



# Diseases Affecting Baby Boomers: COPD, Stroke, BPH, and Hypertension

A pharmacy continuing education supplement derived from an educational program held at the 32nd Annual American Society of Consultant Pharmacists Meeting in Chicago, November 2001

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Dear Pharmacist:

A person in the United States turns 50 every 7 seconds. Currently, more than 75 million people in the United States are over 50 years of age. Within this population, greater than 35 million people are over 65 years of age. This population is responsible for almost 60% of healthcare spending and 77% of prescriptions. This group, the Baby Boomers, will have a significant impact on the future of healthcare.

Four diseases that occur almost exclusively in the older adult include chronic obstructive pulmonary disease, stroke, benign prostatic hyperplasia, and hypertension. A continuing education symposium was held at the 32nd Annual American Society of Consultant Pharmacists meeting in Chicago, Illinois, to discuss the prevalence, diagnosis, prevention, and treatment of these four common diseases. This continuing education program, derived from the symposium, contains current, practical information that can be used by you and your colleagues to reduce the morbidity and mortality associated with these illnesses.

Pharmacy continuing education credit is being provided by Rutgers, The State University of New Jersey Ernest Mario School of Pharmacy. This educational program is being supported through an unrestricted educational grant from Boehringer Ingelheim Pharmaceuticals Inc.

Sincerely,

A handwritten signature in black ink that reads "Thomas C. Snader". The signature is written in a cursive style with a large, prominent 'S' at the end.

Thomas C. Snader, PharmD, FASCP  
Program Chairperson

## Target Audience

*Diseases Affecting Baby Boomers: COPD, Stroke, BPH, and Hypertension* was designed to meet the educational needs of pharmacists in all healthcare delivery settings.

## Learning Objectives

- Identify the prevalence associated with COPD, stroke, BPH, and hypertension in older adults
- Define the morbidities and mortality associated with COPD, stroke, BPH, and hypertension in older adults
- Describe methods to effectively prevent complications associated with COPD, stroke, BPH, and hypertension in older adults
- Determine methods to effectively manage COPD, stroke, BPH, and hypertension in older adults
- Describe new and emerging clinical data that may be useful in the drug therapy decision-making process

## Pharmacy Continuing Education Credits



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# Diseases Affecting Baby Boomers: COPD, Stroke, BPH, and Hypertension

**B**aby Boomers make up one of the fastest growing population segments in the United States, with a person turning 50 years of age every 7 seconds. Along with this aging population comes an increase in disease prevalence. Four diseases that have a higher prevalence in this population—chronic obstructive pulmonary disease (COPD), stroke, benign prostatic hyperplasia (BPH), and hypertension—were discussed in detail at a continuing education symposium that took place at the 32nd Annual American Society of Consultant Pharmacists Meeting in Chicago, November 2001.

## Current and Emerging Therapies for Chronic Obstructive Pulmonary Disease in the Geriatric Patient

Between 12 million and 15 million Americans suffer from chronic obstructive pulmonary disease (COPD), which ranks 3rd in incidence behind congestive heart failure and stroke and is the 4th leading cause of death in the United States.<sup>1,2</sup> COPD claims 25.7 men per 100,000 and 14 women per 100,000 every year. The death rate from COPD has increased by 20% since 1980, with persons older than 55 at particular risk. In addition to advanced age, major risk factors are smoking, male gender, preexisting impaired lung function, and occupational exposure to hazardous substances. Alpha-1 antitrypsin deficiency, a genetic defect, accounts for less than 1% of COPD cases, and is treated with intravenous replacement therapy.

COPD is defined as a spectrum of chronic respiratory diseases characterized by chronic dyspnea and chronic expiratory airflow obstruction. The disease process may lack variability; respiratory function tests may remain stable for months at a time, with acute exacerbations inducing disease progression. Predominant diseases related to COPD are emphysema and chronic bronchitis with airflow limitation. Asthma, which is uncommon in nursing home residents, is a different disease and should be differentiated from COPD (Table 1).

**Table 1. Distinguishing Asthma From COPD**

Asthma	COPD
<ul style="list-style-type: none"> <li>• Airway inflammation</li> <li>• Airway obstruction in response to diverse stimuli</li> <li>• Exacerbation/remission; no inexorable progression</li> <li>• Respiratory distress at rest</li> <li>• Difficulty speaking in sentences</li> <li>• Diaphoresis</li> <li>• Use of accessory respiratory muscles</li> <li>• Pulse rate &gt; 110/minute</li> <li>• Pulsus paradoxus &gt;12 mm Hg</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic dyspnea</li> <li>• Chronic expiratory airflow obstruction</li> <li>• Lacks variability for months, but with acute exacerbations</li> <li>• Inexorable progression</li> <li>• Tests of respiratory function stable for months</li> </ul>

### Verifying the Diagnosis

Appropriate therapy for COPD hinges on accurate diagnosis. Although consultant pharmacists are not diagnosticians, it is essential to verify the proper diagnosis.

Understanding the distinction among respiratory diseases is important to properly critique drug therapy. Results of x-rays, physical exams, and pulmonary function tests provide clues to proper diagnosis. If the diagnosis appears to be inconsistent with the drug therapy plan, it is appropriate for the consulting pharmacist to ask for clarification. Many geriatric physicians “inherit” patients whose histories are absent or very poor, and pharmacists may need to question the diagnosis to ensure that drug therapy is correct.

### COPD Related to Chronic Bronchitis

Patients with COPD due to chronic bronchitis have productive cough with copious amounts of sputum. Patients keep their chest expanded with little movement to get as much air as possible, and thus have a “barrel” chest appearance. On percussion the chest sounds resonant or hollow like a drum, with rhonchi and wheezes. Typically because of edema, weight gain, and cyanosis due to cor pulmonale, these patients are called “blue bloaters.” A key physical examination point is hepatojugular reflex secondary to liver congestion. Sleep apnea is common due to the lack of sensitivity to CO<sub>2</sub> which normally triggers breathing. Therefore, sedative products such as benzodiazepines, barbiturates, or hypnotics should be avoided since they may further depress nighttime breathing.

### COPD Related to Emphysema

Emphysema-related COPD patients are “pink puffers” resulting from extremely rapid respiration in an attempt to get enough oxygen. At rest, dyspnea and tachypnea are prominent, and patients are very thin because they are too busy breathing to maintain adequate food intake. Typically they exhale through pursed lips to increase back pressure, helping to dilate and keep the bronchioles open. Their alveoli coalesce into fewer and larger alveoli, which decreases alveolus surface area, making it difficult to maintain blood oxygenation. In order to increase their air space, emphyse-

ma patients try to hunch over and also lift the shoulders when standing. Percussion of the lungs is even more drumlike, but breath sounds are diminished. These patients have little rhonchi or wheezing and do not have the secretions of chronic bronchitis. Chest radiology shows distended lungs; a lower, flat diaphragm; increased retrosternal air space; long, narrow heart shadow; and bullous lesions. Elderly patients with COPD may have more than one respiratory condition, although it would be rare for a patient to have emphysema in addition to chronic bronchitis and asthma.

### Applying Pulmonary Function Testing to Drug Therapy

Pulmonary function is considered abnormal if results are < 80% of normal values. Pulmonary function testing is essential for determining the severity of the condition, the patient's prognosis, and ongoing response to therapy. However, frail elderly patients may be difficult to test, and some tests are very costly.

The most important tests in terms of assessing therapy are forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>). FVC is reduced in emphysema but not as much as the FEV<sub>1</sub>; therefore the ratio of FEV<sub>1</sub> to FVC decreases. In addition, reductions in FVC and the ratio of FEV<sub>1</sub> to FVC are characteristic of emphysema.

An improvement in FEV<sub>1</sub> of 10% to 15% following a dose of medication demonstrates efficacy. If the patient cannot blow out more air in 1 second than they could before treatment, therapy is ineffective, in addition to possibly exposing the patient to adverse effects associated with drug therapy.

Oximetry, a relatively inexpensive test, uses a simple device (Pulsox<sup>®</sup>) attached to a finger to measure peripheral capillary oxygen concentration. The Pulsox<sup>®</sup> oxygen concentration needs to be below 90% at rest to support oxygen reimbursement by Medicare. Measurement of arterial blood gases—Pao<sub>2</sub>, Paco<sub>2</sub>, and pH—are useful to predict disease severity and prognosis. However, these tests are expensive, uncomfortable for the resident, and are rarely done.

Many physicians feel that the frail elderly are not fit candidates for tolerating spirometry. However, in the right situations it might be worth requesting the test to ensure that drug therapy is benefiting the patient.

### COPD Prevention and Treatment: Facts and Debunked Myths

A number of "homemade" beliefs about treatment are still held, even among healthcare professionals. For example, some believe that smoking cessation will not help once COPD is established. The truth is that at any stage of the disease, minimizing exposure to airway irritants, including cigarette smoke, improves the situation. For clearing secretions, however, increasing fluid intake or thinning the secretions is not helpful unless the patient is dehydrated. Also, contrary to popular belief, the use of nebulized saline, guaifenesin and iodine, or iodinated glycerol has not been proven effective in improving FEV<sub>1</sub>, though iodinated glycerol may improve comfort. Postural drainage is effective in cystic fibrosis patients and possibly in younger patients with chronic bronchitis, but it does not help older patients, and chest percussion may fracture a bone in the osteoporotic elderly patient.

### Rational Therapy of COPD

Acute exacerbations of COPD are treated by attempting to improve the symptoms. Exacerbations result from bronchospasm, increased mucus secretions, and mucus plugging, either because of infections, emboli, pulmonary edema, or pneumothorax. These episodes are managed by administering oxygen, with Pao<sub>2</sub> maintained at 88% to 90%. If given by Venturi mask, the amount should not exceed 3 liters per minute.

A ventilator should be used if Pao<sub>2</sub> remains low and other methods to raise oxygen levels have failed. Unfortunately, ventilators are uncommon in nursing home facilities. Doses of inhaled medications are determined by response and vary due to methods of administration. Many patients will fight the ventilator; sedating drugs may be necessary to calm the patient and to allow the ventilator to be effective so the patient can be weaned off it. There is no risk in this practice because the ventilator is breathing for the patient. The pharmacist should be aware, however, that many problems such as respiratory distress, asynchronous breathing, aspiration, oxygen toxicity, and other issues are associated with ventilators.

Pulmonary infections must be treated early in order to prevent exacerbation of the COPD. Physical signs of infection (fever, white

Figure 1. American Thoracic Society Guidelines for COPD

#### 1. For mild variable symptoms:

- Selective  $\beta_2$ -agonist metered dose inhaler (MDI) aerosol, 1-2 puffs every 2-6 h as needed, not to exceed 8-12 puffs per 24 h

#### 2. For mild to moderate continuing symptoms:

- Ipratropium MDI aerosol, 2-6 puffs every 6-8 h, not to be used more frequently

Plus

- Selective  $\beta_2$ -agonist MDI aerosol, 1-4 puffs as required 4 times daily for rapid relief, when needed, or as regular supplement

#### 3. If response to step 2 is unsatisfactory or there is a mild to moderate increase in symptoms:

- Add sustained release theophylline, 200-400 mg twice daily or 400-800 mg at bedtime for nocturnal bronchospasm

and/or

- Consider use of sustained-release albuterol, 4-8 mg twice daily or at night only

and/or

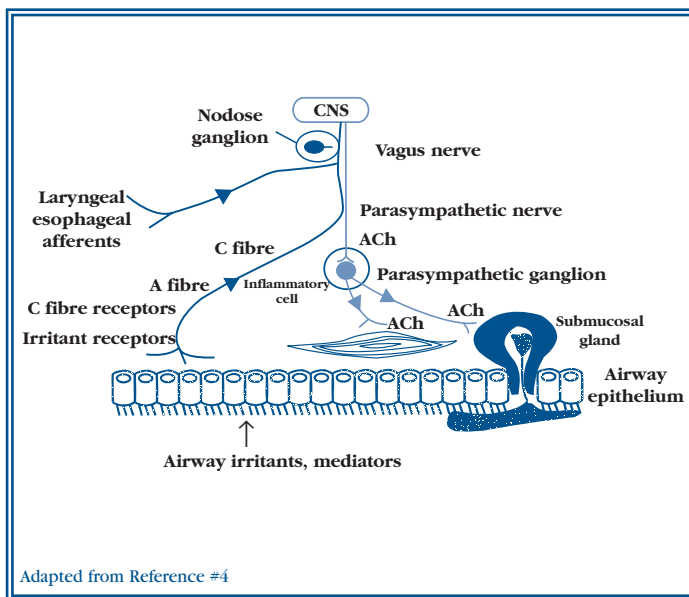
- Consider use of mucokinetic agent

#### 4. If control of symptoms is suboptimal:

- Consider course of oral steroids (eg, prednisone), up to 40 mg/d for 10-14 d
  - If improvement occurs, wean to low daily or alternate-day dose (eg, 7.5 mg)
  - If no improvement occurs, stop abruptly
  - If steroid appears to help, consider possible use of aerosol MDI, particularly if patient has evidence of bronchial hyperactivity

Adapted from Reference #3

Figure 2. Cholinergic Pathways



blood cell changes) may be less obvious if the patient is on steroids. While sensitivity cultures should be done to identify the invading organism, collection of the sample is problematic.

Treatment is often empirical and should be aggressive. Oral quinolones, which produce good serum levels and are effective against organisms commonly seen in institutions, are often the first choice.

Nutritional considerations are an essential part of rational therapy for COPD. Breathing requires a substantial amount of calories in this population. Many people with COPD are underweight because they do not take in sufficient calories to fuel the effort to breathe. Carbohydrates, which increase CO<sub>2</sub> in the blood, should be minimized and proteins and fats substituted.

### Role of Guidelines in Therapy

Therapy of COPD targets 3 basic goals: reduced production of secretions, increased elimination of secretions, and management of acute exacerbations. The American Thoracic Society (ATS) guidelines for drug therapy of COPD, published in 1995, are listed in Figure 1.<sup>3</sup> Unfortunately, healthcare practitioners often jump over the first-line ATS recommendations and move to third- or fourth-line drugs. Often the consultant pharmacist will see an inconsistency between the diagnosis and the application of the medication, either in the order the medications were tried or in optimal doses that were used before moving on to the more toxic, less effective levels of therapy (theophylline and glucocorticoids). In communicating with the physician, the pharmacist can cite the ATS guideline as an authoritative source for suggestions to optimize medications.

The ATS guidelines recommend anticholinergics first for continuing symptoms because these drugs address the pathology of emphysema and COPD more squarely than does a sympathomimetic, which only dilates the bronchials. Anticholinergics affect goblet cells, mucus secretion, and smooth muscle ciliary movement, in addition to the bronchospasm (Figure 2).

### Ipratropium (Atrovent®)

Up to 6 puffs at a time can be used in dosing ipratropium, waiting 1 minute between puffs. The pharmacist should ensure that at least 4 puffs 4 times a day were administered properly before it was decided the drug was ineffective. Often a “spacer” will be needed in the geriatric patient. MDI nebulization can be more effective than mini-nebulizers because the particle size in a mini-nebulizer is larger; the smaller particles dispensed by an MDI have a better chance of reaching the lower bronchi. Often in the long-term care setting nebulization therapy is unsupervised, further reducing the reliability of this form of drug administration. This is especially true in the confused demented resident.

Ipratropium is not to be used as a PRN or rescue drug because of its slow onset, although a PRN order during an acute exacerbation is appropriate to supplement a routinely administered dose. Accidental administration in the eye should be avoided due to anticholinergic effects producing visual disturbances. The only notable side effect is dry mouth. Because ipratropium requires up to 15 minutes to take effect and there are no systemic side effects, patients sometimes falsely believe that the drug has no effect.

### Albuterol (Alupent®)

Albuterol is a relatively selective  $\beta_2$ -adrenergic bronchodilator used PRN as rescue medication for acute attacks. The stimulant side effects of albuterol often give patients the false impression that because they “feel something” the drug is having a therapeutic effect. The drug’s stimulant effects may worsen angina or hypertension, but its benefits usually counterbalance this potentially negative effect—ie, if the patient breathes better, the heart rate will decrease. Thus, albuterol is not necessarily ruled out in the patient with hypertension or angina that is under control with medications. A maximum of 4 puffs 4 times per day is used in older patients.

### Combination Therapy:

#### Ipratropium Plus Albuterol (Combivent®)

This combination therapy produces a 21% to 44% improvement in FEV<sub>1</sub> compared to ipratropium alone, and a 30% to 46% greater response than albuterol alone. The 2 agents have complementary modes of action. Ipratropium is a parasympatholytic anticholinergic bronchodilator, while albuterol is a relatively selective  $\beta_2$ -adrenergic bronchodilator. Typically, the combination, which is packaged as an MDI, is given as 2 to 3 inhalations 4 times a day or as needed, with no more than 12 inhalations in 24 hours. There are no additional adverse effects, and the combination therapy reduces costs and nursing time, and is more convenient for residents.

A 1-month study conducted in 30 nursing homes of the combination inhaler compared to individual ipratropium bromide and albuterol sulfate oral inhalers given sequentially showed average labor time savings of 20 minutes per day and calculated annualized cost savings of approximately \$3,432.90 per resident per year. The medication administration error rate was also significant.

ly lower with the combination inhaler.<sup>5</sup> It is extremely important to optimize this therapy, which represents steps 1 and 2 in the ATS Guidelines, before moving on to steps 3 and 4.<sup>3</sup>

### Salmeterol (Serevant®)

Salmeterol is a long-acting  $\beta_2$ -agonist in the same therapeutic class as albuterol, but is not recommended for rescue therapy. Used primarily for maintenance therapy for prevention of bronchospasm in asthma, salmeterol is given twice daily. The drug may be used in patients who also use short-acting  $\beta_2$ -agonists or parasympatholytic anticholinergic bronchodilators (ipratropium). However, combining salmeterol with albuterol can cause tachyphylaxis (down-regulation of receptor sites in the bronchus). This can lead to increased dosing with increasing side effects, but no additional therapeutic response.

### Theophylline

Theophylline is an effective methylxanthine bronchodilator but should be used with care in patients older than age 60 and those with concurrent illnesses, particularly congestive heart failure, hypothyroidism, and liver disease, all of which may reduce theophylline clearance. Physicians may use reduced doses because lower theophylline doses are believed to provoke improved performance of the diaphragmatic muscles—“digoxin for the diaphragm.” If bronchospasm is present, theophylline at higher doses may help, but side effects can be dangerous.

Theophylline is among the drugs listed as particularly toxic for geriatric patients, and to be avoided if safer alternatives are available (the “Beers criteria”).<sup>6</sup> With some commercially available preparations, the risk of dosage errors and drug interactions is particularly severe. Side effects may include heartburn and esophageal strictures and erosions, which often prompt physicians to add  $H_2$  blockers or proton pump inhibitors (PPIs). At high dose levels, theophylline also may provoke cardiac arrhythmias.

Cimetidine, PPIs, and other  $H_2$  blockers decrease theophylline clearance by inhibiting cytochrome P-450 1A2. Because theophylline interacts with many drugs, a drug review is essential before using this agent in nursing home residents.

### Oral Glucocorticoids

Providers may prescribe oral glucocorticoids for nursing home residents in the belief that some benefit is possible and, at the very least, the oral delivery form ensures that medication has gotten into the patient. However, the benefits of glucocorticoids in COPD are questionable and the side effects numerous. For one example, 2 weeks of oral prednisone at doses > 10 mg per day can lead to atrophy of the adrenal cortex, preventing proper release of glucocorticoid in response to stress.<sup>6</sup> Adrenal suppression can lead to cardiovascular collapse and death. Oral prednisone given to a frail elderly person, especially at higher doses, will worsen osteoporosis, behavioral disorders, hypertension, and diabetes. Another option would be to use an MDI with a high-potency product such as beclomethasone or fluticasone, which have lower systemic absorption than triamcinolone.

### Fluticasone Plus Salmeterol (Advair™)

This product, indicated for the long-term, twice-daily maintenance treatment of asthma, combines the long-acting  $\beta_2$ -agonist salmeterol and the glucocorticoid fluticasone. The most common side effects are upper respiratory tract infection, pharyngitis, upper respiratory tract inflammation, and headaches. The 3 available strengths of the combination inhalation powder are: 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg. The fixed-dose combinations make it difficult to convert those patients receiving separate inhalers of each product since the dosage is 1 inhalation, not 2 puffs. In addition, the drug concentrations are different. As with all inhaled corticosteroids, it is important to have patients rinse the mouth after using inhaled corticosteroids to reduce the risk of thrush.

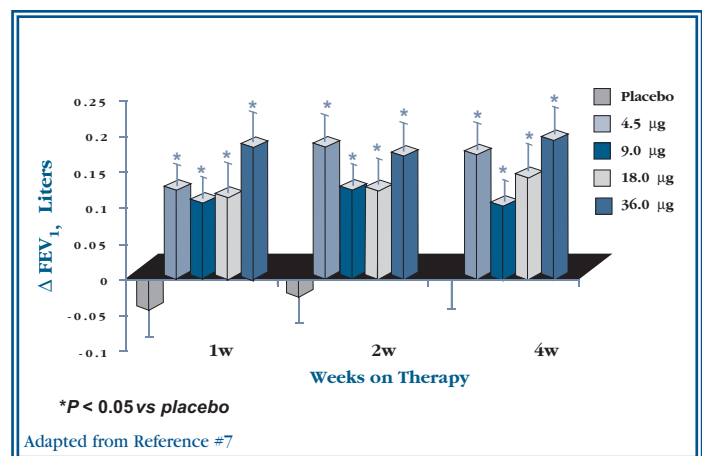
### Advances in Parasympatholytic Therapy: Tiotropium

This product has not yet been approved by the FDA. Tiotropium is a long-acting parasympatholytic anticholinergic bronchodilator targeted for first-line maintenance therapy in COPD. Tiotropium has shown a significant and consistent improvement in lung function over 24 hours in long-term studies. Tiotropium enters the lung, binds there, and remains for an extended period of time. The half-life of tiotropium is nearly 15 times greater than that of ipratropium.

Tiotropium was tested in COPD patients (average age  $64 \pm 7$  years) in a double-blind, randomized, placebo-controlled cross-over study with a 72-hour washout between test days. A dose of 40 mcg produced a > 15% increase in FEV<sub>1</sub>, with a percent change from baseline of  $28 \pm 10\%$ . Figure 3 shows the mean FEV<sub>1</sub> response over 4 weeks.<sup>7</sup>

Tiotropium is administered using an inhaler that has no fluorocarbon propellants. It may be easier for elderly patients to use this device compared to traditional inhalers. Because the patient is only required to suck on it for 1 inhalation, it requires little high-level participation or coordination. The sucking process is fairly primitive and should be much easier for elderly long-term care residents, even in severe cognitively impaired states.

**Figure 3. Tiotropium: Mean FEV<sub>1</sub> Response Over 4 Weeks**



## Medication Administration Challenges

The various inhalation devices in which respiratory medications are packaged present unique challenges in long-term care patients. Some devices provide complicated instructions that require the patient to coordinate breaths with medication intake through the mouth and to count and remember the number of inhalations. This is very difficult, particularly if the patient suffers from dementia.

Even with the help of nursing staff and the use of spacers, medication administration can be difficult. A demented resident often loses focus and may remove the mask or the mouthpiece, thereby reducing the amount of drug delivered. Time is also a factor. It would be unusual for a long-term care nurse to have time to stay with a resident during the entire inhalation administration process—this can average 10 to 20 minutes per use.

MDIs have problems also, but if a spacer is used and the device is administered by a person well trained in proper technique, effective drug delivery is more likely. The newer, simpler delivery devices such as the Handihaler® hold out promise for greater ease of use and more certainty that the medication has reached its intended site.

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## Stroke: Prevention and Treatment

Stroke is the third leading cause of death in the United States. Of the 750,000 strokes recorded annually, 150,000 result in death.<sup>8</sup> Stroke is also the most common debilitating neurologic disorder. Of individuals who survive for 3 months after suffering a stroke, only 50% will live for 5 more years, and only 30% will live for 10 years. Sixty percent will recover and be capable of self-care, and 20% will require institutional care.<sup>9</sup> The cumulative 5-year mortality risk after stroke ranges up to 40%.<sup>10</sup>

The cumulative risk of stroke increases after a transient ischemic attack (TIA). A cerebrovascular occurrence of short duration, TIA is usually due to cerebral or cerebellar thrombosis and may not induce neurologic deficits. It does, though, herald an impending stroke, with a cumulative risk of subsequent stroke up to 29% over time.

A number of stroke risk markers are not modifiable:

- Age: Stroke rate doubles each decade after age 55.
- Gender: Men are at greater risk than women.
- Race/ethnicity: The risk is greater for blacks, Asians, and Hispanics compared to whites.

However, a number of stroke risk factors can be modified<sup>10,11</sup> (Table 2).

### Drug-Induced Risk Factors for Ischemic Stroke

The role of alcohol as a risk factor in ischemic stroke is somewhat controversial because moderate alcohol consumption is thought to be cardioprotective. However, habitual or binge drinking does increase stroke risk. Illicit drugs, including heroin, amphetamines, LSD, PCP, and phenylpropanolamine (PPA), all increase risk of ischemic stroke. Cocaine and crack are particular stroke risks for men younger than age 45. Oral contraceptive (OC) use poses an increased stroke risk, especially at estrogen doses greater than 50 mcg/mL and in women over the age of 35 who also smoke cigarettes. Risks associated with cigarette smoking are generally higher for women than men.

## Summary

COPD is a significant disease in older adults and is a major problem among nursing home residents. Ensuring the correct diagnosis is very important, as elderly patients with respiratory difficulties are often mistakenly thought to suffer from asthma, a relatively uncommon disease among older people. Appropriate drug therapy for COPD patients should follow the American Thoracic Society guidelines, which recommend optimizing therapy with an anticholinergic agent as the first step. The addition of albuterol for PRN use enhances the FEV<sub>1</sub> response to the anticholinergic agent. After these steps have been optimized, it may be appropriate to add other medications. Oral glucocorticoids and theophylline may produce toxicity at therapeutic levels and should ideally be reserved as third- or fourth-line therapy in elderly long-term care residents. In these individuals, it is essential to monitor the effectiveness and safety of therapy and to eliminate toxic or ineffective agents.

**Table 2. Modifiable Risk Factors in Stroke**

- |   |                        |
|---|------------------------|
| • Hypertension (systolic > diastolic)                         | • Hyperlipidemias      |
| • Atrial fibrillation   | • Sickle cell disease  |
| • Mitral stenosis or mitral annular calcification             | • Increased hematocrit |
| • Left ventricular hypertrophy or left arteriolar hypertrophy | • Increased platelets  |
| • History of MI   | • Hyperhomocystinemia  |
| • CHF, endocarditis   | • Migraines            |
| • Carotid bruits  | • Obesity              |
| • Prosthetic cardiac valves                                   | • Stress               |
|   | • Sedentary lifestyle  |

Adapted from References #10, 11

The stroke risk imposed by cardiac and psychotropic prescription drugs is related primarily to the drugs' effects on lipids. Thiazide and loop diuretics and  $\beta$ -blockers increase lipid levels, while  $\alpha_1$ -antagonists have a favorable effect because they lower cholesterol. ACE inhibitors, calcium channel blockers,  $\alpha_2$ -agonists, and indapamide do not affect lipids. Clozapine, olanzapine, risperidone, haloperidol, lithium, valproic acid, and gabapentin can cause weight gain, leading to increased cholesterol, loss of diabetes control, and increased blood pressure.

### Acute Ischemic Stroke: Clinical Presentation and Management

Acute ischemic stroke results from the sudden interruption of focal cerebral blood flow. Ten to 30 percent of all strokes are a result of emboli from the heart.<sup>8</sup> Clinically, acute ischemic stroke

patients may present with limb weakness or paralysis, hemiparesis, sensory complaints such as paresthesias or numbness, facial weakness, aphasia, or visual loss. Other, less obvious manifestations include headaches, seizures, confusion, lightheadedness or vertigo, ataxia, nausea and vomiting, photophobia, or hearing loss.

Tissue plasminogen activator (tPA) therapy works by breaking down (lysing) the clot and enhancing reperfusion. Therapy for ischemic stroke must be initiated within 3 hours of symptom onset. Importantly, the baseline CAT scan should show no evidence of intracranial hemorrhage. Dosage of tPA is calculated at 0.9 mg/kg of body weight, with a maximum of 90 mg, admixed with normal saline. An initial bolus of 10% of the dose is followed by the remaining 90% given as an intravenous bolus over 60 minutes. The patient should receive no antithrombotic or antiplatelet agents during the following 24 hours.

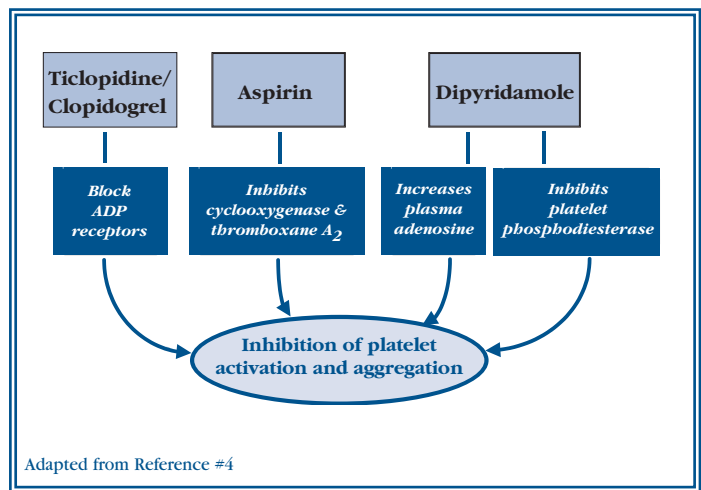
FDA approval of intravenous tPA for urgent treatment of patients who have suffered a stroke was based on The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study (NINDS r-tPA Stroke Study).<sup>12</sup> In part 1 of this study, 624 patients with ischemic stroke were treated with tPA within 3 hours of the onset of symptoms, with a primary endpoint of neurologic improvement within 24 hours. In part 2, the primary endpoint was the odds ratio for complete or near-complete neurologic recovery sustained for 1 year. At 3 months, 31% to 50% of patients had a favorable outcome with tPA, compared to 20% to 38% with placebo. The main risk was hemorrhage, which occurred in 6.4% of tPA-treated patients compared to 0.6% on placebo. Mortality at 1 year was similar between the tPA-treated group (24%) and the placebo-treated group (28%).

### Secondary Prevention/Stroke Prophylaxis

If stenosis caused by large-vessel thromboembolism is 70% or greater, carotid endarterectomy is indicated, but should be preceded by antiplatelet therapy. For stenoses of 50% to 70%, antiplatelet therapy followed by possible endarterectomy may be indicated, depending on the individual patient. For stenosis < 50%, anti-platelet therapy or, if surgery is not done, warfarin is initiated. Warfarin is also given if the event is cardioembolic.

Figure 4 illustrates the mechanisms of action of antiplatelet therapy. Aspirin (ASA) inhibits thromboxane A<sub>2</sub> (a promoter of platelet aggregation) and the cyclooxygenase enzyme in platelets and endothelial cells. Numerous studies of aspirin from doses of 30 mg to 1.5 g daily have been carried out to determine the appropriate dosage. High-dose ASA is associated with gastropathy, ASA triad (asthma, rhinitis, and nasal polyps) leading to bronchospasm, and increased blood pressure. High-dose ASA prior to carotid endarterectomy has also been associated with increased risk of myocardial infarction and stroke in the perioperative period.<sup>13</sup> Early trials were not conclusive in terms of the ASA dose for stroke prevention. ASA doses ranging from 50 to 325 mg daily are currently used for secondary stroke prevention.

**Figure 4. Mechanisms of Action of Antiplatelet Agents**



### Aspirin and Extended-Release Dipyridamole (Aggrenox®)

This combination extended-release gelatin capsule contains an aspirin (ASA): extended-release dipyridamole (ER-DP) ratio of 1:8, providing 25 mg immediate-release ASA and 200 mg ER-DP (ASA+ER-DP). The goal of therapy is to maintain the dipyridamole (DP) level at 1 μmol/mL. DP, a potent vasodilator, increases the effects of adenosine and is effective for chest pain in patients with unstable angina. However, the daily aspirin dose (25 mg BID) may not be adequate to treat cardiac indications.

### The European Stroke Prevention Study 2 (ESPS-2)

Studies reported in the 1980s demonstrated that the combination of aspirin and immediate-release dipyridamole was not more effective than ASA alone for stroke prevention. The ESPS-2 study, however, demonstrated that combination ASA+ER-DP was superior to either agent alone for secondary stroke prevention.<sup>14</sup>

The multicenter, randomized, double-blind, placebo-controlled trial enrolled 6,602 patients. The average age of participants in the ESPS-2 study was 66.7 years, with men comprising 58% and women 42% of the study population. Qualifying events for enrollment were stroke (76.3%) and TIA (23.7%).

Primary endpoints were any type of stroke, fatal or nonfatal, and death from any cause. A secondary endpoint was ischemic events (stroke, MI, or sudden death). Patients who had suffered TIA or stroke were randomized within 3 months of the event to receive daily treatment with either placebo, ASA 25 mg BID, ER-DP 200 mg BID, or combination ASA+ER-DP BID.

The results showed that monotherapy with ASA or ER-DP reduced the risk for stroke compared to placebo; however, the combination of ASA+ER-DP was significantly better than either agent alone (Figure 5). The cumulative stroke rate is shown in Figure 6. The greatest risk reduction occurred with the combination of ASA+ER-DP (37%;  $P < 0.001$ ). Results for all-cause mortality were not significantly different among the treatment groups: placebo, 12.4%; ASA, 11.0%; DP, 11.4%; combination ASA+ER-DP, 11.3%. This suggests that the primary effect of the drugs was the prevention of stroke.<sup>14</sup>

Overall, side effects were relatively comparable for placebo and the 3 active treatment groups. Side effects that were expected with ASA (gastrointestinal events and bleeding) and with ER-DP (headaches) were observed. A very slight, nonsignificant increase in gastrointestinal events was seen with the combination treatment. Headaches were more frequent in the DP-only (37%) and the combination (38%) treatment groups; however, this side effect can be prevented by gradually increasing the dose of ER-DP over several days. While more bleeding occurred in the ASA-alone (8%) and the combination group (8.7%) compared to placebo (4.5%), the incidence of bleeding was not increased by the addition of ER-DP to ASA. Thus, the addition of ER-DP to ASA increased efficacy but did not contribute to increased bleeding risk.

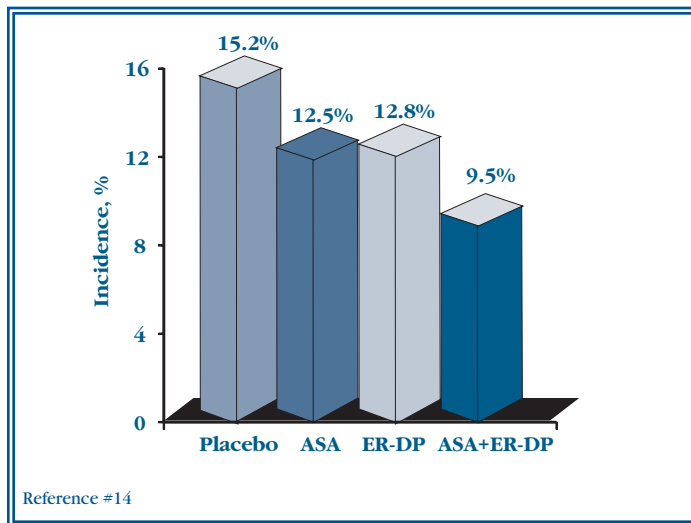
The results of ESPS-2 revealed that the combination of ASA+ER-DP reduces stroke risk and is approximately twice as effective as either ASA or ER-DP alone. Both low-dose ASA (50 mg/d) and ER-DP (400 mg/d) are independently effective and have similar efficacy. Bleeding side effects are similar for the combination and for ASA alone. The combination transiently increases headache incidence and is associated with a very slight nonsignificant increase in gastrointestinal side effects.

A meta-analysis of studies investigating ASA+ER-DP combinations versus ASA alone, which analyzed results by combining the primary endpoints of vascular events, had an inconclusive result because of a wide 95% confidence interval for relative risk (0.75-1.19).<sup>15</sup> However, in the placebo-controlled trials, combination ASA+ER-DP groups did significantly better than placebo-treated patients, with an overall 15% relative risk reduction associated with the combination.

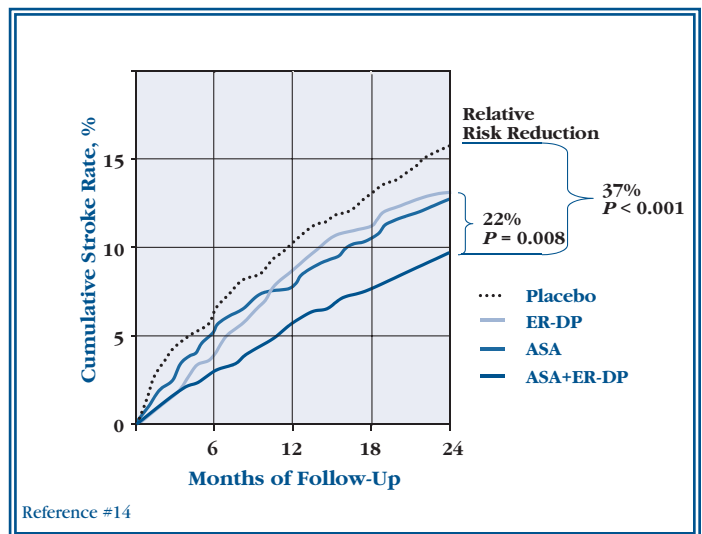
### Clopidogrel (Plavix®)

A prodrug thienopyridine ADP inhibitor, clopidogrel is 50 to 100 times as potent as ticlopidine. The drug is extensively hepatically metabolized, with 50% of metabolites eliminated renally. Caution is recommended with clopidogrel use in patients with hepatic disease. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) Study comparing this agent with

**Figure 5. ESPS-2 Results: Stroke Rates at 24 Months**



**Figure 6. ESPS-2 Results: Cumulative Stroke Rate**



aspirin in preventing stroke, MI, or vascular death was published in 1996.<sup>16</sup> A prospective, multicenter, randomized, blinded trial, CAPRIE included 19,185 patients with atherosclerotic vascular disease randomized to receive either aspirin 325 mg QD or clopidogrel 75 mg QD for up to 3 years; the mean treatment duration was 1.9 years. Patients had either suffered ischemic stroke within 6 months before entering the trial, had an MI within the previous 35 days, or had established peripheral arterial disease. Efficacy was assessed by risk reduction for nonfatal ischemic stroke, MI, primary intracranial hemorrhage, or vascular death. In patients with stroke history, clopidogrel produced a statistically significant reduction in relative risk for stroke, MI, or vascular death of 8.7%. Patients treated with clopidogrel had a 5.32% annual risk of ischemic stroke, MI, or vascular death compared with 5.83% in those treated with aspirin.

Side effects are listed in Table 3. Gastrointestinal bleeding was more common with aspirin and the incidence of gastrointestinal bleeding was statistically significantly greater in the aspirin group. Nonfatal primary intracranial hemorrhage and hemorrhagic deaths were more common in the aspirin group than the clopidogrel group.

Clopidogrel may have notable drug interactions with losartan, phenytoin, nonsteroidal anti-inflammatory drugs (NSAIDs), tamoxifen, tolbutamide, torsemide, S-warfarin, and celecoxib. Older patients should be monitored closely or clopidogrel therapy discontinued when these agents are administered concomitantly with clopidogrel.

### Ticlopidine (Ticlid®)

Ticlopidine is also a thienopyridine ADP inhibitor. It prolongs bleeding time 5-fold, with an onset of action within 4 days. Bleeding times generally normalize 14 days after the agent is discontinued. It is extensively metabolized hepatically to inactive metabolites, of which 50% are eliminated renally.

The Ticlopidine Aspirin Stroke Study (TASS) compared the effects of ticlopidine hydrochloride (500 mg/d) with aspirin (1,300 mg/d) on the risk of stroke or death in 3,069 patients with

**Table 3. CAPRIE Study: Side Effects**

	Clopidogrel, %	ASA, %
<b>GI complaints</b>	<b>15.0</b>	<b>17.6*</b>
<b>Any bleeding disorder</b>	<b>9.3</b>	<b>9.3</b>
<b>Rash</b>	<b>6.0*</b>	<b>4.6</b>
<b>Diarrhea</b>	<b>4.5*</b>	<b>3.4</b>
<b>GI bleeding</b>	<b>2.0</b>	<b>2.7*</b>
<b>Intracranial hemorrhage</b>	<b>0.4</b>	<b>0.5</b>
<b>Severe neutropenia (ANC &lt; 450/mm<sup>3</sup>)</b>	<b>0.05</b>	<b>0.04</b>

\*P < 0.05

Reference #16

recent transient or mild persistent cerebral or retinal ischemia.<sup>17</sup>

Ticlopidine was somewhat more effective than aspirin in reducing the risk of ischemic events, particularly fatal or nonfatal stroke. The most notable ticlopidine side effects were diarrhea (20.4% vs 9.8% for aspirin), rash (11.9% vs 5.2% for aspirin), and severe neutropenia (absolute neutrophil count < 450/mm<sup>3</sup>) (0.9% vs 0.0% for aspirin). A number of drug interactions with ticlopidine may impact therapy in the long-term care setting (Table 4).

Ticlopidine is associated with a number of severe adverse effects. The drug is contraindicated in patients with severe liver impairment and should be used at lower doses in those with renal disease. Neutropenia/agranulocytosis occurs in 2.4% of patients, with a nadir usually at 4 to 6 weeks. This is rarely seen after 3 months of therapy. The drug should be discontinued if absolute neutrophil count is less than 1,200 mm<sup>3</sup>.<sup>18,19</sup> Patients on ticlopidine should have a CBC at baseline and every 2 weeks during therapy. If fever, chills, sore throat, or stomatitis occur, patients should be asked to contact their healthcare providers.

Gastrointestinal disturbances such as diarrhea and, less frequently, nausea and vomiting are seen in 30% to 40% of patients, and may result in discontinuation of therapy. Ticlopidine increases total cholesterol and triglycerides by 10%, an effect that begins after 1 month and persists throughout the course of therapy. The bleeding incidence is similar to that seen with ASA. Rash, with or without pruritus, occurs within the first 3 months and may progress to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.

Thrombotic thrombocytopenic purpura (TTP) is a risk with both ticlopidine and clopidogrel therapy.<sup>19</sup> This life-threatening

**Table 4. Drug Interactions With Ticlopidine**

<ul style="list-style-type: none"> <li>• Cimetidine increases ticlopidine levels by 50%</li> <li>• Ticlopidine increases:                             <ul style="list-style-type: none"> <li>➢ phenytoin levels</li> <li>➢ theophylline levels by 40%</li> <li>➢ R-warfarin by 25%</li> </ul> </li> <li>• Ticlopidine decreases digoxin levels by 15%</li> </ul>
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condition, which is fatal in up to 30% of sufferers, results from the activity of autoantibodies (IgG) against a metalloprotease that degrades von Willebrand factor, resulting in platelet microthrombi. With ticlopidine treatment, TTP occurs in 1 of 1600 to 4000 patients within 3 to 4 weeks after therapy is initiated. Signs and symptoms of TTP include thrombocytopenia, hemolytic anemia, renal dysfunction, neurologic changes, fever, weakness or pallor, purpura or petechiae, dark urine, seizures, dysarthria, jaundice, and schistocytes on smear. TTP is treated with plasma exchange and supportive therapy. Patients receiving ticlopidine or possibly clopidogrel should receive a baseline and biweekly CBC, BUN/creatinine, and liver enzyme tests. A possible association with TTP has been noted in patients on cholesterol-lowering drugs and antiplatelet therapy.

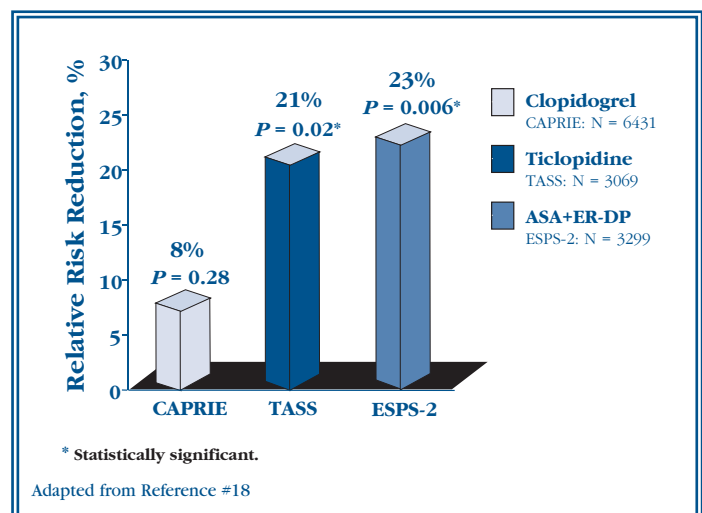
### Indirect Comparison of Therapies Across Studies

Figure 7 illustrates an indirect comparison of relative risk reduction (RRR) for stroke with the use of the antiplatelet agents in the CAPRIE, TASS, and ESPS-2 studies. This comparison shows a 23% RRR in stroke for combination ASA+ER-DR that is statistically significantly greater than the RRR for the other antiplatelet agents.<sup>18</sup> Similarly, an indirect comparison of combined endpoints (all events) from the 3 studies for RRR indicates a statistically significantly better RRR (22%) associated with ASA+ER-DP (Figure 8).

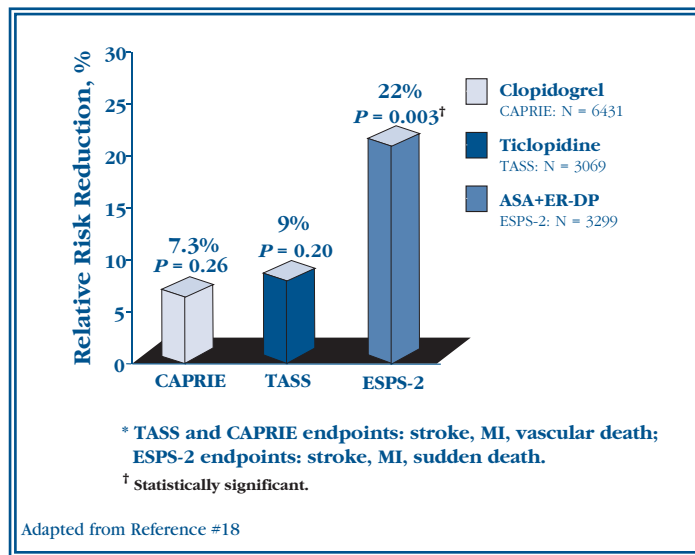
### Monitoring Therapy

Patients receiving antiplatelet and anticoagulant therapy need to be closely monitored for changes in hematology, blood chemistry, and signs of bleeding or TTP. Baseline and periodic tests should include APTT with PT/INR; CBC; liver and renal function tests; and vital signs. Patients should be observed throughout therapy for petechiae, ecchymosis, purpura, hematuria, hematomas, hematemesis, hemoptysis, hematochezia, melena, epistaxis, and gingival hemorrhage.

**Figure 7. Indirect Comparison of RRR for Stroke: CAPRIE, TASS and ESPS-2**



**Figure 8. Indirect Comparison of RRR for Combined Endpoints\*:  
CAPRIE, TASS, ESPS-2**



## Summary

Patients who have had a noncardioembolic stroke or TIA and are at risk of a second event should receive an antiplatelet agent for stroke prevention. If carotid endarterectomy is indicated, platelet therapy should be initiated prior to surgery. An array of effective antiplatelet therapies is available, including ASA, combination ASA+ER-DP, clopidogrel, and ticlopidine. Ticlopidine is more effective than ASA but is associated with a number of severe side effects in large numbers of patients, including hepatotoxicity. Clopidogrel is favored over ticlopidine because of its superior safety profile, but it has not been shown to be significantly more effective than ASA. Combination ASA+ER-DP has a favorable side-effect profile, appears to be more effective than ASA alone, and may be more effective than clopidogrel.

Because of the many clinical studies supporting the safety and efficacy of aspirin, and its comparatively lower cost, it is recommended as the initial therapy for stroke prevention. The dose of aspirin that should be used—ranging from 30 mg/d to 1.5 g/d—is still undetermined. Combination ASA+ER-DP should also be considered when ASA is not recommended.

## Benign Prostatic Hyperplasia: Managing the Older BPH Patient

As the US population ages, 22% of Americans will be over 65 years by the year 2030, 7% of the population will be between the ages of 75 and 84 years, and nearly 3% will be over 85 years. With this demographic shift, disorders associated with aging will become more prevalent. In addition, because physicians can now diagnose and treat conditions that formerly were fatal within a short time, more people are living longer with a greater array of chronic medical conditions. Thus, an average person over 65 years can present with 4 or 5 different chronic conditions that need to be considered when developing a therapeutic plan. It is this same older population that usually presents with benign prostatic hyperplasia (BPH).

BPH is very common in older men. Half of men over 50 years and 90% of men over 85 years have histologically confirmed BPH.<sup>20</sup> In men 80 years of age and older, 90% of BPH cases are confirmed by histologic evidence, 81% have BPH-related symptoms, and 10% develop urinary retention. Only about 25% of these patients receive treatment.

Lower urinary tract symptoms (LUTS) of BPH include progressive difficulty initiating urination, weak stream, incomplete emptying, frequency, and urgency. However, there are several other possible causes for LUTS, the list of which lends itself to the acronym “DRIP DRIP”:

<b>D</b> rugs	<b>D</b> iet
<b>R</b> estricted mobility	<b>R</b> etention of feces
<b>I</b> nfection	<b>I</b> nflammation
<b>P</b> olyuria	<b>P</b> sychological factors

When evaluating a patient with LUTS, even when known to have macroscopic BPH, symptoms attributable to “DRIP DRIP” etiologies should be considered.

### Therapeutic Considerations in the Frail Elderly

Older men with BPH usually present with additional chronic diseases. Some of the most common chronic conditions include hearing impairment, arthritis, heart disease, cataracts, and hypertension. Thus it will be increasingly common to have a man with hypertension present with LUTS from BPH. From the patient’s perspective, management of his symptomatic BPH may be a higher priority than attention to his asymptomatic hypertension. It is important for practitioners to keep in mind the relative importance of these conditions as suggested by the morbidity of untreated disease.

Untreated BPH may lead to urinary retention, renal insufficiency, urinary tract infection, gross hematuria, and bladder stones. In contrast, untreated hypertension is referred to as “the silent killer,” with approximately 50% of deaths due to coronary artery disease, 35% from stroke, and 15% from renal failure. Given that both symptomatic BPH and asymptomatic hypertension therefore become priorities of care, the possibility of using 1 drug to treat 2 conditions is an appealing option.

Approximately 24 million Americans use antihypertensive medications; 1 million use an  $\alpha$ -blocker. Theoretically, it seems rational to use  $\alpha$ -blockade to treat both hypertension and BPH. Alpha-adrenoceptors are located in the prostatic capsule and hyperplastic prostatic tissues. The contraction of prostatic smooth muscle, which regulates the degree of bladder outlet obstruction in BPH, is mediated by  $\alpha_1$ -adrenoceptors. Alpha-adrenergic blocking drugs may decrease the bladder outlet resistance to urinary flow.

The  $\alpha$ -blockers most commonly used to treat LUTS are terazosin, doxazosin, and tamsulosin. In placebo-controlled trials, terazosin 10 mg daily produced statistically significant improvements in LUTS compared to placebo, with maximal therapeutic effect reached 4 to

6 weeks after beginning therapy.<sup>20</sup> Terazosin reduces blood pressure in hypertensive patients but not in normotensive persons.

Doxazosin has also been shown to improve BPH symptoms compared to placebo, and does not adversely affect lipid profiles or glucose tolerance. However, a large study of antihypertensive medications, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), raised significant concerns about the effectiveness and safety of antihypertensive  $\alpha$ -blockers, particularly doxazosin.<sup>21</sup>

A total of 42,500 patients were enrolled in the ALLHAT trial; 24,335 hypertensive patients received either chlorthalidone or doxazosin. The trial was begun in 1994; an interim analysis in 2000 showed that patients on doxazosin had a higher risk of congestive heart failure and combined cardiovascular events compared to those receiving chlorthalidone. The doxazosin treatment arm was then discontinued. Thus, a practitioner who formerly would have prescribed doxazosin to treat a patient with hypertension and BPH would be advised to rethink that strategy, since the ALLHAT study showed that doxazosin failed to provide as much benefit as an antihypertensive in reducing cardiovascular events.

When caring for an older patient, it is also extremely important to consider potential adverse effects that impact activities of daily living. Medication side effects such as postural hypotension, syncope, and dizziness are most hazardous for older patients. “Getting a little dizzy” for the older patient can have dire consequences. It may mean falling down and breaking a hip; 50% of older people who break a hip die within 1 year. BPH itself is often associated with urgency, and in an elderly person the rush to the bathroom may result in a fall. Thus, it is important to recognize that adverse effects of a chosen single medication may negate the potential benefits of avoiding polypharmacy.

Tamsulosin is the most selective, and the first prostate-selective agent in this class of drugs. Tamsulosin has no effect on the vascular system (including hypertension); it affects only the urinary bladder outlet. This is important because patients with BPH who also have hypertension should be treated with an antihypertensive drug that is more effective than doxazosin, while their BPH symptoms can be effectively and safely treated with a highly prostate-selective agent. In a placebo-controlled trial, tamsulosin at doses of 0.1 mg, 0.2 mg, and 0.4 mg improved peak flow rate and BPH symptoms, particularly at the higher doses. The incidence of adverse effects was extremely low. In another larger trial, the incidence of adverse cardiovascular events was comparable between the tamsulosin and placebo groups.<sup>20</sup> Patients treated with tamsulosin maintained improvements in urinary symptoms and peak flow rate for up to 2 years, with no change in the safety profile. Table 5 lists comparative adverse effects of  $\alpha$ -blockers used for LUTS.

## Summary

When older patients with multiple chronic illnesses present to the healthcare practitioner, medication selection requires a number of considerations. For a patient who has both BPH and hypertension, each disease should be treated as a distinct illness. The top priority must be controlling the hypertension, which has potentially

**Table 5. Comparative Adverse Effects of  $\alpha$ -blockers**

	Terazosin	Doxazosin	Tamsulosin
<b>Postural hypotension</b>		17.0%	0%
< 65 years	2.6%		
≥ 65 years	5.6%		
<b>Syncope</b>		—	0.3%
< 65 years	0.3%		
≥ 65 years	1.1%		
<b>Dizziness</b>		15.6%	3.4 - 4.5%
< 65 years	8.3%		
≥ 65 years	10.2%		

Adapted from Reference #20

deadly consequences. Evidence-based medicine suggests that  $\alpha$ -blockers, particularly doxazosin, are less effective than other antihypertensive medications and pose the risk of orthostatic side effects, particularly in older patients.

A number of antihypertensive medications are available that are potentially more safe and effective. The prostate-specific, highly selective  $\alpha$ -blocker tamsulosin can effectively treat BPH with low risk of orthostatic side effects. With this strategy, the treatments do not interfere with each other, the patient’s concern about BPH symptoms is addressed, and the physician’s concern—controlling blood pressure to prevent cardiovascular events—is also addressed without placing the patient at additional risk of adverse effects.

## Hypertension in the Elderly

Hypertension, particularly isolated systolic hypertension (ISH), is extremely common in persons over 60 years of age and is a major risk factor for cardiovascular events, which account for the great majority of deaths in people over 65 years. Data from the National Health and Nutrition Examination Survey (NHANES) for 1994 reveal that 26% of the US population, or 47.4 million people, have hypertension, with the majority (73%) in older age groups (50-80+ years).<sup>22</sup> Older subjects (50+ years) with hypertension comprise 67% of all untreated hypertensives and 86% of all inadequately treated hypertensives. Furthermore, older subjects with ISH comprise 80% of all untreated hypertensives and 80% of all inadequately treated hypertensives.

A projection of the census for 2020 shows that 80% of hypertensives will be over 50 years of age.<sup>23</sup> Among adults over age 50 years, 60% of non-Hispanic whites, 71% of non-Hispanic blacks, and 61% of Mexican Americans are hypertensive.

The overall prevalence of hypertension in older women is higher than in men.<sup>24</sup> Unfortunately, despite these alarming num-

**Table 6. Classification of Blood Pressure in Adults**

Category*	SBP, mm Hg	and	DBP, mm Hg
Optimal	< 120	and	< 80
Normal	< 130	and	< 85
High-normal	130-139	or	85-89
<b>Hypertension</b>			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	≥ 180	or	≥ 110

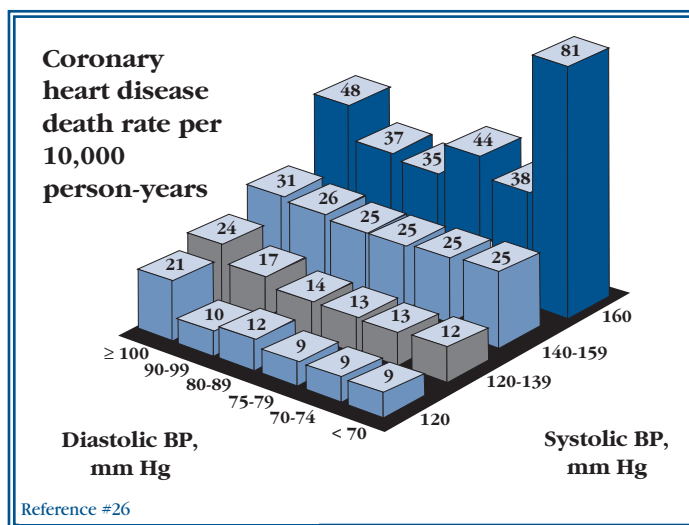
\*When SBP and DBP fall into different categories, use the higher category.  
Reference #25

**Table 7. Treatment Strategies and Risk Stratification**

Blood Pressure Stages (mm Hg)	Risk Group A	Risk Group B	Risk Group C
High-normal (130-139/85-89)	Lifestyle modification	Lifestyle modification	Drug therapy* Lifestyle modification
Stage 1 (140-159/90-99)	Lifestyle modification (up to 12 months)	Lifestyle modification (up to 6 months)**	Drug therapy Lifestyle modification
Stages 2 and 3 (≥ 160/≥ 100)	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification	Drug therapy Lifestyle modification

\*For those with heart failure, renal insufficiency, or diabetes.  
\*\*For those with multiple risk factors, clinicians should consider drugs plus lifestyle modification as initial therapy.  
Reference #25

**Figure 9. Relationship of Systolic and Diastolic Blood Pressure to Risk of Death From CHD**



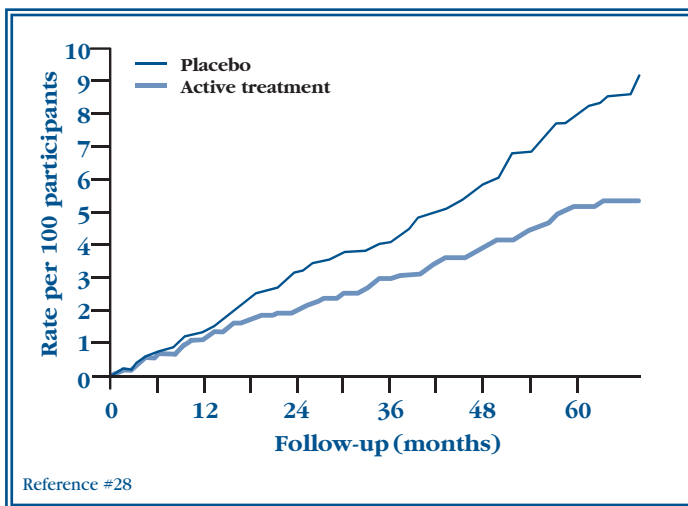
bers as well as ample evidence linking blood pressure control to reduced event rates, there has been little improvement in awareness, treatment, and control of high blood pressure over the years.

Table 6 shows the current classification of BP in adults, according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI).<sup>25</sup> Risk stratification is based on target organ disease (heart disease, stroke or TIA, nephropathy, peripheral artery disease, retinopathy) and risk factors (smoking, dyslipidemia, diabetes mellitus, age > 60 years, sex [men, postmenopausal women], and family history of cardiovascular disease). JNC-VI recommends treatment based on hypertension stage and risk stratification (Table 7). The goal of therapy should be the same in older adults as in younger adults (< 140/90 mm Hg), although in some patients, an interim goal of SBP < 160 mm Hg may be necessary.

ISH is associated with increased systolic pulsatile load, which may lead to increased left ventricular wall stress, decreased coronary flow reserve, impaired left ventricular relaxation, left ventricular hypertrophy, and atherosclerosis. Transmission of increased systolic pulsatile load to the microcirculation can cause impaired autoregulation of cerebral and renal blood flow. Decreased diastolic BP, which often occurs in concert with ISH, can decrease coronary blood flow and increase shear stress, potentially leading to increased plaque rupture, left ventricular dysfunction, and increased endothelial dysfunction.

Figure 9 shows the relationship of systolic and diastolic blood pressure to risk of death from coronary heart disease (CHD). These data are adapted from the Multiple Risk Factor Intervention Trial (MRFIT) of over 300,000 men.<sup>26</sup> Mortality was 81/10,000 person-years among patients with the highest systolic pressure and the lowest diastolic pressure (> 160 mm Hg/< 70 mm Hg), compared to 37/10,000 person-years among patients with blood pressure of 160/90 or 25/10,000 person-years among patients with blood pressure 150/80.<sup>26</sup>

**Figure 10. Cumulative Stroke Rate in SHEP Trial**



### Benefits of Treatment in Older Persons

Treatment of hypertension in older patients has demonstrated major benefits: decreased incidence of stroke, CHD, cardiovascular disease, heart failure, and mortality.<sup>27</sup> Results of 2 major studies, Systolic Hypertension in the Elderly Program (SHEP) and Systolic Hypertension in Europe (SYST-EUR), demonstrated that active treatment of isolated systolic hypertension reduces the incidence of stroke and major cardiovascular events.<sup>28,29</sup>

SHEP was a double-blind, randomized, placebo-controlled trial designed to test whether antihypertensive drug therapy reduces the frequency of new strokes in a multi-ethnic cohort of 4736 men and women aged 60 years or older with ISH (SBP > 160 mm Hg and DBP < 90 mm Hg). Patients were followed for up to 5 years.

Antihypertensive stepped-care drug treatment resulted in a 36% reduction in all strokes (fatal and nonfatal); 27% reduction in MI; 27% reduction in CHD; 32% reduction in all cardiovascular disease; and 13% reduction in total mortality. The incidence of transient ischemic attacks (TIAs) and CHF also decreased with active treatment. Figure 10 shows the cumulative stroke rate compared to placebo in the SHEP trial.<sup>28</sup>

In the SYST-EUR study, a randomized, double-blind, placebo-controlled trial, approximately 700 patients aged 60 years or older with systolic hypertension (defined as SBP 160 to 219 mm Hg and diastolic “clinic BP” of < 95 mm Hg) were enrolled. Active treatment significantly reduced the cumulative stroke rate (fatal and nonfatal); results were very similar to SHEP.<sup>29</sup>

### Drug Therapy for Hypertension

In assessing potential therapy, one should first determine if the hypertension is essential or secondary. Secondary hypertension should be suspected if the condition began when the patient was younger than 30 years or older than 60 years, or is difficult to control with therapy; stable hypertension becomes difficult to control; hypertensive crisis occurs; or the patient shows signs or symptoms of secondary causes (eg, hypokalemia or metabolic alkalosis).

When measuring BP, readings may be falsely high due to excessive vascular stiffness. Some patients have “white coat” hyperten-

sion due to the stress of a doctor visit. Such patients may benefit from readings outside the office. BP should be measured both standing and supine or seated to account for orthostatic changes.

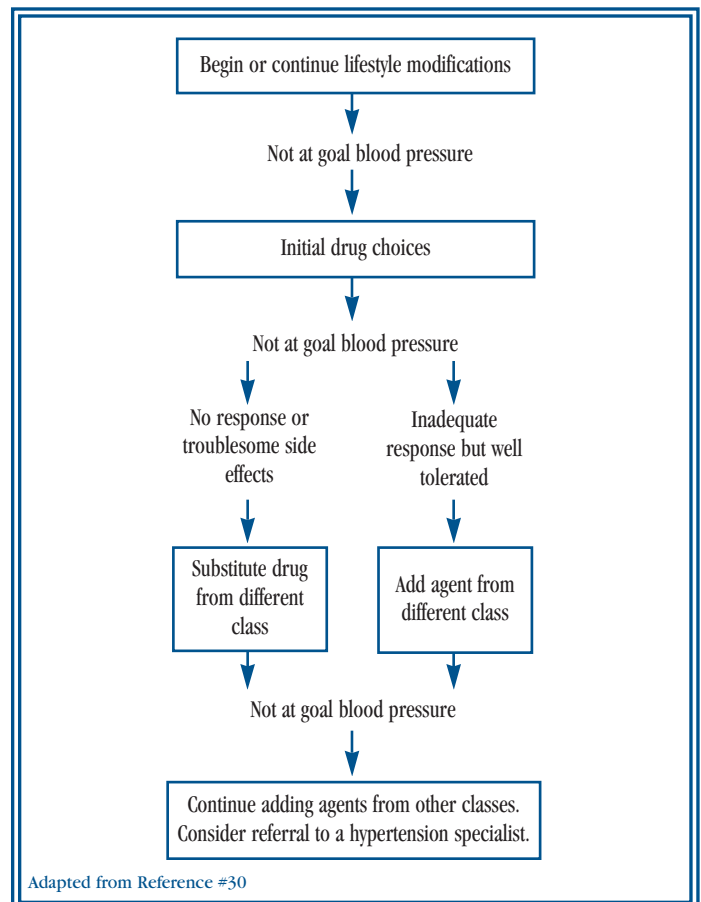
Treatment begins with lifestyle modifications, including appropriate weight, diet, and exercise recommendations. Pharmacotherapy for older patients is started at approximately half the dose used in younger patients. The goal of treatment is the same as in younger patients, ie, 140/90 mm Hg, although it may be necessary to aim for an interim goal of SBP < 160 mm Hg. Before initiating therapy, target organ damage and other risk factors, as well as specific causes of the hypertension, are assessed. Recommended pretherapy lab tests include urinalysis, CBC, blood chemistries (potassium, sodium, creatinine, and fasting glucose), a lipid profile (total and high-density lipoprotein [HDL] cholesterol), and a 12-lead electrocardiogram.

### Selecting Drug Therapy

Antihypertensive drug selection is a challenging process but can be rationally managed with the use of an algorithm for treatment (Figure 11). Specific drug effects may vary by age and ethnic populations. Materson and colleagues showed that most single antihypertensive drugs produce response rates superior to placebo, though the degree of responsiveness varied according to age and race.<sup>30</sup>

Specific drugs are indicated when patients have particular comorbidities. For example, for older patients with ISH, diuretics

**Figure 11. Algorithm for Treatment of Hypertension**



are preferred; long-acting dihydropyridine calcium antagonists are also recommended. Antihypertensive therapy in elderly patients should be reevaluated periodically. Following an adequate trial, failure to attain goal blood pressure should prompt a reevaluation. For patients with type 2 diabetes mellitus, low-dose diuretics are favorable, but for type 1 or 2 diabetes patients with proteinuria, ACE inhibitors are preferred. Some data show favorable effects for calcium antagonists. Details of the treatment algorithm can be found at the NHLBI subsection of the National Institutes of Health Web site.

### Confounders of Care in the Elderly

Older patients may experience physiologic changes as they continue to age. They also have a high prevalence of comorbid conditions and are often receiving concomitant drug therapies. The potential interactions of comorbid conditions and various medications need to be taken into account. In addition, older persons often have increased sensitivity to the adverse effects of treatment.

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### Summary

Recent statistics indicate that 26% of the US population suffers from hypertension. Of this group, 73% are over the age of 50. Older subjects with ISH comprise 80% of all untreated hypertensive patients and are at greater risk of coronary, renal, and vascular events, particularly if they have both ISH and low diastolic pressure. Randomized controlled trials have demonstrated that effective antihypertensive therapy in these older patients could reduce the incidence of cardiovascular deaths, strokes, and coronary events. Appropriate treatment of older hypertensive patients and monitoring of therapy can contribute significantly to the attainment of blood pressure goals and the prevention of cardiovascular events.

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# Diseases Affecting Baby Boomers: COPD, Stroke, BPH, and Hypertension

## Posttest Answer Form

### *Pharmacy Continuing Education*

This course qualifies for 1.5 contact hours of continuing pharmacy credit, which will be awarded via mail within 4 weeks after submission of a successfully completed program posttest. A passing grade of 75% is required. Any participant who fails the examination may be reexamined one additional time. In order to apply for continuing pharmacy education credit, please complete the Posttest Answer Form, and fax or mail to:

**Rutgers, The State University of New Jersey**  
**Ernest Mario School of Pharmacy**  
**Office of Continuous Education**  
**160 Frelinghuysen Road**  
**Piscataway, NJ 08854-8020**  
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**Continuing education processing fees have been covered through an unrestricted grant from Boehringer Ingelheim Pharmaceuticals, Inc.**

*Copies of the form will be accepted. (Please print clearly)*

Name: \_\_\_\_\_

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ACPE# 038-999-02-025-H01

(Please circle the correct answers)

- |                 |                 |
|-----------------|-----------------|
| 1. a. b. c. d.  | 12. a. b. c. d. |
| 2. a. b. c. d.  | 13. a. b. c. d. |
| 3. a. b. c. d.  | 14. a. b. c. d. |
| 4. a. b. c. d.  | 15. a. b. c. d. |
| 5. a. b. c. d.  | 16. a. b. c. d. |
| 6. a. b. c. d.  | 17. a. b. c. d. |
| 7. a. b. c. d.  | 18. a. b. c. d. |
| 8. a. b. c. d.  | 19. a. b. c. d. |
| 9. a. b. c. d.  | 20. a. b. c. d. |
| 10. a. b. c. d. | 21. a. b. c. d. |
| 11. a. b. c. d. |                 |

\*I certify that I completed this CE activity. The actual amount of time that I spent on this activity was:  
\_\_\_ hours \_\_\_ minutes.

Signature:

\_\_\_\_\_

\*No CE credit will be given after May 31, 2005.

## Posttest

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## Posttest Questions

- Risk factors associated with COPD include all the following except:
  - smoking
  - female gender
  - preexisting impaired lung function
  - occupational exposure to hazardous substances
- COPD includes:
  - a spectrum of respiratory diseases
  - chronic dyspnea
  - chronic expiratory airflow obstruction
  - all of the above
- Chronic bronchitis includes all the following except:
  - edema
  - weight loss
  - cyanosis
  - sleep apnea
- A number of "homemade" beliefs about treatment for COPD include:
  - smoking cessation will not help once COPD is established
  - nebulized saline had proven effective
  - pounding on the chest is helpful
  - all of the above
- First-line therapy for COPD includes:
  - anticholinergics
  - inhaled corticosteroids
  - oral corticosteroids
  - theophylline
- The cumulative risk of stroke increases after:
  - eating
  - sleeping
  - a TIA
  - aspirin usage
- Stroke risks that are not modifiable include all the following except:
  - age
  - gender
  - lifestyle
  - race
- Which statement is true regarding aspirin therapy for stroke prevention?
  - Early trials are conclusive.
  - The dose should be 50 mg.
  - The dose ranges from 50 to 325 mg for secondary prevention.
  - Aspirin does not improve mortality.
- ESPS-2 found the following regarding stroke risk reduction:
  - combination aspirin+extended-release dipyridamole was most effective
  - aspirin alone was most effective
  - extended-release dipyridamole alone was most effective
  - all of the above
- The major issue with the use of ticlopidine includes all the following except:
  - efficacy
  - thrombotic thrombocytopenic purpura
  - gastrointestinal disturbances
  - neutropenia/agranulocytosis
- Possible causes for lower urinary tract symptoms include:
  - weak stream
  - incomplete emptying
  - frequency
  - all of the above
- Untreated BPH may lead to:
  - urinary retention
  - renal insufficiency
  - urinary tract infection
  - all of the above
- The most selective  $\alpha$ -blocker is:
  - tamsulosin
  - terazosin
  - doxazosin
  - chlorthalidone
- In older people, the most common form of untreated hypertension is:
  - diastolic
  - isolated systolic
  - combination
  - none of the above
- Treatment of hypertension in older patients has demonstrated major benefits, including a decrease in:
  - stroke
  - coronary heart disease
  - heart failure
  - all of the above
- In older patients, the following therapy is recommended:
  - diuretics for ISH
  - diuretics for type 2 diabetes mellitus
  - an ACE inhibitor for type 2 diabetes mellitus with proteinuria
  - all of the above

## Program Evaluation

- How would you rate this program overall?
  - excellent
  - good
  - fair
  - poor
- To what degree has this program improved your knowledge of the subject matter?
  - extensively
  - moderately
  - somewhat
  - not at all
- How relevant was the program content to your practice?
  - very relevant
  - relevant
  - somewhat relevant
  - not relevant
- How effectively did the program meet the learning objectives?
  - very effectively
  - effectively
  - somewhat effectively
  - not at all
- The program was free from undue commercial bias:
  - strongly agree
  - agree
  - disagree
  - strongly disagree