A GUIDE TO

deprescribing

ANTIHYPERTENSIVE AGENTS

KEY POINTS

- **Lowering blood pressure reduces risk of a range of long-term consequences, this benefit is still evident in the elderly.**
- **Less aggressive control of blood pressure in the elderly gives results equivalent to those achieved with more aggressive control.**
- **Low blood pressure may be associated with increased morbidity and mortality in the elderly.**
- **Patients being treated for hypertension are more likely to fall if they have proven postural hypotension.**
- **Adverse effects of many antihypertensive agents are likely to be more common in the elderly.**
- **Withdrawal of antihypertensives should be gradual.**

CONTEXT

This guide considers the use of antihypertensive medications in the treatment of hypertension.

RECOMMENDED DEPRESCRIBING STRATEGY

- Many patients are receiving multiple agents that lower blood pressure. Reduction and cessation strategies should focus on one agent at a time.
- Reduction or cessation of antihypertensive agents should be considered:
  - In frail elderly and/or immobile patients
  - In patients with a high falls risk
  - In patients with confirmed postural hypotension (>20mmHg fall in systolic on standing, and/or >10mmHg fall in diastolic on standing)

EFFICACY

Multiple studies have shown increased morbidity and mortality in patients with hypertension, with reduction in morbidity and mortality with appropriate treatment of the hypertension. With increasing age, however, the relative benefit of lowering blood pressure is attenuated. In 2002, Lewington et al published data from over 1 million adults from 61 studies on the associations between Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and mortality from stroke and coronary heart disease by age. The associations between both SBP and DBP and mortality from stroke, coronary heart disease and other vascular disease were graded and continuous with the lowest risk at SBP of 115 mmHg and DBP of 75 mmHg (lower BP levels were not reported) and the highest risk at SBP of 175 mmHg and DBP of 105 mmHg (higher levels were not reported). However, these associations were weaker at older age (see **Figure 1** on page 2). [1]

Trials of hypertension management in the elderly are limited and were reviewed by Fleg et al[2] in 2011 and by Muntner et al[3] in 2014. Of 12 studies reviewed by Fleg, five showed statistically significant reductions in cardiovascular events. All five studies showed a relative risk reduction of stroke between 23 and 57%, where starting BP was between 169 and 185mmHg systolic.

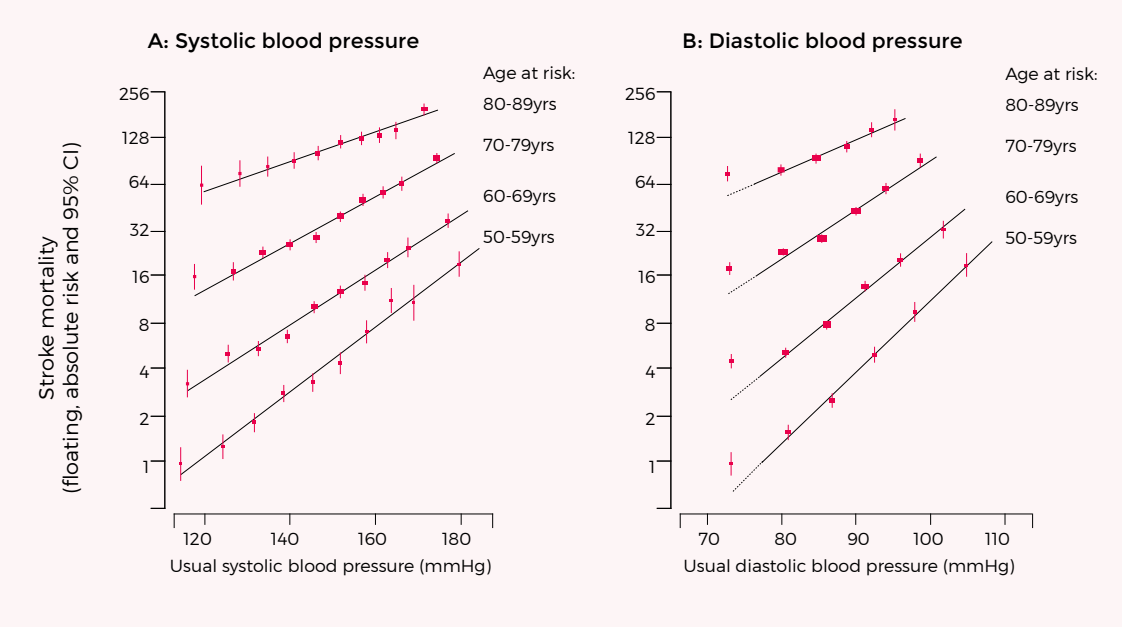

Figure 1: Stroke mortality in each decade of age versus usual blood pressure[1]

Muntner's article reviews three other papers that targeted intensive vs more lenient systolic blood pressure control in older patients:

- A Japanese study of 4418 patients aged 65-84 years compared tight vs lenient control of blood pressure on outcomes. One group achieved 136/75 on average while the other 146/78. Over 2 years of follow-up, there were no differences in the primary composite outcome of cardiovascular disease or renal failure.[4]
- The Valsartan in the Elderly with Isolated Systolic Hypertension (VALISH) study found no difference in 70-84 year olds that achieved 137 vs 142 systolic BPs in terms of stroke, sudden death or myocardial infarction frequency.[5]
- An Italian study of 1111 patients with a mean age of 67 years randomised patients to tight (<130) vs moderate (<140) control of blood pressure. They showed a difference in a composite endpoint of CVD/ renal disease after 2 years of 9.4% in the moderate control group vs 4.8% (ARR 4.6%, NNT= 22 over 2 years).[6]

One additional study (HYVET) looked specifically at patients over 80 years of age.[7] This group randomised patients with a starting systolic BP of 160mmHg or more to indapamide or a placebo. Perindopril was added to the indapamide if the target BP of 150mmHg was not achieved. They reported positive outcomes for the following endpoints after an average 1.8 year follow-up:

- Death from stroke
  - 27/1933 (1.4%) vs 42/1912 (2.2%); OR 0.61 [0.38-0.99]; ARR 0.8% (NNT= 125)
- Death from any cause
  - 196/1933 (10.1%) vs 235/1912 (12.3%); OR 0.79 [0.65-0.95]; ARR 2.2% (NNT= 45)
- Development of Heart Failure
  - 22/1933 (1.14%) vs 57/1912 (2.97%); OR 0.36 [0.22-0.58]; ARR 1.83% (NNT= 54)
- Any cardiovascular event
  - 138/1933 (7.14%) vs 193/1912 (10.09%); OR 0.66 [0.53-0.82]; ARR 2.95% (NNT= 34)

THE SPRINT STUDY

Recently, the SPRINT research group published the results of a randomised trial comparing intensive to standard blood pressure control.[8] They randomly assigned 9361 non-diabetic people with an SBP of 130mmHg or higher to intensive control (target SBP <120mmHg) or standard treatment (target SBP <140mmHg). Approximately 28% of the patients were 75 years old or more (mean age 79.8), of these 1317 received intensive and 1319 received standard treatment. The primary outcome was a composite of MI, ACS, Stroke, acute CCF or death from cardiovascular causes and occurred overall in 5.2% (243/4678) of the intensively treated patients and 6.8% (319/4683) of the standard treatment patients over 3.26 years (ARR over 1 year= 1.6%, NNT=63).

The reduction in the composite outcome with the intensive treatment was also evident in the 75 and over age group, with an event rate of 10.9% (144/1319) in the standard treatment arm and 7.7% (101/1317) of the intensive treatment arm over the median follow-up of 3.26 years (ARR 3.2%, NNT= 31).[8]

When the SPRINT results are examined with the more traditional end point of combined MI, Stroke or cardiovascular death the event rates were 196/4678 (4.2%) for the intensive treatment, compared to 251/4683 (5.4%) for standard treatment (ARR 1.2% over 3.26 years; NNT=85)

As expected, the incidence of serious adverse events was higher in the intensive treatment group. These are summarised in **Table 1** below (it is unclear what proportion of these adverse effects occurred in the 75 year old and over age group).

To summarise the SPRINT results, if 1000 patients were treated with intensive vs standard treatment for 3.26 years, there would be 16 less primary events as used by the authors (or 12 less events if combined MI, Stroke or CV Death is used) while 53 serious adverse events would occur (14 severe hypotensive episodes, 11 more syncopal episodes, 10 more electrolyte disorders and 18 episodes of renal damage).

Thus there seem to be benefits in reducing blood pressure from high systolic blood pressures in the elderly. These relative benefits may be somewhat less than those achieved by a similar level of reduction in younger patients. However, because of increased absolute risks in the elderly, the absolute benefits may be equal to or greater than younger patients.

IMPACT OF FRAILTY

It should be noted that these studies all include relatively fit elderly patients and that frail elderly patients may be more sensitive to the impact of antihypertensive treatment and may or may not obtain the same benefit from antihypertensive therapy.

In an observational study of 2340 adults older than 65 years, the association between blood pressure and mortality was examined according to whether or not individuals were frail (defined as an inability to walk 6 meters in less than 8 seconds).[9] Among frail adults, there was no association between blood pressure and mortality. In addition, a higher blood pressure was associated with a lower risk of death among the most frail (i.e., those who could not walk the distance at all). This was an observational study and there are no randomised controlled trials of treatment of hypertension in frail elderly people.

ADVERSE EVENT*	EVENT RATE OVER MEDIAN 3.26Y FOLLOW-UP; N (%)		DIFFERENCE; % (NNH)
	INTENSIVE TREATMENT	STANDARD TREATMENT	
	N= 4678	N=4683	
Hypotension	158 (3.4)	3 (2.0)	1.4% (71)
Syncope	163 (3.5)	113 (2.4)	1.1 (91)
Electrolyte Abnormality	177 (3.8)	129 (2.8)	1.0 (100)
Acute kidney injury or acute renal failure	204 (4.4)	120 (2.6)	1.8 (56)

* including those resulting in emergency department attendance

Table 1: Incidence of Adverse Events (including those resulting in Emergency Department attendance) in the SPRINT study.[8]

ADVERSE EFFECTS

SUSTAINED HYPOTENSION

Some studies have reported an increased cardiovascular risk at very low systolic or diastolic blood pressures in the elderly.[10,11,12]

Voko et al. reported a J-shaped relationship between incidence of stroke and diastolic (but not systolic) blood pressure in treated hypertensives.[10] In patients receiving treatment for hypertension, diastolic blood pressure of less than 65mmHg was associated with the same stroke risk as patients with a diastolic of >84mmHg, and significantly higher than those with a systolic of 65-74mmHg.

Ogihara et al undertook a 3-year follow-up 2164 patients over 60 who regularly attended their clinician and documented cardiovascular morbidity and mortality as well as achieved blood pressure.[11] In the subgroup of patients aged 75 years or more, patients with an achieved systolic BP of <120mmHg had a significantly higher incidence of total cardiovascular events, as did patients with a systolic BP of >160mmHg (see **Table 2**).

Taken together, the studies from **Table 1** and **Table 2** indicate that low blood pressure may result in increased morbidity and mortality in the elderly. It remains unclear whether the low blood pressure is itself an indicator of poor cardiovascular health, which may be responsible for this observation.

Furthermore, reanalysis of the PROGRESS trial, which originally proposed a J-curve in patients treated for hypertension, concluded that lower blood pressure levels were safe and not associated with a higher stroke risk.[13]

POSTURAL HYPOTENSION

A further potential limiting factor in the treatment of elderly patients is the presence of, or exacerbation by treatment of, postural hypotension. Postural and/or postprandial hypotension is found in up to 20% of elderly patients with isolated systolic hypertension.[14,15,16] Hypertensive older patients with postural hypotension (particularly those with less well-controlled hypertension) are more likely to fall than patients without.[16]

Indeed, antihypertensive treatment has been associated with a 43% increased risk of hip fractures in the elderly in the first 45 days of treatment.[17] Measurement of lying and standing blood pressures are essential prior to commencing or modifying antihypertensive therapy.

OTHER ADVERSE EFFECTS OF ANTIHYPERTENSIVE AGENTS

There are a wide range of differing antihypertensive agents available with multiple mechanisms of action. As a result, there are a wide range of possible adverse effects from these agents, either alone or in combination with other agents being taken by the patient. Metabolic, cardiac and renal effects are seen from many of the antihypertensives, with some agents also exhibiting more specific adverse effects. For the vast majority of adverse effects, the elderly and those with limited reserve are more likely to sustain adverse effects. A summary of the complexity in choosing between drug classes for treatment of hypertension has been undertaken.[18] In **Table 3** (page 5), the main adverse effects with each class of agents are listed.

		<75 YEARS OLD		>= 75 YEARS OLD	
BLOOD PRESSURE ACHIEVED mmHg		NUMBER OF PATIENTS	RELATIVE RISK (*=STATISTICALLY SIGNIFICANT)	NUMBER OF PATIENTS	RELATIVE RISK (*=STATISTICALLY SIGNIFICANT)
Diastolic	<70	158	1.21	98	1.77
	70-79	503	1.00 (reference)	275	1.00 (reference)
	80-89	677	0.99	240	1.02
	>89	161	1.36	52	1.76
Systolic	<120	74	0.43	34	3.40*
	120-139	740	1.00 (reference)	298	1.00 (reference)
	140-159	581	1.49	284	1.74
	>159	104	2.14	49	2.90*

Table 2: Relation between achieved blood pressure and cardiovascular events by age.[11]

DRUG CLASS (COMMON EXAMPLES)	ADVERSE EFFECTS
Thiazide and Loop diuretics (hydrochlorothiazide, indapamide, chlorthalidone, frusemide)	Hypokalemia, hyponatremia, hypomagnesemia
	Volume-depletion and orthostatic hypotension
	Renal impairment, hyperuricemia, gout, lipid alterations, hyperglycemia, insulin resistance
	NSAIDs reduce thiazide potency
	Erectile dysfunction and possibly impotence
	Reduction of lithium excretion and precipitate lithium toxicity
	Potential to increase fatigue and lethargy
	Pro-diabetogenic potential in combination with Beta Blockers
	Increase of urinary frequency, leg cramps
	Decrease of renal blood flow, creatinine clearance, Glomerular Filtration Rate
Potassium Sparing Diuretics (spironolactone, amiloride)	Hyperkalemia, hypotension
Beta Blockers (atenolol, metoprolol, propranolol)	Sinus bradycardia, fatigue, AV-nodal heart block bronchospasm, aggravation of acute heart failure
	Intermittent claudication, confusion, hyperglycemia
	Diabetes mellitus
	Drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, nightmares
	Pulmonary side-effects (increased airway resistance in asthmatics)
	Peripheral vascular side-effects (cold extremities, Raynaud's phenomenon)
	Erectile dysfunction
Angiotensin Converting Enzyme Inhibitors (perindopril, ramipril, fosinopril, trandolapril)	Cough, hyperkalemia
	Angioneurotic edema
	Rash, altered taste sensation, renal impairment
Angiotensin Receptor Blockers (candesartan, irbesartan)	Hyperkalemia, renal impairment
Calcium Channel Blockers (non-dihydropyridines eg. verapamil, diltiazem)	Rash, sinus bradycardia, heart block, heart failure, constipation (verapamil), gingival hyperplasia
	Ankle edema, headache and postural hypotension
Calcium Channel Blockers (dihydropyridines eg. amlodipine, nifedipine)	Peripheral edema, heart failure, tachycardia
	Aggravation of angina pectoris (short-acting agents)
Direct vasodilators (hydralazine)	Tachycardia, fluid retention
	Angina pectoris
Alpha 1 adrenergic blockers (prazosin)	Hypotension
Alpha-beta adrenergic blockers (labetalol)	Hypotension, heart block, sinus bradycardia, bronchospasm
Central acting agents (moxonidine, methyldopa)	Sedation, constipation, dry mouth

Table 3: Most common drug-related side effects of antihypertensive classes[17]

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- Lifestyle modification can achieve significant benefit. In patients where lifestyle modification (exercise, salt and sugar restriction, alcohol, weight loss) are possible, these changes can support the reduction or cessation of antihypertensive agents.
- The benefits of treating hypertension in the >85 age group are unclear; ongoing treatment should be reassessed in light of prognosis–frailty, comorbidities and quality of life.
- Patients who are frail and have a high risk of falls are more likely to fall as a result of antihypertensive treatment and may not derive the same benefit of treatment as non-frail elderly. Reduction or cessation of antihypertensives should be considered in these patients.

AGAINST DEPRESCRIBING

- Agents with an antihypertensive effect may have other benefits in patients with other comorbidities and they may be prescribed more specifically for these other purposes. Beta blockers for heart failure, atrial fibrillation or ischaemic heart disease, ACE inhibitors for heart failure or renal protection and prazosin for prostatic symptoms are examples of where cessation of these agents may worsen the underlying condition.

DISCONTINUATION SYNDROMES

Withdrawal effects may be wide ranging, depending on the specific class of agent and any other conditions being treated. These may include peripheral oedema, tachycardia, rebound hypertension or worsening heart failure or ischaemic heart disease.

As a result, it is recommended that most antihypertensives should be tapered at approximately 25% every month over 3-4 months.

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was written by Dr Peter Tenni and Dr David Dunbabin in consultation with the Deprescribing Clinical Reference Group.

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