

Sympatholytic Agents Centrally acting α_2 sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions. Rebound hypertension is another concern with abrupt cessation of drugs with a short half-life.

Calcium Channel Blockers Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers, α_1 -adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

Direct Vasodilators Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a potent direct vasodilator that has antioxidant and nitric oxide-enhancing actions, and minoxidil is a particularly potent agent and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion. Intravenous nitroprusside can be used to treat malignant hypertension and life-threatening left ventricular heart failure associated with elevated arterial pressure.

COMPARISONS OF ANTIHYPERTENSIVES

Based on pooling results from clinical trials, meta-analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood pressure-lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and α_1 blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients over age 50 may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Early pharmacogenetic studies, utilizing either a candidate gene approach or genome-wide scans, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed.

Currently, in practical terms, the presence of comorbidities often influences the selection of antihypertensive agents.

A meta-analysis of more than 30 randomized trials of blood pressure-lowering therapy indicates that for a given reduction in blood pressure, the major drug classes seem to produce similar overall net effects on total cardiovascular events. In both nondiabetic and diabetic hypertensive patients, most trials have failed to show significant differences in cardiovascular outcomes with different drug regimens as long as equivalent decreases in blood pressure were achieved. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of CHD and nonfatal myocardial infarction, as well as overall mortality, was virtually identical in hypertensive patients treated with either an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine).

However, in specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. In patients with type 2 diabetes, treatment with an ACEI, an ARB, or aliskiren decreases proteinuria and delays the progression of renal disease. In experimental models of hypertension and diabetes, renal protection with aliskiren is comparable to that with ACEIs and ARBs. However, in patients with type 2 diabetes, addition of aliskiren to an ACEI provides no additional protection against cardiovascular or renal disease and may be associated with more adverse outcomes. Among African Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures. In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, the use of diuretics, ACEIs or ARBs, and beta blockers is recommended to improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post-myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a large, double-blind, prospective clinical trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH Trial]) indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly.

After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, has been reported to reduce the rate of recurrent stroke. Some of these apparent differences may reflect differences in trial design and/or patient groups.

There is a recent resurgence of interest in two nonpharmacologic, antihypertensive therapies that interrupt sympathetic outflow: (1) device-based carotid baroreflex activation by electrical stimulation of the carotid sinus; and (2) endovascular radiofrequency ablation of the renal sympathetic nerves. Whereas renal denervation is a minimally invasive procedure, carotid baroreceptor stimulation is a surgical procedure, usually performed under general anesthesia, that currently involves implanting electrodes on both the right and left carotid arteries. Both interventions inhibit sympathetic drive and