cognition and Prognosis in the Elderly (SCOPE) reviewed patients aged 70 to 89 years to candesartan or placebo with open label antihypertensive agents (mostly thiazides) as required. Most participants eventually ended up receiving antihypertensive agents but there was a greater 2.9 mmHg reduction in systolic blood pressure with candesartan, with associated reduced non-fatal strokes and a trend towards reduced all strokes. There were no differences in myocardial infarction, cardiovascular mortality, cognitive decline or incident dementia.\textsuperscript{34}

When analysis was restricted to those with isolated systolic hypertension, which was about a third of the participants, there were no differences in blood pressure reduction but risk of fatal and non-fatal strokes became significant.\textsuperscript{35}

Other Agents – Not Recommended as First Line Therapy for Isolated Systolic Hypertension

**ACE Inhibitors (ACEI):**

Although ACEIs and ARBs appear to have similar benefits in younger patients, the evidence for ACEIs is less clear for older people. The Second Australian National Blood Pressure Study (ANBP2) randomized 65 to 84 years old to ACEIs or diuretics. Although enalapril and hydrochlorothiazide were the recommended agents, actual prescriptions were determined by the family practitioner. While both groups had similar reduction in blood pressure, ACEIs were associated with in reduced cardiovascular events or death, which was limited to male patients only.\textsuperscript{36}

This contradicts ALLHAT which found diuretics superior to ACEIs (comparing chlorthalidone to lisinopril) in terms of cardiac failure and stroke.\textsuperscript{22} With this uncertainty, ACEIs should not be used as first-line hypertension treatment for older people.

**Alpha-Blockers:**

ALLHAT initially included a doxazosin arm in addition to chlorthalidone, amlodipine and lisinopril. An interim analysis four years after recruitment identified that doxazosin was associated with a higher risk of stroke, combined cardiovascular risk and doubling of heart failure risk compared to chlorthalidone. Although
there were no differences in fatal or non-fatal MI or all-cause mortality, due to these identified risks, there were sufficient grounds to discontinue the doxazosin arm.37

Patients assigned to doxazosin had a higher mean systolic blood pressure of 3 mmHg than chlorthalidone. When patients with doxazosin monotherapy or additional antihypertensive medications were compared, risk of heart failure was not eliminated completely suggesting the systolic blood pressure difference does not account fully for this risk.38 Therefore, alpha-blockers are not recommended for hypertension treatment in older people.

**Beta-Blockers:**

Several studies included beta-blockers in combination with diuretics so comparisons are not possible.5,8,21 The LIFE study found losartan superior to atenolol despite similar blood pressure outcomes.33 While this may be due to beneficial effects of ARBs, alternatively atenolol could contribute hazardous effects resulting in this outcome. As there are other preferred agents for hypertension in older people, beta-blockers should not be used as first-line treatment.

**Conclusion**

Ambulatory older people with hypertension should be treated regardless of age, particularly if systolic blood pressure is above 160 mmHg. Treatment should be individualised according to frailty and comorbidities. Non-pharmacological treatment for hypertension in older people, including reduced salt intake and weight loss (if obese) should be recommended. The main drug classes for hypertension treatment in older people are thiazide diuretics, calcium-channel blockers and angiotensin II receptor blockers.

**Declaration of Interest**

The authors have no conflict of interests to declare.

References