



Choice of therapy in essential hypertension: Recommendations

Authors

Norman M Kaplan, MD
Burton D Rose, MD

Section Editor

George L Bakris, MD

Deputy Editor

Alice M Sheridan, MD

Last literature review for version 17.3: September 30, 2009 | **This topic last updated:** July 23, 2009

INTRODUCTION — There is no uniform agreement as to which antihypertensive drugs should be given for initial therapy. The major options are:

- Thiazide-type diuretics
- Angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs)
- Calcium channel blockers
- Beta blockers, which are now used less often for initial therapy in the absence of a specific indication for their use

Recommendations concerning the use of particular agents for the initial treatment of hypertension will be presented here. The efficacy of these agents, the clinical trials that examined their effects upon patient outcomes, particularly cardiovascular morbidity and mortality, and the indications for initiating antihypertensive therapy are discussed separately. (See "[Choice of therapy in essential hypertension: Clinical trials](#)" and "[Hypertension: Who should be treated?](#)".)

RELATIVE EFFICACY OF ANTIHYPERTENSIVE DRUGS — Each of the antihypertensive agents is roughly equally effective in lowering the blood pressure, producing a good antihypertensive response in 30 to 50 percent of patients ([graph 1](#) and [graph 2](#)) [1-5]. There is, however, wide interpatient variability as many patients will respond well to one drug but not to another. (See '[Initial monotherapy](#)' below.)

Importance of attained blood pressure — Meta-analyses published in 2008 and 2009, the 2007 American Heart Association statement on the treatment of blood pressure in ischemic heart disease, and the 2007 European Society of Hypertension/European Society of Cardiology guidelines on the management of hypertension all concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in both younger and older patients with hypertension, NOT the choice of antihypertensive drug [1,2,6,7].

This conclusion was based upon the finding in a number of large randomized trials that, at the same level of blood pressure control, most antihypertensive drugs provide the same degree of cardiovascular protection. As an example, the CAPPP, STOP-Hypertension-2, NORDIL, UKPDS, and INSIGHT trials found little overall difference in outcomes between older (such as diuretics and beta blockers) and newer antihypertensive drugs (such as ACE inhibitors and calcium channel blockers) [3,8]. Similar findings have been noted in the subgroup of patients at increased cardiovascular risk. (See "[Choice of therapy in essential hypertension: Clinical trials](#)" and "[Choice of antihypertensive drug and blood pressure goal in patients at increased risk for a cardiovascular event](#)".)

When differences in outcomes have been noted in trials comparing different antihypertensive drugs, the drug producing better outcomes had better blood pressure control. As examples:

- The ASCOT trial found a lower rate of cardiovascular disease and death with a calcium channel blocker ([amlodipine](#)) compared to a beta blocker ([atenolol](#)). However, patients in the amlodipine arm had a significantly lower mean blood pressure at the end of the study (3/2 mmHg) [[9](#)].

- [Ramipril](#) and [perindopril](#) produced better outcomes than placebo in the HOPE and EUROPA trials of patients at increased cardiovascular risk, but the blood pressure was significantly lower in the treated patients: 3.3/1.4 mmHg (with a greater difference overnight) in HOPE and 5/2 mmHg in EUROPA [[10,11](#)]. (See "[Choice of antihypertensive drug and blood pressure goal in patients at increased risk for a cardiovascular event](#)".)

- In the VALUE trial, [amlodipine](#) produced better outcomes than [valsartan](#) but also greater blood pressure reduction. When 5000 pairs were matched exactly for systolic blood pressure and other risk factors, the two groups had nearly identical rates of cardiovascular events [[12](#)].

Possible exceptions to these general findings were thought to come from the ALLHAT trial of monotherapy and from the ACCOMPLISH trial of combination therapy..

ALLHAT trial — The ALLHAT trial randomly assigned over 41,000 hypertensive patients (mean blood pressure 146/84 mmHg) with at least one other coronary risk factor to one of four initial regimens: [chlorthalidone](#) (12.5 to 25 mg/day), [amlodipine](#), [lisinopril](#), or [doxazosin](#), which was prematurely terminated due to an increased risk of heart failure [[13](#)]. At a mean follow-up of 4.9 years, the primary outcome (fatal coronary heart disease and nonfatal myocardial infarction) was the same in the three arms ([graph 3](#)) [[13](#)]. However, the chlorthalidone arm had a significantly lower rate of heart failure than amlodipine and lisinopril ([graph 4](#)) and a significantly lower rate of combined cardiovascular disease outcomes than lisinopril ([graph 5](#)). (See "[Choice of therapy in essential hypertension: Clinical trials](#)", [section on 'ALLHAT trial'](#).)

It seems likely that the benefits seen with [chlorthalidone](#) were due at least in part to an earlier and greater degree of blood pressure reduction, similar to the findings with [amlodipine](#) in the VALUE trial described in the preceding section [[12](#)]. Chlorthalidone was associated with a small but significantly lower systolic pressure over the course of the study than amlodipine or [lisinopril](#) (133.9 versus 134.7 and 135.9 mmHg, respectively) and a higher proportion of patients who attained the blood pressure goal of less than 140/90 mmHg (68.2 versus 66.3 and 61.2 percent, respectively). The difference in mean systolic blood pressure was most pronounced in the first two years (136.4 versus 137.8 and 139.2 mmHg, respectively).

Twenty-four-hour blood pressure monitoring was not obtained in ALLHAT, which may have been important, since [chlorthalidone](#) is long-acting, while the effect of [lisinopril](#) may diminish toward the end of the day, especially at doses of 10 mg/day.

The findings in ALLHAT led the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), which was published in 2003, and others to conclude that low-dose thiazides (eg, [hydrochlorothiazide](#) or [chlorthalidone](#) at 12.5 mg/day) should be used in the initial drug treatment of most patients with uncomplicated hypertension, unless there is a specific indication for a drug from another class ([table 1](#)) [[14,15](#)]. (See '[Indications for specific drugs](#)' below.)

One cannot exclude that the observed benefits with [chlorthalidone](#) in ALLHAT were due at least in part to the lower attained blood pressure, which is in keeping with the findings in other trials cited in the preceding section.

Looking at the data in another way, there was no difference in the primary end point among the three treated groups ([graph 3](#)), despite the lower attained blood pressure with [chlorthalidone](#). This raises the

possibility that thiazide diuretics may actually be associated with worse outcomes at the same attained blood pressure. Although this may seem to represent manipulation of the data, it is an important consideration given the findings in the ACCOMPLISH trial in which [benazepril](#) plus [hydrochlorothiazide](#) was associated with worse cardiovascular outcomes than benazepril plus [amlodipine](#), despite a trend toward lower 24-hour average blood pressure in the benazepril plus hydrochlorothiazide group. (See '[ACCOMPLISH trial](#)' below.)

Chlorthalidone versus hydrochlorothiazide — [Chlorthalidone](#) at the same dose is approximately 1.5 to 2.0 times as potent as [hydrochlorothiazide](#) [16-18]. Thus, 12.5 mg/day of chlorthalidone is equivalent to 19 to 25 mg/day of hydrochlorothiazide. This may not be so important for efficacy since the dose-response curve for thiazide diuretics in the treatment of essential hypertension is relatively flat ([graph 6](#)) [2,19,20]. However, metabolic complications, such as hypokalemia, glucose intolerance, and hyperuricemia increase with dose ([graph 7](#)) [2,19,20]. In two major trials of low-dose chlorthalidone (12.5 to 25 mg/day), treatment for hypokalemia was required in 7 to 8 percent of patients [13,21]. (See "[Thiazide diuretics in essential hypertension](#)" and "[Diuretic-induced hypokalemia](#)".)

A possibly more important difference than potency is the longer duration of action of [chlorthalidone](#) (24 to 72 hours versus 6 to 12 hours with [hydrochlorothiazide](#)) [16,18]. This may not affect office blood pressure if the medication is taken in the morning but may result in a greater fall in nighttime blood pressure with chlorthalidone compared to baseline (eg, -13.5 mmHg with 12.5 mg/day [force titrated to 25 mg/day] versus -6.4 mmHg with 25 mg/day [force titrated to 50 mg/day] of hydrochlorothiazide in a small randomized, crossover trial) [17].

The importance of the shorter duration of action of [hydrochlorothiazide](#) was also addressed in a study in which 24-hour ambulatory monitoring was performed in 228 patients with essential hypertension [22]. The mean fall in blood pressure with ambulatory monitoring after four weeks of therapy with hydrochlorothiazide 25 mg/day was significantly greater with office blood pressure compared to 24-hour ambulatory measurements (14.3 versus 9.5 mmHg).

There are no randomized trials comparing outcomes in hypertensive patients treated with [hydrochlorothiazide](#) or [chlorthalidone](#). A meta-analysis of trials comparing one of the two drugs to placebo concluded that the magnitude of benefit was similar with the two drugs [23]. However, the daily doses used in the trials that accounted for most of the patients in the meta-analysis were roughly equipotent: 25 to 50 mg of hydrochlorothiazide in combination with [amiloride](#) or [triamterene](#) and 12.5 to, if necessary, 25 mg of chlorthalidone.

Given the lower potency of [hydrochlorothiazide](#) at the same dose and its shorter duration of action, one cannot conclude in the absence of evidence that 12.5 mg/day of hydrochlorothiazide will produce the same cardiovascular benefit as 12.5 mg/day of [chlorthalidone](#). Furthermore, the evidence supporting the efficacy of low-dose thiazide diuretics in the management of hypertension comes primarily from trials using chlorthalidone, such as ALLHAT [13]. There is little if any evidence that hydrochlorothiazide alone in a dose of 12.5 to 25 mg/day reduces cardiovascular events [24-26] and the blood pressure may not be as well-controlled overnight [17,27]. In addition, in the ACCOMPLISH trial, which compared combination therapy with [benazepril](#) plus either hydrochlorothiazide (12.5 to 25 mg/day) or [amlodipine](#), cardiovascular outcomes were worse in the [benazepril-hydrochlorothiazide](#) group. (See '[ACCOMPLISH trial](#)' below.)

Choice of thiazide diuretic — Based on the above observations, we and other experts suggest that [chlorthalidone](#) (12.5 to 25 mg/day) is the low-dose thiazide diuretic of choice [18,24-26]. However, the choice may vary with the clinical setting:

- In most patients not previously treated with a thiazide diuretic, we suggest low-dose [chlorthalidone](#), rather than [hydrochlorothiazide](#). However, among frail older patients who are less than 10 mmHg above

goal blood pressure, some consider low-dose hydrochlorothiazide a reasonable alternative.

- Among patients already treated with low-dose [hydrochlorothiazide](#), the optimal approach has not been defined. Some experts would switch all patients to [chlorthalidone](#) at their next visit, with the possible exception of those who monitor their blood pressure at home and have values below goal on the first morning measurement.

Monitoring for hypokalemia — [Chlorthalidone](#) produced hypokalemia requiring therapy in 7 to 8 percent of patients in large clinical trials including ALLHAT and SHEP [[13,21](#)]. It is possible that hypokalemia is more common with chlorthalidone than [hydrochlorothiazide](#), given its longer duration of action. Concurrent use of a low [salt](#) diet will both contribute to blood pressure lowering and reduce the risk of hypokalemia [[28,29](#)]. (See "[Diuretic-induced hypokalemia](#)".)

Monitoring for the development of hypokalemia is warranted with all thiazide diuretics. In stable patients on a fixed dose of either [chlorthalidone](#) or [hydrochlorothiazide](#), potassium loss, like other diuretic-induced fluid and electrolyte complications, occurs only during the first two weeks of therapy before a new steady state is established ([graph 8](#)). Thus, a stable patient with a normal serum potassium concentration at three weeks is not at risk of late hypokalemia unless the diuretic dose is increased, extrarenal potassium losses increase, or dietary potassium intake is reduced. (See "[The steady state](#)" and "[Time course of diuretic-induced electrolyte complications](#)".)

Issues with chlorthalidone — We recognize that most clinicians, particularly in the United States, have limited, if any, experience with [chlorthalidone](#). The basic principles of monitoring for hypokalemia with chlorthalidone are identical to those with [hydrochlorothiazide](#), as described in the preceding section.

There are three other potential limitations:

- It is not available in all formularies and pharmacies.
- There is no 12.5 mg tablet. Thus, 25 mg tablets of generic [chlorthalidone](#) need to be cut in half. There is a more expensive 15 mg brand name preparation (Thalitone®). This preparation has greater bioavailability than generic chlorthalidone, and clinical studies suggest that its antihypertensive efficacy is closer to 25 mg of generic chlorthalidone.
- In patients who require combination therapy, the current lack of availability (compared to [hydrochlorothiazide](#)) of fixed dose combination pills with ACE inhibitors, angiotensin II receptor blockers, and long-acting calcium channel blockers. (See '[Combination therapy](#)' below.)

ACCOMPLISH trial — Only one major trial, ACCOMPLISH, directly compared different combination regimens in hypertensive patients who require two drugs [[30](#)]. The results of ACCOMPLISH are discussed in detail elsewhere but will be briefly reviewed here. (See "[Choice of therapy in essential hypertension: Clinical trials](#)", section on '[ACCOMPLISH trial](#)'.)

The ACCOMPLISH trial included 11,506 patients with hypertension who were at high risk for a cardiovascular event and, despite prior antihypertensive therapy in 97 percent (most requiring two or more drugs), had a mean baseline blood pressure of 145/80 mmHg [[31](#)]. The patients were randomly assigned to initial combination therapy with [benazepril](#) (20 mg/day) plus either [amlodipine](#) (5 mg/day) or [hydrochlorothiazide](#) (12.5 mg/day). Benazepril was increased to 40 mg/day in both groups at one month. If goal blood pressure was not attained, the amlodipine dose was increased to 10 mg/day and the hydrochlorothiazide dose to 25 mg/day.

The primary end point was measured as the time to the first event, which was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac death and coronary revascularization. The trial was terminated early by

the Data Safety Monitoring Board at a mean follow-up of 36 months when the prespecified stopping rule was exceeded.

The primary end point was achieved significantly less often in the [benazepril-amlodipine](#) group (9.6 versus 11.8 percent, hazard ratio 0.80, 95% CI 0.72-0.90). There was a similar reduction in the secondary end point of cardiovascular death or nonfatal myocardial infarction or stroke (5.0 versus 6.3 percent, hazard ratio 0.79). These benefits increased progressively over the duration of the trial ([graph 9](#)).

The mean office blood pressure was slightly (about 1 mmHg) but significantly lower in the [benazepril-amlodipine](#) group (131.6/73.3 compared to 132.5/74.4 mmHg). However, in contrast to all other major randomized trials that compared the outcomes with different antihypertensive drugs, ACCOMPLISH included 24-hour blood pressure monitoring in a subset of 573 patients. The results were presented at the American Society of Hypertension meeting in May 2009. The 24-hour average blood pressure was nonsignificantly higher (1.6/0.3 mmHg) in the benazepril-amlodipine group. Similar trends were noted with daytime and nighttime average blood pressures.

Thus, the clinical benefits with the [benazepril-amlodipine](#) combination cannot be explained by better blood pressure control. The difference in outcome can be explained in one or both of two ways: there is a beneficial effect of benazepril-amlodipine or an adverse effect of [benazepril-hydrochlorothiazide](#). There is no way to distinguish between these possibilities.

Implications for practice — The ACCOMPLISH trial was large, well designed, and without apparent flaws. In addition, it compared combination regimens using the three classes of antihypertensive drugs that are preferred for initial monotherapy in the absence of a specific indication for a particular drug class. (See '[Initial monotherapy](#)' below and '[Indications for specific drugs](#)' below.)

Some have suggested that confirmatory trials are required before practice recommendations are changed. However, such information is unlikely to be available for many years.

We and our peer reviewers feel that the results of ACCOMPLISH should not be ignored and that they raise the following questions about the use of a long-acting ACE inhibitor/ARB and a long-acting dihydropyridine calcium channel blocker (A/dC):

- Is the A/dC combination the preferred regimen in previously untreated patients who require two drugs because they are more than 20/10 mmHg above goal?
- Should patients being treated with the combination of an ACE inhibitor/ARB and a thiazide diuretic who are at goal and doing well be switched to A/dC? Approximately 75 percent of patients in ACCOMPLISH had previously been treated with two or more antihypertensive drugs [[31](#)].
- In patients being treated with and having responded to a thiazide diuretic who require a second antihypertensive drug, should the thiazide be discontinued and the patient started on A/dC?
- Does ACCOMPLISH affect the choice of monotherapy, with a long-acting ACE inhibitor/ARB or a long-acting dihydropyridine calcium channel blocker being preferred so that the second class can be added if the patient responds but does not reach goal with the initial drug?

These issues will be discussed below. (See '[Combination therapy](#)' below and '[Summary and recommendations](#)' below.)

INITIAL MONOTHERAPY — The goal of antihypertensive therapy in most patients with uncomplicated combined systolic and diastolic hypertension is a blood pressure of less than 140/90 mmHg. A lower goal blood pressure, less than 130/80 mmHg, is indicated in patients with diabetes mellitus, proteinuric

chronic kidney disease, and known atherosclerotic cardiovascular disease. Among patients with isolated systolic hypertension, the goal systolic pressure is less than 140 mmHg, but the diastolic blood pressure should not be reduced to less than 65 mmHg in elderly patients to attain the target systolic pressure. (See "[What is goal blood pressure in treatment of hypertension?](#)".)

Initial monotherapy is successful in most patients with mild essential hypertension. However, single drug therapy is unlikely to attain goal blood pressure in patients whose blood pressures are more than 20/10 mmHg above goal. In such patients, initial combination therapy using two drugs is recommended. (See '[First-line combination therapy](#)' below.)

General principles — Each of the antihypertensive agents is roughly equally effective in lowering the blood pressure, producing a good antihypertensive response in 30 to 50 percent of patients ([graph 1](#) and [graph 2](#)) [1-5]. There is, however, wide interpatient variability as many patients will respond well to one drug but not to another. There are some predictable differences, such as black patients generally responding better to monotherapy with a thiazide diuretic or calcium channel blocker and relatively poorly to an ACE inhibitor or beta blocker ([graph 2](#)). (See '[Monotherapy based upon age and race](#)' below.)

In addition to these general observations, the following findings were noted in a 2009 meta-analysis of randomized trials [2]:

- Defining the standard dose of a class of drugs as the usual maintenance dose in reference pharmacopoeias, the largest reduction in blood pressure was seen at a half standard dose with only modestly greater reductions in systolic and diastolic blood pressures at standard or twice standard doses. As examples, the average fall in systolic blood pressure over 24 hours with half standard, standard, and twice standard doses was 7.1, 9.1, and 10.9 mmHg with data from all classes combined and 7.4, 8.8, and 10.3 mmHg with a thiazide diuretic. (See '[Drug dosing and drug frequency](#)' below.)
- With thiazide diuretics, calcium channel blockers, and beta blockers, the rate of symptomatic and metabolic adverse effects increased significantly with standard or twice standard doses compared to half standard doses. Similar findings have been noted in other studies ([graph 7](#)). In contrast, there was a very low rate of side effects with ACE inhibitors and ARBs with no dose dependence.

Thus, after the initial dose, going to higher doses produced on average relatively small further reductions in blood pressure at the price of an increasing rate of adverse effects. As a result, we generally limit dose titration to one step with a given antihypertensive drug (eg, 12.5 to 25 mg of chlorthalidone and 5 to 10 mg of amlodipine).

These observations suggest that two or even three drugs at half standard doses might have greater antihypertensive efficacy and less toxicity than one drug at standard or twice standard doses and might produce better patient outcomes [2]. Randomized trials to validate this hypothesis have not been performed.

Choice of drug — Some patients have an indication for a specific drug or drugs that is unrelated to essential hypertension (eg, a nondihydropyridine calcium channel blocker or beta blocker for rate control in patients with atrial fibrillation). (See '[Indications for specific drugs](#)' below.)

In the absence of a specific indication, there are three main classes of drugs that have been used for initial monotherapy: thiazide diuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors or angiotensin II receptor blockers (ARBs). Each of these classes of drugs have been equally effective in monotherapy trials if the attained blood pressure is similar. Beta blockers are NOT commonly used for initial monotherapy in the absence of a specific indication, since they may have an adverse effect on some cardiovascular outcomes, particularly in older patients. (See '[Indications for specific drugs](#)' below and '[Importance of attained blood pressure](#)' above and '[Beta](#)

[blockers'](#) below.)

Among patients in whom there is a reasonable likelihood of requiring a second drug (eg, more than 10/5 mmHg above goal), some physicians who practice according to the results of the ACCOMPLISH trial prefer initial therapy with a long-acting ACE inhibitor/ARB or a long-acting dihydropyridine calcium channel blocker, since the second class can be added if additional therapy is required to achieve the desired combination regimen. As described in the next section, the choice between these drug classes may be influenced by age and race. (See '[ACCOMPLISH trial](#)' above.)

This is a change from the current practice of many physicians. Low-dose [hydrochlorothiazide](#) (12.5 to a maximum of 25 mg/day) is widely used and, after publication of the ALLHAT trial, was recommended as initial monotherapy in most patients with mild essential hypertension by JNC 7 and others [[14,15](#)]. However, hydrochlorothiazide appears to be less effective and has a shorter duration of action than [chlorthalidone](#), and there is little, if any, evidence that low-dose hydrochlorothiazide alone reduces cardiovascular events as opposed to the evidence with chlorthalidone. (See '[Chlorthalidone versus hydrochlorothiazide](#)' above.)

Thus, when a thiazide diuretic is used, we and others suggest [chlorthalidone](#) (12.5 to a maximum of 25 mg/day) [[24,25](#)], which produced the best outcomes in ALLHAT, not [hydrochlorothiazide](#) at the same doses. Chlorthalidone is probably associated with somewhat greater risks of hypokalemia, glucose intolerance, and new onset diabetes mellitus than hydrochlorothiazide [[32](#)].

Monotherapy based upon age and race — The likelihood of a good response is increased when two simple clinical characteristics, age and race, are utilized to determine drug treatment. The following patients respond best to different types of antihypertensive agents used as monotherapy [[33,34](#)]:

- Younger patients respond best to angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) and beta blockers. However, beta blockers are not commonly used for initial monotherapy in the absence of a specific indication because of a possible increase in cardiovascular events, particularly in older patients. (See '[Beta blockers](#)' below.)

Support for this differential antihypertensive response in younger patients is supported by a study of 56 young (22 to 51 years) white hypertensive patients who were treated in a crossover rotation with the four main classes of antihypertensive drugs: ACE inhibitor, thiazide diuretic, long-acting dihydropyridine CCB, and beta blocker [[33](#)]. Significantly greater responses in both systolic and diastolic blood pressure levels were noted with the ACE inhibitor and beta blocker than with the CCB or diuretic.

- Black patients ([graph 2](#)) and elderly patients often respond best to a thiazide diuretic or long-acting calcium channel blocker [[5,31](#)]. These different responses may be at least partially related to the baseline plasma renin activity (PRA) [[35](#)]. Older and black hypertensives usually have lower PRA values than younger and white patients. However, many elderly hypertensive patients have a specific indication for an ACE inhibitor or ARB, including heart failure, prior myocardial infarction, and proteinuric chronic kidney disease. (See '[Treatment of hypertension in blacks](#)' and '[Treatment of hypertension in the elderly, particularly isolated systolic hypertension](#)' and '[Indications for specific drugs](#)' below.)

Sequential monotherapy — Each of the recommended first-line agents will normalize the BP in 30 to 50 percent of patients with mild hypertension ([graph 1](#) and [graph 2](#)) [[1-5](#)]. A patient who is relatively unresponsive to one drug has an almost 50 percent likelihood of becoming normotensive on a second drug [[36](#)]. Thus, in a patient who has little or no fall in BP after an adequate dose of drug 1, switching to (rather than adding) drug 2 and, if this is ineffective, switching to drug 3 may allow as many as 60 to 80 percent of patients with mild hypertension to initially be controlled with a single agent [[33,36](#)].

There are no strict guidelines as to how to perform sequential monotherapy. As the dose is increased with most antihypertensive drugs, the antihypertensive response attenuates and side effects become more prominent with the relative exception of ACE inhibitors and ARBs in patients with normal renal function ([graph 10](#)) [37]. As a result, we generally limit dose titration to one step with a given drug (eg, 12.5 to 25 mg of [chlorthalidone](#) and 5 to 10 mg of [amlodipine](#)). Using higher doses may produce a lesser blood pressure response and more toxicity than switching to an initial dose of a second drug. (See '[General principles](#)' above.)

This regimen of trying to find the one drug to which the patient is most responsive may minimize side effects, maximize patient compliance, and is as effective as some forms of combination therapy. However, over time, more than one drug will be needed in many patients who are initially controlled. In ALLHAT, for example, the proportion of patients treated with more than one drug increased from 26 to 33 percent at one year to 40 to 43 percent at five years [13]. (See '[Addition of a second drug](#)' below.)

Drug dosing and drug frequency — Although stepped care therapy has emphasized pushing initial therapy, as necessary, to the maximum recommended dose, the steepest part of the dose-response curve is typically seen at lower doses: good responders generally respond to low doses with few side effects, while higher doses produce more side effects often with little further reduction in blood pressure ([graph 10](#)) [2,38]. (See '[General principles](#)' above.)

As examples, patients often respond as well to 12.5 or 25 mg of [hydrochlorothiazide](#) (or its equivalent) per day as they do to 50 mg ([graph 6](#)), to 50 mg of [atenolol](#) as they do to 100 mg, to 100 mg of [captopril](#) as they do to 450 mg, to 10 to 15 mg of [enalapril](#) as they do to 20 or 40 mg, and to 50 mg of [losartan](#) as they do to 100 mg [19,39-43]. In addition to its efficacy, low-dose hydrochlorothiazide is less likely to produce the metabolic abnormalities that are often seen at higher doses ([graph 7](#)) [19]. (See "[Thiazide diuretics in essential hypertension](#)".)

The issue of dose frequency relates to the possible absence of 24-hour efficacy with shorter-acting drugs [44-46]. Once daily dosing with such drugs gives a greater peak response, but the BP tends to return toward baseline in the early morning hours, well before the next dose. This is a potential concern, since a greater daily BP load and early morning abrupt elevations in BP can increase cardiovascular risk. Giving one-half the dose twice a day produces a lesser peak effect but a more sustained response; however, patient compliance may be reduced [46,47]. (See "[Ambulatory blood pressure monitoring and white coat hypertension in adults](#)", section on '[Influence on therapy of hypertension](#)'.)

Thus, drugs that are longer acting are preferred [48]. It is prudent to check the BP in the morning prior to the next dose whenever a once daily regimen is used [49].

Indications for specific drugs — The general recommendations for initial therapy should be amended in patients with specific underlying conditions in whom specific agents might offer particular benefit independent of blood pressure control ([table 1](#)) [6,14,50]. These indications include the demonstration that ACE inhibitors improve outcomes in a number of high risk settings and that beta blockers improve survival in patients with systolic heart failure or a prior myocardial infarction [6]. (See "[Indications for use of and contraindications to specific antihypertensive drugs](#)", and topics on the specific disorders).

ACE inhibitors — ACE inhibitors are first-line therapy in all patients who have HF or asymptomatic LV dysfunction, in all patients who have had an ST elevation MI, in patients with a non-ST elevation MI who have had an anterior infarct, diabetes, or systolic dysfunction, and in patients with proteinuric chronic kidney disease. (See "[ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use](#)" and "[Angiotensin II receptor blockers in heart failure due to systolic dysfunction: Therapeutic use](#)" and "[Angiotensin converting enzyme inhibitors and receptor blockers in acute myocardial infarction: Recommendations for use](#)" and "[Antihypertensive therapy and progression of nondiabetic chronic kidney disease](#)".)

It has been suggested that ACE inhibitors and ARBs have a cardioprotective effect independent of blood pressure lowering in patients at high risk for a cardiovascular event. However, as mentioned above and described in detail elsewhere, the available evidence suggests that the attained blood pressure, not the drug used, is of primary importance in such patients. (See ['Importance of attained blood pressure'](#) above and ["Choice of antihypertensive drug and blood pressure goal in patients at increased risk for a cardiovascular event"](#).)

Angiotensin II receptor blockers — The specific indications for and efficacy of angiotensin II receptor blockers (ARBs) are similar to those with ACE inhibitors. (See ["Angiotensin II receptor blockers in heart failure due to systolic dysfunction: Therapeutic use"](#) and ["Angiotensin converting enzyme inhibitors and receptor blockers in acute myocardial infarction: Recommendations for use"](#) and ["Antihypertensive therapy and progression of nondiabetic chronic kidney disease"](#).)

There is at least one setting in which ARBs have specific benefit and in which similar trials have not been performed with ACE inhibitors: severe hypertension with ECG evidence of left ventricular hypertrophy in LIFE [39]. An ARB can be used instead of an ACE inhibitor in such patients, although it is highly likely that an ACE inhibitor is equally effective. We would not switch such a patient who is already receiving and tolerating an ACE inhibitor to an ARB.

An ARB is particularly indicated in patients who do not tolerate ACE inhibitors (mostly because of cough). (See ["Differences between angiotensin converting enzyme inhibitors and receptor blockers"](#).)

Thiazide diuretics — The preferred thiazide diuretic in patients with essential hypertension is [chlorthalidone](#) (12.5 to 25 mg/day), since major trials such as ALLHAT have shown benefit with this regimen. There is little, if any, evidence that [hydrochlorothiazide](#) at this dose improves cardiovascular outcomes. Hydrochlorothiazide is both less potent and shorter acting than chlorthalidone. (See ['Chlorthalidone versus hydrochlorothiazide'](#) above and ['Initial monotherapy'](#) above.)

One problem with low-dose [chlorthalidone](#) is that there is no 12.5 mg tablet. Thus, 25 mg tablets of generic chlorthalidone need to be cut in half. There is a more expensive 15 mg brand name preparation (Thalitone®). This preparation has greater bioavailability than generic chlorthalidone, and clinical studies suggest that its antihypertensive efficacy is closer to 25 mg of generic chlorthalidone [51]. Another problem with chlorthalidone compared to [hydrochlorothiazide](#) is the current lack of availability of fixed dose combination pills with ACE inhibitors, angiotensin II receptor blockers, and long-acting calcium channel blockers.

Diuretics should also be given for volume control in patients with heart failure or chronic kidney disease, with or without nephrotic syndrome; these settings usually require loop diuretics. In addition, an aldosterone antagonist ([spironolactone](#) or [eplerenone](#)) is indicated in selected patients with advanced HF who have relatively preserved renal function and, in patients with less severe disease, for the prevention or treatment of hypokalemia. (See ["Use of diuretics in heart failure"](#).)

Calcium channel blockers — There are no absolute indications for calcium channel blockers in hypertensive patients. Long-acting dihydropyridines are most commonly used. Like beta blockers, the non-dihydropyridine calcium channel blockers ([verapamil](#), [diltiazem](#)) can be given for rate control in patients with atrial fibrillation or for control of angina. Calcium channel blockers also may be preferred in patients with obstructive airways disease. (See ["Treatment of hypertension in asthma and COPD"](#).)

Beta blockers — A beta blocker without intrinsic sympathomimetic activity should be given after an acute myocardial infarction and to stable patients with heart failure or asymptomatic left ventricular dysfunction (beginning with very low doses to minimize the risk and degree of initial worsening of myocardial function). The use of beta blockers in these settings is in addition to the recommendations for ACE inhibitors in these disorders. (See ["Beta blockers in the management of acute coronary syndrome"](#) and ["Use of beta blockers in heart failure due to systolic dysfunction"](#).)

Beta blockers are also given for rate control in patients with atrial fibrillation, for control of angina, and for symptom control in a number of other disorders ([table 1](#)).

In the absence of such indications, we and others suggest that beta blockers should NOT be used for initial antihypertensive therapy [[32,52,53](#)], particularly in patients over age 60. Compared to other antihypertensive drugs in the primary treatment of hypertension, beta blockers (not all trials used [atenolol](#)) may be associated with a higher rate of stroke (particularly among smokers) [[54,55](#)], coronary disease [[55](#)], all cardiovascular events [[55](#)], and perhaps, with atenolol, a small increase in mortality [[56](#)]. These effects are primarily seen in patients over age 60 [[55,57,58](#)]. Beta blockers are also associated with impaired glucose tolerance and an increased risk of new onset diabetes [[32](#)], with the exception of vasodilating beta blockers such as [carvedilol](#) and [nebivolol](#) [[59,60](#)].

The data supporting these conclusions are presented separately. (See "[Choice of therapy in essential hypertension: Clinical trials](#)", section on 'Beta blockers as initial therapy?' and "[Treatment of hypertension in diabetes mellitus](#)", section on 'Beta blockers'.)

Alpha blockers — The ALLHAT trial cited above included a [doxazosin](#) arm that was terminated prematurely because of a significantly increased risk of heart failure compared to [chlorthalidone](#) (relative risk 2.0 after adjusting for a 3 mmHg higher in-trial systolic pressure with doxazosin) noted during an interim analysis [[61](#)] and a higher rate of cardiovascular events [[62](#)]. Thus, an alpha blocker is not recommended for initial monotherapy, with the possible exception of older men with symptoms of prostatism, particularly if they are not at high cardiovascular risk. (See "[Medical treatment of benign prostatic hyperplasia](#)".)

COMBINATION THERAPY — There are two issues related to combination therapy: use as first-line therapy; and addition of a second drug when the goal blood pressure is not achieved with monotherapy. The following discussion assumes that the patient does not have an indication for the use of specific drugs. (See '[Indications for specific drugs](#)' above.)

Recommendations for combination therapy were made in the 2003 JNC 7 report, the 2004 British Hypertension Society guidelines, and the 2007 European Societies of Hypertension and Cardiology guidelines [[14,34,63](#)]. However, the guidelines were published well before the ACCOMPLISH trial, which we feel provides the best evidence for combination therapy.

First-line combination therapy — Administering two drugs as initial therapy should be considered when the blood pressure is more than 20/10 mmHg above goal, as recommended in the JNC 7 report [[14](#)]. This strategy may increase the likelihood that target blood pressures are achieved in a reasonable time period. Fixed-dose combination preparations are available that may improve patient compliance and, if both drugs are given at lower doses, reduce side effects [[2,37,64,65](#)].

Supine and standing pressures should be measured prior to the initiation of combination therapy in patients at increased risk for orthostatic (postural) hypotension, such as elderly patients and those with diabetes. Orthostatic hypotension is diagnosed when, within two to five minutes of quiet standing, one or more of the following is present:

- At least a 20 mmHg fall in systolic pressure
- At least a 10 mmHg fall in diastolic pressure
- Symptoms of cerebral hypoperfusion, such as dizziness

(See "[Mechanisms and causes of orthostatic and postprandial hypotension](#)".)

Based upon the results of the ACCOMPLISH trial [[30](#)], we recommend the use of a long-acting dihydropyridine calcium channel blocker plus a long-acting ACE inhibitor/ARB (such as [amlodipine](#) plus [benazepril](#) as used in ACCOMPLISH). In addition, in patients already being treated with and doing well on

the combination of a thiazide diuretic and a long-acting angiotensin inhibitor, we suggest replacing the thiazide diuretic with a long-acting dihydropyridine calcium channel blocker. (See '[ACCOMPLISH trial](#)' above.)

Addition of a second drug — As noted above, each of the recommended first line agents will normalize the BP in up to 30 to 50 percent of patients with mild hypertension [5]. In the patient who is relatively unresponsive to one drug, sequentially trying different agents may allow 60 to 80 percent of patients with mild hypertension to be initially controlled with a single agent [33,36]. These issues are discussed in detail above. (See '[Initial monotherapy](#)' above.)

We generally limit dose titration to one step with a given drug (eg, 12.5 to 25 mg of [chlorthalidone](#) or 5 to 10 mg of [amlodipine](#)). Using higher doses generally produces a lesser blood pressure response and more toxicity than switching to an initial dose of a second drug ([graph 10](#)) [5,37,66].

Over time, more than one drug will be needed in many patients who are initially controlled. In ALLHAT, for example, the proportion of patients treated with more than one drug increased from 26 to 33 percent at one year to 40 to 43 percent at five years [13].

Based upon the results of the ACCOMPLISH trial [30], we suggest that combination therapy consist of a long-acting dihydropyridine calcium channel blocker plus a long-acting ACE inhibitor/ARB (such as [amlodipine](#) plus [benazepril](#)). Thus, if the patient is being treated with one of the drugs, add the other. In patients being treated with a thiazide diuretic, we suggest discontinuing the thiazide and starting combination therapy. Approximately 75 percent of patients in ACCOMPLISH had previously been treated with two or more antihypertensive drugs. (See '[ACCOMPLISH trial](#)' above.)

Beta blockers are now used less often as initial therapy except for patients with another indication for their use. The preferred second drug in patients who are treated with a beta blocker are a thiazide diuretic or a dihydropyridine calcium channel blocker [50]. An alpha blocker would be chosen only if there is another reason for its use, such as symptomatic benign prostatic hyperplasia.

An ACE inhibitor or ARB is likely to be less effective in patients treated with a beta blocker, since beta blockers reduce renin secretion and therefore angiotensin II formation [67], and a beta blocker should be used with caution in combination with [verapamil](#) and to a lesser degree [diltiazem](#). These drugs can potentiate the cardiac depressant effect of the beta blocker, possibly leading to or exacerbating bradycardia or heart block.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See '[Patient information: High blood pressure in adults](#)' and '[Patient information: High blood pressure treatment in adults](#)' and '[Patient information: High blood pressure, diet, and weight](#)'.) We encourage you to print or e-mail these topic reviews, or to refer patients to our public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY AND RECOMMENDATIONS — The amount of blood pressure reduction is generally the major determinant of a decrease in cardiovascular risk in patients with hypertension, not the specific antihypertensive drug(s). However, this may not apply to combination therapy. In the ACCOMPLISH trial, [amlodipine](#) plus [benazepril](#) was associated with a 20 percent lower rate of cardiovascular events compared to [hydrochlorothiazide](#) plus benazepril, despite slightly higher 24-hour blood pressures in the amlodipine arm. (See '[Importance of attained blood pressure](#)' above and '[ACCOMPLISH trial](#)' above.)

Some hypertensive patients have underlying conditions for which specific antihypertensive drugs might offer particular benefit independent of blood pressure control. The following recommendations do not apply to such patients. (See '[Indications for specific drugs](#)' above.)

Monotherapy — Among hypertensive patients without an indication for a specific drug, the major

classes of drugs that have been used for monotherapy are a low dose thiazide diuretic, long-acting angiotensin converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARBs), or a long-acting dihydropyridine calcium channel blocker.

- Given the preference for an ACE inhibitor/ARB plus a dihydropyridine calcium channel blocker in patients requiring combination therapy, we suggest use of one of these drug classes as initial therapy so that the other can be added, if necessary (**Grade 2C**). If this approach is chosen, an ACE inhibitor/ARB may be more effective in younger patients, and a dihydropyridine calcium channel blocker may be more effective in elderly and black patients. (See '[Initial monotherapy](#)' above and '[Monotherapy based upon age and race](#)' above.)

- If a thiazide-type diuretic is chosen, we suggest [chlorthalidone](#) rather than [hydrochlorothiazide](#) (**Grade 2B**). Most clinicians, particularly in the United States, have limited, if any, experience with chlorthalidone, which may be somewhat more likely to induce hypokalemia than hydrochlorothiazide at the same dose. The basic principles of monitoring for hypokalemia with chlorthalidone are identical to those with hydrochlorothiazide. (See '[Choice of thiazide diuretic](#)' above and '[Choice of thiazide diuretic](#)' above and '[Issues with chlorthalidone](#)' above.)

- We recommend that patients who have a minimal or no response to the initial antihypertensive drug be treated with sequential monotherapy (**Grade 1B**). (See '[Sequential monotherapy](#)' above.)

Combination therapy

- Among patients who have an initial blood pressure more than 20/10 mmHg above goal, we recommend therapy with the combination of a long-acting ACE inhibitor/ARB plus a long-acting dihydropyridine calcium channel blocker ([benazepril](#) plus [amlodipine](#) was used in the ACCOMPLISH trial) (**Grade 1B**). (See '[ACCOMPLISH trial](#)' above and '[First-line combination therapy](#)' above.)

- Among patients who are already being treated with an ACE inhibitor/ARB plus a thiazide diuretic and have attained goal blood pressure, we suggest stopping the thiazide and switching to a long-acting dihydropyridine calcium channel blocker (**Grade 2B**). We suggest continuing therapy in patients who are well controlled on combinations other than an ACE inhibitor/ARB plus a thiazide (**Grade 2C**).

- Among patients being treated with a thiazide diuretic as monotherapy who have responded but have not attained goal blood pressure, we suggest stopping the thiazide and switching to a long-acting ACE inhibitor/ARB plus a long-acting dihydropyridine calcium channel blocker (**Grade 2B**).

Use of *UpToDate* is subject to the [Subscription and License Agreement](#).

REFERENCES

1. Turnbull, F, Neal, B, Ninomiya, T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008; 336:1121.
2. Law, MR, Morris, JK, Wald, NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338:b1665.
3. Staessen, JA, Wang, JG, Thijs, L. Cardiovascular prevention and blood pressure reduction. *J Hypertens* 2003; 21:1055.
4. Neaton, JD, Grimm, RH Jr, Prineas, RJ, et al. Treatment of Mild Hypertension Study: Final results.

JAMA 1993; 270:713.

5. Materson, BJ, Reda, DJ, Cushman, WC, et al. Single-drug therapy for hypertension in men. a comparison of six antihypertensive agents with placebo (correction - N Engl J Med 1994; 330:1689). N Engl J Med 1993; 328:914.
6. Rosendorff, C, Black, HR, Cannon, CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007; 115:2761.
7. Mancia, G, De Backer, G, Dominiczak, A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28:1462.
8. Neal, B, MacMahon, S, Chapman, N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000; 356:1955.
9. Dahlof, B, Sever, PS, Poulter, NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366:895.
10. Yusuf, S, Sleight, P, Pogue, J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342:145.
11. Fox, KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003; 362:782.
12. Weber, MA, Julius, S, Kjeldsen, SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE trial. Lancet 2004; 363:2049.
13. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981.
14. Chobanian, AV, Bakris, GL, Black, HR, Cushman, WC. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003; 289:2560.
15. Appel, LJ. The verdict from ALLHAT--thiazide diuretics are the preferred initial therapy for hypertension. JAMA 2002; 288:3039.
16. Carter, BL, Ernst, ME, Cohen, JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. Hypertension 2004; 43:4.
17. Ernst, ME, Carter, BL, Goerdts, CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006; 47:352.
18. Sica, DA. Chlorthalidone: has it always been the best thiazide-type diuretic?. Hypertension 2006; 47:321.
19. Carlsen, JE, Kober, L, Torp-Pedersen, C, Johannsen, P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. BMJ 1990; 300:975.
20. Flack, JM, Cushman, WC. Evidence for the efficacy of low-dose diuretic monotherapy. Am J Med 1996; 101(Suppl 3A):53S.
21. Franse, LV, Pahor, M, Di Bari, M, et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 2000; 35:1025.
22. Finkelstein, JD, Schwartz, GL, Chapman, AB, et al. Lack of agreement between office and ambulatory blood pressure responses to hydrochlorothiazide. Am J Hypertens 2005; 18:398.
23. Psaty, BM, Lumley, T, Furberg, CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. JAMA 2004; 292:43.

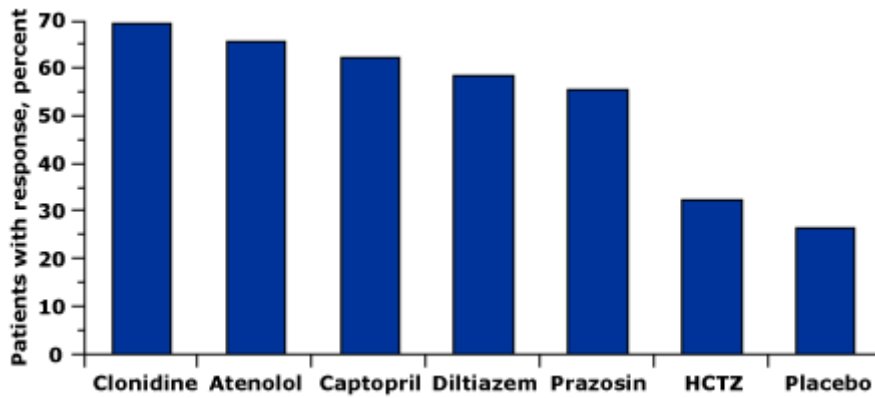
24. Messerli, FH, Bangalore, S. Antihypertensive efficacy of aliskiren: is hydrochlorothiazide an appropriate benchmark?. *Circulation* 2009; 119:371.
25. Ernst, ME, Carter, BL, Basile, JN. All thiazide-like diuretics are not chlorthalidone: Putting the ACCOMPLISH study into perspective. *J Clin Hypertens (Greenwich)* 2009; 11:5.
26. A diuretic for initial treatment of hypertension?. *Med Lett Drugs Ther* 2009; 51:9.
27. Lacourciere, Y, Poirier, L, Lefebvre, J, et al. Antihypertensive effects of amlodipine and hydrochlorothiazide in elderly patients with ambulatory hypertension. *Am J Hypertens* 1995; 8:1154.
28. Ram, CV, Garrett, BN, Kaplan, NM. Moderate sodium restriction and various diuretics in the treatment of hypertension. Effects on potassium wastage and blood pressure control. *Arch Intern Med* 1981; 141:1015.
29. Langford, HG, Schlundt, D, Levine, K. Sodium restriction in hypertension. *Compr Ther* 1984; 10:6.
30. Jamerson, K, Weber, MA, Bakris, GL, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. *N Engl J Med* 2008; 359:2417.
31. Morgan, TO, Anderson, AI, MacInnis, RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens* 2001; 14:241.
32. Messerli, FH, Bangalore, S, Julius, S. Risk/benefit assessment of beta-blockers and diuretics precludes their use for first-line therapy in hypertension. *Circulation* 2008; 117:2706.
33. Dickerson, JEC, Hingorani, AD, Ashby, MJ, et al. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; 353:2008.
34. Williams, B, Poulter, NR, Brown, MJ, et al. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; 328:634.
35. Blaurock, MD, Lee, HB, Davis, B, et al. Renin predicts the blood pressure response to nonpharmacologic and pharmacologic therapy. *JAMA* 1992; 267:1221.
36. Materson, BJ, Reda, DJ, Preston, RA, et al. Response to a second single antihypertensive agent used as monotherapy for hypertension after failure of the initial drug. *Arch Intern Med* 1995; 155:1757.
37. Epstein, M, Bakris, G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med* 1996; 156:1969.
38. Kaplan, NM. The appropriate goal of antihypertensive therapy: Neither too much nor too little. *Ann Intern Med* 1992; 116:686.
39. Dahlof, B, Devereux, RB, Kjeldsen, SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:995.
40. Lindholm, LH, Ibsen, H, Dahlof, B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:1004.
41. Low-dose captopril for the treatment of mild to moderate hypertension. I. Results of a 14-week trial. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med* 1984; 144:1947.
42. Salvetti, A, Arzilli, F. Chronic dose-response curve of enalapril in essential hypertensives. An Italian multicenter study. *Am J Hypertens* 1989; 2:352.
43. Saunders, E, Weir, MR, Kong, BW, et al. A comparison of the efficacy and safety of a β -blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med* 1990; 150:1707.
44. Neutel, JM, Schnaper, H, Cheung, DG, et al. Antihypertensive effects of β -blockers administered once daily: 24-hour measurements. *Am Heart J* 1990; 120:166.
45. Sarafidis, P, Bogojevic, Z, Basta, E, et al. Comparative efficacy of two different beta-blockers on 24-hour blood pressure control. *J Clin Hypertens (Greenwich)* 2008; 10:112.
46. Meredith, PA, Donnelly, R, Elliott, HL, et al. Prediction of the antihypertensive response to enalapril.

J Hypertens 1990; 8:1085.

47. Cramer, JA, Mattson, RH, Prevey, ML, et al. How often is medication taken as prescribed? A novel assessment technique. *JAMA* 1989; 261:3273.
48. Eguchi, K, Kario, K, Hoshide, Y, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. *Am J Hypertens* 2004; 17:112.
49. Kario, K. Time for focus on morning hypertension: pitfall of current antihypertensive medication. *Am J Hypertens* 2005; 18:149.
50. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21:1011.
51. Vardan, S, Mehrotra, KG, Mookherjee, S, et al. Efficacy and reduced metabolic side effects of a 15-mg chlorthalidone formulation in the treatment of mild hypertension. A multicenter study. *JAMA* 1987; 258:484.
52. Cutler, JA, Davis, BR. Thiazide-type diuretics and beta-adrenergic blockers as first-line drug treatments for hypertension. *Circulation* 2008; 117:2691.
53. National Institute for Health and Clinical Excellence. Hypertension: management of hypertension in adults in primary care (NICE clinical guideline update). Available at: <http://www.nice.org.uk>. Accessed January 21, 2009.
54. Lindholm, LH, Carlberg, B, Samuelsson, O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366:1545.
55. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ* 1992; 304:405.
56. Carlberg, B, Samuelsson, O, Lindholm, LH. Atenolol in hypertension: is it a wise choice?. *Lancet* 2004; 364:1684.
57. Khan, N, McAlister, FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. *CMAJ* 2006; 174:1737.
58. Messerli, FH, Grossman, E, Goldbourt, U. Are β -blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998; 279:1903.
59. Bakris, GL, Fonseca, V, Katholi, RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; 292:2227.
60. Sarafidis, PA, Bakris, GL. Antihypertensive treatment with beta-blockers and the spectrum of glycaemic control. *QJM* 2006; 99:431.
61. Davis, BR, Cutler, JA, Furberg, CD, et al. Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: Further analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial. *Ann Intern Med* 2002; 137:313.
62. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000; 283:1967.
63. Mancia, G, De Backer, G, Dominiczak, A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25:1105.
64. Bangalore, S, Kamalakkannan, G, Parkar, S, Messerli, FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007; 120:713.
65. Brixner, DI, Jackson KC, 2nd, Sheng, X, et al. Assessment of adherence, persistence, and costs among valsartan and hydrochlorothiazide retrospective cohorts in free-and fixed-dose combinations. *Curr Med Res Opin* 2008; 24:2597.
66. Bakris, GL. Maximizing cardiorenal benefit in the management of hypertension: achieve blood pressure goals. *J Clin Hypertens (Greenwich)* 1999; 1:141.
67. Pickering, TG. The use of angiotensin converting enzyme inhibitors in combination with other

antihypertensive agents. *Am J Hypertens* 1991; 4:73S.

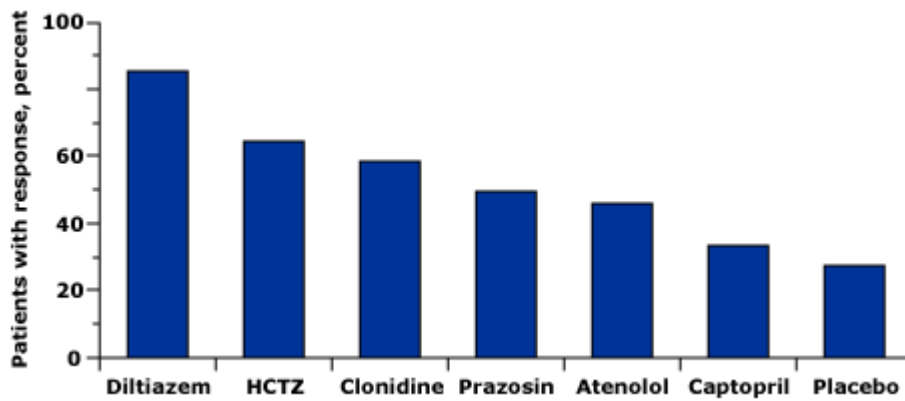
GRAPHICS

Antihypertensive response to different drugs in whites

Response rates to single drug therapy for hypertension in whites under the age of 60. There were no significant differences in response, except that hydrochlorothiazide (HCTZ) appeared to be least effective. A response was defined as a diastolic pressure below 90 mmHg at the end of the titration phase and below 95 mmHg at one year. The pattern of response was similar but the success rate for each drug was reduced by five to 15 percent if goal diastolic pressure were less than 90 mmHg at one year. There were between 30 and 39 patients in each group.

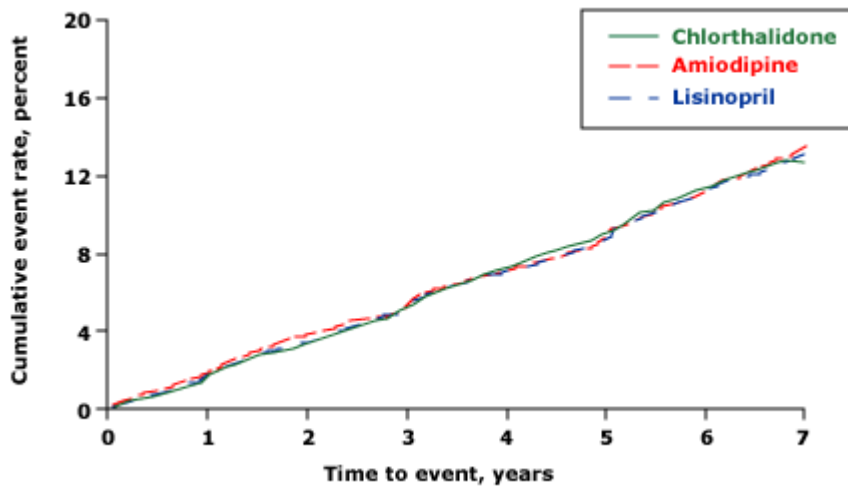
Data from Materson, BJ, Reda, DJ, Cushman, WC, et al, N Engl J Med 1993; 328:914. Correction and additional data: Am J Hypertens 1995; 8:189.

Antihypertensive response to different drugs in blacks



Response rates to single drug therapy for hypertension in blacks over the age of 60 years. The highest response was seen with diltiazem and hydrochlorothiazide (HCTZ) and the lowest with captopril. A response was defined as a diastolic pressure below 90 mmHg at the end of the titration phase and below 95 mmHg at one year. The pattern of response was similar but the success rate for each drug was reduced by five to 15 percent if goal diastolic pressure were less than 90 mmHg at one year. There were between 42 and 53 patients in each group.

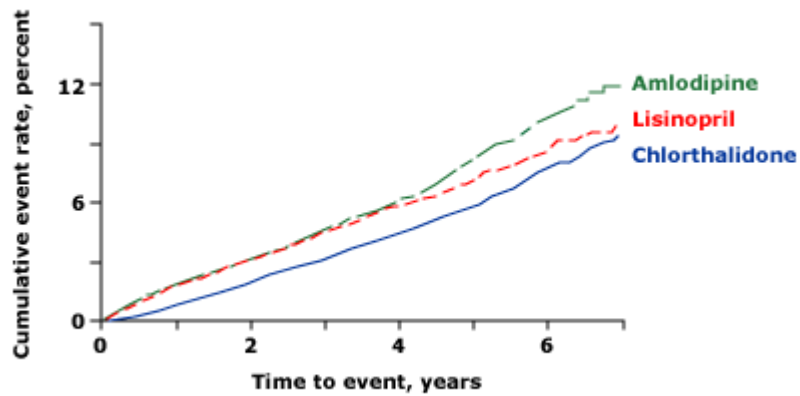
Data from Materson, BJ, Reda, DJ, Cushman, WC, et al, N Engl J Med 1993; 328:914. Correction and additional data: Am J Hypertens 1995; 8:189.

Choice of antihypertensive drug does not predict outcome

In the ALLHAT trial, cumulative event rates for the primary outcome (fatal coronary heart disease or nonfatal myocardial infarction) according to primary treatment with chlorthalidone, amlodipine, or lisinopril. Compared to chlorthalidone, there was no significant difference with amlodipine (relative risk 0.98) or lisinopril (relative risk 0.99 percent) at a mean of 4.9 years.

Data from *The ALLHAT Officers, JAMA 2002; 288:2981.*

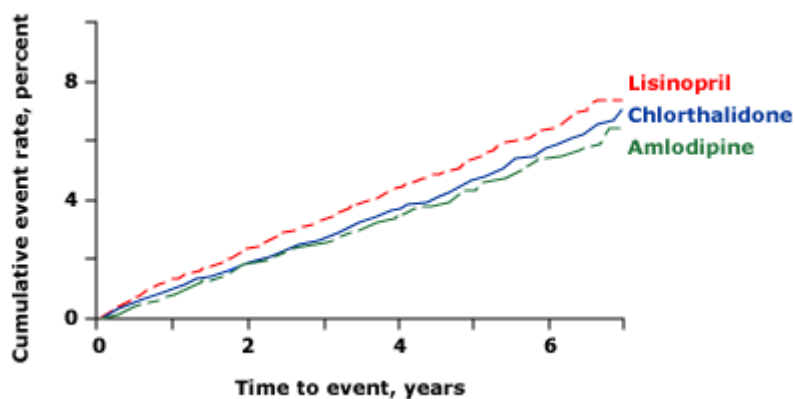
Amlodipine, lisinopril, and increased risk of HF



In the ALLHAT trial, cumulative event rates for the development of heart failure (HF) according to primary treatment with chlorthalidone, amlodipine, or lisinopril. Compared to chlorthalidone, there were significant increases in the six year rate of HF with both amlodipine (10.2 versus 7.7 percent, relative risk 1.38, 95 percent CI 1.25 to 1.52) and lisinopril (8.7 versus 7.7 percent, relative risk 1.19 95 percent CI 1.07 to 1.31).

Data from *The ALLHAT Officers, JAMA 2002; 288:2981.*

Lisinopril and increased risk of stroke



In the ALLHAT trial, cumulative event rates for the development of stroke according to primary treatment with chlorthalidone, amlodipine, or lisinopril. Compared to chlorthalidone, there was a significant increase in the six year rate of stroke with lisinopril (6.3 versus 5.6 percent, relative risk 1.15 95 percent CI 1.02 to 1.30).

Data from *The ALLHAT Officers, JAMA 2002; 288:2981.*

Considerations for individualizing antihypertensive therapy

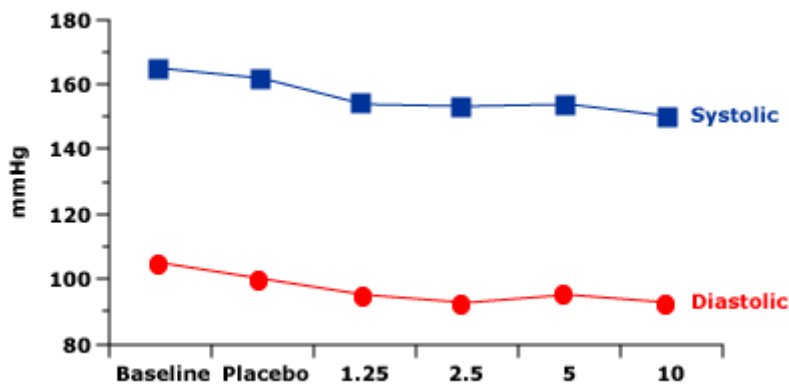
Indication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Systolic heart failure	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Post-myocardial infarction	ACE inhibitor, beta blocker, aldosterone antagonist
Proteinuric chronic renal failure	ACE inhibitor and/or ARB
High coronary disease risk	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)
Diabetes mellitus (no proteinuria)	Diuretic (ALLHAT), perhaps ACE inhibitor (HOPE)
Angina pectoris	Beta blocker, calcium channel blocker
Atrial fibrillation rate control	Beta blocker, nondihydropyridine calcium channel blocker
Atrial flutter rate control	Beta blocker, nondihydropyridine calcium channel blocker
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hypertrophy	Alpha blocker
Essential tremor	Beta blocker (noncardioselective)
Hyperthyroidism	Beta blocker
Migraine	Beta blocker, calcium channel blocker
Osteoporosis	Thiazide diuretic
Perioperative hypertension	Beta blocker
Raynaud's syndrome	Dihydropyridine calcium channel blocker
Contraindications	
Angioedema	ACE inhibitor
Bronchospastic disease	Beta blocker
Depression	Reserpine
Liver disease	Methyldopa
Pregnancy	ACE inhibitor, ARB (includes women likely to become pregnant)
Second or third degree heart block	Beta blocker, nondihydropyridine calcium channel blocker
May have adverse effect on comorbid conditions	
Depression	Beta blocker, central alpha agonist
Gout	Diuretic
Hyperkalemia	Aldosterone antagonist, ACE inhibitor, ARB
Hyponatremia	Thiazide diuretic
Renovascular disease	ACE inhibitor or ARB

* A survival benefit from an aldosterone antagonist has only been demonstrated in patients with advanced heart failure; in patients with less severe disease, an aldosterone antagonist is primarily given for hypokalemia

Adapted from *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of*

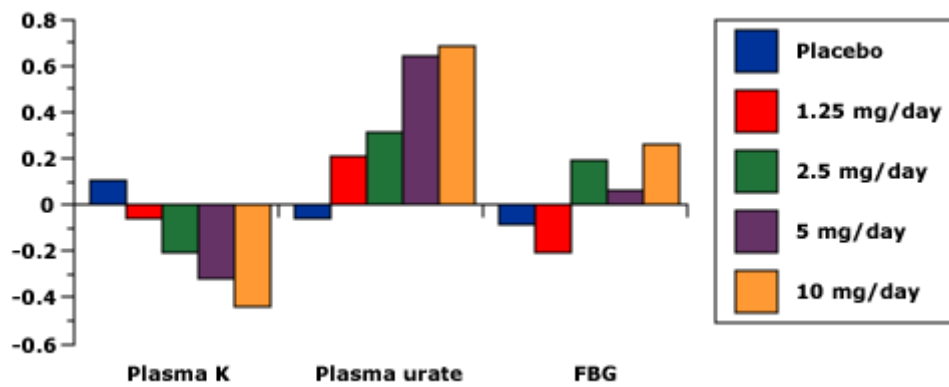
High Blood Pressure, JAMA 2003; 289:2560.

Efficacy of low-dose thiazide therapy



Antihypertensive response to bendrofluazide in relation to daily dose (in mg, multiply by 10 to get approximate equivalent doses of hydrochlorothiazide). The initial dose of 1.25 mg/day lowers the blood pressure in comparison to placebo; however, higher doses produced little further antihypertensive response. Each treatment group contained approximately 52 patients.

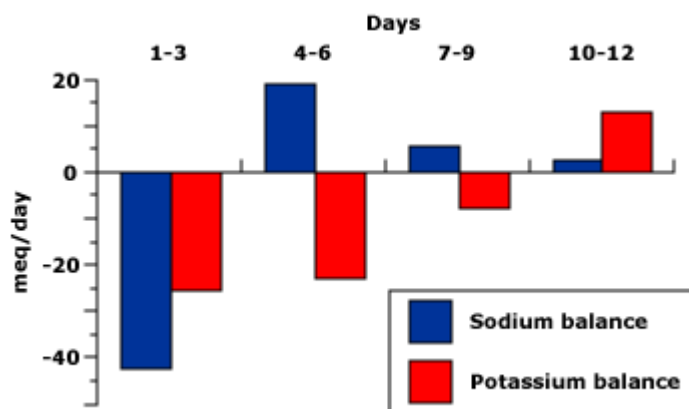
Data from Carlsen, JE, Kober, L, Torp-Pedersen, C, Johannsen, P, BMJ 1990; 300:975.

Dose-dependence of thiazide-induced side effects

Metabolic complications induced by bendroflumazide in relation to daily dose (multiply by 10 to get equivalent doses of hydrochlorothiazide). Increasing the dose led to progressive hypokalemia and hyperuricemia and a greater likelihood of a mild elevation in the fasting blood glucose (FBG), all without a further reduction in the systemic blood pressure. Each treatment group contained approximately 52 patients.

Data from Carlsen, JE, Kober, L, Torp-Pedersen, C, Johannsen, P, BMJ 1990; 300:975.

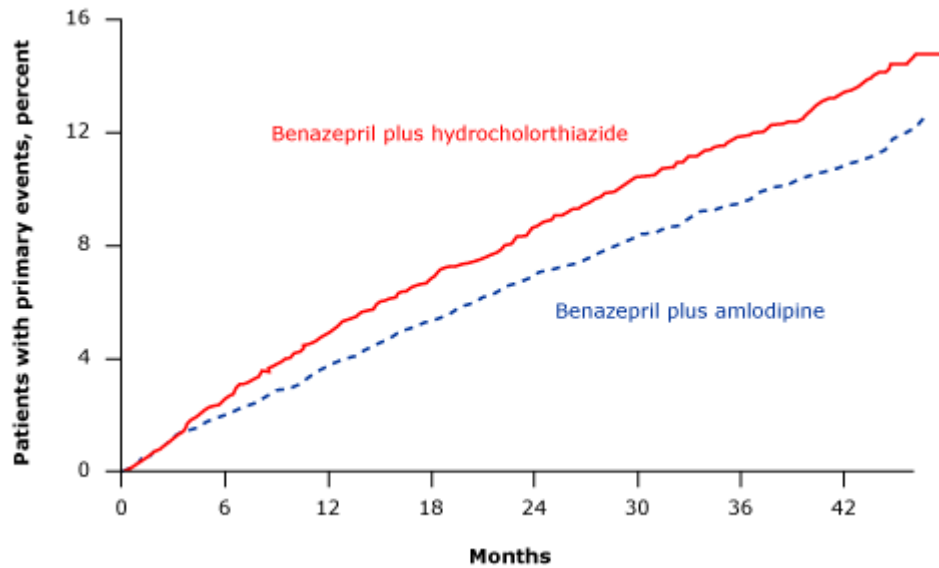
Steady state after thiazide therapy



Changes in sodium and potassium balance (intake minus excretion) after the administration of 100 mg of hydrochlorothiazide to 3 normal subjects. Negative balance persisted for only three days for sodium and six days for potassium before a steady state was reestablished in which intake and excretion were roughly equal.

Data from Maronde, RF, Milgrom, M, Vlachakis, ND, Chan, L, JAMA 1983; 249:237.

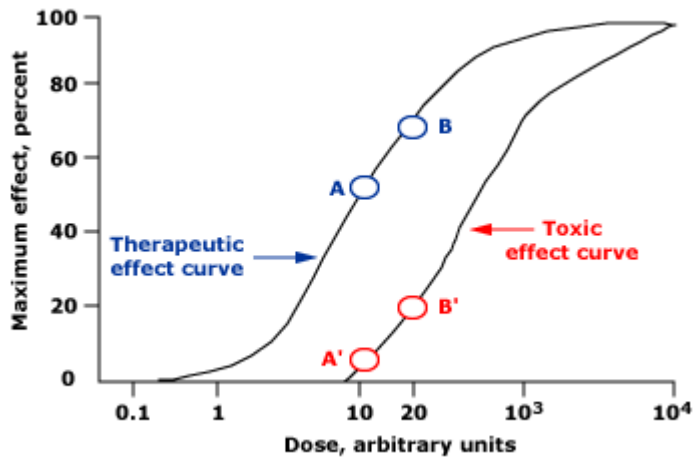
Kaplan-Meier curves for time to first primary composite end point



There were 552 patients with events (9.6 percent) in the benazepril-amlodipine group, as compared with 679 patients with events (11.8 percent) in the benazepril-hydrochlorothiazide group. The relative risk reduction was 20 percent (hazard ratio, 0.80; 95 percent CI 0.72-0.90; $p < 0.001$).

Reproduced with permission from: Jamerson, K, Weber, M, Bakris, G, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359:2417. Copyright ©2008 Massachusetts Medical Society. All rights reserved.

Dose relation between therapeutic effect and toxicity with antihypertensive drugs



The theoretical therapeutic and toxic effect curves of antihypertensive agents vary based upon the administered dose. The theoretical effects of a single drug given at two different doses (10 and 20 units) are shown. At a dose of 10 units, the antihypertensive agent has a minimal toxic effect (A') and a moderate therapeutic effect (A). Doubling the dose, however, is associated with substantial toxic effects (B') but little increase in therapeutic efficacy (B).

Redrawn from Epstein, M, Bakris, G, Arch Intern Med 1996; 156:1969.

© 2010 UpToDate, Inc. All rights reserved. | [Subscription and License Agreement](#) | Support Tag: [ecapp0603p.utd.com-212.25.67.206-383641440A-251928]
Licensed to: **Hillel Yaffe Med Centre**