Traditional First-Line Therapy
Overview of Medical Benefits and Side Effects
Ray W. Gifford Jr. and Raymond A. Borazanian

When diuretic-based stepped care was first advocated for the treatment of hypertension, there were fewer classes of antihypertensive medication than there are today. In 1984, the third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) for the first time suggested an alternative initial treatment with a β-blocker in selected hypertensive patients, and the fourth JNC report has recommended the alternatives of calcium channel blockers or angiotensin converting enzyme inhibitors for step-one therapy as well. However, only the diuretic drugs and β-blockers have been shown to reduce cardiovascular morbidity and mortality in prospective, long-term, controlled trials. Moreover, 30 years’ experience with diuretic agents and 20 years’ experience with β-blockers have defined the advantages, disadvantages, and potential side effects of these drugs more precisely than is possible for newer agents. The diuretic drugs and β-blockers remain excellent choices in the management of hypertension. (Hypertension 1989;13(suppl 1):I-119–I-124)

The thiazide diuretics and more recently the β-blockers have been the traditional first-step agents in the stepped care approach to therapy of arterial hypertension. Stepped care therapy was not intended to be a rigid algorithm for selection of drugs that had to be followed in all cases, but rather, this therapeutic approach was intended as a set of guidelines for treatment based on experience and arrived at by consensus. When stepped care was introduced, the only options other than diuretic agents for initial therapy were methyldopa, reserpine, guanethidine, or hydralazine, and the diuretic drugs were much preferable to any of the other drugs. In 1984, the third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) suggested an alternative: either a thiazide diuretic drug at less than a full dose or a β-blocker at less than a full dose. The fourth JNC report recommends other alternatives for step one, including calcium channel blockers and angiotensin converting enzyme inhibitors. Nevertheless, 30 years after the introduction of thiazide diuretic agents and 20 years after the introduction of β-blockers, these agents remain a viable choice for step-one therapy and possess many attributes of the ideal step-one drug (Table 1).

Advantages of Diuretic Agents and β-Blockers as Step-One Drugs
Diuretic drugs are effective as monotherapy in at least 50% of unselected mildly hypertensive patients (Table 2). In a Veterans Administration double-blind study comparing propranolol and hydrochlorothiazide for the initial treatment of hypertension in men with diastolic blood pressures between 95 and 114 mm Hg, 65.5% of those receiving hydrochlorothiazide achieved a goal diastolic blood pressure of less than 90 mm Hg compared with 52.8% of those receiving propranolol (p < 0.03). Black patients responded better to hydrochlorothiazide than to propranolol.4 β-Blockers seem to be more effective in younger patients than in older patients.5 Diuretic agents are easy to titrate and are less expensive than the alternatives including the β-blockers. The usual initial dosage is 12.5 or 25 mg/day of hydrochlorothiazide or its equivalent in other diuretic drugs. If this dose is not effective, the dosage can be increased to 50 mg/day. Above the 50-mg/day dosage, the dose–response curve becomes flat, and most authorities agree that there is no advantage to a further increase. The next step is to add another drug to the regimen or to use a substitute. This approach results in fewer office visits for the patient and consequent lower health care costs. Unfortunately, cost is a real concern for many patients, particularly those on limited incomes. Most diuretic agents and some β-blockers can be given as a once-daily dose, a regimen that enhances patient compliance. Titration usually requires more than two or three steps for most β-blockers except for atenolol (25–50–100 mg).
In cases where diuretic drugs are not effective as monotherapy, they have the virtue of potentiating the effect of any agent that may subsequently be added to the regimen. In the case of the direct vasodilators and the sympathetic inhibitors (other than the β-blockers), concomitant use of a diuretic drug will prevent the gradual accumulation of sodium and water that leads to the pseudotolerance that occurs when the vasodilators or sympathetic inhibitors are used alone. Prevention of salt and water accumulation cannot entirely explain this enhancing effect of the diuretic drugs, since such enhancement also occurs when the diuretics are given in combination with β-blockers, calcium channel blockers, and converting enzyme inhibitors, which do not cause pseudotolerance. In any event, when a diuretic drug is included in the regimen, lower doses of other drugs are effective, and side effects of other drugs can be minimized. This is also true to a lesser extent for the β-blockers.

The precise mechanism of the hypotensive action of the diuretic agents is not known. It has been established that these drugs reduce plasma volume during the first few weeks of therapy; thereafter, the decrease in plasma volume is less obvious but seems to persist as long as the diuretic drug is administered. During chronic therapy, diuretic agents reduce total peripheral vascular resistance but have no effect on cardiac output. This effect may be diuretic drug hemodynamically appropriate for most patients with essential hypertension, which is characterized by increased total peripheral resistance and normal cardiac output.

Most β-blockers reduce blood pressure by reducing cardiac output and by leaving total peripheral resistance unchanged, making them ideal for the treatment of young hypertensive individuals with hyperkinetic circulation characterized by increased cardiac output. The β-blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) and especially the β-blocker with α-adrenergic receptor-blocking properties (labetalol) decrease total peripheral resistance with a lesser effect on cardiac output than do the β-blockers without these properties.

The major advantage of the β-blockers that is not shared by any other class of antihypertensive drugs is the β-blockers' unique cardioprotective effect after a myocardial infarction, although β-blockers with intrinsic sympathomimetic activity may not have this cardioprotective effect. β-Blockers also have an antianginal effect, some have a prophylactic effect against migraine, and they may also be helpful in controlling senile tremor.

Only the diuretic agents and the β-blockers have been shown to decrease total cardiovascular morbidity and mortality in long-term prospective trials (Table 3). The European Working Party on Hypertension in the Elderly trial is the only placebo-controlled clinical trial that demonstrated a significant reduction in coronary mortality. No placebo-controlled trial with a β-blocker as step-one therapy has shown a primary protective effect against coronary events, although these agents have been shown to be effective in the secondary prevention of coronary events. Nevertheless, it is impressive that between 1970 and 1985 the US age-adjusted death rate for coronary disease and

**Table 2. Advantages of Diuretic Drugs and β-Blockers as Step-One Therapy**

<table>
<thead>
<tr>
<th>Advantages of a Diuretic Drug</th>
<th>Advantages of a β-Blocker</th>
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<tbody>
<tr>
<td>Inexpensive</td>
<td>Effective in ≥50% of mild hypertensive patients</td>
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<tr>
<td>Effective in ≥50% of mild hypertensive patients</td>
<td>Cardioprotective after myocardial infarction</td>
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<tr>
<td>One dose daily</td>
<td>Antianginal drug</td>
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<tr>
<td>Easy to titrate</td>
<td>Reduces cardiac output in hyperkinetic circulation</td>
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<tr>
<td>Well tolerated</td>
<td>Reduces cardiovascular mortality</td>
</tr>
<tr>
<td>Enhances potency of all other agents</td>
<td>One dose daily</td>
</tr>
<tr>
<td>Effective in reducing cardiovascular mortality</td>
<td>No pseudotolerance</td>
</tr>
<tr>
<td>No pseudotolerance</td>
<td>Migraine prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Reduces senile tremor</td>
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The decrease in the mortality rates for these diseases can be attributed to a variety of factors, one of which is the control of hypertension, and during this time, most hypertensive patients were treated with diuretic-based stepped care. No other class of drugs has been as intensely scrutinized for so long as the diuretic drugs, and today, they are the standard against which other classes of agents must be measured.

**Side Effects**

With the possible exception of the calcium channel blockers and converting enzyme inhibitors, diuretic agents and β-blockers produce fewer symptomatic side effects than other classes of antihypertensive drugs and are well tolerated by most patients. In the Medical Research Council trial25, the most troublesome side effect of bendrofluazide was sexual dysfunction, which was reported by 22.6% of the men receiving this diuretic agent for 2 years compared with 10.1% of the men receiving placebo (p<0.05) and 13.2% of the men receiving propranolol. This side effect, however, was reversible. Sexual dysfunction was the most frequent reason that men withdrew from diuretic therapy, while nausea, dizziness, or headache were the most frequent side effects cited by women. In all, 17.1% of men and 12.8% of women were withdrawn from diuretic therapy during the 5-year period of the trial, although not all subjects were withdrawn because of symptomatic side effects. In the propranolol group, 15.5% of the men and 18% of the women were withdrawn. Table 4 lists the most common side effects reported by participants in this study.

In the Systolic Hypertension in the Elderly Program 1-year feasibility trial,26 none of the symptomatic side effects reported by subjects receiving chlorthalidone 25–50 mg/day were significantly more frequent than those in the placebo group. Only six of 443 participants on chlorthalidone and two of 108 participants in the placebo group were withdrawn from the study because of symptomatic side effects. Diuretic drugs were reserved for the second step if blood pressure could not be controlled by monotherapy in a double-blind study that compared the effects of propranolol, methyldopa, and captopril on various parameters of quality of life in 626 men.27 The investigators found that captopril interfered with quality of life less frequently than did the others. The addition of a diuretic agent detracted from the quality of life, but without the diuretic, the study might not have been completed because 36%, 31%, and 22% of patients in the captopril, methyldopa, and propranolol groups, respectively, required the addition of a diuretic agent by the 16th week to maintain normotension.

**Disadvantages of Diuretic Agents and β-Blockers as Step-One Drugs**

The major concern about diuretic agents concerns their metabolic side effects: hypokalemia,
TABLE 5. Disadvantages of a Diuretic Drug as Step-One Therapy

<table>
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<tr>
<th>Metabolic side effects</th>
<th>Disadvantages of a β-Blocker as Step-One Therapy</th>
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<tr>
<td>Decreases potassium and magnesium</td>
<td>Does not reduce total peripheral resistance</td>
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<tr>
<td>Increases urate, calcium, glucose, and lipids</td>
<td>Central nervous system side effects</td>
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<tr>
<td></td>
<td>Metabolic side effects</td>
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<tr>
<td></td>
<td>Decreases high density lipoprotein cholesterol</td>
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<tr>
<td></td>
<td>Increases glucose</td>
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<td></td>
<td>Sexual dysfunction in men</td>
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<tr>
<td></td>
<td>Multiple contraindications and precautions</td>
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<td></td>
<td>Greater than first-degree heart block</td>
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<td></td>
<td>Asthma</td>
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<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Intermittent claudication</td>
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<td></td>
<td>Insulin-dependent diabetes mellitus</td>
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hyponatremia, hyperuricemia, hyperglycermia, and hyperlipidemia. Hypokalemia is not usually a problem because it can easily be avoided by the concomitant use of a potassium-sparing diuretic agent if the patient is at risk of ventricular ectopy due to digitalis therapy, a history of cardiac arrhythmias, or an abnormal resting electrocardiogram, particularly left ventricular hypertrophy. If the patient is not at particular risk, diuretic-induced hypokalemia has not been harmful, 28 Hyperuricemia is not harmful if the patient is asymptomatic, 29 and hypercalcemia is not life-threatening and occurs only infrequently.

Long-term use of thiazide diuretic agents can increase the concentration of fasting plasma glucose and can impair glucose tolerance, but these changes usually do not reach abnormal levels. Glucose tolerance is not usually impaired during the 1st year of thiazide treatment, 30 although impairment was apparent at 10 weeks in a Veterans Administration study 31 but was only apparent at 2–3 years in the European Working Party on Hypertension in the Elderly trial and after 6 years in a Medical Research Working Party on Hypertension in the Elderly trial 32 and after 6 years in a Medical Research Council study. 33 At 14 years, glucose tolerance had deteriorated even more than at 6 years. 34 These changes were reversible after the diuretic agent was discontinued even after 14 years. 34 On the other hand, Berglund and Andersson 35 found that fasting blood glucose and 1-hour blood glucose concentrations decreased after 6 years of treatment with bendroflumethiazide.

Although the thiazide diuretic agents can aggravate preexisting diabetes in some susceptible patients and can precipitate diabetes in predisposed persons, 36 most diabetic patients can tolerate a thiazide diuretic drug with little or no change in the control of their diabetes.

The most serious criticism of diuretic agents concerns their effects on serum lipids. Most short-term studies have shown an increase in serum cholesterol, triglycerides, and low density lipoprotein cholesterol in previously untreated individuals when diuretic therapy is started. 37–39 These effects occur in about 60% of patients, with the other 40% experiencing no adverse effect on their serum lipid levels. 37 These effects are blunted by adjustments in the diet 38 and appear to be dose related. 37 In most studies, higher doses of diuretic agents were used than are now customarily prescribed. It is now unusual to use more than 50 mg hydrochlorothiazide or its equivalent per day. In long-term trials, serum cholesterol concentrations have decreased to or below baseline after the 1st year. 3, 26, 35, 40–42

The β-blockers have the disadvantage of producing a high incidence of central nervous system side effects, which may not be related to relative lipophilicity. 43 In the Veterans Administration Trial, 3 propranolol caused significant increases in the concentrations of total cholesterol and serum triglycerides, which (unlike the effect of hydrochlorothiazide) persisted for the duration of the 58-week trial. In this same study, the adverse effect of propranolol on glucose tolerance persisted longer than that produced by hydrochlorothiazide after conclusion of the trial. 31 The high density lipoprotein cholesterol has been suppressed by β-blocker therapy even when the total serum cholesterol concentration has not been significantly altered. The intrinsic sympathomimetic activity β-blockers and the α- and β-blocking drug labetalol apparently do not have an adverse effect on serum lipids, yet these agents have not been shown to have the cardioprotective effect after a myocardial infarction that the conventional β-blockers have.

Summary

The traditional drugs for initial therapy of hypertension, the diuretic agents and β-blockers, have many of the desirable attributes of the ideal step-one drug, not the least of which is their demonstrated effect in reducing cardiovascular morbidity and mortality. Time and experience may well temper the original enthusiasm for calcium channel blockers and converting enzyme inhibitors as step-one agents.

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