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Treating Hypertension in Older Adults
Safety Considerations

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Contents

Abstract

This article discusses the efficacy, use and adverse effects of antihypertensive drug therapy in older adults. Numerous double-blind, randomized, placebo-controlled studies have demonstrated that antihypertensive drug therapy reduces cardiovascular events in older adults. All antihypertensive drugs may predispose older patients to the development of symptomatic orthostatic hypotension and postprandial hypotension, and syncope or falls. Adverse effects of diuretics, β-adrenergic receptor antagonists, ACE inhibitors, angiotensin receptor antagonists, calcium channel antagonists, α-adrenergic receptor antagonists, centrally acting drugs and direct vasodilators are discussed. The adverse effects depend on the antihypertensive drugs used, the doses used, the co-morbidities present in older patients taking these drugs and drug-drug interactions.

Hypertension in older persons is a major risk factor for coronary events,[1-3] stroke,[1,4-6] congestive heart failure (CHF)[1,7,8] and peripheral arterial disease.[9-12] Older persons are more likely to have hypertension and isolated systolic hypertension, to have target organ damage and clinical cardiovascular disease, and to develop new cardiovascular events, and are less likely to have their hypertension controlled.

It should be emphasized that the elderly are a very heterogeneous group. Frailty is a condition in which a person has an impaired ability to carry out routine activities that exceeds normal age-related physiological deterioration.[13] Barriers to

treatment of hypertension include physicians not understanding that frail older patients should be treated according to recommended guidelines to reduce cardiovascular morbidity and mortality. In fact, some physicians have recommended against treating very old persons with antihypertensive drugs.[14-16]

Older patients with hypertension that is treated appropriately will have a greater absolute decrease in cardiovascular events (such as major coronary events, stroke, CHF) and renal insufficiency than younger patients, and may have a greater reduction in dementia.[17] However, not all trials have shown a reduction in dementia with antihypertensive drug therapy.[18]

Some older patients living in the community may not be able to afford their antihypertensive medications.[19] The cost of medications is very dependent on the healthcare system of the country in which they live. There is also the issue of adherence and polypharmacy, which, although not a barrier to treatment, may affect control rates of hypertension.

In this article, the efficacy, use and adverse effects of antihypertensive drug therapy in older adults are discussed.

1. Efficacy of Antihypertensive Drug Therapy in Older Adults

Numerous prospective, double-blind, randomized, placebo-controlled studies have demonstrated that antihypertensive drug therapy reduces the development of new coronary events, stroke and CHF in older patients.[20] Therapy with antihypertensive drugs reduces the incidence of all strokes by 38% in women, 34% in men, 36% in older patients and 34% in those older than 80 years.[5] The overall data suggest that reduction of stroke in older persons with hypertension is related more to a decrease in BP than to the type of antihypertensive drugs used.[5]

In HYVET (Hypertension in the Very Elderly Trial), 3845 patients aged 80 years and older (mean age 83.6 years) with a sustained systolic BP of 160 mmHg or higher were randomized to indapamide (sustained release 1.5 mg) or matching placebo.[21] Perindopril (2 or 4 mg), or matching placebo, was added if needed to achieve the target BP of 150/80 mmHg. Median follow-up was 1.8 years. Antihypertensive drug treatment reduced the incidence of the primary endpoint (fatal or nonfatal stroke) by 30% ($p = 0.06$). Furthermore, it reduced fatal stroke by 39% ($p = 0.05$), all-cause mortality by 21% ($p = 0.02$), death from cardiovascular causes by 23% ($p = 0.06$) and heart failure by 64% ($p < 0.001$). The significant 21% reduction in all-cause mortality by antihypertensive drug treatment was unexpected. The benefits of treatment began to be apparent during the first year of follow-up.

The prevalence of baseline cardiovascular disease was only 12% in the patients in HYVET. In a cohort of hypertensive patients with a mean age of 80 years seen in a university geriatrics practice, 70% had baseline cardiovascular disease, target organ damage or diabetes mellitus.[22] An older population such as this with a high prevalence of cardiovascular disease would be expected to have a greater absolute reduction in cardiovascular events resulting from antihypertensive drug therapy.

2. Use of Antihypertensive Drug Therapy in Older Adults

I agree with the recommendations of the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of Hypertension (JNC 7)[20] that the goal of treatment of hypertension in older persons is to lower BP to <140/90 mmHg and to <130/80 mmHg in older persons with diabetes or chronic renal insufficiency.

Most older persons with hypertension need two or more antihypertensive drugs to control their BP.[19,20,23] It is important to measure BP in both arms and to use the arm with the higher BP during follow-up of treatment.[24] It is also very important to measure BP in older persons in the upright position as well as in the sitting position. Repeat measurements are important given the increased variability of BP with age.

I also agree with the recommendations of JNC 7 that diuretics should be used as initial drugs in the treatment of older persons with

hypertension and no associated medical conditions because these drugs have been demonstrated to reduce cardiovascular events and mortality in controlled clinical trials.[20] However, older persons with hypertension have a very high prevalence of associated medical conditions.[22] The selection of antihypertensive drug therapy in these patients therefore depends on their associated medical conditions.[20] If the BP is more than 20/10 mmHg above the goal BP, drug therapy should be initiated with two antihypertensive drugs, one of which should be a thiazide-type diuretic.[20]

The initial antihypertensive drug should be administered at the lowest dose and gradually increased to the maximum dose. If the antihypertensive response to the initial drug is inadequate after reaching the maximum dose, a second drug from another class should be given if the person is tolerating the initial drug. If the person is having no therapeutic response or is experiencing significant adverse effects, a drug from another class should be substituted. If a diuretic is not the initial drug, it is usually indicated as the second drug. Diuretics can take up to 6 weeks to have their full effect. If the antihypertensive response is inadequate after reaching the maximum dose of two classes of drugs, a third drug from another class should be added.[20]

Before adding new antihypertensive drugs, the physician should consider possible reasons for inadequate response to therapy, including nonadherence, pseudoresistance, volume overload, uncontrolled pain, drug interactions (use of NSAIDs, caffeine, antidepressants, nasal decongestants, sympathomimetics, etc.) and associated conditions such as increasing obesity, smoking, excessive intake of alcohol and insulin resistance.[20] Causes of secondary hypertension should be identified and treated.[20,25]

Falls or syncope in older persons may be due to orthostatic or postprandial hypotension.[26] Management of orthostatic and postprandial hypotension in older persons is discussed in detail elsewhere.[26] The dose of antihypertensive drug may need to be decreased or another antihypertensive drug given.

Older frail persons are most susceptible to orthostatic and postprandial hypotension.[26] Measurements of BP in the upright position, especially after eating, are indicated in these persons.

3. Adverse Effects of Antihypertensive Drug Therapy

All antihypertensive drugs, especially diuretics, ACE inhibitors, angiotensin receptor antagonists (ARAs), calcium channel antagonists and nitrates, may predispose the older person to develop symptomatic orthostatic hypotension and postprandial hypotension, and syncope or falls.[27-31] Diuretics may cause volume depletion. Vasodilators such as ACE inhibitors, ARAs, calcium channel antagonists, hydralazine, nitrates and prazosin may cause a reduction in systemic vascular resistance and venodilation.

With aging, left ventricular stiffness is increased, left ventricular compliance is reduced, left ventricular wall thickness is increased, left ventricular diastolic filling is decreased and left ventricular relaxation is impaired.[32] This may result in hypotension if preload is reduced. An age-related increase in systolic BP also impairs left ventricular diastolic filling, leading to hypotension if preload is decreased.

The reduction in baroreflex sensitivity with age and with systemic hypertension leads to an impaired baroreflex-mediated increase in total systemic vascular resistance and to an inability to increase heart rate.[33] Therefore, older persons with systemic hypertension have a greater impairment in baroreflex sensitivity and are more likely to develop orthostatic and postprandial hypotension.

3.1 Diuretics

Serum electrolytes need to be closely monitored in older patients treated with diuretics. Hypokalaemia and/or hypomagnesaemia, both of which may precipitate ventricular arrhythmias and/or digitalis toxicity, can occur with thiazide or loop diuretic therapy.[34] Hyponatraemia is not uncommon in older persons treated with diuretics, particularly when thiazide-like or loop diuretics are being used.[35] Older patients with

CHF are especially sensitive to volume depletion with dehydration, hypotension and prerenal azotaemia occurring in the face of excessive diuretic effect. Older patients with CHF and normal left ventricular ejection fraction (LVEF) should receive diuretics more cautiously. NSAIDs may reduce the antihypertensive and natriuretic effect of loop diuretics.[36]

Compared with ACE inhibitors and calcium channel antagonists, thiazide diuretics cause an increase in fasting blood glucose and in new-onset diabetes.[37] Whether this would lead to an increased incidence of cardiovascular events at very long follow-up is unknown but it was not found at the 14.3-year follow-up in the Systolic Hypertension in the Elderly Program.[38]

Thiazide diuretics may precipitate hyperuricaemia and gout.[39] Therefore, thiazide diuretics should be avoided or used cautiously in patients with a history of gout.[20]

Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalaemia.[20] These drugs should be avoided if the serum potassium level is >5.0 mEq/L, or the serum creatinine level is >2.5 mg/dL in men, or >2.0 mg/dL in women.[20,40] The incidence of gynaecomastia in men is less with eplerenone[41] than with spironolactone.[42] However, eplerenone is not licensed for the treatment of hypertension in all countries.

3.2 β-Adrenergic Receptor Antagonists

The benefit of β-adrenergic receptor antagonists (β-blockers) in reducing new coronary events in older patients with prior myocardial infarction is especially increased in older patients with diabetes,[43] peripheral arterial disease,[44] abnormal LVEF,[45] complex ventricular arrhythmias with abnormal LVEF[46] or normal LVEF,[47] and CHF with abnormal LVEF[48] or normal LVEF.[49] β-Blockers should also be used to treat older patients with hypertension who have angina pectoris,[50] myocardial ischaemia,[51] supraventricular tachyarrhythmias such as atrial fibrillation with a rapid ventricular rate,[52,53] hyperthyroidism,[54] preoperative hypertension,[20] migraine[20] or essential tremor.[20]

However, β-blockers depress the sinus node and the atrioventricular node and are contraindicated in patients with severe sinus bradycardia, sinoatrial disease and marked first-, second- and third-degree atrioventricular block.[55] β-Blockers should also not be administered to patients with bronchial asthma or with lung disease with severe bronchospasm.[55] Patients with very severe peripheral arterial disease with pain at rest should also not be treated with β-blockers. In addition, caution is needed in treating patients with brittle diabetes and a history of hypoglycaemic events, because β-blockers may mask the symptoms of hypoglycaemia.[55] β-Blockers may also cause depression or confusion in older adults. There is now less support for the use of β-blockers as first-line antihypertensive drugs in persons with uncomplicated hypertension.[20]

3.3 ACE Inhibitors and Angiotensin Receptor Antagonists

Diuretics and ACE inhibitors are recommended in JNC 7 to prevent recurrent stroke in older persons with hypertension.[20] In addition to β-blockers, older persons with CHF should be treated with diuretics and ACE inhibitors.[40] ACE inhibitors or angiotensin II type 1 receptor antagonists should be administered to older persons with diabetes, chronic renal insufficiency or proteinuria.[20] Compared with amlodipine, ramipril significantly decreased progression of renal disease in a study of 1094 African-Americans with hypertensive nephrosclerosis.[56] If the older patient cannot tolerate an ACE inhibitor because of cough, angioneurotic oedema, rash or altered taste sensation as seen with captopril or other ACE inhibitors containing a sulfhydryl group, an angiotensin II type 1 receptor antagonist should be administered.[57]

In one study, the addition of telmisartan to ramipril, compared with ramipril alone, in patients (mean age 67 years) with vascular disease or high-risk diabetes did not improve the efficacy in the primary outcome of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure after a median follow-up of 56 months, but increased hypotensive symptoms

(4.8% vs 1.7%), syncope (0.3% vs 0.2%) and renal dysfunction (1.1% vs 0.7%).[58] In patients treated with either ramipril or telmisartan, the drug was stopped because of hypotensive symptoms in 1.7% versus 2.7% of patients, respectively, syncope in 0.2% versus 0.2%, cough in 4.2% versus 1.1%, angioneurotic oedema in 0.3% versus 0.1% and renal impairment in 0.7% versus 0.8%.[58]

Cough occurs in 5–20% of patients treated with ACE inhibitors.[59] The mechanism may involve accumulation of prostaglandins, bradykinin or substance P. Angioneurotic oedema occurs in 0.1–0.2% of patients receiving ACE inhibitors.[59]

To avoid hyperkalaemia, potassium-sparing diuretics should not be administered to patients receiving ACE inhibitors or ARAs.[20] Risk factors for renal insufficiency in patients receiving ACE inhibitors or ARAs include renal artery stenosis (usually bilateral), polycystic renal disease, reduced absolute or effective arterial blood volume, use of NSAIDs, ciclosporin or tacrolimus, and sepsis.[60,61] However, reversible renal failure may occur in elderly patients treated with ACE inhibitors or ARAs who are dehydrated or salt depleted.[62] ACE inhibitors or ARAs can cause an azotaemic response when there is an absolute decrease in intravascular volume due to aggressive diuresis, poor oral intake or gastroenteritis, or an effective decrease in intravascular volume due to severe CHF.[60]

3.4 Calcium Channel Antagonists

Short-acting dihydropyridine calcium channel antagonists have the potential to increase cardiovascular events and should be avoided.[63] Verapamil and diltiazem depress the sinus node and the atrioventricular node and are contraindicated in patients with severe sinus bradycardia, sinoatrial disease and marked first-, second- and third-degree atrioventricular block.[64]

Verapamil and diltiazem are also contraindicated in treating postinfarction patients with an abnormal LVEF because they will increase coronary events and mortality as well as CHF.[65-67] Calcium channel antagonists such as nifedipine, diltiazem and verapamil exacerbate heart failure in patients with CHF and abnormal LVEF.[68] The most common adverse effect in patients treated for hypertension with verapamil or diltiazem is constipation.[69]

The vasoselective calcium channel antagonists amlodipine[70] and felodipine[71] did not significantly affect survival in patients with CHF and abnormal LVEF. In these studies, there was a significantly higher incidence of pulmonary oedema in patients treated with amlodipine[70] (15%) than in those treated with placebo (10%), and a significantly higher incidence of peripheral oedema in patients treated with amlodipine[70] or felodipine[71] than in those administered placebo.

3.5 α-Adrenergic Receptor Antagonists

α-Adrenergic receptor antagonists (α-blockers) include doxazosin, prazosin and terazosin.[20] In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the doxazosin arm involving 9067 patients was prematurely stopped at a median treatment duration of 3.3 years.[37] Compared with the diuretic chlortalidone, doxazosin significantly increased CHF by 104%, stroke by 19% and combined cardiovascular disease (coronary heart disease death, nonfatal myocardial infarction, stroke, angina pectoris, coronary revascularization, CHF or peripheral arterial disease) by 25%, as well as angina pectoris by 16% and coronary revascularization by 15%.[37]

In an observational study of older patients (mean age 80 years) with prior myocardial infarction and hypertension, patients treated with α-blockers had, at 40 months' mean follow-up, a significant increase in new coronary events of 1.69 times compared with β-blockers, 1.50 times compared with ACE inhibitors and 1.35 times compared with diuretics.[67] α-Blockers cause a high incidence of orthostatic hypotension, especially in patients receiving diuretics or other vasodilator drugs.[72]

3.6 Centrally Acting Drugs

Centrally acting drugs include clonidine, methyldopa, reserpine, guanfacine, moxonidine, guanethidine, hexamethonium, mecamylamine and phenoxybenzamine.[20] Centrally acting drugs

should not be used as monotherapy in older patients because they cause a high incidence of sedation, precipitate or exacerbate depression, and cause constipation.[72]

3.7 Direct Vasodilators

Direct vasodilator drugs include hydralazine and minoxidil.[20] They may cause headache, fluid retention and tachycardia, and aggravate angina pectoris. Hydralazine caused a lupus-like syndrome in 6.7% of 281 patients treated with the drug for 3 years.[73] The incidence was 0% in patients taking hydralazine 50 mg daily, 5.4% in those taking 100 mg daily and 10.4% in those taking 200 mg daily. Minoxidil may cause hirsutism and a pericardial effusion.[74]

4. Conclusions

Numerous prospective, double-blind, randomized, placebo-controlled studies have demonstrated that antihypertensive drug therapy reduces the development of new coronary events, stroke and CHF in older persons. However, antihypertensive drug therapy may cause adverse effects, as discussed in this article. The adverse effects depend on the antihypertensive drugs used, the doses of these drugs, the co-morbidities in the older patients taking these drugs, and drug-drug interactions.

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