Educational Objectives

The goal of this program is to improve the management of hypertension and diabetes. After hearing and assimilating this program, the clinician will better be able to:

1. Discuss the risks associated with hypertension and diagnose hypertension using office and home measurements.
2. Describe the mechanisms by which obesity influences hypertension.
3. Prescribe appropriate antihypertensive medications to address the different mechanisms that contribute to hypertension, and use the correct target blood pressure when treating patients with diabetes and hypertension.
4. Increase adherence to antihypertensive medication regimens by prescribing affordable drugs (eg, generic formulations).
5. Recommend practical steps patients can take to adopt a Mediterranean-style diet.

Online Resources

Standards of Medical Care in Diabetes, 2013
http://care.diabetesjournals.org/content/36/Supplement_1

www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm

United States Department of Agriculture Food Guidance System
www.choosemyplate.gov

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio-Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in healthcare and not a proprietary business or commercial interest. For this program, the following was disclosed: Dr. Anderson reported relationships with Amylin Pharmaceuticals (B), Daichii Sankyo Company (B), Eli Lilly and Company (B), Novo Nordisk (B), and sanofi-aventis US (A); Dr. Mende reported relationships with Boehringer Ingelheim GmbH (B), Forest Laboratories (B); Eli Lilly and Company (B), and Novartis Pharmaceuticals Corporation (B); Dr. Cooper-deHoff, Ms. Boucher and the members of the planning committee reported nothing to disclose.

A=Advisory panel  B=Speakers bureau  C=Consultant  G=Grant or other research support
Mechanisms

About 70% of people with hypertension have an overactive renin-angiotensin aldosterone system (RAAS), *ie*, too much renin is produced with angiotensin II or too much aldosterone. About 50% of hypertensive patients are sensitive to salt, and ≥50% have elevations in the sympathetic nervous system (SNS); *ie*, they have higher production of catecholamine (although metanephrines and catecholamines remain in the normal range on a 24-hr urine test).

Physicians should examine resting pulse rate in hypertensive patients because β-blockers do not control blood pressure (BP) in patients with an elevated pulse rate (*eg*, 80 beats per min) and normal thyroid function. A consistently elevated resting pulse rate suggests an overactive SNS.

Risk

Data from the Framingham Heart Study show that in patients <50 yr of age, diastolic BP (DBP) correlates better with risk for myocardial infarction (MI), cerebrovascular accident (CVA), congestive heart failure (CHF), arteriosclerosis, and other complications. At ≥50 yr of age, systolic BP (SBP) is the better predictor of these events.

Un-treated BP of 155/95 mm Hg is associated with 4-fold higher risk (compared with 115/75). Every increase of 20/10 mm Hg doubles the risk for cardiovascular (CV) mortality. Lowering SBP over ≥10 yr reduces CV risk by 50%. Reduction in BP produces 25% decrease in MIs, 35% to 40% decrease in strokes, and >50% decrease in CHF. Ninety percent of patients with a new diagnosis of CHF have inadequately treated hypertension.

Lowering SBP in 11 patients with stage I hypertension (*ie*, SBP 140–160 mm Hg) by 12 mm Hg for 10 yr prevents one death. This is the lowest number needed to treat (NNT) for any drug treatment. For patients with underlying CV disease, the NNT is 1 in 9.

Home BP measurement

National Institute for Health and Clinical Excellence guidelines from Britain recommend taking two BP measurements per day for ≥4 days at home; after discarding data from the first day, BP ≥140/90 mm Hg is considered hypertension. Data show that home BP measurement is twice as accurate in predicting CV events as measurements taken in the physician’s office.

Ten-year follow-up data from the Prevention of Progression Arteriosclerosis (PAMELA) study indicate that office hypertension (*ie*, white coat syndrome) does not increase CV risk. Home measurement can also detect hypertension in the 5% to 8% of hypertensive patients with masked hypertension (*ie*, normal BP in the physician’s office).

Several studies show that patients who measure their BP weekly at home are more likely to adhere to their medication regimen and to keep follow-up appointments. Patients should be advised to initially measure BP in the morning and evening. Subsequently, BP should be measured only at the peak time (usually in the morning) 1 to 2 times per week.

Timing of medication

Antihypertensive medications (except diuretics) should be taken at bedtime. Calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors taken at bedtime can convert 85% of “ nondippers” to “dippers” (*ie*, BP drops by 10%-20% in the early morning). A Spanish study of ≥5000 patients who had ambulatory BP measurements found that 23% of patients with SBP >160 mm Hg were normotensive at home. Patients with SBP of 140 to 160 mm Hg may be normotensive at home.

Obesity

Obesity is the main secondary cause of hypertension. In the United States, 68% of adults are overweight (body mass index [BMI] >25), 33% are obese, and 33%-38% have metabolic syndrome. Seventy-five percent of obese people (so 33% of all adults >18 yr of age) have hypertension. Half of all patients with hypertension have a BMI >30.

There is a linear relationship between weight (from BMI 25 to 35) and BP (both increasing and decreasing). Every 10 lb of weight gained increases SBP by 4.5 to 5 mm Hg. Monotherapy with any antihypertensive drug lowers BP by an average of 10 mm Hg (equivalent to loss of 20 lb).

Mechanisms of obesity effect

The RAAS is activated in people who are overweight or obese. Adipocytes (especially intra-abdominal fat in the omentum and liver) produce >30 hormones, including a substance that releases aldosterone from the adrenals, angiotensinogen and angiotensin II, and leptin (which activates the SNS). Sensitivity to salt increases, partly because fat in the renal pelvis and around the renal capsule compresses the kidney, creating a minimal Goldblatt mechanism.

Treatment

No guidelines exist for treating hypertension and obesity. Options that address the mechanisms include RAAS blockers, diuretics, and vasodilating β-blockers. However, inexpensive β-blockers (*eg*, atenolol, metoprolol) should not be used because they create diabetes in 25% of patients after 5 yr of treatment, due to reduced blood flow to muscle. Muscle is the key organ for uptake of insulin and glucose. Exercising for 25 to 30 min reduces insulin resistance by 10% to 15% in 24 hr.

Salt sensitivity and hypertension

According to a Cochrane review, Asians are the most sensitive to salt. Among patients with stage I hypertension (SBP 150–160 mm Hg), the gain between 6 and 9 g of salt is 5 mm Hg. The conversion factor of salt to sodium is 0.4 (*eg*, 6 g of salt is equivalent to 2.4 g of sodium). Eighty percent of salt intake comes from food, with the highest salt content in bread.

There is no test for salt sensitivity, which occurs in:

- 85% of black patients with hypertension
- Most patients with BMI >30
- White patients with ratio of triglycerides to high-density lipoprotein (HDL) cholesterol >3.5
- Latino patients with ratio of triglycerides to HDL cholesterol >3.0
- Black patients with ratio of triglycerides to HDL cholesterol >2.5

Two studies showed that reduction of salt intake to <3 g in healthy individuals activates the RAAS and increases CV events. Salt intake for all people should be 3 to 6 g.
Potassium counteracts excessive salt intake. The Dietary Approaches to Stop Hypertension (DASH) diet, which is high in potassium (eg, from watermelon, cantaloupe, bananas), was shown to reduce stage I hypertension by 11.6/5 mm Hg and to reduce BP by 3 to 4 mm Hg in normotensive individuals.

Reasons to reduce salt and increase potassium:
- Excess sodium causes retention of water and volume expansion.
- Excess sodium and low potassium block the cellular sodium pump, allowing entry of calcium into smooth muscle cells, which causes vasoconstriction. CCBs reduce the inflow of calcium into the smooth muscle cell and vasodilate it.
- Serum sodium >144 mmol/L or potassium <4 mmol/L interferes with the plasticity of endothelial cells, as measured by atomic tonometry, and reduces release of nitric oxide.
- Hypokalemia counteracts the effects of antihypertensive drugs.

Blood pressure goals
Lowering SBP to <130 mm Hg in people with diabetes does not reduce CV risk, except for stroke. In patients with transient ischemic attack, strong family history of stroke, or previous stroke, reducing SBP to <130 mm Hg remains the target.

Clinical Pearl
New guidelines from the American Diabetes Association (ADA) suggest that the BP goal for most people ≥50 yr of age with diabetes, prediabetes, or chronic kidney disease is 135/80 mm Hg.

A European study of ≈6000 patients with coronary artery disease (66%), claudication (33%), or diabetes (16.67%) followed for >5 yr found that reducing BP to <130 mm Hg increased the incidence of CV events.

Drug therapy for hypertension
Start antihypertensive treatment with monotherapy if SBP is <20 mm Hg from target. If BP is >20/10 mm Hg above goal or the patient is ≥70 yr of age, start with 2 drugs. If BP is 140 to 160 mm Hg, monotherapy will reduce blood pressure by ≤10/5 mm Hg. For greater effect, two drugs are needed. Seventy-five percent of patients with hypertension require two drugs, because 80% of hypertensive patients have ≥2 systems upregulated (eg, overactive RAAS plus sodium and water retention or overactive RAAS plus overactive SNS).

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared benazepril (ACE inhibitor) combined with a diuretic vs benazepril plusamlodipine (CCB). Outcomes at 5 yr showed 20% lower incidence of MI’s and CVAs and a 50% decrease in loss of renal function in favor of the CCB plus ACE inhibitor combination.

Combinations to avoid:
- β-Blocker plus verapamil or diltiazem may cause excessive bradycardia.
- Long-term use of a β-blocker plus clonidine may cause complete heart block, especially in the elderly.
- ACE inhibitors and angiotensin receptor blockers (ARBs) used together were shown in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) to produce little improvement in BP and to cause increased hyperkalemia and increased renal dysfunction.
- Aliskiren (Tekturna) plus an ACE inhibitor or ARB had similar effects. The combination of spironolactone (Aldactone) with an ACE inhibitor or ARB is acceptable. However, if potassium is 4.5 mmol/L, patients can develop hyperkalemia when spironolactone is added to an ACE inhibitor.

Track 2:
Generic Drugs to Treat Resistant Hypertension

Interview with:
Rhonda Cooper-deHoff, PharmD, Associate Professor of Pharmacy and Medicine, University of Florida, Gainesville

Resistant hypertension
Patients who have BP >140/90 mm Hg despite use of ≥3 antihypertensive medications and patients who require ≥4 antihypertensive medications to achieve BP <140/90 mm Hg have resistant hypertension.

Patient preference and generic drugs
If the cost of a medication is covered by insurance, many patients prefer branded products. However, when patients are responsible for the entire cost, they prefer generics.

Under Medicare Part D (the prescription drug plan), patients who incur drug expenses over the course of a year that exceed a certain monetary threshold enter what is called the “doughnut hole,” meaning that they must pay the entire cost of their medications (rather than just a copay) until they hit another threshold, at which point the cost of medications is again covered.

Over the past 3 years, the use of generic drugs for chronic diseases requiring medication has increased, and the use of branded products has decreased.

Pricing and legal issues
When a branded drug goes off patent, the cost of a generic version is only slightly less until ≥2 generic compounds are available, at which point the price may decrease by 50%. When ≥10 generic formulations of a drug are available, the cost may drop to 10% of the cost of the branded product.

The courts have determined that generic drug manufacturers cannot be sued for hazardous outcomes from taking generic drugs.

Pros and cons of generic combination drugs
Generic versions of combination drugs are easier for patients to take, which improves adherence. However, they tend to be more expensive, so some Medicare beneficiaries may enter the doughnut hole sooner. Some generic combination drugs are inexpensive, and these should be chosen by the prescriber if possible.

Discount generic programs
Several large retail stores offer discount generic drug programs, which can cost as little as $4 for a 30-day supply or $10 for a 90-day supply. Choices on the formularies vary from store to store. Therefore, when prescribing medications for chronic conditions it is helpful to collect information about the formularies of the retail stores patients are likely to use. None of these programs have any long-acting CCB on the formulary.

Chlorthalidone vs hydrochlorothiazide
There are data to suggest that chlorthalidone is more effective at lowering BP
than hydrochlorothiazide. Chlorothalidone can be associated with decreased potassium and increased glucose levels. Therefore, it is necessary to monitor potassium and glucose. Generic versions of chlorthalidone are available, as are generic combination products that contain chlorthalidone (eg, atenolol/chlorthalidone).

**Take-home message**

Physicians should ask patients whether they have difficulty paying for their medications. If they don’t fill their prescriptions, they will not lower their BP. When possible, prescribe generic drugs to help patients afford their medications. Ask patients where they plan to get their prescriptions filled and choose medications from that formulary. Patients with several chronic conditions can stagger their prescription filling to distribute the cost of copays over several months.

**Track 3: BENEFITS OF THE MEDITERRANEAN DIET**

**Interview with:**

Jackie L. Boucher, MS, RD, LD, CDE, Vice President for Education, Minneapolis Heart Institute Foundation, Minneapolis, MN

**The Mediterranean diet**

The Mediterranean diet has been studied mostly for its effect on preventing and managing heart disease. These studies did not all include people with diabetes. Some modest evidence supports use of the diet for people with diabetes, but so far there is little evidence that it improves glycemic control. There is evidence showing that following the Mediterranean diet decreases BP and triglycerides and increases HDL cholesterol levels.

The Mediterranean diet is an eating pattern that is high in fruits, vegetables, whole grains, legumes (eg, lentils, beans), olive oil, and nuts. It includes moderate amounts of dairy products and alcoholic drinks (mostly red wine) and limited amounts of red meat and sweets. In countries surrounding the Mediterranean Sea, people tend to get a high proportion of calories from fat (eg, 40% in Greece, 30% in Italy), mostly from olive oil, which is a monounsaturated fat.

**Similar to other dietary recommendations**

The Mediterranean diet follows similar principles as the DASH diet, which has been shown to lower BP and help with weight loss. Few studies have looked at the DASH diet for people with diabetes. The Mediterranean diet is also similar to recommendations from the National Heart, Lung, and Blood Institute for lowering cholesterol levels (ATP III), although the Mediterranean diet contains more monounsaturated fats (eg, olive oil, flax seed, nuts) and includes moderate alcohol consumption.

The Greek word for diet means “way of living,” which is a different concept than in the United States, where a diet is more prescriptive and often has negative connotations. In Mediterranean countries the diet also includes lifestyle components (eg, physical activity, socializing). Most people in Mediterranean countries eat meals with other people.

**Wine with dinner**

People living in Mediterranean countries typically drink wine with a meal, whereas in the United States people often drink alcohol at times and places other than at the dinner table (eg, “happy hour” at a bar). This may lead to excessive drinking. Research has shown that one alcoholic drink per day has health benefits — even greater benefits than consuming no alcoholic drinks. Yet nondrinking patients should not be encouraged to start drinking alcohol, because there are risks from drinking.

In the Mediterranean region, meals take longer and are more social. Dessert tends to be foods like nuts, fruit, and cheese rather than high-sugar, high-fat treats. The Mediterranean diet is low in saturated fat (eg, butter, shortening) and high in omega-3 fatty acids (eg, fish, flax seed, nuts).

**Mediterranean diet and diabetes**

Walter Willett, MD, created a Mediterranean diet pyramid, modeled on the 1990s food pyramid created by the US Department of Agriculture (USDA), which contains more specific information about servings. For people with diabetes who follow the Mediterranean diet, however, it is most important to count carbohydrates and match the amount with the diabetes medication.

Because the Mediterranean diet emphasizes eating more fruits and vegetables and less meat and dairy, it is in line with many national nutrition recommendations for preventing and managing diabetes.

It may help to start with simple steps. For example, encourage patients to have a fruit or vegetable at every meal and to eat one meatless meal per week. Ask them what type of fat they are using in preparing foods and encourage them to use monounsaturated fat (eg, olive oil). Refer patients to a dietitian, community-based education program, or cooking school so they can learn to prepare healthy foods. Emphasize moderation and small portions. While nuts are healthy, 1 cup of peanuts contain ≈900 calories. A handful is enough.

“**When you take time to prepare food and you eat more like the Mediterranean diet — fruits and vegetables, whole grains, beans, legumes — you feel fuller, more satisfied.”**

People in the Mediterranean often start the main meal with a cup of soup, which research has shown leads to eating less food overall, most likely due to the fluid volume. The USDA food guidance system (choosemyplate.gov) corresponds fairly well with the Mediterranean diet. The USDA recommends filling half the plate with fruits and vegetables and considering meat a side dish. Essentially, it involves eating the same kinds of foods but in different proportions.

**Part of a family plan**

Rather than create two separate meals, one for the adult with diabetes and another for the children in the family, parents should start their children at a young age eating...
healthy meals that are high in fruits and vegetables.

**Role of the clinician**

Patients look to their primary care providers for advice and resources. Therefore, physicians should be prepared to refer patients to a dietitian or diabetes educator for help with dietary issues. They should address nutritional issues regularly with patients and offer feedback and advice, even if it is just a small tip. Taking the time to discuss diet with patients can make a big difference.

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**Suggested Reading**


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**Cultural and linguistic resources:** In compliance with California Assembly Bill 1195, Audio-Digest Foundation offers selected cultural and linguistic resources on its website. Please visit this site: www.audiodigest.org/CLCresources.

**Estimated time to complete the educational process:**

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
1. Which class of antihypertensive drug should not be prescribed for a patient with a resting pulse rate of 90 beats per min and normal thyroid function?
   (A) Angiotensin converting enzyme (ACE) inhibitor
   (B) Beta-blocker
   (C) Diuretic
   (D) Calcium channel blocker

2. Lowering systolic blood pressure in _______ patients with stage I hypertension by 12 mm Hg for 10 yr prevents one death.
   (A) 11 (B) 36 (C) 52 (D) 99

3. Blood pressure measurements taken in the physician’s office are twice as accurate in predicting cardiovascular events as measurements taken by patients at home.
   (A) True (B) False

4. Which of the following antihypertensive drugs increases the risk for diabetes and should be avoided in patients who are obese?
   (A) Hydrochlorothiazide
   (B) Captopril
   (C) Carvedilol
   (D) Atenolol

5. Salt intake in the range of _______ is ideal for most people.
   (A) 0 to 3 g
   (B) 0 to 6 g
   (C) 3 to 6 g
   (D) 4 to 10 g

6. According to the American Diabetes Association, what is the systolic blood pressure goal for people ≥50 yr of age with diabetes, prediabetes, or chronic kidney disease?
   (A) 125 mm Hg
   (B) 130 mm Hg
   (C) 135 mm Hg
   (D) 140 mm Hg

7. When treating hypertension with two drugs, which combination should be avoided?
   (A) Ramipril plus telmisartan
   (B) Benazepril plus amlodipine
   (C) Benazepril plus hydrochlorothiazide
   (D) Enalapril plus hydrochlorothiazide

8. When prescribing chlorthalidone for hypertension it is necessary to monitor:
   (A) Potassium (B) Glucose (C) Lipids (D) A and B

9. There is strong evidence that adoption of the Mediterranean diet has all the following effects, except:
   (A) Reduces blood pressure
   (B) Reduces triglycerides
   (C) Improves glycemic control
   (D) Increases high-density lipoprotein cholesterol

10. Which of the following is the primary source of fat in a Mediterranean diet?
    (A) Butter (B) Lard (C) Margarine (D) Olive oil