Contents

Treatment

Summary approach

Goals of treatment

- The main aim of treatment is to reduce the risk of clinically overt cardiovascular disease
- Blood pressure should be reduced to less than 140/90 mm Hg in the absence of comorbidities, including diabetes mellitus , chronic kidney disease , or existing coronary heart disease or heart failure
- Blood pressure should be reduced to less than 130/80 mm Hg in patients with diabetes, chronic kidney disease, or established cardiovascular disease
- Blood pressure should be reduced to less than 120/80 mm Hg in patients with heart failure
- Blood pressure should not be viewed in isolation; rather, the whole cardiovascular risk profile of the patient, including smoking , dyslipidemia, obesity , and diabetes, should be considered

Immediate action

Depending on the level of blood pressure, urgent and aggressive treatment may be required in the following emergencies:

- Hypertensive encephalopathy

- Stroke
- Unstable angina
- Acute myocardial infarction
- Acute left ventricular failure with pulmonary edema
- Dissecting aortic aneurysm
- Hypertension in pregnancy with eclampsia or preeclampsia
- Hypertension in the perioperative period in patients scheduled for vascular surgery
- Malignant hypertension

Blood pressure should be lowered within hours in other hypertensive urgencies such as:

- Blood pressure greater than 180/110 mm Hg without ongoing target organ damage
- Perioperative hypertension in patients imminently undergoing nonvascular surgery

Summary of therapies

- Therapy should be dictated by the patient's overall cardiovascular risk and the presence or absence of comorbid conditions such as diabetes or chronic kidney disease, not by the blood pressure alone
- Lifestyle modifications are indicated in all hypertensive patients; in those patients with a relatively low cardiovascular risk, lifestyle modifications may be all that are required

- While thiazide diuretics are the cornerstone of antihypertensive therapy, choices about pharmacologic therapies should take into account any coexisting disease, since this may favor or limit the use of particular medications (*eg* , calcium-channel blockers or β-blockers may be preferred in patients with angina; angiotensin-converting enzyme [ACE] inhibitors are preferred in patients with diabetes)
- To increase the likelihood of a good response to therapy, treatment choices should also take into account age and race. Frailty should be considered in appropriate elderly patients to prevent polypharmacy and iatrogenic syncope
- If goal blood pressure (<140/90 mm Hg in most patients; <130/80 mm Hg in patients with diabetes, coronary heart disease, or chronic kidney disease) is not reached with initial treatment, combining medications from different classes frequently provides better control of blood pressure with fewer adverse effects than does increasing the dose of a single agent
- Treatments for resistant hypertension include device-related therapies such as carotid baroreceptor stimulation and radiofrequency ablation of renal nerves

Pharmacologic management of essential hypertension:

- Thiazide diuretics are considered first-line therapy for uncomplicated hypertension unless there is a specific indication for a medication from another class. They have been shown to be effective at lowering blood

pressure and improving cardiovascular outcomes in randomized, controlled trials (RCTs)

- If thiazide monotherapy does not achieve target blood pressure, one of the following medications either may be added to thiazide therapy or substituted: angiotensin-converting enzyme (ACE) inhibitor ; angiotensin-II receptor blocker (ARB); β-blocker ; or a calcium-channel blocker
- ACE inhibitors are commonly used and are particularly suitable for patients with heart failure, diabetes, chronic kidney disease, and proteinuria
- ARBs have similar indications to ACE inhibitors, including some benefits in patients with heart failure, albeit with a better adverse effect profile (less risk of persistent cough) compared with ACE inhibitors
- β-blockers should not be considered first-line therapy for uncomplicated hypertension in the absence of a specific indication for their use, such as post-myocardial infarction, heart failure, or atrial fibrillation
- Calcium-channel blockers are divided into three classes: dihydropyridines , benzothiazepines , and phenylalkylamines . Dihydropyridine calcium-channel blockers such as nifedipine are effective and well tolerated in lowering blood pressure and are of particular benefit in preventing stroke in elderly patients with systolic hypertension. Diltiazem , a benzothiazepine, and verapamil , a phenylalkylamine, have effects on the myocardium as well as blood vessels and are preferable in patients with angina or supraventricular tachycardia

- Loop diuretics are generally reserved for fluid control in patients with heart failure or chronic renal disease and are often given in combination with medications from other classes
- Potassium-sparing diuretics that block the epithelial sodium channel, such as amiloride and triamterene, are used as second-line drugs for patients taking other diuretics, such as the thiazide diuretics
- α1-blockers are effective in lowering blood pressure, although their long-term effects on cardiovascular risk are unknown; they may be suitable for patients with coexisting benign prostatic hyperplasia . However, α1-blockers should not be used as monotherapy to treat hypertension, since the risk of congestive heart failure is increased
- Methyldopa may be used in the management of moderate to severe hypertension and has an important place in the management of hypertension in pregnancy
- Minoxidil is a vasodilator that may have a role when standard medications have failed to control blood pressure. It can be used in combination with a β-blocker and a diuretic in severe hypertension resistant to other agents
- Hydralazine is a vasodilator and can be used in combination with other medications in moderate to severe hypertension, but its adverse effect profile (like that of minoxidil) makes it generally unsuitable as monotherapy
- Clonidine , a centrally acting α2-agonist, is a potent antihypertensive and is useful in patients resistant to other therapies
- Nonselective aldosterone antagonists such as spironolactone inhibit aldosterone action as well as inhibit other receptors, leading to adverse

effects such as gynecomastia . The selective aldosterone receptor antagonist eplerenone is associated with significantly reduced cardiovascular morbidity and mortality in post-myocardial infarction patients

- Aliskiren is the first of a new class of antihypertensives, direct renin inhibitors, approved by the Food and Drug Administration (FDA) for the treatment of essential hypertension either as monotherapy or in combination with other antihypertensives. Aliskiren lowers blood pressure by inhibiting renin, in contrast with current non–renin-angiotensin system antihypertensives, which act at later stages of the blood pressure regulation process. Its clinical utility appears similar to that of ACE inhibitors and ARBs. In 2012, the FDA added a new contraindication against the use of aliskiren with ARBs or ACE inhibitors in patients with diabetes because of the risk of renal impairment, hypotension, and hyperkalemia; the FDA further stated that the use of aliskiren with ARBs or ACE inhibitors should be avoided in any patient with moderate to severe renal impairment (*ie* , where glomerular filtration rate <60 mL/min)

Management of perioperative hypertension:

- For patients with known preexisting hypertension, continue all antihypertensives in the perioperative period except ACE inhibitors and ARBs, which are associated with excessive hypotension during surgery and should be used with caution. Diuretics are typically withheld on the day of surgery

- For patients presenting with newly diagnosed hypertension, elective surgery should be delayed only in those with extremes of hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg), or hypertension associated with signs of end-organ failure
- Acute control of hypertension perioperatively can usually be achieved with administration of a single small dose of an oral β-blocker such as atenolol
- Controversy exists about the routine perioperative administration of β-blockers to patients with increased cardiovascular risk, with many studies suggesting a significantly positive impact on morbidity and mortality, but some suggesting that the effects may be agent-specific. More information is needed. Patients most likely to benefit from perioperative β-blockers are those with increased cardiovascular risk undergoing intermediate or high-risk surgery
- Patients should be referred for standard care for hypertension, including a search for underlying causes, risk assessment, and therapeutic intervention

Efficacy of therapies

- Response to antihypertensive medication is variable: while some patients' blood pressure will normalize quickly after starting treatment, others will take many months and possibly several medication regimens before blood pressure stabilizes at an acceptable level
- Long-term treatment of hypertension reduces the risk of cardiovascular events in hypertensive patients

- When blood pressure is more than 10 to 20 mm Hg above goal, it is reasonable to consider initiating therapy with a combination-drug approach, either as two separate agents or in a fixed-dose combination formulation

Medications

Thiazide diuretics

Indication

- First-line treatment for uncomplicated hypertension

Dose information

Chlorothiazide :

- 250 to 500 mg orally once or twice a day

Hydrochlorothiazide :

- Oral: 12.5 to 50 mg once a day

Indapamide :

- Oral: 1.25 to 5 mg once a day

Chlorthalidone :

- Oral: 12.5 to 50 mg once a day

Major contraindications

- Anuria
- Sulfonamide hypersensitivity
- Thiazide diuretic hypersensitivity

Comments

- Readily available, safe, and efficacious
- Recommended first-line drug therapy for most patients with uncomplicated hypertension either alone or in combination with ACE inhibitors, ARBs, β-blockers, or calcium-channel blockers

Evidence

Diuretics, ACE inhibitors, ARBs, β-blockers, and calcium-channel blockers have all been found to reduce stroke and events secondary to ischemic heart disease compared with placebo, and no drug class has proven more effective than low-dose thiazide when compared with placebo or no treatment.

- A systematic review of 24 RCTs including 58,040 patients compared the effects on mortality, stroke, coronary heart disease, cardiovascular events, decrease in systolic and diastolic blood pressure, and withdrawals due to adverse events of low- and high-dose thiazides, β-blockers, ACE

inhibitors, and calcium-channel blockers, each compared with placebo or no treatment. The authors concluded that low-dose thiazides were associated with improved outcomes for all indicators measured; ACE inhibitors and calcium-channel blockers were similarly effective but not as thoroughly studied; β-blockers and high-dose thiazides were less effective than low-dose thiazides. [1] *Level of evidence: 1*

- An RCT assessing various cardiovascular end points in 3,845 patients aged 80 or older with elevated systolic blood pressure treated with the diuretic indapamide versus placebo, plus the addition of perindopril versus placebo, to achieve a target blood pressure of 150/80 mm Hg. After 2 years, the treated group had a significant 39% reduction in rate of death from stroke, a 21% reduction in the rate of death from any cause, and a 64% reduction in rate of heart failure compared with the placebo group. There were also fewer adverse events in the treated group versus the placebo group. [2] *Level of evidence: 1*
- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*

- A meta-analysis of 26 RCTs involving 223,313 patients with hypertension or high cardiovascular risk found that diuretics were the most effective in preventing heart failure, followed by ACE inhibitors and ARBs, while calcium-channel blockers were among the least effective in heart failure prevention, together with β-blockers and α-blockers. [4] *Level of evidence: 1*

Evidence from various systematic reviews suggests no advantage in terms of total mortality, cardiovascular mortality, and rates of myocardial infarction when classes of antihypertensive drugs are compared with each other.

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found no significant difference in terms of total mortality, cardiovascular mortality, myocardial infarction, and cardiovascular events. It found that heart failure occurred more frequently with the newer agents compared with the older agents. [5] *Level of evidence: 1*
- In a follow-up study, the same authors updated their quantitative overview with new information from secondary prevention trials published before 2005. In this review, the authors found that dihydropyridine calcium-channel blockers may have a slight benefit in the prevention of stroke, and that inhibitors of the renin-angiotensin system may be of benefit in the prevention of heart failure. For

prevention of myocardial infarction, the published results were inconclusive. [6] *Level of evidence: 1*

- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. [7] *Level of evidence: 1*

Further evidence suggests the benefit of certain antihypertensive agents versus others in terms of improvements in particular outcomes other than total mortality. Some of the differences, however, may in part be due to the differences in blood pressure in the treatment groups.

Chlorthalidone versus lisinopril, amlodipine, or doxazosin:

- An RCT, ALLHAT, enlisted 33,357 people aged 55 years or older with hypertension and at least one other coronary heart disease risk factor, and compared chlorthalidone to lisinopril, amlodipine, or doxazosin. It found that all interventions reduced blood pressure, but to varying degrees. The primary outcomes of coronary heart disease mortality and nonfatal myocardial infarction rates for chlorthalidone, lisinopril, and amlodipine were similar. Chlorthalidone was better at preventing combined cardiovascular events and stroke than doxazosin, better at preventing

heart failure than amlodipine, and resulted in lower rates of combined cardiovascular disease events, stroke, and heart failure compared with lisinopril. [8] *Level of evidence: 1*

- Final results of ALLHAT, an RCT comparing chlorthalidone with doxazosin in additional 9,232 patient-years, showed that after a mean of 3.2 years, there was no difference in combined occurrence of fatal coronary heart disease or nonfatal myocardial infarction between the two groups. However, the doxazosin group experienced a significantly higher risk of stroke and combined cardiovascular disease. [9] *Level of evidence: 1*
- A propensity score–matched observational cohort study with up to 5 years of follow-up comparing the effectiveness and safety of chlorthalidone and hydrochlorothiazide in older adults (N = 29,873) found that patients on chlorthalidone were more likely to be hospitalized with hypokalemia (adjusted hazard ratio, 3.06 [CI, 2.04 to 4.58]) or hyponatremia (adjusted hazard ratio, 1.68 [CI, 1.24 to 2.28]). [10] *Level of evidence: 2*

Thiazide diuretics versus β-blockers:

- A systematic review of 42 long-term RCTs involving 192,478 patients compared the efficacy of various antihypertensive agents (diuretics, β-blockers, ACE inhibitors, ARBs, calcium-channel blockers, and α1-blockers) as first-line agents in the treatment of hypertension. There was no significant difference between thiazide diuretics and β-blockers in terms of total mortality. There was a nonsignificant benefit in terms of cardiovascular disease mortality, stroke, congestive heart failure, and

coronary heart disease with diuretics versus β-blockers. [11] *Level of evidence: 1*

Thiazide diuretics versus ACE inhibitors:

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found a significant difference in stroke with ACE inhibitors compared with the older agents. [5] *Level of evidence: 1*
- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. However, there was a trend toward increased stroke with ACE inhibitors compared with the older agents. [7] *Level of evidence: 1*
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- A systematic review of 28 trials compared the incidence of coronary heart disease and stroke in 179,122 patients with hypertension who were randomly prescribed either ACE inhibitors or calcium-channel blockers, or were prescribed diuretics, β-blockers, or placebo. ACE inhibitors resulted in additional decreased incidence of coronary heart disease. Concentrating on the combined outcomes of coronary heart disease and stroke, the study was unable to identify a significant difference between ACE inhibitors and older agents (diuretics, β-blockers, or both). [12] *Level of evidence: 1*
- A randomized, open-label, prospective trial of 6,083 elderly patients with hypertension was designed to assess the efficacy of ACE inhibitors and diuretics over a median of 4.1 years. There were fewer cardiovascular events or deaths from any cause among patients taking ACE inhibitors compared with patients taking diuretics; this is particularly true for elderly men. [13] *Level of evidence: 1*
- An RCT involving 508 hypertensive, hypercholesterolemic patients with asymptomatic carotid atherosclerosis comparing the efficacy of hydrochlorothiazide and fosinopril, each with and without pravastatin. Progression of atherosclerosis occurred only in the group of patients receiving only hydrochlorothiazide; there was no progression in the fosinopril group and no progression in the two other groups receiving either drug with pravastatin. [14] *Level of evidence: 2*

Thiazide diuretics versus calcium-channel blockers:

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel

blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found that calcium-channel blockers were associated with a trend toward a reduced incidence of stroke, but with a significantly increased incidence of congestive heart failure compared with the older agents. [5] *Level of evidence: 1*

- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. However, calcium-channel blockers were associated with a trend toward a reduced incidence of stroke, but with a significantly increased incidence of congestive heart failure compared with the older agents. [7] *Level of evidence: 1*
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- A systematic review of 28 trials compared the incidence of coronary heart disease and stroke in 179,122 patients with hypertension who were randomly prescribed either ACE inhibitors or calcium-channel blockers, or were prescribed diuretics, β-blockers, or placebo. Calcium-channel

blockers resulted in additional decreased incidence of stroke. [12] *Level of evidence: 1*

- Using major cardiovascular events as an end point, a systematic review evaluated calcium-channel blockers versus other antihypertensive agents. The authors identified 18 trials with a total of 141,807 subjects. They found no differences in all-cause mortality between calcium-channel blockers and any other antihypertensive agent, but with calcium-channel blockers there was an increase in total cardiovascular deaths compared with diuretics. Calcium-channel blockers also increased the incidence of congestive heart failure compared with diuretics. [15] *Level of evidence: 1*
- The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a large randomized, double-blind trial enrolling a total of 11,506 patients with hypertension at high risk for cardiovascular events, showed that the combination of the ACE inhibitor benazepril plus the calcium-channel blocker amlodipine is superior to the combination of benazepril plus the thiazide diuretic hydrochlorothiazide in terms of cardiovascular and renal outcomes. [16] *Level of evidence: 1*

Thiazide diuretics versus ARBs:

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found that ARBs were associated with a

significant reduction in stroke and cardiovascular events compared with the older agents. [5] *Level of evidence: 1*

- A systematic review of 42 long-term RCTs involving 192,478 patients compared the efficacy of various antihypertensive agents (diuretics, β-blockers, ACE inhibitors, ARBs, calcium-channel blockers, and α1-blockers) as first-line agents in the treatment of hypertension. There was a trend toward a decreased incidence of stroke with ARBs compared with diuretics. [11] *Level of evidence: 1*

Thiazide diuretics versus α1-blockers:

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found that α1-blockers were associated with an increase in congestive heart failure, an increase in cardiovascular events, and a slight increase in stroke compared with the older agents. [5] *Level of evidence: 1*
- A systematic review of 42 long-term RCTs involving 192,478 patients compared the efficacy of various antihypertensive agents (diuretics, β-blockers, ACE inhibitors, ARBs, calcium-channel blockers, and α1-blockers) as first-line agents in the treatment of hypertension. There was an increase in congestive heart failure and cardiovascular events with α1-blockers compared with diuretics. [11] *Level of evidence: 1*

Thiazide diuretics have been found effective as a second drug in patients whose blood pressure is not controlled on monotherapy with another antihypertensive agent.

- A systematic review identified 53 double-blind RCTs with a total of 15,129 subjects in whom a thiazide was added to another agent to reduce blood pressure. The mean baseline blood pressure was 156/101 mm Hg. The addition of a thiazide at the recommended starting dose resulted in a mean reduction of 6 mm Hg systolic pressure and 3 mm Hg diastolic pressure; twice the recommended starting dose resulted in a drop of 8 mm Hg and 4 mm Hg, respectively. [17] *Level of evidence: 1*

References

Angiotensin-converting enzyme (ACE) inhibitors

Indications

- Effective in reducing blood pressure and particularly useful in the following circumstances: patients who do not respond to or do not tolerate diuretics or β-blockers; in combination with diuretics in patients not adequately controlled on diuretics alone; coexisting heart failure ; diabetes mellitus ; and proteinuria
- Also used as initial therapy, particularly in patients with hypertension who are not black

- Ramipril is specifically indicated to reduce risk of myocardial infarction , stroke , and cardiovascular death in patients aged 55 years or older who are at risk due to a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and at least one other cardiovascular risk factor. Evidence supporting ramipril may be a class effect that is often generalized to all ACE inhibitors in the class
- First choice in those with other indications for ACE inhibitors such as heart failure, diabetes, or coronary disease

Dose information

Benazepril :

- 10 to 40 mg orally once daily
- Maximum: 80 mg/d

Captopril :

- Initially, 12.5 to 25 mg orally two or three times a day; increase dose to 50 mg three times a day after 1 to 2 weeks depending on response
- Maximum: 450 mg/d

Enalapril :

- 2.5 to 5 mg orally once daily
- Maximum: 40 mg/d

Fosinopril :

- 10 to 40 mg orally once daily
- Maximum: 80 mg/day

Lisinopril :

- 10 to 40 mg orally once daily
- Maximum: 80 mg/d (rarely more effective than 40 mg/d)

Moexipril :

- 7.5 mg orally once daily
- Maximum: 30 mg/d

Perindopril :

- 2 to 8 mg orally once daily
- Maximum: 16 mg/d

Quinapril :

- 10 to 20 mg orally once daily
- Maximum: 80 mg/d

Ramipril :

- 2.5 to 20 mg orally once daily
- Maximum: 20 mg/d

Trandolapril :

- 1 to 4 mg orally once daily
- Maximum: 8 mg/d

Major contraindications

- Angioedema
- ACE inhibitor hypersensitivity

Comments

- Considered the therapy of choice in many patients with hypertension and are associated with decreased morbidity and mortality, and regression of left ventricular remodeling
- U.S. guidelines recommend ACE inhibitors as initial therapy in patients in need of antihypertensive drug therapy when there are compelling indications for their use or benefits in terms of management of comorbidities
- Compelling indications for use as a first-line treatment in patients with hypertension include coexisting heart failure , diabetes mellitus , or chronic kidney disease . Other indications include past history of myocardial infarction and patients with high risk of coronary heart disease
- Well-tolerated, but moderately expensive medications
- A significant number of patients develop some form of hypersensitivity to these agents, and they are the one antihypertensive agent that is contraindicated in the perioperative period

Evidence

ACE inhibitors are effective as initial therapy for hypertension, especially in patients with comorbid conditions such as heart failure, diabetes, or chronic renal failure.

- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. At least two thirds of patients with hypertension were randomly assigned to receive ACE inhibitors or ARBs versus placebo or other antihypertensive agents. Therapy with ACE inhibitors resulted in a significant 10% reduction in all-cause mortality, while ARB treatment did not result in further reduction in mortality. [7] *Level of evidence: 1*
- A pooled analysis of 20 RCTs evaluated cardiovascular morbidity and mortality in 158,998 patients with hypertension treated with a renin-angiotensin-aldosterone system inhibitor. With ACE inhibitors, there was 10% reduction in all-cause mortality. [18] *Level of evidence: 2*

There is evidence that ACE inhibitors lower blood pressure even at the lower end of the dosing range.

- A systematic review identified 92 RCTs including 12,954 subjects in which patients with hypertension took either an ACE inhibitor or placebo. Follow-up in most studies was approximately 6 weeks. The average effect was a reduction of 8 mm Hg systolic and 5 mm Hg diastolic pressure. Although this analysis examined placebo-controlled trials and not direct comparisons, the authors noted no apparent differences between the various agents in the class in efficacy versus placebo. They also concluded that higher doses result in only modest increases in blood pressure reduction, estimating that 70% of the maximum efficacy can be achieved at the lower end of the dosage range. [19] *Level of evidence: 1*

Diuretics, ACE inhibitors, β-blockers, and calcium-channel blockers have all been found to reduce stroke and events secondary to ischemic heart disease compared with placebo.

- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*

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groups. However, the doxazosin group experienced a significantly higher risk of stroke and combined cardiovascular disease. [9] *Level of evidence: 1*

ACE inhibitors versus calcium-channel blockers:

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Thiazide diuretics (or older agents) versus ACE inhibitors:

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found a significant increase in stroke with ACE inhibitors compared with the older agents. [5] *Level of evidence: 1*
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- A randomized, open-label, prospective trial of 6,083 elderly patients with hypertension was designed to assess the efficacy of ACE inhibitors and diuretics over a median of 4.1 years. There were fewer cardiovascular events or deaths from any cause among patients taking ACE inhibitors

compared with patients taking diuretics; this is particularly true for elderly men. [13] *Level of evidence: 1*

References

Angiotensin-II receptor blockers (ARBs)

Indication

- Alternative therapy to ACE inhibitors for hypertension

Dose information

Candesartan :

- 8 to 32 mg/d orally in one or two divided doses

Eprosartan :

- 400 to 800 mg/d orally in one or two divided doses

Irbesartan :

- 150 to 300 mg orally once daily

Losartan :

- 25 to 100 mg/d orally in one or two divided doses

Olmesartan :

- 5 to 40 mg orally once daily

Telmisartan :

- 20 to 80 mg orally once daily

Valsartan :

- 80 to 320 mg orally once daily

Comments

- Readily available but more expensive
- Shown to be superior to β-blockers in patients with left ventricular hypertrophy and in patients with diabetes mellitus type 2 and diabetic nephropathy , but are not superior in patients with congestive heart failure or after myocardial infarction
- Compelling indications for use as a first-line treatment in patients with hypertension include coexistent heart failure, diabetes mellitus, or chronic kidney disease
- Calcium-channel blockers give more rapid and persistent antihypertensive effects and better protection against myocardial infarction and stroke, but ARBs reduce heart failure and new onset diabetes

- In general, experts suggest that ACE inhibitors should remain the primary medication of choice for treatment of hypertension, with ARBs used only if ACE inhibitor intolerance (or coughing) develops

Evidence

There is evidence for the efficacy of ARBs in treating hypertension and some evidence for the efficacy of ARBs in improving cardiovascular outcome.

- A systematic review identified 46 RCTs including 13,451 subjects in which patients with hypertension took either an ARB or placebo. Follow-up in most studies was approximately 7 weeks. The average effect was a reduction of 8 mm Hg systolic and 5 mm Hg diastolic pressure. Although this analysis examined placebo-controlled trials and not direct comparisons, the authors noted no apparent differences between the various agents in this class in efficacy when compared with placebo. They also concluded that higher doses result in only modest increases in blood pressure reduction, estimating that 70% of the maximum efficacy can be achieved at the lower end of the dosage range. [20] *Level of evidence: 1*
- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found no significant difference

in terms of total mortality, cardiovascular mortality, myocardial infarction, and cardiovascular events. [5] *Level of evidence: 1*

- A systematic review of 97 studies directly comparing ACE inhibitors with ARBs supports the equivalence of ACE inhibitors and ARBs in blood pressure control and outcomes. Compared with ACE inhibitors, ARBs appear to have fewer short-term adverse effects, mostly cough. [21] *Level of evidence: 1*
- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*
- A meta-analysis and trial sequential analysis of 37 RCTs including 147,020 patients with a total follow-up of 485,166 patient-years showed that ARBs reduce the risk of stroke, heart failure, and new-onset diabetes mellitus, but not all-cause mortality, angina, or myocardial infarction compared with placebo or other active treatment. [22] *Level of evidence: 1*
- A pooled analysis of 20 RCTs evaluated cardiovascular morbidity and mortality in 158,998 patients with hypertension treated with a

renin-angiotensin-aldosterone system inhibitor. With ARBs, there was no reduction in all-cause mortality compared with placebo. [18] *Level of evidence: 2*

β-blockers versus ARBs:

- An RCT enlisted 9,193 adults aged 55 to 80 years with essential hypertension and known left ventricular hypertrophy to assess prevention of cardiovascular morbidity and mortality while on atenolol or losartan as initial drug treatment. After four years, there was no significant difference between atenolol and losartan as initial drug treatment in patients with hypertension for the outcomes of myocardial infarction, revascularization procedures, heart failure, or angina. It found a nonsignificant reduced incidence of stroke, new-onset diabetes, and overall mortality with losartan compared with atenolol. [23] *Level of evidence: 1*

Calcium-channel blockers versus ARBs:

- An RCT comparing valsartan with amlodipine in 15,245 people with high coronary heart disease risk and hypertension found no significant difference in cardiac morbidity and mortality between the two therapy groups. During the first month, the blood pressure effects were more pronounced in the amlodipine arm, but the differences between the two drugs was minimal at 1 year. The trial found a significant decrease in myocardial infarction with amlodipine versus valsartan. [24] *Level of evidence: 1*

ACE inhibitors versus ARBs:

- A systematic review of 61 studies involving thousands of patients showed that ACE inhibitors and ARBs have similar effects on blood pressure. There were no clear difference in outcomes such as death, cardiovascular diseases, or quality of life, but data on these long-term outcomes were more limited. [25] *Level of evidence: 1*
- An RCT involving 16,118 patients with vascular disease or high-risk diabetes compared telmisartan with the ACE-inhibitor ramipril. Telmisartan was not inferior in preventing new cardiovascular disease. [26] *Level of evidence: 1*

References

β-blockers

Indication

- Treatment of hypertension where there are also other indications for their use (*eg* , post- myocardial infarction , heart failure , atrial fibrillation)

Dose information

Acebutolol :

- 400 to 1,200 mg orally once daily

Atenolol :

- 25 to 100 mg orally once daily

Betaxolol :

- 10 to 20 mg orally once daily

Bisoprolol :

- 2.5 to 20 mg orally once daily

Carteolol :

- 2.5 to 10 mg orally once daily

Carvedilol :

- 6.25 mg orally twice a day (immediate release)
- 20 to 80 orally once daily (extended-release CR formulation)

Labetalol :

- 100 to 400 mg orally twice a day

Metoprolol :

- 100 to 450 mg orally once daily

Nadolol :

- 40 to 80 mg orally once daily

Nebivolol :

- 5 to 40 mg orally once daily

Penbutolol :

- 20 to 80 mg orally once daily

Pindolol :

- 10 to 30 mg/d orally in two or three divided doses

Propranolol :

- 40 to 160 mg orally twice a day

Timolol :

- 10 to 20 mg orally twice a day

Major contraindications

- Angioedema (carvedilol)
- Asthma (carvedilol, labetalol, nadolol, penbutolol, pindolol, propranolol, timolol)

- AV block
- β-blocker hypersensitivity (metoprolol)
- Bradycardia
- Cardiogenic shock
- Chronic obstructive pulmonary disease (timolol)
- Heart failure (acebutolol, atenolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, pindolol, timolol)
- Hepatic disease (carvedilol, nebivolol)
- Hypotension (labetalol, metoprolol)
- Pheochromocytoma (metoprolol)
- Sick sinus syndrome (betaxolol, carvedilol, metoprolol, nebivolol, propranolol)

Comments

- Readily available, efficacious, and relatively inexpensive
- The risk-to-benefit ratio is good, and patient acceptability is high
- Not usually recommended as first-line treatment for uncomplicated hypertension
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends that thiazide diuretics be used in drug treatment for most patients with uncomplicated hypertension, but certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes such as β-blockers. Compelling indications to consider β-blockers as initial antihypertensive drug therapy include patients with a high

coronary heart disease risk, past history of myocardial infarction, heart failure, or young women of child-bearing potential. β-blockers are useful when patients requiring antihypertensive drug therapy also have atrial tachyarrhythmias or fibrillation, migraine , thyrotoxicosis (short-term), essential tremor, or perioperative hypertension, but they should be avoided in patients with asthma , reactive airway disease, or second- or third-degree heart block

- The British Hypertension Society in combination with National Institute for Health and Clinical Excellence (NICE) guidelines do not recommend β-blockers as an initial therapy for hypertension except in younger people with intolerance of ACE inhibitors and ARBs, women of child-bearing potential, and people with evidence of increased sympathetic drive. There was less evidence for the reduction of major cardiovascular events, particularly of stroke, with β-blockers versus other comparator drugs, and there was increasing evidence that some β-blockers are associated with an unacceptable risk of provoking type 2 diabetes
- The Canadian Hypertension Education Program do not recommend β-blockers as first-line therapy for patients aged 60 years or older with no other compelling indications
- While historically β-blockers have been considered contraindicated in heart failure, newer evidence suggests that they can be beneficial in heart failure associated with diastolic dysfunction
- Compared with placebo, β-blockers reduce stroke and heart failure but without reduction in coronary artery disease or cardiovascular or total mortality

- Associated with increased cardiovascular events compared with diuretic agents
- Atenolol has been shown to be less effective in stroke prevention compared with a variety of other antihypertensive agents
- May be poorly tolerated in the elderly or frail

Evidence

Diuretics, ACE inhibitors, β-blockers, and calcium-channel blockers have all been found to reduce stroke and events secondary to ischemic heart disease compared with placebo.

- A systematic review of 13 studies assessed the safety and efficacy of β-blockers in 91,561 patients with hypertension. With β-blockers, there was a decrease in incidence of stroke but either no difference or an increase in incidence of total cardiovascular disease and all-cause mortality when compared with diuretics, calcium-channel blockers, and renin-angiotensin-aldosterone system inhibitors. However, 75% of subjects were taking atenolol, and it is not clear whether the same conclusions can be made about other subtypes of β-blocker. [27] *Level of evidence: 1*
- A systematic review of 20 RCTs found that β-blockers added as a second-line drug to either a thiazide diuretic or a calcium-channel blocker in 3,744 patients with hypertension was effective in reducing blood pressure by a mean of 6/4 mm Hg when prescribed at the recommended starting dose and 8/6 mm Hg when the dose was doubled. [28] *Level of evidence: 1*

- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*

Evidence from various systematic reviews suggests no advantage in terms of total mortality, cardiovascular mortality, and rates of myocardial infarction when classes of antihypertensive drugs are compared with each other.

- A systematic review of 13 studies assessed the safety and efficacy of β-blockers in 91,561 patients with hypertension. With β-blockers, there was a decrease in incidence of stroke but either no difference or an increase in incidence of total cardiovascular disease and all-cause mortality when compared with diuretics, calcium-channel blockers, and renin-angiotensin-aldosterone system inhibitors. However, 75% of subjects were taking atenolol, and it is not clear whether the same conclusions can be made about other subtypes of β-blocker. [27] *Level of evidence: 1*

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found no significant difference in terms of total mortality, cardiovascular mortality, myocardial infarction, and cardiovascular events. It found that heart failure occurred more frequently with the newer agents compared with the older agents. [5] *Level of evidence: 1*
- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. It found that heart failure occurred more frequently with the newer agents compared with the older agents. [7] *Level of evidence: 1*
- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already

present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*

Further evidence suggests the benefit of certain antihypertensive medications versus others in terms of improvements in particular outcomes other than total mortality. Some of the differences, however, may in part be due to the differences in blood pressure in the treatment groups.

β-blockers versus diuretics:

- A systematic review of 13 studies assessed the safety and efficacy of β-blockers in 91,561 patients with hypertension. With β-blockers, there was a decrease in incidence of stroke but either no difference or an increase in incidence of total cardiovascular disease and all-cause mortality when compared with diuretics, calcium-channel blockers, and renin-angiotensin-aldosterone system inhibitors. However, 75% of subjects were taking atenolol, and it is not clear whether the same conclusions can be made about other subtypes of β-blocker. [27] *Level of evidence: 1*
- A systematic review of 42 long-term RCTs involving 192,478 patients compared the efficacy of various antihypertensive agents (diuretics, β-blockers, ACE inhibitors, ARBs, calcium-channel blockers, and α1-blockers) as first-line agents in the treatment of hypertension. There was no significant difference between thiazide diuretics and β-blockers in terms of total mortality. There was a

nonsignificant benefit in terms of cardiovascular disease mortality, stroke, congestive heart failure, and coronary heart disease with diuretics versus β-blockers. [11] *Level of evidence: 1*

β-blockers versus ARBs:

- A systematic review of 13 studies assessed the safety and efficacy of β-blockers in 91,561 patients with hypertension. With β-blockers, there was a decrease in incidence of stroke but either no difference or an increase in incidence of total cardiovascular disease and all-cause mortality when compared with diuretics, calcium-channel blockers, and renin-angiotensin-aldosterone system inhibitors. However, 75% of subjects were taking atenolol, and it is not clear whether the same conclusions can be made about other subtypes of β-blocker. [27] *Level of evidence: 1*
- An RCT enlisted 9,193 adults aged 55 to 80 years with essential hypertension and known left ventricular hypertrophy to assess prevention of cardiovascular morbidity and mortality while on atenolol or losartan as initial drug treatment. After four years, there was no significant difference between atenolol and losartan as initial drug treatment in patients with hypertension for the outcomes of myocardial infarction, revascularization procedures, heart failure, or angina. It found a nonsignificant reduced incidence of stroke, new-onset diabetes, and overall mortality with losartan compared with atenolol. [23] *Level of evidence: 1*

β-blockers versus calcium-channel blockers:

- A systematic review of 13 studies assessed the safety and efficacy of β-blockers in 91,561 patients with hypertension. With β-blockers, there was a decrease in incidence of stroke but either no difference or an increase in incidence of total cardiovascular disease and all-cause mortality when compared with diuretics, calcium-channel blockers, and renin-angiotensin-aldosterone system inhibitors. However, 75% of subjects were taking atenolol, and it is not clear whether the same conclusions can be made about other subtypes of β-blocker. [27] *Level of evidence: 1*
- Using major cardiovascular events as an end point, a systematic review evaluated calcium-channel blockers versus other antihypertensive agents. The authors identified 18 trials with a total of 141,807 subjects. They found no differences in all-cause mortality between calcium-channel blockers and any other antihypertensive agent, but with calcium-channel blockers there was an increase in total cardiovascular deaths compared with β-blockers. [15] *Level of evidence: 1*
- The blood pressure lowering arm of ASCOT, a multicenter RCT involving 19,257 patients with hypertension and with additional high risk for cardiovascular disease, found no significant difference in terms of cardiovascular events or all-cause mortality between β-blockers and calcium-channel blockers for initial drug therapy in patients with hypertension. There was a trend toward decreased incidence of major cardiovascular events and induction of less diabetes with calcium-channel

Calcium-channel blockers (dihydropyridines)

Indication

- Effective in reducing blood pressure and particularly useful in the following circumstances: patients who do not respond to or do not tolerate diuretics or β-blockers; in combination with selected β-blockers in patients not adequately controlled on β-blockers alone; or in elderly patients with isolated systolic hypertension

Dose information

Amlodipine :

- 5 to 10 mg orally once daily

Clevidipine :

- 4 to 32 mg/h intravenously

Felodipine :

- 5 to 10 mg orally once daily

Isradipine :

- 5 to 20 mg orally once daily

Nicardipine :

- 20 to 40 mg orally three times a day (regular-release)
- 30 to 60 mg twice a day(sustained-release)

Nifedipine :

- 30 to 120 mg orally once daily

Nisoldipine :

- 17 to 34 mg orally once daily

Major contraindications

- Aortic stenosis (clevidipine, nicardipine)
- Cardiogenic shock (nifedipine)
- Dihydropyridine hypersensitivity (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine)
- Egg hypersensitivity (clevidipine)
- Hyperlipidemia (clevidipine)
- Pancreatitis (clevidipine)
- Soya lecithin hypersensitivity (clevidipine)

Comments

- Shown to be safe, effective, and relatively inexpensive
- Patients with diabetes mellitus type 2 who are treated with calcium-channel blockers appear to do better than those treated with diuretics
- Appear to not have adverse effects on blood glucose or lipid metabolism, unlike some diuretics
- Long-acting calcium-channel blockers are a suitable alternative to β-blockers for the initial treatment of hypertensive patients with stable angina
- Cause less fatigue than β-blockers and can be used in patients with asthma
- Outcome studies show that calcium-channel blockers are associated with reduced incidence of stroke , coronary heart disease, major cardiovascular events, and cardiovascular death compared with placebo, and are equally efficacious to conventional therapy with diuretics and/or β-blockers in reducing cardiovascular death, total mortality, and heart failure
- Associated with significantly lower rates of new-onset diabetes than therapy with β-blockers or diuretics
- May cause significant edema and may require the use of diuretic in combination with therapy

Evidence

Note: Of the calcium-channel blockers, the dihydropyridines have been studied most extensively, and most of the following evidence is derived largely from those studies, although some systematic reviews and meta-analyses also include data from studies that include the other classes.

Diuretics, ACE inhibitors, β-blockers, and calcium-channel blockers have all been found to reduce stroke and events secondary to ischemic heart disease compared with placebo.

- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*

Evidence from various systematic reviews suggests no advantage in terms of total mortality, cardiovascular mortality, and rates of myocardial infarction when classes of antihypertensive drugs are compared with each other.

- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found no significant difference in terms of total mortality, cardiovascular mortality, myocardial infarction, and cardiovascular events. It found that heart failure occurred more frequently with the newer agents compared with the older agents. [5] *Level of evidence: 1*

- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. It found that heart failure occurred more frequently with the newer agents compared with the older agents. [7] *Level of evidence: 1*
- A systematic review involving 156,766 patients with hypertension found a significant increase in diagnosis of heart failure in the group treated with calcium-channel blockers compared with those treated with other medications. [32] *Level of evidence: 1*
- A meta-analysis of 147 trials included 464,000 patients divided into three groups: no history of vascular disease; a history of coronary heart disease; and a history of stroke. It evaluated the efficacy of various blood pressure medication classes (thiazides, β-blockers, ACE inhibitors, ARBs and calcium-channel blockers) and showed that all classes of medications lowered blood pressure and similarly reduced coronary heart disease and stroke regardless of pretreatment levels or whether cardiovascular disease is already present. β-blockers offer added protection just after an acute myocardial infarction, and calcium-channel blockers may have an added effect in stroke prevention. [3] *Level of evidence: 1*
- A meta-analysis of 26 RCTs published from 1997 to 2009 and involving 223,313 patients with hypertension or high cardiovascular risk, with hypertension a predominant proportion, found that diuretics were the

most effective in preventing heart failure, followed by ACE inhibitors and ARBs, while calcium-channel blockers were among the least effective in heart failure prevention, together with β-blockers and α-blockers. [4] *Level of evidence: 1*

Evidence from various systematic reviews suggests no advantage in terms of total mortality, cardiovascular mortality, and rates of myocardial infarction when classes of antihypertensive drugs are compared with each other.

Chlorthalidone versus lisinopril, amlodipine, or doxazosin:

- An RCT, ALLHAT, enlisted 33,357 people aged 55 years or older with hypertension and at least one other coronary heart disease risk factor, and compared chlorthalidone to lisinopril, amlodipine, or doxazosin. It found that all interventions reduced blood pressure, but to varying degrees. The primary outcomes of coronary heart disease mortality and nonfatal myocardial infarction rates for chlorthalidone, lisinopril, and amlodipine were similar. Chlorthalidone was better at preventing combined cardiovascular events and stroke than doxazosin, better at preventing heart failure than amlodipine, and resulted in lower rates of combined cardiovascular disease events, stroke, and heart failure compared with lisinopril. [8] *Level of evidence: 1*
- Final results of ALLHAT, an RCT comparing chlorthalidone with doxazosin in additional 9,232 patient-years, showed that after a mean of 3.2 years, there was no difference in combined occurrence of fatal coronary heart disease or nonfatal myocardial infarction between the two groups. However, the doxazosin group experienced a significantly higher

risk of stroke and combined cardiovascular disease. [9] *Level of evidence: 1*

ACE inhibitors versus calcium-channel blockers:

- A systematic review of 29 trials involving 162,341 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers and ACE inhibitors) with older agents (diuretics and β-blockers). It found no significant difference among any of the medications with respect to reduction in total major cardiovascular events. Whatever the medication used, the regimens that targeted the lower blood pressure goals resulted in the largest reduction in total major cardiovascular events. However, there was a significant decrease in heart failure and a significant increase in stroke with ACE inhibitors compared with calcium-channel blockers. [7] *Level of evidence: 1*

β-blockers versus calcium-channel blockers:

- Using major cardiovascular events as an end point, a systematic review evaluated calcium-channel blockers versus other antihypertensive agents. The authors identified 18 trials with a total of 141,807 subjects. They found no differences in all-cause mortality between calcium-channel blockers and any other antihypertensive agent, but with calcium-channel blockers there was an increase in total cardiovascular deaths compared with β-blockers and with diuretics. Calcium-channel blockers reduced stroke compared with ACE inhibitors and ARBs but increased incidence of congestive heart failure compared with diuretics. [15] *Level of evidence: 1*

- The blood pressure lowering arm of ASCOT, a multicenter RCT involving 19,257 patients with hypertension and with additional high risk for cardiovascular disease, found no significant difference in terms of cardiovascular events or all-cause mortality between β-blockers and calcium-channel blockers for initial drug therapy in patients with hypertension. There was a trend toward decreased incidence of major cardiovascular events and induction of less diabetes with calcium-channel blockers. [29] *Level of evidence: 1*
- An RCT involving 2,344 patients with hypertension compared the efficacy of lacidipine and atenolol on the progression of asymptomatic carotid atherosclerosis. There was a significant 40% reduction in carotid intima-media thickness in the lacidipine group compared with the atenolol group. There was a trend toward decreased relative risk for stroke, major cardiovascular events, and mortality in the lacidipine group. [30] *Level of evidence: 1*
- A randomized, open-label study involved 22,576 patients with hypertension and coronary artery disease treated with either sustained-release verapamil or atenolol, with trandolapril and/or hydrochlorothiazide added to achieve blood pressure according to guidelines of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. After a mean of 2.7 patient-years, both drug regimens were clinically effective. [31] *Level of evidence: 2*

Calcium-channel blockers versus ARBs:

- An RCT comparing valsartan with amlodipine in 15,245 people with high coronary heart disease risk and hypertension found no significant difference in cardiac morbidity and mortality between the two therapy groups. During the first month, the blood pressure effects were more pronounced in the amlodipine arm, but the differences between the two drugs was minimal at 1 year. The trial found a significant decrease in myocardial infarction with amlodipine versus valsartan. [24] *Level of evidence: 1*

References

Calcium-channel blockers (benzothiazepines)

Indication

- Benzothiazepine calcium-channel blockers (*eg* , diltiazem) are preferable in treating hypertensive patients with angina or supraventricular tachycardia and are more effective in reducing proteinuria associated with hypertensive nephropathy

Dose information

- 30 to 120 mg orally three or four times a day (regular-release)
- 120 to 480 mg once a day (extended-release)

Major contraindications

- Acute myocardial infarction
- AV block
- Cardiogenic shock
- Hypotension
- Lown-Ganong-Levine syndrome
- Sick sinus syndrome
- Ventricular tachycardia
- Wolff-Parkinson-White syndrome

Comments

- Preferred medication in patients with contraindications to β-blockers
- Does not have detrimental effects on lipid profiles or serum glucose levels, making it good for patients with diabetes mellitus or metabolic syndrome
- May be particularly useful in patients with other indications for calcium-channel blockers, such as angina or supraventricular tachycardia
- Calcium-channel blockers cause less fatigue than β-blockers and offer better protection against stroke than ACE inhibitors

Evidence

Diltiazem has been shown to be as effective as diuretics and β-blockers, alone or combined, in the treatment of hypertension and the prevention of cardiovascular morbidity and mortality.

- In a prospective, randomized, open study, 10,881 patients with a diastolic blood pressure of 100 mm Hg or more were randomly assigned to receive diltiazem, a β-blocker, a diuretic, or a combination of the latter two drugs. Diltiazem resulted in significantly greater decreases in systolic blood pressure compared with the other groups; there was no difference between the treatment arms in the extent to which diastolic pressures were reduced. A primary end point (stroke, myocardial infarction, cardiovascular death) occurred in 403 patients in the diltiazem group and in 400 patients in the other group. [33] *Level of evidence: 1*

References

Calcium-channel blockers (phenylalkylamines)

Indication

- Phenylalkylamine calcium-channel blockers (*eg* , verapamil) are preferable in treating hypertensive patients with angina or supraventricular tachycardia and are more effective in reducing proteinuria associated with hypertensive nephropathy

Dose information

- 80 to 480 mg/d orally in three divided doses (immediate-release)

- Individualize dosage depending on the specific extended-release formulation

Major contraindications

- AV block
- Cardiogenic shock
- Heart failure
- Hypotension
- Lown-Ganong-Levine syndrome
- Sick sinus syndrome
- Ventricular dysfunction
- Ventricular tachycardia
- Wolff-Parkinson-White syndrome

Comments

- Preferred medication in patients with contraindications to β-blockers
- Does not have detrimental effects on lipid profiles or serum glucose levels, making it good for patients with diabetes mellitus or metabolic syndrome
- May be particularly useful in patients with other indications for calcium-channel blockers, such as angina or supraventricular tachycardia
- Calcium-channel blockers cause less fatigue than β-blockers and offer better protection against stroke than ACE inhibitors
- May be less well tolerated than other calcium channel blockers. Can cause significant constipation

Evidence

Verapamil is as effective as β-blockers or thiazide diuretics in controlling blood pressure.

- A prospective, double-blind, RCT compared controlled-onset extended-release verapamil to either atenolol or hydrochlorothiazide in 16,602 patients with hypertension. The reduction in blood pressure was similar in the two groups, but verapamil treatment was associated with more cardiovascular events, death due to cardiovascular events, and all-cause mortality. [34] *Level of evidence: 1*
- A randomized, open-label study involved 22,576 patients with hypertension and coronary artery disease treated with either sustained-release verapamil or atenolol, with trandolapril and/or hydrochlorothiazide added to achieve blood pressure according to guidelines of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. After a mean of 2.7 patient-years, both drug regimens were clinically effective. [31] *Level of evidence: 2*

References

Loop diuretics

Indication

- Generally reserved for the treatment of fluid control in patients with heart failure or chronic kidney disease

Dose information

Bumetanide :

- 0.5 to 2 mg orally once daily
- Maximum: 10 mg/d
- Hypertension is an off-label indication

Ethacrynic acid :

- 25 to 100 mg orally once daily
- Maximum: 400 mg/d
- Hypertension is an off-label indication

Furosemide :

- 20 to 80 mg/dose orally initially; increase dose by 20 to 40 mg/dose increments every 6 to 8 hours according to response
- Maximum: 600 mg/d

Torsemide :

- 5 mg orally once daily
- Maximum: 10 mg/d

Major contraindications

- Anuria
- Diarrhea (ethacrynic acid)
- Electrolyte imbalance (bumetanide)
- Hepatic encephalopathy (bumetanide)
- Infants (ethacrynic acid)
- Neonates (ethacrynic acid)
- Sulfonylurea hypersensitivity (torsemide)

Comments

- Furosemide is readily available, effective, and inexpensive
- Patient acceptability is high and the main risks such as orthostatic hypotension and hypokalemia are usually easily managed
- JNC7 states that a loop diuretic is often required for people with advanced renal disease (estimated glomerular filtration rate <30 mL/min per 1.73 m^2corresponding to a serum creatinine of 2.5-3.0 mg/dL), usually in combination with other drug classes
- Tachyphylaxis with the need for escalating doses can occur

Evidence

Loop diuretics are of moderate efficacy in decreasing diastolic and systolic blood pressure.

- A systematic review of nine trials involving 460 subjects evaluated the efficacy of loop diuretics in reducing blood pressure. The average reduction in systolic pressure was found to be 8 mm Hg and in diastolic pressure was found to be 4 mm Hg. [35] *Level of evidence: 1*

References

Potassium-sparing diuretics

Indication

- Adjunctive treatment with thiazide or loop diuretics to treat heart failure or hypertension, when it is clinically important to prevent hypokalemia or when persistent hypokalemia has been documented

Dose information

Amiloride :

- Initially, 5 to 10 mg/d orally. Titrate the dosage to achieve clinical goals
- Maximum: 20 mg/d

Triamterene :

- Initially, 50 to 100 mg orally twice daily. Use lower initial doses when used in combination with another diuretic or antihypertensive agent
- Maximum: 300 mg/d

Major contraindications

- Anuria
- Diabetic nephropathy
- Hepatic disease (triamterine)
- Hyperkalemia
- Renal disease
- Renal failure
- Renal impairment

Comments

- Carefully monitor serum potassium and electrolyte balance

Evidence

- A systematic review examining the efficacy of potassium-sparing diuretics (that block epithelial sodium channel, or ENaC) for primary hypertension did not find trials evaluating the blood pressure–lowering efficacy of ENaC blockers as monotherapy in patients with primary hypertension. Only 6 trials evaluated the blood pressure–lowering efficacy of low doses of amiloride and triamterene as a second drug in 496 participants with a baseline blood pressure of 151/102 mm Hg. The reviewers conclude that ENaC blockers do not have a statistically or clinically significant blood pressure–lowering effect at low doses but trials at higher doses are not available. [36] *Level of evidence: 2*

References

α1-blockers

Indication

- Effective in reducing blood pressure and particularly useful in patients who do not respond sufficiently to or do not tolerate diuretics or β-blockers; in combination with β-blockers in patients not adequately controlled on β-blockers alone; or coexisting benign prostatic hyperplasia
- Usually not prescribed as initial hypertensive therapy unless there is a compelling indication, because α1-blockers confer less cardiovascular benefit compared with chlorthalidone based on the results of ALLHAT

Dose information

Doxazosin :

- 1 to 8 mg orally once daily
- Maximum: 16 mg/d

Prazosin :

- Initially, 1 mg orally two or three times a day
- Maximum: 20 mg/d

Terazosin :

- 1 to 5 mg orally once daily
- Maximum: 20 mg/d

Comments

- Effective in lowering blood pressure but may do so at the cost of reflex increased heart rate, an effect that can be particularly detrimental in patients with ischemic heart disease
- May be more likely to benefit patients who have diabetes mellitus or metabolic syndrome because of a lack of metabolic adverse effects
- Provide symptomatic relief in men with benign prostatic hypertrophy
- Taper dose; can cause a rebound of hypertension if stopped abruptly

Evidence

α 1 -blockers are moderately effective in controlling systolic and diastolic hypertension. Cardiovascular adverse-effect profile might limit use in some patients.

- A systematic review evaluated the efficacy of α1-blockers in lowering blood pressure. Ten trials involving 1,175 subjects were identified. The average reduction in systolic pressure was 8 mm Hg and in diastolic pressure, 5 mm Hg [37] *Level of evidence: 1*
- A systematic review of 15 trials involving 120,574 patients with hypertension compared newer antihypertensive agents (calcium-channel blockers, ACE inhibitors, ARBs, and α1-blockers) with older agents (diuretics and β-blockers). It found that α1-blockers were associated with an increase in congestive heart failure and cardiovascular events, and a

slight increase in stroke, compared with the older agents. [5] *Level of evidence: 1*

- A systematic review of 42 long-term RCTs involving 192,478 patients compared the efficacy of various antihypertensive agents (diuretics, β-blockers, ACE inhibitors, ARBs, calcium-channel blockers, and α1-blockers) as first-line agents in the treatment of hypertension. There was a similar increase in congestive heart failure and cardiovascular events with α1-blockers versus diuretics. [11] *Level of evidence: 1*

References

Methyldopa

Indication

- Methyldopa is used in the management of moderate to severe hypertension; particularly useful in the management of hypertension in pregnancy

Dose information

- 250 mg orally two to three times a day
- Maximum: 3,000 mg/d

Major contraindications

- Hepatic disease

- Hepatitis
- Monoamine oxidase inhibitor therapy

Comments

- Still used despite adverse central nervous system effects and potentially serious hepatic and blood adverse effects
- Lowers blood pressure without losing heart rate and is relatively inexpensive

Evidence

Methyldopa is moderately effective in managing systolic and diastolic hypertension, but reduction in cardiovascular and total mortality may only extend to subsets of patients.

- A systematic review found that methyldopa and reserpine reduced the incidence of congestive heart failure in people with initial diastolic blood pressure levels above 110 mm Hg by 86% compared with placebo. In the subgroup of people aged 60 years or younger, there was a significant reduction in stroke but no difference in total mortality with reserpine or methyldopa versus placebo. In the subgroup of people aged 60 years or older, there was a significant reduction in stroke, coronary heart disease events, cardiovascular disease deaths, congestive heart failure, and total mortality with methyldopa or β-blockers compared with placebo. [38] *Level of evidence: 1*
- A systematic review of 12 trials including 595 patients with essential hypertension on methyldopa 500 to 2,250 mg daily compared with

placebo found that while methyldopa lowers blood pressure by a mean of 13/8 mm Hg, there is no evidence assessing benefit or risk on cardiovascular outcomes. [39] *Level of evidence: 1*

References

Minoxidil

Indication

- Minoxidil is used when standard medications have failed to control blood pressure
- Can be used in combination with a β-blocker and a diuretic in severe hypertension resistant to other agents

Dose information

- Initially, 5 mg orally once daily; increase dose by 5 to 10 mg/d at intervals of 3 days or longer to usual dose of 10 to 40 mg/d
- Maximum: 100 mg/d

Major contraindications

- Pheochromocytoma

Comments

- Long-acting and efficacious in lowering blood pressure
- Usually limited mainly to men with severe refractory hypertension or renal insufficiency
- Causes profuse hirsutism , an adverse effect that limits its use in women
- It is associated with intense renal sodium retention requiring administration of loop diuretics to overcome; dilates renal arterioles; and has positive effects on renal function in hypertensive nephropathy

Evidence

Minoxidil has been studied primarily in patients with refractory hypertension, to whom it is given in combination with other antihypertensive agents. Data are limited to small trials.

- In an older comparative study, 238 hypertensive patients whose blood pressure was uncontrolled by a β-blocker plus a diuretic were randomly assigned to receive one of the following additional drugs: placebo, minoxidil, hydralazine, methyldopa, prazosin, or labetalol (the latter prescribed instead of the original β-blocker). All of the antihypertensive drugs reduced blood pressure more effectively than placebo, and minoxidil was superior in efficacy to any of the others but was not well tolerated. [40] *Level of evidence: 3*

References

Hydralazine

Indication

- Hydralazine is used in combination with other medications in the treatment of moderate to severe hypertension

Dose information

- 10 mg orally four times a day; increase to 25 mg four times a day for the first week. For second and subsequent weeks, increase to 50 mg four times a day
- Maximum: 300 mg/d

Major contraindications

- Coronary artery disease (in selected patients)
- Rheumatic heart disease

Comments

- Inexpensive and used widely, particularly in underdeveloped countries
- Has been largely been replaced in developing countries by calcium-channel blockers or other vasodilators because of the lack of evidence for regression of left ventricular hypertrophy with treatment and concerns about the development of lupus
- Useful in combination with nitrates in ACE inhibitor intolerant patients

Evidence

There is a lack of published evidence on the efficacy of hydralazine for blood pressure control.

- A systematic review sought to evaluate the efficacy of hydralazine in reducing blood pressure and to determine the nature and extent of adverse effects, but no RCTs meeting selection criteria in which hydralazine monotherapy was compared with placebo could be identified. [41] *Level of evidence: 1*

References

Clonidine

Indication

- Clonidine is useful in patients with hypertension that is resistant to other therapies

Dose information

Immediate-release:

- Initially, 0.1 mg orally twice a day; increase by 0.1 to 0.2 mg/d every 2 to 4 days as necessary
- Maximum: 2.4 mg/d

Extended-release:

- Initially, 0.1 mg orally once daily at bedtime; increase by 0.1 mg/day at weekly intervals as necessary
- Maximum: 0.6 mg/d

Transdermal:

- Available in topical preparation (Topical Therapeutic System, or TTS), which produces steady trough levels of the oral doses of 0.1 mg twice a day (TTS-1), 0.2 mg twice a day (TTS-2), or 0.3 mg twice a day (TTS-3)

Comments

- Very effective in lowering blood pressure across age and racial groups. However, intolerance to the medication limits its use in up to 14% of patients
- Clonidine withdrawal is a serious problem if stopped suddenly, and adverse central nervous system effects include worsening of depression
- Has been implicated in bradycardic spells in some patients

Evidence

The efficacy of clonidine versus placebo and other antihypertensive agents has been studied in several large trials.

- A randomized, double-blind study that enrolled 1,292 men with hypertension randomly assigned subjects to receive placebo, hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, or prazosin.

Patients were treated for a year, and doses were adjusted toward a goal diastolic blood pressure of 90 mm Hg or less. The proportion of patients reaching the goal in each treatment group was as follows: diltiazem, 59%; atenolol, 51%; clonidine, 50%; hydrochlorothiazide, 46%; captopril, 42%; prazosin, 42%; and placebo, 25%. Black patients responded more successfully to diltiazem (64%). Younger white men responded more successfully to captopril (55%), and older white men responded more successfully to atenolol (68%). Drug intolerance occurred most frequently with clonidine. [42] *Level of evidence: 2*

- In a continuation of the above study that enrolled 1,292 men with hypertension and randomly assigned subjects to receive placebo, hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem, or prazosin, patients were treated for a year, and doses were adjusted toward a goal diastolic blood pressure of 90 mm Hg or less. In the second phase of the study, 352 of the 410 patients who failed to reach the target blood pressure with the first agent were randomly assigned to receive one of the other drugs. Target blood pressure control was achieved in 173 of the 352 patients, with the proportion reaching the goal in each group as follows: diltiazem, 63%; clonidine, 59%; prazosin, 47%; hydrochlorothiazide, 46%; atenolol, 41%; and captopril, 37%. [43] *Level of evidence: 2*

References

Aldosterone antagonists

Indication

- Used as monotherapy or in combination with other medications in moderate to severe hypertension

Dose information

Spironolactone :

- 50 to 100 mg/d orally

Eplerenone :

- 50 mg/d orally

Major contraindications

- Anuria (spironolactone)
- Hyperkalemia
- Renal disease (eplerenone)
- Renal failure

Comments

- Eplerenone is effective in reducing morbidity and mortality in post-myocardial infarction heart failure
- In combination with an ACE inhibitor, eplerenone is effective in reducing left ventricular hypertrophy and improving diastolic dysfunction
- A major risk is hyperkalemia , and potassium levels warrant close monitoring at the initiation of therapy

- In contrast to spironolactone, antiandrogenic adverse effects such as gynecomastia and erectile dysfunction , and antiprogestational effects such as oligomenorrhea are reduced with eplerenone

Evidence

Spironolactone is an effective fourth-line antihypertensive agent.

- A meta-analysis of five crossover studies involving 137 patients with hypertension found that spironolactone (100-500 mg/d) results in a significant reduction of 20 mm Hg in systolic and 6.7 mm Hg in diastolic blood pressure compared with placebo. A dose of 25 mg/day did not statistically significantly reduce systolic or diastolic blood pressure compared with placebo. [44] *Level of evidence: 2*
- As part of ASCOT, a multicenter RCT studying cardiovascular outcomes in 19,257 patients with hypertension and with additional high risk for cardiovascular disease, one arm of 1,411 hypertensive patients received spironolactone as fourth-line antihypertensive agent. After a median of 1.3 years, spironolactone, in primarily 25 to 50 mg dosing, showed a powerful antihypertensive effect, reducing blood pressure 21.9/9.5 mm Hg. [45] *Level of evidence: 2*

Eplerenone has been found effective as monotherapy for hypertension and as a second agent in an incompletely effective regimen.

- An RCT compared eplerenone versus losartan versus placebo in 751 patients with mild to moderate hypertension during a 16-week period. The study found that eplerenone was superior to both losartan and placebo in reducing systolic blood pressure in black patients and as effective as losartan in reducing systolic blood pressure in white patients. [46] *Level of evidence: 2*
- An RCT compared eplerenone versus placebo in 341 hypertensive patients treated with either ACE inhibitors or ARBs whose blood pressure was not controlled. The study found that the addition of eplerenone nonsignificantly lowered systolic blood pressure in both groups and diastolic blood pressure in the ARB patients compared with placebo. [47] *Level of evidence: 2*

References