Options for subsequent antihypertensive therapy

- Not at goal blood pressure (<140/<90 mm Hg); lower goal in patients with diabetes mellitus or renal disease
  - No response or troublesome side effects
  - Inadequate response but well tolerated
  - Substitute another drug from a different class
  - Add a second agent from a different class (diuretic if not already used)
- Not a goal blood pressure
- Continue adding agents from other classes
- Consider referral to a hypertension specialist

FIGURE 7-52
Options for subsequent antihypertensive therapy. The majority of patients with mild to moderate hypertension can be controlled with one drug. If, after a 1- to 3-month interval, the response to the initial choice of therapy is inadequate, however, three options for subsequent antihypertensive drug therapy may be considered: 1) increase the dose of the initial drug, 2) discontinue the initial drug and substitute a drug from another class, or 3) add a drug from another class (combination therapy). Recommendations from the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) are provided [17].

COMBINATION THERAPIES

Mild to moderate (stage 1 or 2) hypertension
- Addition of low-dose thiazide-type diuretic to:
  - ACE inhibitor
  - β1-adrenergic antagonist
  - α1-adrenergic antagonist
  - Angiotensin III receptor antagonist
  - Severe (Stage 3) hypertension
  - Classic triple drug therapy
  - Diuretic
  - β1-adrenergic antagonist
  - Direct-acting vasodilator
  - ACE inhibitor plus calcium antagonist
  - β1-adrenergic antagonist plus α1-adrenergic antagonist
  - β1-adrenergic antagonist plus dihydropyridine calcium antagonist

Severe (Stage 3) hypertension
- Classic triple drug therapy
- ACE—angiotensin-converting enzyme; JNC—Joint National Committee.
Pharmacologic Treatment of Hypertension

JNC VI LIFE STYLE MODIFICATIONS

Lose weight if overweight
Limit alcohol intake to no more than 1 oz (30 mL) ethanol (eg, 24 oz [720 mL] beer, 10 oz [300 mL] wine, or 2 oz [60 mL] 100-proof whiskey) per day or 0.5 oz (15 mL) ethanol per day for women and lighter weight people
Increase aerobic physical activity (30 to 45 minutes most days of the week)
Reduce sodium intake to no more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride)
Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
Maintain adequate intake of dietary calcium and magnesium for general health
Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health

CAUSES OF RESISTANT HYPERTENSION

Patient’s failure to adhere to drug therapy
Physician’s failure to diagnose a secondary cause of hypertension
Renal parenchymal hypertension
Renovascular hypertension
Mineralocorticoid excess state (eg, primary aldosteronism)
Pheochromocytoma
Drug-induced hypertension (eg, sympathomimetic, cyclosporine)
Illicit substances (eg, cocaine, anabolic steroids)
Glucocorticoid excess state (eg, Cushing’s syndrome)
Coarctation of the aorta
Hormonal disturbances (eg, thyroid, parathyroid, growth hormone, serotonin)
Neurologic syndromes (eg, Guillain-Barré syndrome, porphyria, sleep apnea)
Physician’s failure to recognize an adverse drug–drug interaction
See Physician’s Desk Reference
Physician’s failure to recognize the development of secondary drug resistance
Sodium retention with pseudotolerance, secondary to diuretic resistance or excess sodium intake
Increased heart rate, cardiac output secondary to drug-induced reflex tachycardia
Increased peripheral vascular resistance secondary to drug-induced stimulation of the renin-angiotensin system

FIGURE 7-54
Follow-up in antihypertensive therapy. During follow-up visits, pharmacologic therapy should be reconfirmed or readjusted. As a rule, antihypertensive therapy should be maintained indefinitely. Cessation of therapy in patients who were correctly diagnosed as hypertensive is usually (but not always) followed by a return of blood pressure to pretreatment levels. After blood pressure has been controlled for 1 year and at least four visits, however, attempts should be made to reduce antihypertensive drug therapy “in a deliberate, slow, and progressive manner;” such “step-down therapy” may be successful in patients following lifestyle modification [17]. Patients for whom drug therapy has been reduced or discontinued should have regular follow-up, since blood pressure may increase again to hypertensive levels. JNC—Joint National Committee.

FIGURE 7-55
Resistant hypertension. Causes of failure to achieve or sustain control of blood pressure with drug therapy are listed [6,9].
Hypertension and the Kidney

FIGURE 7-56
Diuretic resistance. Diuretic resistance may result from patient noncompliance, impaired bioavailability in an edematous syndrome, impaired diuretic secretion by the proximal tubule, protein binding in the tubule lumen (e.g., nephrotic syndrome), reduced glomerular filtration rate, or enhanced sodium chloride reabsorption [7,8]. Resultant fluid retention will attenuate the effectiveness of most antihypertensive drugs. Renal mechanisms, problems, and solutions are provided in this table [6,8,9].

### DIURETIC RESISTANCE

<table>
<thead>
<tr>
<th>Problem</th>
<th>Mechanism</th>
<th>Solution</th>
</tr>
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<tbody>
<tr>
<td>Limits active transport of diuretics into proximal tubular fluid, reducing inhibitory effect at a more distal intraluminal membrane site</td>
<td>Reduced renal blood flow</td>
<td>Use of large doses of a diuretic and appropriate dosing interval to achieve a therapeutic tubular drug concentration</td>
</tr>
<tr>
<td>Limits absolute amount of sodium filtered</td>
<td>Reduced glomerular filtration rate</td>
<td>Use loop diuretics with steep dose response curve and/or block multiple sites of sodium reabsorption: loop diuretic with thiazide-like diuretic</td>
</tr>
<tr>
<td>Sodium recaptured at late distal tubule and collecting duct</td>
<td>Secondary hyperaldosteronism</td>
<td>Addition of a potassium-sparing diuretic to above, to maintain urine sodium/potassium ratio &gt; 1</td>
</tr>
</tbody>
</table>

### References