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EXPERT CONSENSUS DOCUMENT

ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents

Developed in Collaboration With the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension

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Preamble

This document has been developed as an expert consensus document by the American College of Cardiology Foundation (ACCF), and the American Heart Association (AHA), in collaboration with the American Academy of Neurology (AAN), the American College of Physicians (ACP), the American Geriatrics Society (AGS), the American Society of Hypertension (ASH), the American Society of Nephrology (ASN), the American Society for Preventive Cardiology (ASPC), the Association of Black Cardiologists (ABC), and the European Society of Hypertension (ESH). Expert consensus documents are intended to inform practitioners, payers, and other interested parties of the opinion of ACCF and document cosponsors concerning evolving areas of clinical practice and/or technologies that are widely available or new to the practice community. Topics chosen for coverage by expert consensus documents are so designed because the evidence base, the experience with technology, and/or clinical practice are not considered sufficiently well developed to be evaluated by the formal ACCF/AHA practice guidelines process. Often the topic is the subject of considerable ongoing investigation. Thus, the reader should view the expert consensus document as the best attempt of the ACCF and document cosponsors to inform and guide clinical practice in areas where rigorous evidence may not yet be available or evidence to date is not widely applied to clinical practice. When feasible, expert consensus documents include indications or contraindications. Typically, formal recommendations are not provided in expert consensus documents as these documents do not formally grade the quality of evidence, and the provision of "Recommendations" is felt to be more appropriately within the purview of the ACCF/AHA practice guidelines. However, recommendations from ACCF/AHA practice guidelines and ACCF appropriate use criteria are presented where pertinent to the discussion. The writing committee is in agreement with these recommendations. Finally, some topics covered by expert consensus documents will be addressed subsequently by the ACCF/AHA Task Force on Practice Guidelines.

The ACCF Task Force on Clinical Expert Consensus Documents makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing committee are asked to provide disclosure statements of all such relationships that might be perceived as relevant to the writing effort. This information is documented in a table, reviewed by the parent task force before final writing committee selections are made, reviewed by the writing committee in conjunction with each conference call and/or meeting of the group, updated as changes occur throughout the document development process, and ultimately published as an appendix to the document. External peer reviewers of the document are asked to provide this information as well. The disclosure information for writing committee members and peer reviewers is listed in Appendixes 1 and 2, respectively, of this document. Disclosure information for members of the ACCF Task Force on Clinical Expert Consensus Documents—as the oversight group for this document development process—is available online at www.

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Executive Summary

This document was written with the intent to be a complete reference at the time of publication on the topic of managing hypertension in the elderly. Given the length of the document, the writing committee included this executive summary to provide a quick reference for the busy clinician. Because additional detail is needed, please refer to the sections of interest in the main text. The tables and figures in the document also delineate important considerations on this topic, including the treatment algorithm in Section 4.2.2.1.

General Considerations

Our population is aging, and as hypertension affects most elderly people (≥65 years of age), these individuals are more likely to have organ damage or clinical cardiovascular disease (CVD). They represent management dilemmas because most hypertension trials had upper age limits or did not present age-specific results. However, because the Hypertension in the Very Elderly Trial (HYVET) documented antihypertensive therapy benefits in persons ≥80 years of age, it is timely to place into perspective issues relevant to hypertension management in elderly patients.

Pathophysiology of Hypertension in the Elderly

Age-associated increases in hypertension prevalence derive from changes in arterial structure and function accompanying aging. Large vessels become less distensible, which increases pulse wave velocity, causing late systolic blood pressure (SBP) augmentation and increasing myocardial oxygen demand. Reduction of forward flow also occurs, limiting organ perfusion. These undesirable alterations are enhanced with coronary stenosis or excessive drug-induced diastolic blood pressure (DBP) reduction. Autonomic dysregulation contributes to orthostatic hypotension (a risk factor for falls, syncope, and cardiovascular [CV] events) and orthostatic hypertension (a risk factor for left ventricular hypertrophy [LVH], coronary artery disease [CAD], and cerebrovascular disease). Progressive renal dysfunction, because of glomerulosclerosis and interstitial fibrosis with a reduction in glomerular filtration rate (GFR) and other renal homeostatic mechanisms such as membrane sodium/potassium–adenosine triphosphatase, fosters hypertension through increased intracellular sodium, reduced sodium–calcium exchange, and volume expansion. Microvascular damage contributes to chronic kidney disease (CKD) as reduced renal tubular mass provides fewer transport pathways for potassium excretion; thus elderly hypertensive patients are prone to hyperkalemia. Secondary causes of hypertension should be considered, such as renal artery stenosis (RAS), obstructive sleep apnea, primary aldosteronism, and thyroid disorders. Lifestyle, substances, and medications (tobacco, alcohol, caffeine, nonsteroidal anti-inflammatory drugs [NSAIDs], glucocorticoids, sex hormones, calcium, and vitamins D and C) can also be important contributors.

End-Organ Effects

The following are highly prevalent among the elderly and associated with poor blood pressure (BP) control: cerebrovascular disease (ischemic stroke, cerebral hemorrhage, vascular dementia, Alzheimer's disease, and accelerated cognitive decline); CAD (including myocardial infarction [MI] and angina pectoris); disorders of left ventricular (LV) structure and function (including LVH and heart failure [HF]); cardiac rhythm disorders (atrial fibrillation [AF] and sudden death); aortic and peripheral arterial disease [PAD]) (including abdominal aortic aneurysm [AAA], thoracic aortic aneurysm, acute aortic dissection and occlusive PAD); CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2; ophthalmologic disorders (including hypertensive retinopathy, retinal artery occlusion, nonarteritic anterior ischemic optic neuropathy, age-related macular degeneration, and neovascular age-related macular degeneration); and quality of life (QoL) issues.

Interactions Between Aging and CV Risk Conditions Associated With Hypertension

Because dyslipidemia and hypertension are common among the elderly, it is reasonable to be aggressive with lipid lowering in elderly hypertensive patients. Elderly patients with hypertension and diabetes mellitus have a higher mortality risk than similarly aged nondiabetic controls. Hypertension is an insulin-resistant state because SBP, fasting glucose, and thiazide diuretic and/or beta-blocker use are independent risk factors for incident diabetes mellitus. Albuminuria is a predictor of higher mortality risk among those with diabetes mellitus. Obesity is associated with increases in LV wall thickness, volume, and mass, independent of BP. Adipose tissue produces all components of the renin-angiotensin-aldosterone system (RAAS) locally, leading to development of obesity-related hypertension. Increased angiotensin II (AII) may contribute to insulin resistance. Activation of tissue RAAS contributes to vascular inflammation and fibrosis. Renin and aldosterone may also promote atherosclerosis and organ failure. Microalbuminuria is associated with CAD, HF, and mortality. Screening for albuminuria is recommended for all elderly hypertensive patients with concomitant diabetes mellitus and for those with mild and moderate CKD. Gout incidence rates are 3 times higher in hypertensive patients versus normotensive patients; thiazide diuretics increase serum uric acid levels and may provoke gout. Serum uric acid independently predicts CV events in older hypertensive persons; therefore, monitoring serum uric acid during diuretic treatment is reasonable. Arthritis is a common prob-

lem in the elderly, with implications for hypertension and adverse outcomes related to medications. NSAIDs are implicated in BP elevation, and a chronic inflammatory burden may lead to increased arterial stiffness. Other drugs such as cyclo-oxygenase-2 inhibitors, glucocorticoids, and some disease-modifying antirheumatic drugs (e.g., cyclosporine, leflunomide) may increase BP.

Clinical Assessment and Diagnosis

Diagnosis of hypertension should be based on at least 3 different BP measurements, taken on ≥2 separate office visits. At least 2 measurements should be obtained once the patient is seated comfortably for at least 5 minutes with the back supported, feet on the floor, arm supported in the horizontal position, and the BP cuff at heart level. Pseudohypertension is a falsely increased SBP that results from markedly sclerotic arteries that do not collapse during cuff inflation (e.g., "noncompressible"). Although this occurs more commonly in the elderly, the actual prevalence is unclear. Identification of pseudohypertension is necessary to avoid overtreating high BP and should be suspected in elders with refractory hypertension, no organ damage, and/or symptoms of overmedication. White-coat hypertension is more common in the elderly and frequent among centenarians. Ambulatory BP monitoring is recommended to confirm a diagnosis of white-coat hypertension in patients with persistent office hypertension but no organ damage. Ambulatory BP monitoring (ABPM) is indicated when hypertension diagnosis or response to therapy is unclear from office visits, when syncope or hypotensive disorders are suspected, and for evaluation of vertigo and dizziness. The case for using out-of-office BP readings in the elderly, particularly home BP measurements, is strong due to potential hazards of excessive BP reduction in older people and better prognostic accuracy versus office BP.

Recommendations for Management

General Considerations. Because there is limited information for evidence-based guidelines to manage older hypertension patients, the following recommendations are based on expert opinion that we believe provide a reasonable clinical approach. Evaluation of the elderly patient with known or suspected hypertension must accurately determine BP, and if elevated: 1) identify reversible and/or treatable causes; 2) evaluate for organ damage; 3) assess for other CVD risk factors/comorbid conditions affecting prognosis; and 4) identify barriers to treatment adherence. Evaluation includes a history, physical exam, and laboratory testing. It is most important to focus on aspects that relate to hypertension, including details concerning the duration, severity, causes, or exacerbations of high BP, current and previous treatments including adverse effects, assessment of target organ damage, and other CVD risk factors and comorbidities, as noted in the preceding text. There is limited evidence to support routine laboratory testing. Instead, a more deliberative, reasoned approach to testing is recommended: 1) urinalysis for evidence of renal damage, especially albuminuria/microalbuminuria; 2) blood chemistries (especially potassium and creatinine with eGFR); 3) total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; 4) fasting blood sugar (including hemoglobin A1c if there are concerns about diabetes mellitus); and 5) electrocardiogram (ECG). In selected elderly persons, 2-dimensional echocardiography is useful to evaluate for LVH and LV dysfunction that would warrant additional therapy (i.e., angiotensin-converting enzyme inhibitors [ACEIs], beta blockers).

BP Measurement and Goals. Reliable, calibrated BP measurement equipment is essential for hypertension management. The BP should also be measured with the patient standing for 1 to 3 minutes to evaluate for postural hypotension or hypertension. The general recommended BP goal in uncomplicated hypertension is <140/90 mm Hg. However, this target for elderly hypertensive patients is based on expert opinion rather than on data from randomized controlled trials (RCTs). It is unclear whether target SBP should be the same in patients 65 to 79 years of age as in patients >80 years of age.

QoL and Cognitive Function. Because symptomatic well-being, cognitive function, physical activity, and sexual function are diminished by aging and disease, it is important to give particular attention to QoL areas when making therapeutic decisions.

Nonpharmacological Treatment. Lifestyle modification may be the only treatment necessary for milder forms of hypertension in the elderly. Smoking cessation, reduction in excess body weight and mental stress, modification of excessive sodium and alcohol intake, and increased physical activity may also reduce antihypertensive drug doses. Weight reduction lowers BP in overweight individuals, and combined with sodium restriction, results in greater benefit. BP declines from dietary sodium restriction are generally larger in older than in young adults. Increased potassium intake, either by fruits and vegetables or pills, also reduces BP, especially in individuals with higher dietary sodium intake. Alcohol consumption of >2 alcoholic drinks per day is strongly associated with BP elevations, and BP generally declines after reduced alcohol intake, though evidence is limited among older adults. Exercise at moderate intensity elicits BP reductions similar to those of more intensive regimens.

Management of Associated Risk Factors and Team Approach. Many risk stratification tools calculate risk estimates using an overall or "global" instrument like the Framingham Risk Score for predicting MI, stroke, or CVD. These instruments emphasize age and classify all persons >70 or 75 years of age as high risk (i.e., ≥10% risk of CAD in next 10 years), or very high risk (e.g., those with diabetes mellitus or CAD), thus deserving antihypertensive therapy. Furthermore, analyses have not suggested that elderly subgroups differed from younger subgroups in response to multiple risk

interventions. Patient management is often best accomplished by employing a health care team that may include clinical pharmacists, nurses, physician assistants, clinical psychologists, and others (as necessary). Technology enhancements to assist in achieving and maintaining goals range from simple printed prompts and reminders to telemedicine and text messaging.

Considerations for Drug Therapy

Drug treatment for elderly hypertensive patients has been generally recommended but with a greater degree of caution due to alterations in drug distribution and disposal and changes in homeostatic CV control, as well as QoL factors. However, patients in most hypertension trials were <80 years of age. Pooling the limited number of octogenarians from several trials mainly composed of younger patients, treated patients showed a reduction in both stroke and CV morbidity, but a trend toward increased all-cause mortality compared to controls. Thus, the overall benefits of treating octogenarians remain unclear despite epidemiological evidence that hypertension remains a potent CV risk factor in this age group. Results of HYVET, documenting reduced adverse outcomes with antihypertensive drugs in persons ≥80 years of age, requires updating previous recommendations.

Initiation of Drug Therapy

The initial antihypertensive drug should be started at the lowest dose and gradually increased, depending on BP response, to the maximum tolerated dose. An achieved SBP <140 mm Hg, if tolerated, is recommended except for octogenarians (see special populations in the following text). If the BP response is inadequate after reaching "full dose" (not necessarily maximum recommended dose), a second drug from another class should be added provided the initial drug is tolerated. If there are adverse effects or no therapeutic response, a drug from another class should be substituted. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching full doses of 2 classes of drugs, a third drug from another class should be added. When BP is >20/10 mm Hg above goal, therapy should be initiated with 2 antihypertensive drugs. However, treatment must be individualized in the elderly. Before adding new antihypertensive drugs, possible reasons for inadequate BP response should be examined. On average, elderly patients are taking >6 prescription drugs, so polypharmacy, nonadherence, and potential drug interactions are important concerns.

Specific Drug Classes

Thiazide diuretics (hydrochlorothiazide [HCTZ], chlorthalidone, and bendrofluazide [bendrofluomethiazide]) are recommended for initiating therapy. They cause an initial reduction in intravascular volume, peripheral vascular resistance, and BP, and are generally well tolerated. Several trials demonstrate reduced CV, cerebrovascular, and renal adverse outcomes in the elderly. Aging-related physiological changes can be exacerbated with diuretics. The elderly generally have contracted intravascular volumes and impaired baroreflexes. Diuretics cause sodium and water depletion and may promote orthostatic hypotension. Older people have a high prevalence of LVH, which predisposes them to ventricular arrhythmias and sudden death. Thiazide diuretics can cause hypokalemia, hypomagnesemia, and hyponatremia, which increase arrhythmias. The elderly have a tendency toward hyperuricemia, glucose intolerance, and dyslipidemia, all of which are exacerbated by thiazides. Nevertheless, thiazides reduce CV events in the elderly to a similar extent as other drug classes.

Non-Thiazide Diuretics. Indapamide is a sulfonamide diuretic used for hypertension. This drug increases blood glucose, but not uric acid, and can cause potassium-independent prolongation of the QT interval. Caution is advised when used with lithium. Furosemide and analogs (bumetanide or torsemide) are loop diuretics sometimes used for hypertension complicated by HF or CKD. They increase glucose and may cause headaches, fever, anemia, or electrolyte disturbances. Mineralocorticoid antagonists (spironolactone and eplerenone) and epithelial sodium transport channel antagonists (amiloride and triamterene) are useful in hypertension when combined with other agents. In contrast to thiazides and loop diuretics, these drugs cause potassium retention and are not associated with adverse metabolic effects.

Beta blockers have been used for hypertension, but evidence for a benefit in the elderly has not been convincing. They may have a role in combination therapy, especially with diuretics. Beta blockers are indicated in the treatment of elderly patients who have hypertension with CAD, HF, certain arrhythmias, migraine headaches, and senile tremor. Although earlier beta blockers have been associated with depression, sexual dysfunction, dyslipidemia, and glucose intolerance, these side effects are less prominent or absent with newer agents. Although the efficacy of alpha blockers is documented, their usefulness is very limited because doxazosin showed excess CV events compared with chlorthalidone in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (greater than a 2-fold increase in HF and ~20% increase in stroke). Based on these findings, alpha blockers should not be considered as first-line therapy for hypertension in older adults.

Calcium antagonists (CAs) have widely variable effects on heart muscle, sinus node function, atrioventricular conduction, peripheral arteries, and coronary circulation. They include phenylalkylamines (verapamil); benzothiazepines (diltiazem); and dihydropyridines (nifedipine, nicardipine, nimodipine, amlodipine, felodipine, isradipine, nitrendipine). Results of controlled trials have demonstrated the safety and efficacy of CAs in elderly patients with hypertension. They appear well suited for elderly patients, whose hypertensive profile is based on increasing arterial stiffness, decreased vascular compliance, and diastolic dysfunction. Because they have multiple applications, including treat-

ment of angina and supraventricular arrhythmias, CAs are useful for elderly hypertensive patients with these comorbid CV conditions. Most adverse effects of dihydropyridines relate to vasodilation (e.g., ankle edema, headache, postural hypotension). Postural hypotension is associated with an increased risk of dizziness and falls and a serious concern for elderly patients. Short-acting rapid-release dihydropyridines must be avoided. Verapamil and diltiazem can precipitate heart block in elderly patients with underlying conduction defects. First-generation CA (nifedipine, verapamil, and diltiazem) should be avoided in patients with LV systolic dysfunction.

ACEIs block conversion of AI to AII, both in tissue and plasma to lower peripheral vascular resistance and BP without reflex stimulation of heart rate and contractility. They reduce morbidity and mortality in patients with HF, reduce systolic function post-MI, and retard progression of diabetic renal disease and hypertensive nephrosclerosis. Main adverse effects include hypotension, chronic dry cough, and, rarely, angioedema or rash. Renal failure can develop in those with RAS. Hyperkalemia can occur in patients taking potassium supplements, as well those with renal insufficiency. Rarely, neutropenia or agranulocytosis can occur; close monitoring is suggested during the first months of therapy. Angiotensin receptor blockers (ARBs) selectively block AT1-receptor subtype and, overall, are similar to other agents in reducing BP, are well tolerated, protect the kidney, and reduce mortality and morbidity in HF patients. In elderly hypertensive patients with diabetes mellitus, ARBs are considered first line and as an alternative to ACEI in patients with hypertension and HF who cannot tolerate ACEIs.

Direct Renin Inhibitors. Aliskiren is as effective as ARBs or ACEIs for BP lowering without dose-related increases in adverse events in elderly patients. Combined with HCTZ, ramipril, or amlodipine, aliskiren causes greater BP lowering than with either agent alone. Evidence is lacking combining aliskiren with beta blockers or maximal dose ACEIs, and only limited data are available in black hypertensive patients. In patients >75 years of age, including those with renal disease, aliskiren appears well tolerated. The major side effect is a low incidence of mild diarrhea, which usually does not lead to discontinuation. There are no data on treating patients with an eGFR below 30 mL/min/1.73 m^2.

Nonspecific Vasodilators. Because of their unfavorable side effects, hydralazine and minoxidil are fourth-line antihypertensive agents and only used as part of combination regimens. As a monotherapy, both drugs cause tachycardia, and minoxidil causes fluid accumulation and atrial arrhythmias. Centrally acting agents (e.g., clonidine) are not first-line treatments in the elderly because of sedation and/or bradycardia. Abrupt discontinuation leads to increased BP and heart rate, which may aggravate ischemia and/or HF. These agents should not be considered in noncompliant patients but may be used as part of a combination regimen if needed after several other agents are deployed.

Combination therapy provides more opportunity for enhanced efficacy, avoidance of adverse effects, enhanced convenience, and compliance. It is important to consider the attributes of ACEIs, ARBs, and CAs, in addition to BP lowering. Some combinations of these agents may provide even more protective effects on the CV system. One trial of high-risk hypertensive elders, ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension), found an ACEI–long-acting CA combination superior to an ACEI–HCTZ combination in reduction of morbidity and mortality.

Uncomplicated Hypertension

The 2009 updated European Society of Hypertension guidelines recommend initiating therapy in the elderly with thiazide diuretics, CAs, ACEIs, ARBs, or beta blockers based on a meta-analysis of major hypertension trials (23). Most elderly persons with hypertension will need ≥2 drugs. When BP is >20/10 mm Hg above goal, consideration should be given to starting with 2 drugs.

Complicated Hypertension

In elderly patients who have CAD with hypertension and stable angina or prior MI, the initial choice is a beta blocker. A long-acting dihydropyridine CA should be administered in addition to the beta blocker when the BP remains elevated or if angina persists. An ACEI should also be given, particularly if LV ejection fraction is reduced and/or if HF is present. A verapamil SR–trandolapril-based strategy is as clinically effective, in terms of BP control and adverse outcomes, as an atenolol–HCTZ-based strategy in hypertensive elderly CAD patients including those with prior MI. Angina was better controlled with the verapamil SR–trandolapril strategy. With acute coronary syndromes, hypertension should be treated with beta blockers and ACEI, with additional drugs added as needed for BP control. Verapamil and diltiazem should not be used with significant LV systolic dysfunction or conduction system disease. Although some guidelines recommend reducing BP to <130/80 mm Hg in CAD patients, there is limited evidence to support this lower target in elderly patients with CAD. Observational data show the nadir BP for risk was 135/75 mm Hg among CAD patients 70 to 80 years of age and 140/70 mm Hg for patients ≥80 years of age. Beta blockers with intrinsic sympathomimetic activity must not be used after MI.

Hypertension associated with LVH is an independent risk factor for CAD, stroke, PAD, and HF. A large meta-analysis found ACEIs more effective than other antihypertensive drugs in decreasing LV mass. However, all agents except for direct-acting vasodilators reduce LV mass if BP is controlled.

Elderly patients with hypertension and systolic HF should receive a diuretic, beta blocker, ACEI, and an aldosterone antagonist, in the absence of hyperkalemia or significant renal dysfunction, if necessary. If a patient cannot tolerate an ACEI, an ARB should be used. Elderly black

hypertensive patients with HF may benefit from isosorbide dinitrate plus hydralazine. Based on expert opinion, the BP should be reduced to <130/80 mm Hg in HF patients with CAD. Elderly patients with hypertension and asymptomatic LV systolic dysfunction should be treated with ACEIs and beta blockers. Because HF may improve in hypertensive elderly patients with RAS after renal revascularization, a search for RAS should be considered when HF is refractory to conventional management. Diastolic HF is very common in the elderly. Fluid retention should be treated with loop diuretics, hypertension should be adequately controlled, and when possible, comorbidities should be treated.

Although "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" recommends that elderly hypertensive patients with cerebrovascular disease (prior stroke or transient ischemic attack) should be treated with a diuretic plus an ACEI (22), reduction of stroke risk among elderly persons with hypertension is related more to reduction in BP than to type of antihypertensive drug.

Presence of aortic aneurysm requires very intense BP control to the lowest tolerated level. Therapy should include an ACEI or ARB plus a beta blocker because, in addition to lowering BP, beta blockers decrease peak LV ejection rate. In acute aortic dissection (acute aortic syndrome), control of BP with multiple drugs, including beta blockers, is needed for both type A and B (not involving the ascending aorta) dissections. For PAD, lifestyle interventions include smoking cessation, weight loss, and a structured walking program. Management of hypertension as well as coexistent CAD and HF are essential, as is control of blood glucose and lipids. ACEIs or ARBs, and antiplatelet therapy are required.

In the absence of RCT data, guidelines recommend that patients with diabetes mellitus should have a BP <130/80 mm Hg. If tolerated, multiple drugs are often required. However, RCT data among those ≥65 years of age from the ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial found no additional benefit from a target SBP <120 mm Hg versus a target of 140 mm Hg. Observational data from extended follow-up of the predominantly elderly INVEST (INternational VErapamil SR/Trandolapril Study) diabetes cohort suggest an increase in mortality when on-treatment SBP is <115 mm Hg or DBP <65 mm Hg. Reduction of macrovascular and microvascular complications in elderly hypertensive diabetic patients depends more on reducing BP than on type of drugs used. Drug choice depends on associated comorbidities. However, thiazide diuretics will increase hyperglycemia. Elderly persons with diabetes mellitus, hypertension, and nephropathy should be treated initially with ACEIs or ARBs. In ACCOMPLISH, over the background of ACEI, diabetic patients treated with amlodipine had a 21% relative risk reduction and 2.2% absolute risk reduction in CV events compared with HCTZ plus the ACEI. In elderly persons with prediabetes/metabolic syndrome, attempts should be made to reduce BP using lifestyle modification. If drugs are needed, thiazide diuretics increase risk for incident diabetes mellitus, which has been associated with increased HF hospitalizations and other CV events in elderly patients with hypertension.

Based on expert opinion and observational data, elderly hypertension patients with CKD should have a target BP <130/80 mm Hg, if tolerated. Drug regimens including ACEIs or ARBs are more effective than regimens without them in slowing progression of CKD. ACEIs are indicated in patients with nondiabetic nephropathy. However, there are no data on outcomes with any class of antihypertensive agent among elderly patients with hypertension and CKD. Without proteinuria >300 mg/d, there are no data that ACEIs or ARBs are better than BP control alone with any other antihypertensive agent. ACEIs or ARBs should be administered to elderly hypertensive patients with CKD if proteinuria is present. Hypertension and HF are both associated with a more pronounced decline in renal function in older age. With the recognition of early renal dysfunction, more patients should benefit from aggressive therapy. In an observational study of elderly patients who were hospitalized with acute systolic HF and advanced CKD, ACEI use was associated with reduced mortality. A retrospective cohort of elderly individuals with CKD and acute MI found benefit from aspirin, beta blockers, and ACEIs.

Aortorenal bypass has been used to treat hypertension, preserve renal function, and treat HF and unstable angina in RAS patients with ischemic nephropathy. Advanced age and HF are independent predictors of mortality. Percutaneous transluminal renal artery balloon angioplasty with stenting has replaced angioplasty alone because the stenosis usually involves narrowing of the ostium. However, there is uncertainty regarding the benefit of stenting on BP control and CKD.

Other Conditions/Special Populations

Among elderly persons with osteoporosis and calcium regulatory disorders, thiazide diuretics may preserve bone density and raise blood calcium levels. Loop diuretics can decrease serum calcium. Epithelial sodium transport channel antagonists may decrease urinary calcium and may be considered for people with calcium oxalate kidney stones. Beta blockers and heart rate–slowing CAs (verapamil or diltiazem) should be used for ventricular rate control with supraventricular tachyarrhythmias in elderly persons with hypertension. Beta blockers should be used for elderly patients with hypertension, complex ventricular arrhythmias, HF, hyperthyroidism, preoperative hypertension, migraine, or essential tremor.

Blacks: RAAS inhibitors appear less effective than other drug classes in decreasing BP in elderly blacks, unless combined with diuretics or CAs. The initial agent in blacks with uncomplicated hypertension should be a thiazide diuretic. CAs effectively lower BP in blacks and decrease CV events, especially stroke. A diuretic or CA plus an ACEI would be a reasonable combination in blacks. Blacks, many of whom have severe and complicated hypertension, usually will not achieve control with monotherapy. Aldo-

sterone antagonists (spironolactone and eplerenone) are often beneficial in resistant hypertension, including blacks.

Hispanics: Recommendations for pharmacological management of elderly Hispanic patients are the same as for elderly patients in general.

Women: There is no evidence that elderly women respond differently than elderly men to antihypertensive drugs.

Available data from HYVET (4) and other RCTs suggest that treatment of hypertension in octogenarians may substantially reduce CV risk and mortality, but benefits on cognitive function are less certain. Although a BP <140/90 mm Hg is recommended for all patients in "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," except for a lower level in special populations (22), randomized trial evidence to support this BP level in the very elderly is not robust. Secondary analyses from INVEST and ACCOMPLISH showed no difference in effects of antihypertensive drug therapy on outcomes among those ≥80 years of age versus those <80 years of age. However, ACCORD BP found no additional benefit, and increased drug-related adverse experiences, targeting a SBP of 120 versus 140 mm Hg in high-risk patients with diabetes mellitus who were >55 years of age. Observational data from INVEST in hypertensive CAD patients showed a nadir for adverse outcomes at a mean on-treatment SBP of 135 mm Hg for patients 70 to 79 years of age and at 140 mm Hg for those ≥80 years of age.

The following recommendations are offered for persons ≥80 years of age. Initiate treatment with a single drug followed by a second drug if needed. Achieved SBP 140 to 145 mm Hg, if tolerated, can be acceptable. Low-dose thiazides, CAs, and RAAS blockers are preferred, but concomitant conditions often dictate which drugs are most appropriate. Octogenarians should be seen frequently with the medical history updated at each visit. Standing BP should always be checked for excessive orthostatic decline. Although BP values below which vital organ perfusion is impaired in octogenarians are not known, SBP <130 and DBP <65 mm Hg should be avoided.

Resistant hypertension (e.g., BP that remains above goal when patient adheres to lifestyle measures and maximum tolerated doses of complementary antihypertensive agents, including a diuretic) is associated with increasing age. Reasons include higher arterial stiffness, decreased antihypertensive medication efficacy, higher baseline BP, higher incidence of organ damage and comorbidities, excess salt intake, weight, alcohol, nicotine, poor treatment compliance, volume overload, pseudohypertension, and NSAID use. Elderly patients with higher baseline SBP typically have more severe or longer duration of hypertension that makes it more difficult to treat because it is often associated with autonomic dysfunction and organ damage. Volume overload is commonly due to excessive salt intake, inadequate kidney function, or insufficient diuretic therapy. Physicians are less aggressive treating very elderly patients as many believe that hypertension treatment in an 85 year old has more risks than benefits. Pseudohypertension represents another reason for resistant hypertension. Increased arterial stiffness due to heavily calcified arteries that cannot be fully compressed makes BP readings falsely higher than the intra-arterial BP.

Although therapy of resistant hypertension must be individualized, a combination of a RAAS blocker, a CA, and an appropriately dosed diuretic is frequently effective. These agents must be given in adequate dosages at appropriate time intervals. Lifestyle modifications (e.g., weight reduction, sodium restriction, reduction in alcohol intake, and the DASH [Dietary Approaches to Stop Hypertension] diet) may be useful, and secondary causes of hypertension should be considered.

Adherence to Pharmacological Therapy. Adherence, defined as extent to which a patient takes medication as prescribed, is a major issue in antihypertensive therapy in all age groups. A large proportion of elderly patients will discontinue or take the drugs inappropriately. Nonadherence often results in failing to reach recommended BP targets and impacts outcomes. Older age, previous nonadherence, low risk for CV events, competing health problems, nonwhite race, low socioeconomic status, treatment complexity (e.g., multiple dosing, pill burden), side effects, and cost of medications predict nonadherence.

Treatment Initiation and Goals. Elderly patients who have hypertension are candidates for nonpharmacological interventions; if they remain hypertensive, drug therapy should be considered. Achieved SBP values <140 mm Hg are appropriate goals for most patients ≤79 years of age; for those ≥80 years of age, 140 to 145 mm Hg, if tolerated, can be acceptable.

Future Considerations

Prevention of Hypertension and Its Consequences. Research should include both fundamental and clinical investigation defining pathogenesis of increased vascular and LV stiffness; RCTs to define appropriate treatment thresholds and goals; comparative effectiveness trials testing various treatment strategies (i.e., different regimens and different intensities of lifestyle modification); and assessing the relative safety and efficacy of these approaches in the prevention of mortality and morbidity.

1. Introduction

1.1. Document Development Process and Methodology

1.1.1. Writing Committee Organization

The writing committee consisted of acknowledged experts in hypertension among elderly patients representing the ACCF, AHA, AAN, ABC, ACP, AGS, ASH, ASN, ASPC, and ESH. Both the academic and private practice sectors were represented. Representation by an outside organization does not necessarily imply endorsement.

1.1.2. Relationships With Industry and Other Entities

Prior to finalizing writing committee membership, all potential authors reported their relevant relationships with industry and other entities pertinent to this writing effort that began 24 months prior to receiving their invitation letter to participate. This information was organized into a table and reviewed by the ACCF Task Force on Clinical Expert Consensus Documents for writing committee balance across a series of elements including relationships with industry and other entities, regional distribution, sex, race, and specialty area. The ACCF Task Force on Clinical Expert Consensus Documents approved the constitution of this group. On each full-committee conference call, authors were asked to review the disclosure table and verbally disclose any additions to their information. As noted in the Preamble, relevant relationships with industry and other entities of writing committee members are published in Appendix 1 of this document. In addition, in the spirit of full transparency, author comprehensive disclosure information (relationships the author deemed not applicable to this document) is made available online as a supplement to this document. For detailed information regarding ACCF's disclosure policy, including the definitions of relevant relationships with industry, visit www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

1.1.3. Consensus Development

Prior to the first writing committee conference call, an outline of the document was drafted, and preliminary writing assignments were made. During the committee's first call, the timeline, draft outline and writing assignments, definition of hypertension, and relationships with industry were discussed and finalized. A thorough literature review was undertaken on hypertension and the elderly, results were distributed to authors, and primary authors drafted their sections for review by secondary authors prior to submitting their sections for incorporation into the master draft. The co-chairs edited the manuscript and sent it back to committee members for further editing. Several additional conference calls with the entire committee were held to discuss document issues in order to achieve consensus. Smaller subgroup meetings were held when necessary to focus on a particular area (e.g., management of the patient). Each individual contributor of the document had his or her initial full written presentation critiqued by all other members of this writing committee. Considerable discussion among the group focused on the best and most proper way to manage the elderly patient with hypertension as the clinical data are limited for this population. The writing committee arrived at consensus on the document and signed off on the draft for external peer review.

1.1.4. External Peer Review

The document was reviewed by 2 official reviewers nominated by each of the participating societies in this document, as well as 5 content reviewers, totaling 25 reviewers in all. A task force lead reviewer was assigned to the review process to ensure that the writing committee reviewed and responded to all reviewer comments in a reasonable and balanced manner. A complete listing of peer reviewers and their relevant relationships with industry are listed in Appendix 2.

1.1.5. Final Writing Committee and Task Force Approval of the Document

The writing committee formally approved the final document. Subsequently, the task force lead reviewer signed off on the completeness of the external review process, and the ACCF Task Force on Clinical Expert Consensus Documents reviewed the document for completeness and approved the document to be sent for final organizational review.

1.1.6. Document Approval

The document was approved for publication by each of the following participating societies: ACCF, AHA, AAN, AGS, ASPC, ASH, ASN, and ESH. This document will be considered current until the task force revises or withdraws it from distribution.

1.1.7. Document Methodology

An extensive literature search was conducted using the U.S. National Library of Medicine's PubMed database that led to the incorporation of 741 references. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included but were not limited to *hypertension, aged, elderly, pharmaceutical preparations, cost, compliance, diagnosis, physical examination, tobacco, smoking, drug therapy, family history, premature CVD, risk factors, complications, dyslipidemia, obesity, cerebrovascular disease, HF, MI, angina, PAD, diabetes mellitus, lifestyle, J-curve, adverse drug event, renal revascularization, osteoarthritis, hypokalemia, prognosis, microalbuminuria,* and *retinopathy*. Additional relevant references have also been identified by personal contacts of the writing committee members, and substantial efforts were made to identify all relevant manuscripts that were currently in press. References selected and published in this document are representative and not all-inclusive.

The writing committee agreed uniformly that the definition of *elderly* would include those ≥65 years of age. Recommendations for management of hypertension in the elderly are largely based on randomized controlled trials and meta-analyses. However, specific data as they pertain directly to the elderly population remain limited in some areas, including specific BP recommendations for patients with comorbid conditions such as diabetes mellitus, CKD, and PAD. Recommendations made in these and other areas

may be based on expert consensus opinion or on the limited data available from observational studies.

The recommendations listed in this document are, whenever possible, evidence-based. Unlike ACCF/AHA guidelines, there is not a large body of peer-reviewed published evidence to support most recommendations, which will be clearly indicated in the text. To ensure concordance across ACCF clinical documents, the writing committee reviewed documents related to the subject matter previously published by the ACCF. Prior ACCF/AHA guidelines contain recommendations for BP management, but none of these recommendations are directed to the elderly.

1.2. Purpose of This Expert Consensus Document

Our population is aging, and hypertension in elderly patients is increasing in prevalence. Approximately 34 million Americans are currently ≥65 years of age; this number is expected to reach 75 million by 2040, representing more than >20% of the U.S. population. Individuals >85 years of age are the largest growing subset in the United States (1), and there have been dramatic improvements in life expectancy in older adults (2). Also, the clinical importance of treating this subgroup is emphasized from the National Hospital Discharge Survey (2000) where the far majority of patients admitted to CV services are >65 years of age, and nearly 80% to 90% of those who die on our services are >65 years of age. Hypertension in elderly patients is a complex CV disorder that affects women more than men and occurs in essentially all races, ethnic groups, and countries. Although it appears to be underdiagnosed in general and particularly among women, minorities, and underserved populations, clearly it is also undertreated. Elderly persons are more likely to have hypertension and isolated systolic hypertension (ISH), organ damage, clinical CVD, develop new CV events, and are less likely to have hypertension controlled.

Hypertension is a very prevalent disorder (about 1 billion people worldwide) (3), and as such, it is the most common modifiable risk factor for conditions such as atherosclerosis, stroke, HF, AF, diabetes mellitus, sudden cardiac death, acute aortic syndromes, CKD, and may cause death and disability in patients of all ages. Because it increases with aging and is also compatible with longevity, there is often uncertainty about its management in older patients. Indeed, hypertension in elderly patients represents a management dilemma to CV specialists and other practitioners. Furthermore, with the wide adoption of multiple drug treatment strategies targeting subgroups of hypertension patients with specific risk conditions to lower BP beyond traditional goals, difficult questions arise about how vigorously elderly patients should be treated. Until very recently, this was a particular dilemma for the very elderly because most hypertension management trials had upper age thresholds for enrollment and/or did not present age-specific results. However, HYVET documented major benefit in those ≥80 years of age (4), and consequently, it seems particularly timely to clarify and place into perspective clinical issues relevant to the management of hypertension in elderly patients. Prior to HYVET, although some clinicians favored treating hypertension in the very elderly (5), others did not (6,7).

1.3. General Considerations

This clinical scientific statement represents the consensus of a panel of experts appointed by the ACCF, AHA, AAN, ABC, ACP, AGS, ASH, ASN, ASPC, and ESH. The writing group is composed of CV specialists with extensive experience in hypertension among elderly patients. The panel focused largely on management of this complex disease and derived practical and contemporary treatment strategies for the many subgroups of patients comprising the broad disease spectrum. Because of limited published clinical trial data in elderly patients, the level of evidence governing management decisions for drugs or other strategies has often been derived from nonrandomized and observational-type investigations. Many studies, such as those that have provided important answers regarding management of CAD and/or HF, had often limited enrollment of elderly patients. Therefore, treatment strategies have necessarily evolved based on available data from younger populations or from observational data, sometimes obtained in relatively small patient groups, or from the accumulated clinical experience of individual investigators. Consequently, construction of strict clinical algorithms designed to assess prognosis and dictate treatment decisions for elderly patients with hypertension has been challenging and with their multiple comorbidities, management decisions must be individualized to the particular patient. This data gap seems to be closing as many recent trials have included older patients. The age details of these trials are summarized in Table 1.

Understanding of the clinical course and optimal management of hypertension and associated CVD is increasing. There is growing awareness of the heterogeneity of patients with hypertension and the many patient subgroups that inevitably influence considerations for treatment. Some management strategies are evolving, and this document cannot, in all instances, convey definitive assessments of their role in treatment. For some uncommon subsets, there are limited data currently available to definitively guide therapy. With these considerations in mind, the panel has aspired to create a document that is not only current and pertinent, but also has the potential to remain relevant for years.

1.4. Nomenclature, Definitions, and Clinical Diagnosis

The usual definitions of hypertension and target BP levels might not be applicable to the elderly hypertensive population. Criteria for categorizing BP vary (22–25) and have not been further characterized for the elderly. In the United States, a clinical diagnosis of hypertension is established by demonstrating a SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg on at least 2 occasions as summarized in "The Seventh Report of the Joint National Committee on Pre-

Table 1. Trials of Antihypertensive Treatment in the Elderly

Trial Name (Reference)	N	Age Range (y)	Mean Age (y)	Drug(s)	% Risk Reduction						
					CVA	MI	Hospitalization for CHF	Total CVD (or All CV Events)	All-Cause Mortality	CV Mortality	Response to Therapy Same Above Mean Age
ACCOMPLISH (8)	11,506	≥55	68	(Benazepril amlodipine) versus (benazepril + HCTZ)	16	NR	↑ 4	17*	10	20*	Yes†
ALLHAT (9)	33,357	≥55	67	Amlodipine versus chlorthalidone	7	No difference	↑ 38*	↑ 4	4	NR	Yes
				Lisinopril versus chlorthalidone	↑ 15*	↑ 5	↑ 19*	↑ 10*	No difference	NR	Yes
ANBP 2 (10)	6,083	65–84	72	ACE inhibitors versus diuretics	↑ 2	14	15	11*	10	NR	Yes
Coope and Warrender (11)	884	60–79	68	Atenolol + bendrofluazide	42*	−3	32	24	3	22	Stroke only
EWPHE (12)	840	≥60	72	HCTZ + triamterence + methyldopa	36	20	22	29	9	27*	NR
HYVET (4)	3,845	80–105	84	Indapamide + perindopril	30	NR	64*	34*	21*	23	Yes‡
INVEST (13)	22,576	≥50	66	Verapamil versus atenolol	No difference	No difference	No difference	No difference	No difference	No difference	Yes§
LIFE (14)	9,193	55–80	67	Losartan versus atenolol	25*	NR	3	13*	10	11	NR
MRC (15)	4,396	65–74	70	Atenolol + HCTZ or amiloride	25*	19	NR	17*	3	9	Yes‡
SHEP (16)	4,736	≥60	72	Chlorthalidone	36*	25	55	32	13	20	NR
STONE (17)	1,632	60–79	67	Nifedipine	57*	6	68	60*	45	26	Yes‡
STOP-HTN (18)	1,627	70–84	76	Atenolol + HCTZ or amiloride or metroprolol or pinodolol	47	13	51	40	43	50	Yes‡
Syst-China (19)	2,394	≥60	67	Nitrendipine captopril HCTZ	38*	33	38	37*	39*	39*	All but CV mortality
Syst-Eur (20)	4,695	≥60	70	Nitrendipine	42	26	36	31	14	27	NR
VALUE (21)	15,245	≥50	67	Amlodipine versus valsartan	↑ 15	NR	11	↑ 6	↑ 4	NR	NR

*Statistically significant; †≥65 years of age, HR=0.81, >70 years of age, HR=0.79; ‡Specific data not reported; §≤70 years of age, RR=1.06, ≥70 years of age, RR=0.93.

ACE indicates angiotensin-converting enzyme; ACCOMPLISH, Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure study; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; EWPHE, European Working Party on High Blood Pressure in the Elderly; HCTZ, hydrochlorothiazide; HYVET, Hypertension in the Very Elderly; INVEST, International Verapamil SR/Trandolapril Study; LIFE, Losartan Intervention For Endpoint; MI, myocardial infarction; MRC, Medical Research Council; N, number of randomized patients; NR, not reported; SHEP, Systolic Hypertension in the Elderly Program; STONE, Shanghai Trial of Nifedipine in the Elderly; STOP-HTN, Swedish Trial in Old Patients with Hypertension; Syst-China, Systolic Hypertension in China; Syst-Eur, Systolic Hypertension in Europe; VALUE, Valsartan Long-term Use Evaluation; and ↑, increase.

Table 2. American Heart Association Recommendations for Prevention and Management of Ischemic Heart Disease: Blood Pressure Targets

Patient Type	Goal BP (mm Hg)
Left ventricular dysfunction	<120/80
Diabetes mellitus	<130/80
Chronic renal disease	<130/80
CAD or CAD risk equivalents*	<130/80
Carotid artery disease	<130/80
Peripheral arterial disease	<130/80
Abdominal aortic aneurysm	<130/80
High-risk (10-y FRS ≥10%)	<130/80
Uncomplicated hypertension (none of above)	<140/90

*CAD risk equivalents include diabetes mellitus, peripheral arterial disease, carotid arterial disease, and abdominal aortic aneurysm.

BP indicates blood pressure; CAD, coronary artery disease; and FRS, Framingham Risk Score. Modified from Rosendorff et al. (26).

vention, Detection, Evaluation, and Treatment of High Blood Pressure" (22). In addition, considerable evidence has evolved to classify SBP >130 mm Hg but <140 mm Hg as less than optimal for individuals with certain conditions. Specific BP goals based on coexisting conditions (Table 2) have been recommended for prevention and management of CAD (26). These conditions include HF or asymptomatic LV dysfunction (27) with a BP goal of <120/80 mm Hg. For patients with diabetes mellitus (and impaired glucose tolerance without clinical diabetes mellitus or "prediabetes" and metabolic syndrome) and/or CKD, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (22), the American Diabetes Association (28), and the National Kidney Foundation (29) recommend a BP goal <130/80 mm Hg. Many also consider patients with CAD, as well as those with coronary risk equivalents (i.e., CAD, PAD, aortic or intracerebral artery aneurysm) in this category. Evidence is evolving to support the suggestion that targeting a BP lower than traditional goals may prevent or delay progression or promote stabilization of atherosclerosis (30,31). Thus, although the traditional BP ≥140/90 mm Hg will be used herein to define hypertension, for special populations (Table 2), a lower BP target may be considered optimal. However, BP targets are based primarily on observational data in middle-aged patients, and optimal targets for elderly patients, especially those with systolic hypertension and normal or low DBP (e.g., ISH) remain to be defined from randomized trial data. Importantly, ACCORD BP found among patients with type 2 diabetes mellitus at high risk for CV events targeting SBP <120 mm Hg, as compared with <140 mm Hg, did not reduce the rate of fatal and nonfatal major CV events at the expense of an increase in adverse experiences attributed to BP medications. Furthermore, results were the same among the subgroup of 1,617 patients ≥65 years of age (32).

It is also important to note that, although a specific BP level may be used to classify a person as hypertensive, a finite BP level, per se, is only a biomarker that is somewhat removed from the complex CV disorder termed hypertension. In the future, improved descriptors more closely linked to the disorder itself may evolve to better define who has the disorder, to better predict those at risk for adverse outcomes, and also to better target treatment.

Criteria to define elderly also vary, because it is not possible to develop a specific age-based definition derived from physiological or pathological data because aging is a continuous and progressive process for both sexes in all cultures. In addition, vascular aging rates vary considerably among individuals as a result of genetic, cultural, environmental, behavioral, and disease-related factors. It is therefore not possible to define *elderly* on a purely physiological basis, and any definition is inherently arbitrary and subjective. For this document, writing committee members agreed to use the traditional demographic definition of ≥65 years of age to define the elderly population. However, recognizing that there are clinically relevant physiological differences between the "young old" (65 to 74 years of age), the "older old" (75 to 84 years of age), and the "oldest old" (≥85 years of age), age-specific subgroup data are presented when available, and limitations of existing data are noted. It may also be important to determine whether the elderly individual requires "assisted living" or is "ambulant and free-living" because these qualifiers begin to describe physiological impairments and comorbidities associated with the aging process.

1.5. Magnitude and Scope of the Problem

1.5.1. Epidemiology of Hypertension Related to Aging

Between 1999 and 2004, the prevalence of hypertension in the U.S. population (>18 years of age) was 27% for both men and women, (33) and prevalence increases progressively with age, so the majority of elderly are hypertensive (Figure 1) (34). In the Framingham Heart Study (FHS), 90% of participants with a normal BP at age 55 years eventually developed hypertension (35). Hypertension prevalence is

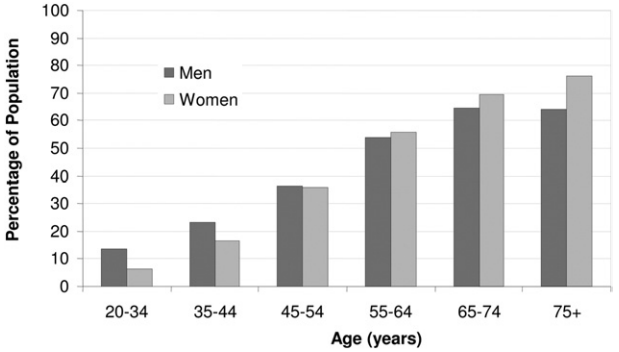

Figure 1. Prevalence of High Blood Pressure in Adults by Age and Sex (NHANES: 2005–2006)

NHANES indicates The National Health and Nutrition Examination Survey. Modified from Lloyd-Jones et al. (34).

greater in older African Americans, especially women, than in older non-Hispanic whites, and somewhat higher in non-Hispanic whites than in Hispanic Americans (34).

In older Americans, hypertension is the most important risk factor for CVD, with estimates that 69% of patients with an incident MI, 77% with incident stroke, and 74% with incident HF have antecedent hypertension (34). In addition, hypertension is a major risk factor for incident diabetes mellitus (36), as well as for AF (37) and CKD (34). In 2005, hypertension was the primary cause of death for 57,356 Americans, and a primary or contributory cause for >300,000 of the 2.4 million total deaths that year (34). Moreover, hypertension death rates increased 25.2% from 1995 to 2005, and the actual number of deaths rose by 56.4%, in part reflecting increasing numbers of older Americans and high prevalence of hypertension at older age (34). In 2009, total direct and indirect costs attributable to hypertension were estimated to be $73.4 billion (34).

People ≥65 years of age currently comprise 13.0% of the U.S. population (38). With aging of the "baby boomer" generation, it is anticipated that by 2030, the number of people in this age group will increase by almost 80%, and that approximately 1 in 5 Americans will be ≥65 years of age (Table 3) (34). Although older patients with hypertension are more likely to be aware of their condition and receiving treatment than middle-aged patients (Figure 2), BP control rates are lower in the elderly, especially after age 80 years (34). The marked growth in size of the older population anticipated over the next decades means the societal burden of hypertension will rise progressively if we do not develop more effective strategies for enhancing BP control rates.

1.5.1.1. ISOLATED SYSTOLIC HYPERTENSION

Aging is associated with a progressive increase in aortic stiffness, in part, related to increased collagen with cross-linking and degradation of elastin fibers. Consequently, SBP rises gradually throughout adult life, although DBP peaks and plateaus in late middle-age, declining slightly thereafter (Figure 3) (39). So, the proportion of hypertensive patients with ISH increases with age—65% of patients with hypertension >60 years of age (39) and over 90% >70 years of age (Figure 4) (40). The prevalence of ISH is higher in women than in men, whereas the proportion of hypertension attributable to ISH in older adults is similar across racial and ethnic groups (34).

In decades past, the apparently inexorable rise in SBP with increasing age fostered the view that this was an adaptive response essential to support organ perfusion, and an empiric formula "100 + age" was often used to estimate the "appropriate" SBP. However, data from the FHS and other epidemiologic investigations provide compelling evidence that SBP is a strong independent risk factor for incident CV events in all decades of life (41,42). Furthermore, as discussed in Section 4.2, randomized trials document that treatment of elevated SBP substantially reduces CV risk in cohorts of elderly patients. As a result, beginning with "The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (43), the focus of management shifted from a primary emphasis on controlling DBP to progressively greater emphasis on controlling SBP, particularly in older patients (22).

Table 3. Population Projections by Selected Age Groups and Sex for the United States: 2010 to 2050 (in 1,000s)

Population	Year 2010	Year 2030	Year 2050
Both sexes			
≥65 y of age	40,229 (13.0%)	72,092 (19.3%)	88,547 (20.2%)
≥85 y of age	5,751 (1.9%)	8,745 (2.3%)	19,041 (4.3%)
Total	310,233	373,504	439,010
Men			
≥65 y of age	17,292 (11.3%)	32,294 (17.6%)	39,917 (18.5%)
≥85 y of age	1,893 (1.2%)	3,284 (1.8%)	7,458 (3.5%)
Total	152,753	183,870	215,825
Women			
≥65 y of age	22,937 (14.6%)	39,798 (21.0%)	48,630 (21.8%)
≥85 y of age	3,859 (2.5%)	5,461 (2.9%)	11,583 (5.2%)
Total	157,479	189,634	223,185

Modified from U.S. Census Bureau (38).

1.5.1.2. SYSTOLIC AND DIASTOLIC HYPERTENSION AND PULSE PRESSURE

After age 70 years, diastolic hypertension accounts for <10% of all patients with hypertension (Figure 4) (40). In addition, the relationship between DBP and CV risk is bimodal in older individuals, with DBPs of ≥90 mm Hg associated with similar increased risk as that associated with DBPs lower than about 70 mm Hg (40,45). As a result, at any given level of SBP, CAD risk increases as DBP decreases (Figure 5) (46,47).

An important implication of this observation is that pulse pressure (i.e., difference between SBP and DBP), which increases with age (Figure 5) and is a measure of the degree of age-related vascular stiffness, emerges as a potent risk factor for CAD events in older individuals. Pulse pressure has been identified as a stronger risk factor than SBP, DBP, or mean pressure in older adults in some studies (48–50). In the FHS, with increasing age, there was a gradual shift from DBP to SBP and then to pulse pressure as the strongest predictor of CAD risk. In patients <50 years of age, DBP was the strongest predictor. Age 50 to 59 years was a transition period when all 3 BP indexes were comparable predictors, and from 60 to 79 years of age, DBP was negatively related to CAD risk so that pulse pressure became superior to SBP (49).

1.5.1.3. SPECIAL POPULATIONS

From the standpoint of epidemiology, pathophysiology, and treatment, there are important subgroups with distinctive characteristics, including elderly women, blacks, Hispanics, and Asians that require additional focus. These populations

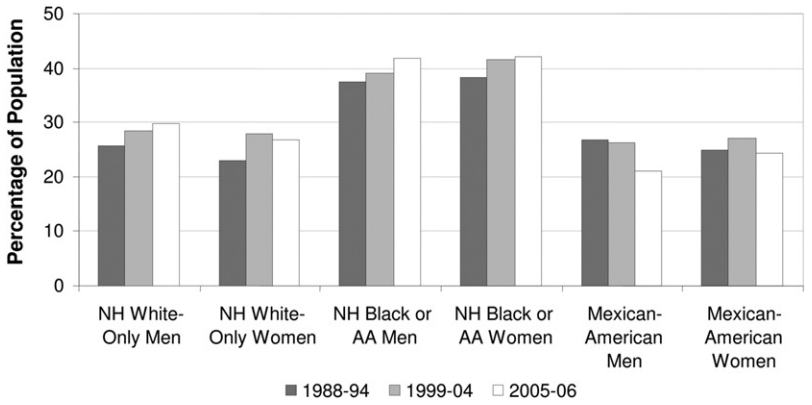

Figure 2. Extent of Awareness, Treatment, and Control of High Blood Pressure by Age (NHANES: 2005–2006)

Hypertension is defined as ≥140/90 mm Hg. AA indicates African American; NH, non-Hispanic; and NHANES, The National Health and Nutrition Examination Survey. Modified from Lloyd-Jones et al. (34).

are discussed in more detail in Section 1.5.2 on pathophysiology and Section 4 on management.

1.5.1.3.1. ELDERLY WOMEN. Among elderly women, hypertension is a major risk factor for CAD and stroke and a major contributor to CV and renal morbidity and mortality (51). Hypertension prevalence is less in women than in men until 45 years of age, is similar in both sexes from 45 to 64 years of age, and is much higher in women than men >65 years of age (52). Age-adjusted hypertension prevalence, both diagnosed and undiagnosed, from 1999 to 2002, was 78% for older women and only 64% for older men (53). Both the prevalence and severity of hypertension increase markedly with advancing age in women, such that after age 60 years, a majority of women have stage 2 hypertension (BP ≥160/100 mm Hg) or receive antihypertensive treatment (54–57). A substantial proportion of elderly women also have prehypertension or stage 1 hypertension, so the prevalence of normal BP in this group is very low (15% of those 60 to 79 years and 6% of those ≥80 years of age in the FHS cohort) (55).

Further, BP control is difficult to achieve in elderly women. Data from the FHS showed an age-related decrease in BP control rates that was more pronounced in women than men (55). Among the oldest participants (>80 years of age) with hypertension, only 23% of women (versus 38% of men) had BP <140/90 mm Hg. Gender differences in the pattern of antihypertensive medications prescribed were noted in this cohort: 38% of women but only 23% of men were taking thiazide diuretics. Whether the age-related decline in BP control among women is related to inadequate intensity of treatment, inappropriate drug choices, lack of compliance, true treatment resistance because of biological factors, or to other factors is unclear.

Data from the NHANES (U.S. National Health and Nutrition Examination Survey) highlight a likely contributory factor to poor BP control in elderly women: an increased prevalence of other CV risk factors, including central obesity, elevated total cholesterol, and low high-density lipoprotein cholesterol levels (57). Among adults

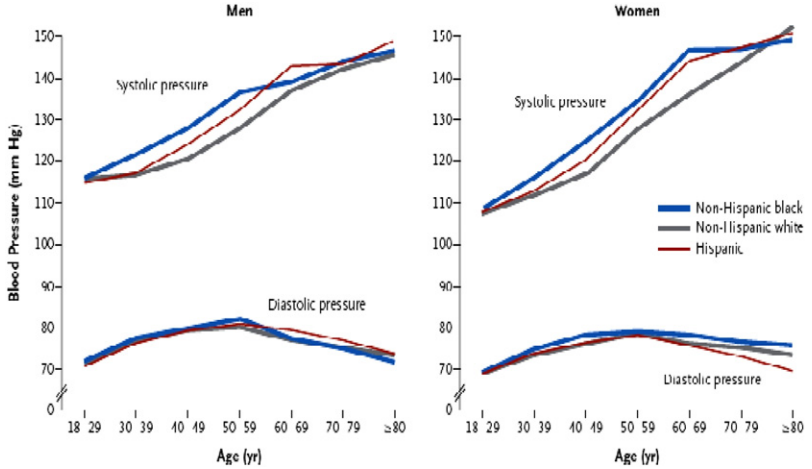

Figure 3. Mean Blood Pressure According to Age and Ethnic Group in U.S. Adults

Reprinted from Chobanian et al. (44).

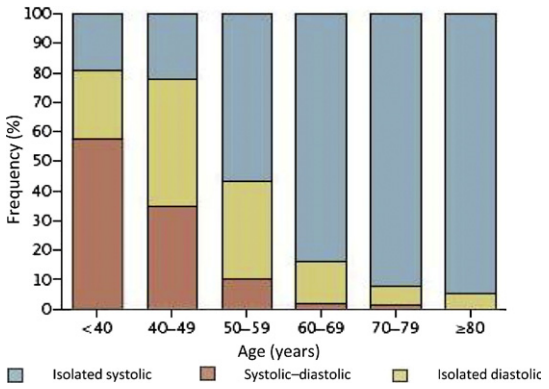

Figure 4. Frequency of Untreated Hypertension According to Subtype and Age

Reprinted from Chobanian et al. (44).

with hypertension in NHANES 1999 to 2004, women were at higher CV risk compared with men: 53% of women, but only 41% of men had >3 of the 6 risk factors studied ($p<0.001$).

Contributions of postmenopausal hormonal changes to BP elevation in elderly women are controversial, in large part because determining the role of sex hormones (or their withdrawal) on BP is complex and confounded by effects of aging and related alterations in CV risk factors such as body weight and lipid levels (58–64). Conversely, there is strong evidence from prospective longitudinal studies that menopause-related BP elevation is dependent on increased body mass index (BMI) and aging, rather than ovarian failure, per se (51,62). The pathophysiology of the menopause-related increase in BP has been inferred from studies in animals (65,66) and human subjects (58). Endothelial dysfunction, increased arterial stiffness, activation of RAAS, increased salt sensitivity, oxidative stress, obesity, and genetic factors have been implicated (58).

1.5.1.3.2. ELDERLY BLACKS. Blacks have the highest age-adjusted hypertension prevalence in the United States: about 40% of African-American men and women, versus about 27% of white men and women (33). Hypertension among blacks is earlier in onset, more severe and uncontrolled, and contributes to the highest CAD mortality rates in the United States, in addition to highest morbidity and mortality attributable to stroke, LVH, HF, and CKD (22). Hypertension is a significant factor in the disproportionate decreased life expectancy for blacks: African-American men, 70.0 years versus 75.9 years for white men, and African-American women, 76.8 years versus 80.8 years for white women (67).

Approximately 9 million, or 13.7%, of the total U.S. hypertensive population is black, 21.2% higher than expected, based on the percentage of U.S. population (11.3%) (68). From the NHANES III (1988 to 1994) versus NHANES 1999 to 2004, there was a significant increase in hypertension among non-Hispanic black men aged 60 to 69 years and ≥70 years old, from 65.0% and 69.6% to 74.2% and 83.4%, respectively odds ratio ([OR]: 1.14; 1.20; $p<0.05$) (33). For non-Hispanic black women, aged 60 to 69 years and >70 years, hypertension prevalence increased from 73.7% and 71.7% to 84.1% and 83.1%, respectively (OR: 1.14, 1.16; $p<0.01$ and $p<0.05$) (33). Overall, age-standardized hypertension rates are increasing, not completely explained by obesity. Interestingly, non-Hispanic black men and women showed 14% and 7% significant improvement in hypertension treatment rates, possibly as a result of focused efforts in that community (33). Although awareness and treatment have increased, control rates for those ≥70 years of age did not significantly improve from NHANES III to NHANES 1999 to 2004 (21.5% and 28.6%, respectively; p=NS).

Compared with whites, blacks are more likely to have hypertension, more likely to be aware of it, and more likely to be pharmacologically treated, but less likely to achieve BP control, especially in middle age (Table 4) (69). Hypertension awareness was higher among blacks than whites ≥60 years of age in NHANES III and NHANES 1999 to 2002 (76.9% versus 68.3% in 1998 to 1994 and 81.7% versus 72.3% in 1999 to 2002). Hypertension treatment rates were also higher in older blacks versus whites (74.0% versus 64.8%, respectively) (69). Despite improved control rates, there remains a racial disparity in BP control, especially in younger blacks (69). In the group >70 years of age, control groups were 20.7% in blacks but 30.0% in whites.

Education is associated with improved BP control; less than high school graduate status is an independent risk factor and a possible proxy for decreased health literacy (69). Control rates among non-Hispanic blacks >60 years of age were 36.8% in NHANES III (1988 to 1994) and 47.4% in NHANES 1999 to 2002, a 28.7% change in BP control

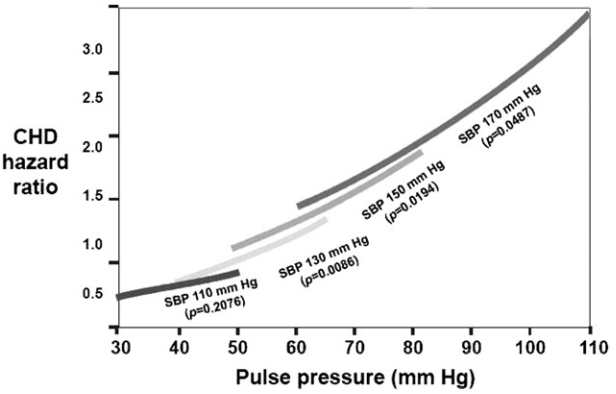

Figure 5. Joint Influences of Systolic Blood Pressure and Pulse Pressure on Coronary Heart Disease

Joint influences of SBP and pulse pressure on CHD risk, from the Framingham Heart Study. CHD hazard ratio was determined from level of pulse pressure within SBP groups. Hazard ratios were set to a reference value of 1.0 for SBP values of 110, 130, 150, and 170 mm Hg, respectively. All estimates were adjusted for age, sex, body mass index, cigarettes smoked per day, glucose intolerance, and total cholesterol/high-density lipoprotein. The p values refer to the CHD hazard ratios determined from the level of pulse pressure within the SBP groups. CHD indicates coronary heart disease; SBP, systolic blood pressure.
Reprinted from Franklin et al. (46).

Table 4. Hypertension Awareness, Treatment, and Control in the U.S. Adult Hypertensive Population (NHANES 1999–2004)

NHANES Population (by Age, y)	Awareness 1999–2004, %	Treatment 1999–2004, %	Control 1999–2004, %
MA men, 50–69	67.3	56.1	28.4
NHW men, 50–69	76.5	68.1*	48.1*
NHB men, 50–69	80.7	72.9*	39.6*
MA men, ≥70	71.2	62.7	25.1
NHW men, ≥70	73*	65.7*	34.8*
NHB men, ≥70	75.1	70.2	28.6
MA women, 50–69	72.2	60.0	28.0
NHW women, 50–69	79.6	68.9	39.6
NHB women, 50–69	87.7*	80.3	43.0*
MA women, ≥70	66.4	58.5*	19.0*
NHW women, ≥70	70.7	63.9*	25.8
NHB women, ≥70	81.6	77.7*	26.0

*Statistically significant.

MA indicates Mexican American; NHANES, The National Health and Nutrition Examination Survey; NHB, non-Hispanic black; and NHW, non-Hispanic white.

Modified from Cutler et al. (33).

over time ($p<0.01$). This was not significantly different from whites over the same period (38.4% and 50.4%), a 30.3% increase in the same age group ($p<0.001$).

Blacks have increased rates of overweight and obesity, physical inactivity, and inadequate potassium intake, especially in a high sodium dietary environment. Environmental factors affect differences in rates of elevated BP in populations of African descent, related to increased BMI and ratio of sodium-to-potassium intake (70). Sodium restriction, weight maintenance or loss, increased aerobic activity, decreased alcohol intake, and high potassium/low sodium diets, such as the DASH diet, rich in fruits, vegetables, and low-fat dairy products have all been shown to be beneficial in reducing BP, as in other populations (22). The beneficial effect of sodium restriction increased with age in blacks; however, the mean age of DASH participants was 44±10 years (71). Reduced sodium intake and DASH diet should be advocated for prevention and treatment of hypertension, especially in blacks, and response to reduced sodium strengthens with increasing age.

1.5.1.3.3. ELDERLY HISPANICS. Hispanics constitute the largest growing ethnic group in the United States, comprising approximately 15% of the population with a growth rate almost 4 times that of the total population (72). Strategies to reduce morbidity and mortality from hypertension among elderly Hispanics are therefore essential.

Hypertension prevalence, treatment, and control rates are often thought to be worse in Hispanics than in non-Hispanic whites and blacks; however, data are conflicting (73). This difference, in part, is because Hispanics are not a homogeneous group in terms of genetics, sociodemographics, and health-related lifestyles. Accordingly, certain Hispanic subpopulations are characterized by low levels of hypertension awareness, treatment, and control. In addition, different Hispanic subgroups may have different levels and frequencies of other CVD risks and health outcomes. For example, Puerto Ricans have a worse health status than Mexican Americans and Cuban Americans (74), including consistently higher hypertension-related mortality rates than other Hispanic subpopulations and non-Hispanic whites (73). Much of this disparity appears driven by sociodemographic and health-related lifestyle factors. Poverty, language issues, lack of education, diet, increased social stress, and high prevalence of diabetes mellitus and obesity all contribute.

Mexican-American men age 60 to 69 years had a lower hypertension prevalence than non-Hispanic white men and non-Hispanic black men (33) (Figure 6), and those ≥70 years of age had a greater prevalence than non-Hispanic white men but less than non-Hispanic black men. For Mexican-American women 60 to 69 years of age, the

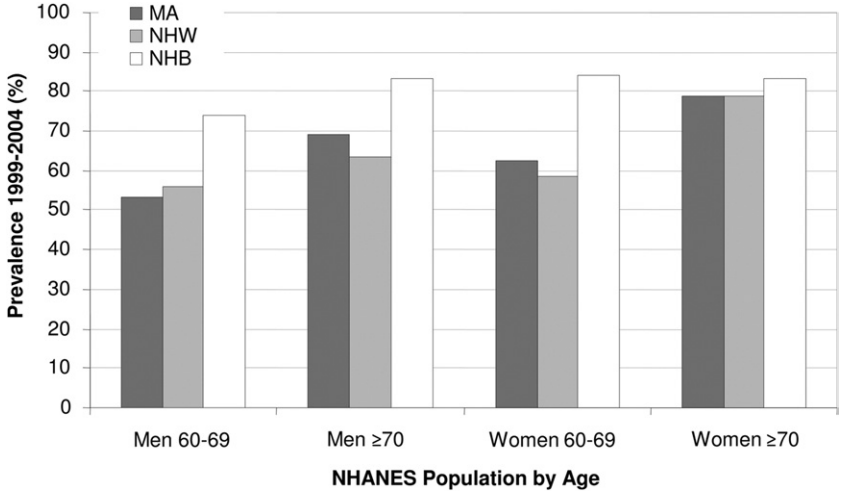

Figure 6. Age-Specific Prevalence of Hypertension in U.S. Adults (NHANES 1999–2004)

MA indicates Mexican American; NHANES, The National Health and Nutrition Examination Survey; NHB, Non-Hispanic Black; and NHW, Non-Hispanic White.
Modified from Cutler et al. (33).

prevalence was greater than non-Hispanic white women but less than non-Hispanic black women. For Mexican-American women ≥70 years of age, the prevalence was the same as non-Hispanic white women but less than non-Hispanic black women. In NHANES 1999 to 2004, hypertension awareness, treatment, and control rates in Mexican-American men 50 to 69 years of age were 67.3%, 56.1%, and 28.4%, respectively, and consistently less than in non-Hispanic whites and non-Hispanic blacks (Table 4).

Older (age ≥70 years) Mexican and Mexican-American women have a greater prevalence of hypertension than male counterparts (75). Also, older Mexican women who migrated to the United States have greater risk for hypertension than female counterparts in Mexico (75). Conversely, older Mexican-American men that immigrated have a lower risk than male counterparts in Mexico.

Although population-based studies often reveal BP prevalence, treatment, and control rates that are worse in Hispanics than in non-Hispanic whites, these disparities often disappear when Hispanics are provided with affordable and easy access to appropriate medical care. Older Hispanics have achieved similar BP control as non-Hispanic whites and blacks (76–82), and no differences were seen in BP responses or outcomes in those above the mean age (65.9 years for Hispanics and 68.5 for non-Hispanics). For example, the INVEST compared 8,045 Hispanic with 14,531 non-Hispanic hypertensive CAD patients randomized to a CA-based or beta-blocker–based strategy (76) with an ACEI or HCTZ as needed for BP control or organ protection. After 61,835 patient-years follow-up and adjusting for baseline BP values, Hispanic patients had better BP control (defined as the proportion with <140/90 mm Hg) than non-Hispanic patients at 24 months ($p<0.001$). They also experienced significantly fewer deaths, nonfatal MIs, or nonfatal strokes. Recommendations for pharmacological management of elderly Hispanic patients are the same as for elderly patients in general, as described in Section 4.

1.5.1.3.4. ELDERLY ASIANS. Asian Americans (familial origin Far East, Southeast Asia, or Indian subcontinent) are rapidly growing in percentage in the United States, and CVD is their leading cause of death, with perhaps higher stroke mortality than whites (83). Asians constitute approximately 5% of the U.S. population; 23.8% are Chinese, 18.3% Filipino, 16.2% Asian Indian, 10.9% Vietnamese, 10.5% Korean, and 7.8% Japanese, with the remaining in other groups (84). In the 2004 to 2006 National Health Interview Survey, Filipino adults (27%) and Japanese adults (25%) were more likely than Chinese (17%) or Korean adults (17%) to have ever been told they have hypertension, with overall rates similar to whites (85). The 1999 to 2004 NHANES indicated the prevalence of hypertension in Asian Americans was 16.1% and that of white Americans was 28.5% (83). Among community-dwelling Asian Americans, mean age 74 years, hypertension rate, awareness rate, and treatment rate were 51.9%, 37.9%, and 24.9%, respectively. Hypertension control was worst among the oldest persons (86).

There may be some differences in responses and side effects to antihypertensive treatments in AsianAmericans versus whites. Japanese appear to have a higher frequency of salt sensitivity than whites (87), possibly influenced by more prevalent polymorphisms of the angiotensinogen, alpha-adducing, and aldosterone synthase genes. Beta blockers and CAs may give more robust BP response at lower dosages, and ACEI-associated cough may be more common than in whites. Chinese may have greater sensitivity to BP-lowering and bradycardic effects of propranolol than whites. Genetic variants in the $beta_1$-adrenergic receptor gene might contribute (88). Eplerenone is very effective at lowering SBP in Japanese patients with hypertension, including those with low-renin hypertension (89). A study in Hong Kong found that patients with hypertension had a larger decrease in BP in response to isradipine than seen in whites in the United States (90).

The Systolic Hypertension in China trial (19) assigned 2,394 patients ≥60 years of age (mean 66 years of age) with SBP 160 to 219 mm Hg and DBP <95 mm Hg to either nitrendipine (10 to 40 mg/d) or placebo, with addition of captopril (12.5 to 50.0 mg/d), and/or HCTZ (12.5 to 50 mg/d) as needed for BP control. Stepwise treatment, starting with nitrendipine, improved prognosis, particularly in patients with diabetes mellitus. At 2 years, the between-group differences were 9.1 mm Hg SBP (95% CI: 7.6 to 10.7 mm Hg) and 3.2 mm Hg DBP (95% CI: 2.4 to 4.0 mm Hg). Active treatment reduced total stroke 38% ($p=0.01$), all-cause mortality 39% ($p=0.003$), CV mortality 39% ($p= 0.03$), stroke mortality 58% ($p=0.02$), and all fatal and nonfatal CV events 37% ($p=0.004$). The adjusted relative risk for fatal and nonfatal CV events continued to decline as age increased. They concluded that treatment of 1,000 Chinese patients for 5 years could prevent 55 deaths, 39 strokes, or 59 major CV events. After 5 years of treatment, the number needed to treat to prevent 1 major CV event was 16.9 in the Systolic Hypertension in China trial (19), and 18.9 in the Systolic Hypertension in Europe trial, which involved white Europeans (20).

1.5.2. Pathophysiology of Hypertension in the Elderly

1.5.2.1. AORTA AND LARGE ARTERIES

The marked age-associated increase in hypertension prevalence is largely attributable to changes in arterial structure and function that accompany aging. Large vessels such as the aorta become less distensible (91), and although the precise mechanisms are incompletely understood, they primarily involve structural changes within the media, such as fatigue fracture of elastin, collagen deposition (92), and calcification (93), resulting in increases in vessel diameter and intima-medial thickness. Calcification may occur in the intima (in conjunction with atherosclerosis), as opposed to the media (arteriosclerosis); although there is an association between these processes, they are pathologically distinct

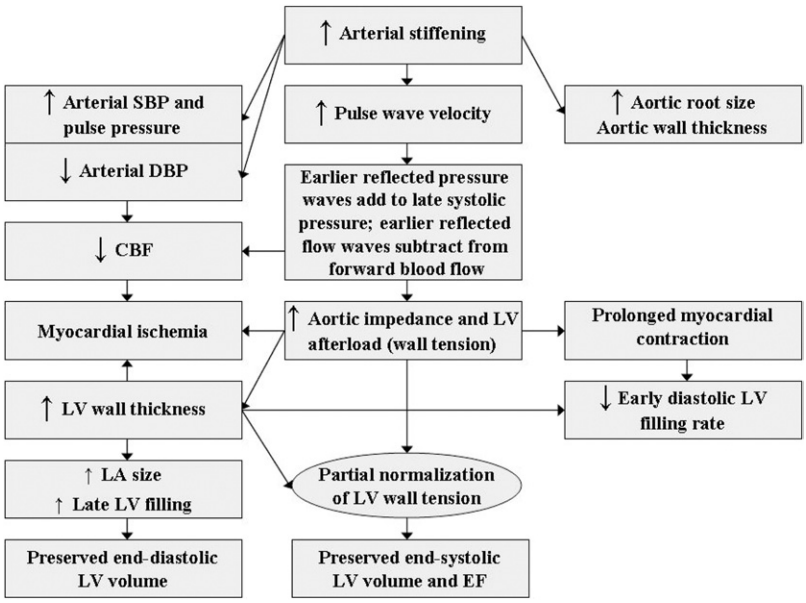

Figure 7. Conceptual Framework for Cardiovascular Adaptations to Arterial Stiffening That Occur With Aging

CBF indicates coronary blood flow; DBP, diastolic blood pressure; EF, ejection fraction; LA, left atrial; LV, left ventricular; SBP, systolic blood pressure; ↑, increased; and ↓, decreased. Modified from Fleg (146).

(94,95). Aortic calcification, in addition to hypertension and aging, is associated with diabetes mellitus, LVH (Section 1.6.3.2), and CKD (Section 1.6.6). (96–99). Arterial stiffness is not only a product of structural changes in the arterial wall but is also induced by circulating and endothelium-derived vasoactive mediators such as norepinephrine and endothelin 1 (100). In a group of elderly patients (68±6 years of age) compared with young patients (37±9 years of age), endothelial dysfunction and decreased nitric oxide availability was associated with increased arterial stiffness and development of ISH (101).

In addition to structural changes, a number of functional alterations impact the aging CV system. The increased stiffening increases pulse wave velocity, which has functional consequences (Figure 7). One is a change in arterial pulse contour caused by earlier return of reflected waves from the periphery to the proximal aorta. These returning waves summate with anterograde waves to produce late SBP augmentation quantified as the augmentation index (102,103). The late SBP peak creates an additional load against which the older heart must eject blood thereby increasing LV wall tension. Another functional alteration with aging is a decline in flow-mediated arterial dilation, primarily caused by a decrease in endothelium-derived nitric oxide (104). Reduction in flow-mediated vasodilator capacity further compromises the ability of aged arteries to buffer flow-related increases in SBP such as during vigorous exercise (105).

As a result of these and other less well-understood structural and functional arterial aging changes, there is a gradual rise in SBP across the adult age span (40,106), which persists even when overtly hypertensive individuals are excluded (106). The decline in DBP in older adults (Section 1.5.1.1) is related to blunted ability of the stiffer aorta and other capacitance arteries to expand in systole and contract during diastole, to augment DBP. Thus aging, even in normotensive individuals, is characterized by an increased pulse pressure, creating greater pulsatile stress on the arterial system (107–109). In contrast to younger patients with hypertension, in whom elevated BP is determined primarily by increased peripheral arterial resistance, the isolated or predominant elevation of SBP seen in older adults is mediated by increased conduit artery stiffness.

Because the heart is coupled to the vasculature, the age-associated increase in arterial stiffness has critically important effects on cardiac structure and function in the elderly (Figure 7). A consistent finding (110–112) is a modest age-associated increase in LV diastolic wall thickness, even among normotensive individuals. Consequent normalization of systolic wall stress by the thickened LV wall, in combination with prolonged contractile activation in the older heart, helps preserve resting LV systolic function (113). However, prolonged contractile activation results in less complete myocardial relaxation at the time of mitral valve opening, reducing the early diastolic LV filling rate (114,115). Conversely, late LV filling caused by atrial contraction increases with age (114–116). This augmented atrial contribution to LV filling, accomplished by a modest increase in left atrial size (111), preserves LV end-diastolic volume across the age span (110,117). Notably, these aging changes in cardiac structure and function, including increased LV wall thickness, preserved systolic LV function, and reduced early diastolic filling with increased late filling from a larger left atrium, mimic changes observed in mild hypertension among

younger patients. Such changes also contribute to age-related increase in AF prevalence (Section 1.6.4).

Cardiac output is lower and peripheral vascular resistance is higher in older patients with hypertension than in younger ones, but postural decreases in cardiac output, stroke volume, and LV filling pressure in the upright posture are less pronounced in elderly patients. Elderly patients may also have reduced venous capacitance, which leads to reduced blood volume in the lower body during upright posture (118).

Stiffening of the aorta also negatively influences myocardial perfusion (119). Because oxygen extraction from blood perfusing myocardium is very high, an increase in myocardial oxygen supply can only be met by an increase in coronary flow. Because most (>80%) myocardial blood flow occurs in diastole, central aortic DBP amplitude and duration of diastole are the principal noncoronary determinants of myocardial perfusion. Minor changes in diastolic duration may have as much effect on coronary flow as a severe coronary stenosis (120). As central arterial stiffness and wave reflection amplitude increase, SBP rises, pulse pressure widens, and myocardial systolic wall stress and oxygen demand increase while diastolic (e.g., coronary perfusion) pressure decreases (121). Such changes in ventricular/vascular coupling unbalance the supply/demand ratio and promote myocardial ischemia. With normal coronary vessels, however, flow is maintained over a wide range of perfusion pressures by autoregulation (e.g., as perfusion pressure declines, vasodilation maintains flow) (122). In the presence of LVH and other conditions associated with increased myocardial oxygen demand (e.g., increased SBP, tachycardia), coronary flow increases to meet demands. When the LV ejects into a stiff aorta, SBP, and hence myocardial oxygen demand, increases while DBP decreases, but coronary flow increases to maintain contractile function (123–125). However, increased aortic stiffness decreases coronary flow reserve, and during increases in myocardial contractility, endocardial flow becomes impaired, resulting in subendocardial ischemia (124). These undesirable alterations are enhanced with coronary stenosis or during reductions in DBP (123,125,126). In patients with stable angina, there is an inverse relationship between central aortic stiffness and coronary flow (127).

Although age-associated increases in arterial stiffness and SBP are often considered an immutable aging change in industrialized societies, there is accumulating evidence that these "normative" aging changes are markedly attenuated in populations not exposed to a lifestyle of high sodium, high-calorie diets, low physical activity levels, and increasing obesity rates. For example, populations with habitually low sodium intake demonstrate less arterial stiffening with age than those with high sodium consumption (128). Improvement in arterial distensibility has been observed after a low sodium diet (129). In addition, arterial distensibility (102) and flow-mediated vasodilator capacity are enhanced (130) in older endurance athletes compared with their sedentary peers of similar age. A less atherogenic lipid profile, thinner carotid artery wall, markedly lower BP, and better preserved early diastolic LV filling have been observed in lean middle-aged and older adults practicing voluntary caloric restriction of approximately 30% for several years compared with persons with more typical dietary patterns (131,132). It is therefore likely that the striking age-associated rise in SBP and incident hypertension in developed countries, and certain individuals in the United States, could be substantially reduced by adoption of a healthier lifestyle.

1.5.2.2. AUTONOMIC DYSREGULATION

Age-associated reduction in baroreflex function and increase in venous insufficiency contribute to a high prevalence of orthostatic hypotension in the elderly, which is a risk for CV events as well as falls and syncope (133–137). In contrast, orthostatic hypertension, where BP increases with postural change, is also prevalent among the elderly (138–142). This is part of the orthostatic BP dysregulation associated with aging. The orthostatic SBP increase can exceed 20 mm Hg. These patients are generally older, have a greater frequency of LVH, CAD, and silent cerebrovascular disease by magnetic resonance imaging (MRI) than elderly patients with hypertension with or without orthostatic hypotension. The orthostatic BP increase is blocked by alpha-adrenergic blockade, indicating that alpha-adrenergic activity may be a predominant pathophysiological mechanism (143).

Yet the neurohormonal plasma profile of older patients with hypertension is similar to that observed in normotensive older individuals. Plasma norepinephrine increases with age, though to a greater degree in normotensive patients (144,145). The age-associated rise in plasma norepinephrine is thought to be a compensatory mechanism for reduction in beta-adrenergic responsiveness with aging (145,146). In contrast, plasma renin activity declines with age and is lower in older than younger patients with hypertension (144,146); this has been attributed to the effect of age-associated nephrosclerosis on the juxtaglomerular apparatus. Thus, hypertension in the elderly is usually associated with low plasma renin levels. Plasma aldosterone levels also decline with age, resulting in greater risk for hyperkalemia, especially when coupled with an age-associated decline in GFR (146).

1.5.2.3. RENAL FUNCTION AND CATION BALANCE

Between 30 and 85 years of age, renal mass, particularly the cortex, declines 20% to 25% (147). The aging kidney is characterized by progressive development of glomerulosclerosis and interstitial fibrosis, which is associated with a decline in GFR and reduction of other renal homeostatic mechanisms (147,148). Age-associated declines in membrane sodium/potassium–adenosine triphosphatase may also contribute to geriatric hypertension because this results in increased intracellular sodium that may reduce sodium–calcium exchange and thereby increase intracellular calcium and vascular resistance. Reductions in cellular calcium efflux caused by reduced calcium–adenosine triphosphatase activity may similarly increase intracellular calcium and vascular

resistance (149). Latent volume expansion in the elderly also contributes to suppression of plasma renin activity and low aldosterone levels (148).

Renal hemodynamics are impaired in elderly patients with untreated ISH. Lower GFR and effective renal plasma flow characterize the older hypertension patient with a BMI >26.5 kg/m^2 (150). In the elderly, pulse pressure is inversely related to GFR, suggesting that increased vascular stiffness may accelerate age-related decline of GFR and renal plasma flow, which is a probable reflection of preglomerular resistance. In elderly patients with untreated ISH (151), increasing SBP was associated with the greatest risk of decline in renal function; whereas DBP, pulse, and mean arterial pressure had no significant association with decline in kidney function. Thus, elevated SBP and pulse pressure are strong risk factors for declining kidney function among older persons with ISH. Because renal arterial resistance is very low, high flow and low resistance to flow expose the small vessels to large pressure fluctuations that may increase up to 4-fold with aging (152). This exposure to high flow and pulsatile pressure causes microvascular damage, contributing to CKD.

1.5.2.3.1. SODIUM. Mechanisms underlying hypertensive responses to high salt intake and salt sensitivity are controversial. Earlier studies have shown the central role that kidneys play in BP control, as well as the relationship between alterations in BP and the ability of kidneys to modulate fluid volume through rapid increase in natriuresis or "pressure natriuresis" (153). Salt sensitivity, characterized by an increase in BP in response to positive salt balance, occurs in obese and elderly populations (154). Low natriuretic activity in salt-sensitive individuals may stimulate the RAAS; thus, together with vasoconstrictor effects of endothelin, inhibition of nitric oxide regulation of renal flow, natriuresis, and increase in SNS activity may explain the relationship between sodium sensitivity, obesity, and aging and hypertension (155). The capacity of the kidney to excrete a sodium load is impaired with age, contributing to BP elevation (148,156). Increased fractional reabsorption of sodium in the proximal tubule in the elderly may contribute to their tendency to exhibit an expanded sodium space resulting in salt-sensitive BP, and eventually fluid overload (148,156). There is a significant positive association between 24-hour sodium excretion as well as urinary sodium/potassium ratio and SBP (157). The relation between sodium excretion and SBP is stronger for older than younger adults, perhaps reflecting longer exposure with aging or diminished capacity to handle sodium.

A chronic high-sodium diet in elderly individuals with hypertension is associated with an increase in BP that is more marked for SBP than DBP (158). Moderate sodium restriction in elderly patients with hypertension significantly decreases SBP (159,160).

Age-related increases in salt sensitivity result, in part, from reduced ability to excrete a salt load due to reduction in both kidney function and generation of natriuretic substances such as prostaglandin E2 and dopamine (149). Failure of a sodium pump inhibitor, marinobufagenin, in older persons may be involved in the increased salt sensitivity with aging (161). An increase in BP with increasing salt load appears most pronounced in ISH and could be modulated by angiotensin genotype (162). Additionally, the cytoskeleton protein alpha-adducin polymorphism has been associated with excess risk among elderly patients with hypertension and CAD (163). This polymorphism is implicated in renal sodium handling and BP regulation (164), elastic properties of conduit arteries (165), and hypertension (166), as well as ischemic stroke in elderly women (167).

1.5.2.3.2. POTASSIUM. Potassium excretion is limited in the aged normal individual (147). The decrease in kidney mass that occurs with aging includes reduction in tubular mass, providing fewer transport pathways for potassium excretion (147). Plasma aldosterone levels also decline with age, consequently, elderly patients with hypertension are more prone to drug-induced hyperkalemia (147).

1.5.3. Secondary Causes of Hypertension Important in the Elderly

1.5.3.1. RENAL ARTERY STENOSIS

The demographics of patients with RAS are shifting toward older ages and more severe comorbid disease. The incidence of RAS increases with age, and RAS is a risk factor for poor kidney function, but there is very limited evidence-based information about effective screening or treatment strategies.

RAS occurs in ostial segments extending from adjacent aortic plaque (168). Hemodynamically significant RAS is defined as >70% diameter narrowing of the renal artery that results in significant reduction of renal blood flow (>70%), decreased intraglomerular pressure, activation of the RAAS to increase BP, and decreased kidney size. Increases in plasma AII levels result in vasoconstriction and increase BP. A key role for AII is to maintain perfusion pressure within the intraglomerula through constriction of efferent arterioles and increases in systemic BP (168). Increases in intrarenal AII also cause transient sodium retention, through AII effects on proximal tubules, which culminates in pressure natriuresis secondary to increases in BP over time and reestablishes sodium balance. When RAS is bilateral, the mechanism of hypertension is through volume expansion.

In autopsy studies, RAS prevalence ranges from 4% to 50% and increases with increasing age. A population-based study of subjects >65 years of age (mean 77.2 years of age) without recognized kidney disease, found RAS (>60% lumen narrowing by ultrasound) in 6.8% (169,170). Elderly patients with widespread PAD have RAS rates ranging from 35% to 50% (171). Evaluation of the entire renal arterial tree of both kidneys (172) showed a RAS prevalence of 87% for those ≥75 years of age with PAD. Aortic angiography identified RAS in 38% of patients with aortic aneurysm, 33% of those with PAD, and 39% of those with lower limb occlusive disease (173).

The functional significance of RAS in older adults is unclear. When elderly patients (mean age 73.2±8.1 years, median eGFR 51.2 mL/min/1.73 m^2) undergoing nonemergent coronary angiography were angiographically screened for RAS, and those with >50% RAS referred for nuclear renography, about half had evidence of reduced perfusion to 1 kidney (174,175). Of these, 13% were discordant with the angiographic lesion, and only 9% had positive captopril renograms. A positive captopril renogram was associated with severe (>70%) unilateral RAS. Thus, presence of known anatomic lesions does not correlate with captopril renogram positivity. It is unclear whether nuclear renography is a poor functional test in this population or the stenotic lesions are not functionally significant (174).

The importance of "incidental" RAS identified at nonemergent cardiac angiography has been examined (175). Patients with ≥50% stenosis underwent nuclear renography and were managed with or without stenting as recommended by their nephrologist and/or cardiologist. Of the 140 patients, 67 (48%) were stented, mostly for "preservation of kidney function" (70.1%) and/or resistant hypertension (53.7%). Patients who received stents were younger and had higher SBP and more severe RAS. After follow-up (median 943 days), there was no difference between groups in rate of GFR decline; presence of cerebrovascular disease was the only factor associated with a poor outcome. Although there was no evidence of either harm or benefit of stenting, the significance of these lesions and how they are best managed remains unclear (175). The ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial of 806 patients found substantial risks, but no evidence of meaningful clinical benefit from revascularization in patients with atherosclerotic RAS (669). Additional information should come from the ongoing CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial to determine whether stenting atherosclerotic RAS in patients reduces cardiovascular and/or renal events (www.coralclinicaltrial.org). Knowledge about natural history of atherosclerotic RAS in the elderly is limited because of variation of study cohorts and potential selection and/or follow-up (survivor) bias. Data on progression of RAS were provided from the Cardiovascular Health Study using follow-up renal ultrasound for an elderly cohort (mean age 82.8±3.4 years [277]). The overall estimated change in renovascular disease among all 235 kidneys studied was 14.0%, with progression to significant RAS in only 4.0%. Longitudinal increase in DBP and decrease in kidney size were significantly associated with progression to new (i.e., incident) significant renovascular disease but not prevalent disease. This was the first prospective, population-based estimate of incident renovascular disease and progression of prevalent disease among elderly Americans living in the community. In contrast to previous reports among selected patients with hypertension, these participants had a low frequency of hypertension and an annualized rate of only 1.3% per year for significant RAS and 0.5% per year for progression to significant RAS as no prevalent RAS progressed to occlusion over 8 years (176).

The risks of RAS are related both to declining kidney function and to accelerated CVD, with increased morbidity and mortality (177). Recent studies reemphasize the predictive value of clinical variables, including age, symptomatic vascular disease, elevated serum cholesterol, and presence of abdominal bruit, as the most powerful predictors of detecting lesions of at least 50% stenosis (178,179). Additional clues include hypertension requiring ≥3 agents that is controlled only to have significant increases in BP over the next 4 to 6 months requiring higher doses or additional medications. Another clue is "flash pulmonary edema," when BP spikes occur. Bilateral RAS may be signaled by a serum creatinine increase >50% within the first month after starting RAAS blockers. This serum creatinine increase can be associated with hyperkalemia. If testing fails to reveal RAS, intrarenal ischemia must be considered. Antihypertensive therapy, especially with RAAS blockers, may result in underperfusion of the kidneys and loss of function (177). This is particularly true when bilateral stenosis is present or in those with a solitary kidney.

1.5.3.2. OBSTRUCTIVE SLEEP APNEA

Approximately 30% of adults with hypertension have obstructive sleep apnea (180), and its prevalence more than doubles for each 10-year increase in age in both sexes (181). Obstructive sleep apnea is associated with a high prevalence of isolated diastolic hypertension (182), and there is a significant association between the incidence of combined systolic and diastolic hypertension and obstructive sleep apnea in patients <60 years of age but not in older patients (183,184). Thus, elderly obstructive sleep apnea patients may be less susceptible to consequent hypertension than younger patients. Alternatively, these findings may represent survivor bias for a life-threatening disorder. Interestingly, a population-based study, investigating stroke risk in people 70 to 100 years of age, found severe obstructive sleep apnea independently associated with increased stroke risk (adjusted HR: 2.52) over 6 years (185).

1.5.3.3. PRIMARY ALDOSTERONISM

Although most cases are in younger patients, rare cases with primary aldosteronism in elderly patients have been reported (186,187). Primary aldosteronism prevalence varies from 1% to 11%, increases according to hypertension severity (188), and cross-sectional and prospective studies report primary aldosteronism in >10% of patients with hypertension (189), with approximately 70% caused by adrenal adenomas (190). The adenoma is usually unilateral and comprised of glomerulosa cells in the adrenal cortex. Rarely, primary aldosteronism is caused by adrenal carcinoma or hyperplasia. Adrenal hyperplasia is more prevalent among older men, and both adrenals are overactive without adenoma. Diagnosis is suspected in patients with hypertension with persistent hypokalemia confirmed by elevated plasma aldosterone levels and low plasma renin activity (PRA) without

drugs that affect the RAAS (e.g., ACEIs, ARBs, beta blockers, even thiazide diuretics).

Laparoscopic adrenalectomy is recommended for tumors shown to be aldosterone-secreting by adrenal vein sampling. After adenoma removal, BP decreases in all patients, with complete hypertension remission in 50% to 70%. With adrenal hyperplasia, however, approximately 70% will remain hypertensive after bilateral adrenalectomy, so surgery is not recommended. Medical recommendations include a mineralocorticoid receptor antagonist (Section 4.2.2.1.1.2).

1.5.3.4. THYROID STATUS AND HYPERTENSION

With aging, changes in thyroid homeostasis interact with age-related CV factors to complicate the usual interactions between thyroid homeostasis and BP regulation. In a study of 688 consecutive patients (ages 15 to 70 years) referred for hypertension management, 3.8% were found to have unrecognized hyperthyroidism, whereas 3.6% had serum levels indicative of hypothyroidism (191).

1.5.3.4.1. HYPERTHYROIDISM AND BLOOD PRESSURE. Relatively few studies have investigated BP alterations in hyperthyroidism in older patients. Although the prevalence of hypertension itself increases with age, no studies indicate an age-related alteration in prevalence of hypertension with hyperthyroidism. Subclinical hyperthyroidism, defined as reduced thyroid stimulating hormone (TSH) in the presence of normal serum thyroid hormone levels, has a prevalence in patients older than 60 estimated between 1% and 5% (192). The link between risk of hypertension in patients with subclinical hyperthyroidism remains controversial. One study (4,087 German subjects, mean age 49 years, range 35 to 63) found no association between suppressed TSH levels and hypertension (193), but there was a trend toward higher pulse pressures in older ages, independent of TSH levels. Another study (2,033 patients ages 17 to 89 years) found a higher prevalence of hypertension in patients with subclinical hyperthyroidism than in euthyroid subjects (194). It is likely that inclusion of elderly patients in the latter study increased the power to detect an association.

1.5.3.4.2. HYPOTHYROIDISM AND BLOOD PRESSURE. The prevalence of subclinical hypothyroidism clearly increases with age: a study of 3,607 community-living Japanese (ages 17 to 89 years) found 14.6% of subjects age 70 to 80 years and 20.1% of subjects >80 years of age with elevated TSH and normal free T3 and free T4 (195). In this study, no association was found between subclinical hypothyroidism and BP.

In other studies, hypothyroidism was associated with diastolic hypertension (196), which may return to normal with thyroxine treatment (191). Hypertension incidence increased with age in both euthyroid and hypothyroid women with thyroiditis, but hypothyroid patients had significantly higher DBP in the fifth and sixth decades of life than did euthyroid controls. Patients who achieved therapeutic levels of L-thyroxine replacement (13 of 14) exhibited reductions in BP (157±5/99 ± 6 mm Hg versus 143±3/90±3 mm Hg) (197). A study of subjects not being treated for hypertension or thyroid disease (mean age 56±14 years, range 29 to 89 years) showed an association between SBP and DBP with increasing TSH within the normal range of TSH levels (198). Another study of community-dwelling subjects (4,140 of whom were ≥70 years of age) found a small but consistent rise in SBP (approximately 2 mm Hg) and DBP (approximately 1.5 mm Hg) with increases in TSH levels which remained within the reference range. Interestingly, men >70 years of age with increased TSH levels failed to show an increase in SBP, while still manifesting the increase in DBP.

Studies in primary care settings have yielded differing results. In a study of postmenopausal women ≥50 years of age, 45.4% had hypertension, and 10.9% had hypothyroidism. Although hypertension was correlated with diabetes mellitus and use of NSAIDs, no association was observed between hypertension and either untreated or treated hypothyroidism (199). A study of patients referred to an academic geriatrics clinic identified elevated TSH levels in 122 patients; compared with age-matched controls, the hypothyroid patients showed no significant difference in SBP or DBP, and linear regression analysis of TSH and DBP showed no association (200).

Although lower levels of T4/T3 or higher TSH levels seem to be associated with a rise in DBP, this effect may be blunted in the oldest old (201). Treatment of overt hypothyroidism can reduce DBP levels to normal. However, the literature describing asymptomatic, subclinical hypothyroidism does not show a consistent, clinically significant association with hypertension, especially in older patients.

1.5.3.5. LIFESTYLE, SUBSTANCES, AND MEDICATIONS THAT AFFECT BLOOD PRESSURE

1.5.3.5.1. TOBACCO. Tobacco use is the most common avoidable cause of death and illness in our society, and 4.5 million adults >65 years of age smoke cigarettes (202). There are complex interactions between hypertension and smoking that increase the risk of CVD, PAD, cerebrovascular disease, and kidney disease at all BP levels. Smoking increases vascular damage by increasing sympathetic tone, platelet aggregability and reactivity, free radical production, damage to endothelium, and surges in arterial pressure (203). Smoking increases SBP, especially in those >60 years of age (204), and smoking cessation reduces SBP (205). These hemodynamic changes are caused, in part, by changes in sympathetic nervous system activity. Elderly patients have a longer duration of exposure to these risk factors, as well as a diminished capacity to adjust to them, resulting in an increased incidence of CV events at any level of CVD risk factors compared with younger candidates (206).

CAD, the most common cause of death in individuals with hypertension, occurs at a rate 2 to 3 times higher in hypertensive versus normotensive individuals, and smoking increases this risk by an additional 2- to 3-fold. For every increment of 10 cigarettes smoked per day, CV mortality

increases by 18% in men and 31% in women (207). In a Chinese study involving patients ≥60 years of age (mean age 67 years) followed for 3 years (median), both smoking and SBP were associated with a higher risk of stroke (208). Smoking 10 to 20 or >20 cigarettes per day increased stroke risk about 2-fold (risk ratios [RR]: 1.78 and 2.23, respectively). When moderate (10 to 20 cigarettes per day) and heavy (>20 cigarettes per day) smokers were combined and compared with those that had never smoked, the risk ratio for fatal stroke was 2.66. Smoking >20 cigarettes per day also increased the risk of all-cause mortality, non-CV mortality, and cancer mortality (RR: 2.04, 4.66, and 4.74, respectively).

1.5.3.5.2. ALCOHOL. Several mechanisms have been suggested for the relationship between alcohol and elevated BP, but these are not known to differ among the elderly. Proposed mediators include: neurohormonal (sympathetic nervous system, endothelin, RAAS, insulin/insulin resistance, corticotrophin, or cortisol); inhibition of vascular relaxing substances (nitric oxide); calcium depletion; magnesium depletion; increased intracellular calcium or other electrolytes in vascular smooth muscle cells; and increased plasma acetaldehyde (209). Drinking, especially outside meals, is significantly associated with hypertension. There is no difference in risk between beer, wine, and liquor.

1.5.3.5.3. CAFFEINE/COFFEE. Because of the greater proportion of adipose tissue to lean body mass in older subjects, and because caffeine is distributed through lean body mass, a dose of caffeine expressed as milligrams per kilogram of total bodyweight may result in a higher plasma and tissue concentration in elderly compared with younger individuals (210). Metabolism of, and physiological responses to, caffeine are similar in elderly and younger individuals, but there is limited evidence that responses to caffeine in some systems may be greater in the elderly at doses in the 200- to 300-mg range (210). One small study found a 4.8 mm Hg ($p=0.03$) higher mean 24-hour SBP and a 3.0 mm Hg ($p=0.010$) mean 24-hour DBP in elderly coffee drinkers compared with abstainers. Findings suggest restriction of coffee intake may be beneficial in some older individuals with hypertension (211).

1.5.3.5.4. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS. NSAIDs, including cyclo-oxygenase-2 inhibitors, are frequently used to provide analgesia and anti-inflammatory benefits (212), but are not without adverse effects in elderly hypertensive patients (213). In fact, NSAIDs may negatively impact hypertension control in elderly individuals as NSAID users have higher SBP versus nonusers that are not explained by age, weight, and type or dose of antihypertensive regimen (214). In persons ≥65 years of age, NSAID use increased the risk for initiation of antihypertensive therapy. Compared with nonusers, low daily NSAID doses significantly increased the risk 1.55 times, medium daily doses increased risk 1.64 times, and high daily doses increased risk 1.82 times (213). A meta-analysis found that NSAIDs elevated mean supine BP by 5.0 mm Hg (95% CI: 1.2 to 8.7 mm Hg) (215). Not all NSAIDs affect BP in the same way. Rofecoxib significantly increases SBP compared with celecoxib (216). Piroxicam seems to produce more marked elevation in BP (6.2 mm Hg) compared with sulindac or aspirin (215).

There are several mechanisms by which NSAIDs may influence BP elevation. Use of NSAIDs or cyclo-oxygenase-2 inhibitors influences production of prostaglandins: This decreases inflammation but also results in renal side effects (217). In the setting of physiological stress, renal function becomes dependent upon prostaglandins, and NSAID use may be associated with acute deterioration of kidney function, including sodium retention, decreased GFR, edema, hyperkalemia, and/or papillary necrosis, as well as hypertension (218–221).

NSAIDs may also contribute to increased vascular resistance due to increased ET-1 synthesis and/or altered arachidonic metabolism (222–226). They also interfere with BP control in the elderly through partial reversal of antihypertensive effects of diuretics (218,227–230), beta-receptor antagonists, and ACEIs (231–233) and ARBs, but not CAs. NSAIDs antagonize antihypertensive effects of beta blockers more than vasodilators or diuretics (234). Effects of NSAIDs on antihypertensive drug effects vary with the specific NSAID and dose (235).

Caution must be taken when prescribing NSAIDs to elderly patients with hypertension. Close monitoring for BP changes, weight gain, fluid retention, and kidney dysfunction are required. Changing class of antihypertensive drug, keeping NSAID doses as low as possible, or up-titrating antihypertensive drugs may be necessary.

1.5.3.5.5. GLUCOCORTICOIDS. Glucocorticoid-induced hypertension occurs more often in the elderly (236) compared with younger patients. Oral glucocorticoids can increase SBP as much as 15 mm Hg within 24 hours (236). Mineralocorticoids and other compounds, such as licorice and carbenoxolone, that inhibit 11-beta hydroxysteroid dehydrogenase enzyme increase exchangeable sodium and blood volume, induce hyperkalemia and metabolic alkalosis, and suppress plasma renin and AII (236).

Potential complications of corticosteroid use among elders (mean age 67 years) with Crohn's disease (237) include an increased risk for developing BP ≥160/90 (RR: 1.46, 95% CI: 1.09 to 1.95). Analyses stratified by patient age showed a similar risk of complications for patients <65 years of age and patients >65 years of age.

1.5.3.5.6. SEX HORMONES. Estradiol treatment effects on SBP in healthy postmenopausal women (238) differ significantly by age, suggesting an increase in SBP in younger postmenopausal women, while having the opposite effect in older postmenopausal women. (Section 1.5.1.3.2)

In a cohort of men 60 to 80 years of age who did not have diabetes mellitus, did not smoke, were not obese, and were untreated for hypertension, testosterone levels decreased

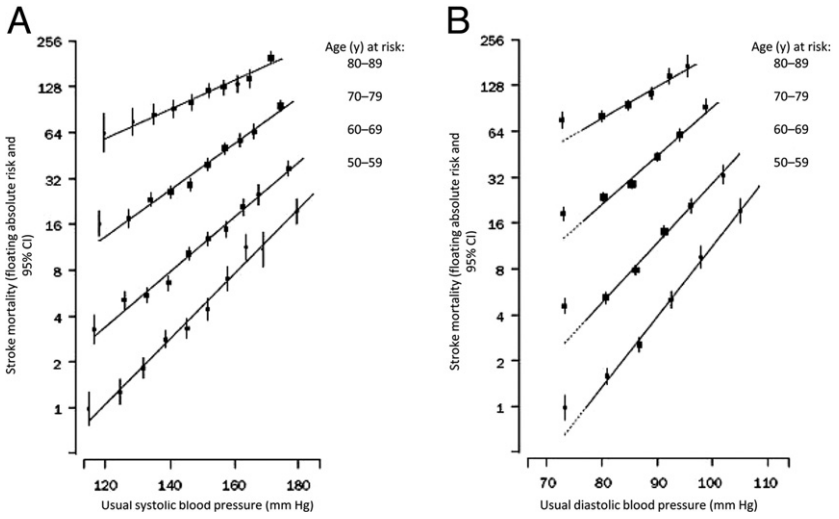

Figure 8. Absolute Risk of Stroke Mortality in Relation to Blood Pressure

(A) Systolic blood pressure. **(B)** Diastolic blood pressure. Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade. Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. For diastolic blood pressure, each age-specific regression line ignores the left-hand point (i.e., at slightly <75 mm Hg), for which the risk lies significantly above the fitted regression line (as indicated by the broken line below 75 mm Hg). The y-axis is logarithmic. CI indicates confidence interval. Reprinted from Lewington et al. (42).

with increasing age in normotensive individuals, those with elevated SBP and DBP hypertensive treatments, and those with elevated SBP only (ISH) (239). Testosterone levels were significantly lower in hypertensive treatments (−15%) and ISH men (−21%) than in normotensive men ($p<0.05$). Adjusting for BMI confirmed a significant difference in plasma testosterone levels between ISH and normotensive men, but not between hypertensive treatments and normotensive men. Multiple regression analysis confirmed a strong relationship between testosterone levels and SBP in all 3 groups, whereas a significant relationship between testosterone levels and DBP was found only in normotensive men. Although further studies are needed, findings suggest that in elderly men with ISH, reduced plasma testosterone levels may contribute to increased arterial stiffness typical of these subjects. However, available data do not suggest a significant effect of testosterone supplementation on BP (240). The relationship between serum testosterone levels, testosterone replacement, and arterial BP and other clinical outcomes among elderly men is under investigation in a large randomized by trial by the National Institutes of Health's National Institute on Aging.

1.5.3.5.7. CALCIUM AND VITAMINS D AND C. Investigators examined the effect of calcium plus vitamin D supplementation on BP and the incidence of hypertension in postmenopausal women (241); calcium plus vitamin D3 supplementation did not reduce either BP or risk of developing hypertension over 7 years of follow-up. Others have found high intakes of ascorbic acid in older adults may have modest effects on lowering high SBP (242). With increasing baseline BP, the magnitude of the decline in BP with vitamin C supplementation increased.

1.6. End-Organ Effects of Hypertension in the Elderly

1.6.1. Cerebrovascular Disease and Cognitive Impairment

Hypertension in the elderly is a risk factor for both ischemic stroke and cerebral hemorrhage. ISH is as an important component of BP-related stroke risk (243). The strength of the association between BP level and stroke decreases with increasing age (244). But because of the increased risk of stroke-related mortality and morbidity with increasing age (Figure 8) (42), and evidence of benefit from antihypertensive treatment, hypertension remains critically important relative to stroke risk in the elderly.

The benefit of BP reduction for stroke risk was demonstrated in SHEP (Systolic Hypertension in the Elderly Program) evaluating active treatment of ISH with chlorthalidone with or without atenolol or reserpine (with nifedipine as third-line therapy) compared with placebo (RR: 0.64; 95% CI: 0.50 to 0.82; $p=0.003$) on nonfatal and fatal stroke with active treatment for over 5 years (16). Patients in the active treatment arm had reduced incidence of both ischemic (37%) and hemorrhagic stroke (54%) (245). In the PROGRESS (Perindopril Protection Against Recurrent Stroke Study), over 4 years of perindopril plus indapamide significantly reduced ischemic stroke 24% (10% to 35%) and hemorrhagic stroke 50% (26% to 87%) compared with placebo (246). The Syst-Eur trial of patients (mean age was 70.2 years) with ISH confirmed stroke prevention with BP control using nitrendipine with possible addition of enalapril, HCTZ, or both. This study was stopped after 2 years instead of the planned 5 years because of a 42% reduction in total stroke in the treatment arm ($p<0.003$) (20). A large

number of these patients were then enrolled in a 4-year follow-up study with open-label treatment that assessed the benefits of early or delayed treatment on stroke risk. The placebo arm from the earlier study received active treatment as the delayed treatment arm. The initial treatment group continued active treatment as the early treatment arm. Early treatment remained more protective against stroke than delayed treatment, with a 28% reduction in stroke ($p=0.01$) (247). These findings support the suggestion that earlier antihypertensive treatment is associated with better outcome. The LIFE (Losartan Intervention For Endpoint Reduction) study showed a 25% reduced overall risk of stroke in the losartan arm versus atenolol, despite similar reduction in BP in both groups (14).

Patients in the aforementioned studies consisted predominantly of the "early elderly." In HYVET, patients in the "late elderly" group (≥80 years of age with elevated SBP) were randomized to indapamide, with addition of perindopril if needed, or placebo and followed over 2 years. Patients in the indapamide arm had a 30% risk reduction in fatal or nonfatal stroke ($p=0.06$). Although there have been consistent benefits in reduction of stroke with antihypertensive therapy in elderly patients, some reports have suggested that these benefits may be offset by an increase in death in treated patients (248,249). The HYVET, however, found benefits consistent with a 21% risk reduction (95% CI: 4% to 35%; $p=0.02$) of all-cause death in the indapamide arm (4).

In the majority of studies to date, benefits in stroke reduction appear related to BP reduction, as a 10 mm Hg reduction in SBP was associated with a 20% to 30% lower risk of stroke in individuals ≥70 years of age. Furthermore, there is greater benefit with greater reduction in BP (9,250). It is unclear whether the benefits are related solely to BP reduction or whether there are additional benefits conferred by class of BP medication. Although there is consistent benefit in stroke reduction when drugs were compared with placebo, there is little difference between drug classes (250). In addition, there are no differences in benefits conferred by different classes of antihypertensive agents comparing younger and older adults. A meta-analysis of 31 randomized trials showed no difference between younger (<65 years of age) and older patients (>65 years of age) in protection against major vascular events provided by major drug classes (251).

The prevalence of both hypertension and dementia increases with advancing age. Hypertension is considered a risk factor for vascular dementia and Alzheimer's disease. Poor BP control is associated with an even greater cognitive decline (252,253). Observational studies report a long-term increased SBP with paradoxical BP reduction in years immediately preceding dementia onset (254,255). In older patients with hypertension, nocturnal nondipping of BP occurred in 35% and was associated with mild cognitive impairment in about half of the cases compared to dippers (256), where this impairment occurred in only 13%.

Three randomized studies evaluated dementia as an outcome with treatment of hypertension in elderly patients. In Syst-Eur and PROGRESS, active treatment was associated with 50% and 19% reduction in dementia incidence, respectively (246,257). The SCOPE (Study on Cognition and Prognosis in the Elderly) assessed candesartan compared with placebo in 70 to 89 year olds with hypertension, and over 44 months (mean); there were no differences in cognitive outcome between the 2 groups (258). However, a SCOPE post hoc analysis reported less cognitive decline among those with only mild cognitive impairment (Mini-Mental State Exam score 24 to 28) at baseline in the candesartan-treated group ($p=0.04$) (259). The SHEP showed no significant difference in dementia incidence between active and placebo; however, the SBP target was 160 mm Hg, and results indicated that in those with mild cognitive impairment, better BP control may reduce cognitive decline. The HYVET-COG, a HYVET substudy, found a nonsignificant 14% decrease in dementia with active treatment versus placebo (260). Although no specific class of antihypertensive drugs have been definitively linked with cognitive decline in the elderly, inadequate BP reduction is associated with cognitive decline.

There is a theoretical risk that BP control may impair cerebral perfusion and negatively impact cognitive function. Although benefits in HYVET-COG were limited to CV outcomes, hypertension treatment was not associated with negative effects on cognition. Although there is clear evidence of the benefits of hypertension treatment in reduction of both ischemic and hemorrhagic stroke, the benefits in reducing cognitive impairment and dementia have only been demonstrated in the early elderly. In patients, mean age 64±10 years, in PROGRESS, a perindopril-based BP-lowering regimen among patients with previous ischemic stroke or transient ischemic attack significantly reduced stroke-related dementia (34%) and severe cognitive decline (19%) (261).

1.6.2. Coronary Artery Disease

CAD is highly prevalent among the elderly. Elderly patients with hypertension have a higher prevalence of MI than elderly patients without hypertension. According to 2004 AHA statistics, 83% of CAD deaths occurred in persons ≥65 years of age (34). The median age of occurrence of a first MI is approximately 65 years for men and 74 for women. In the very old, the male predominance in MI observed among younger elderly is attenuated as the rate in women approximates that of men. Among autopsies in persons with average age 80 years, the age-related increase in atherosclerosis was evident even after age 80 (262). Atherosclerosis was more severe in men than in women 60 to 70 years of age, but this gender difference diminished with increasing age and disappeared in the nineties. Centenarians have lower prevalence of CVD and are less likely to have the usual CV risk factors. This has been attributed

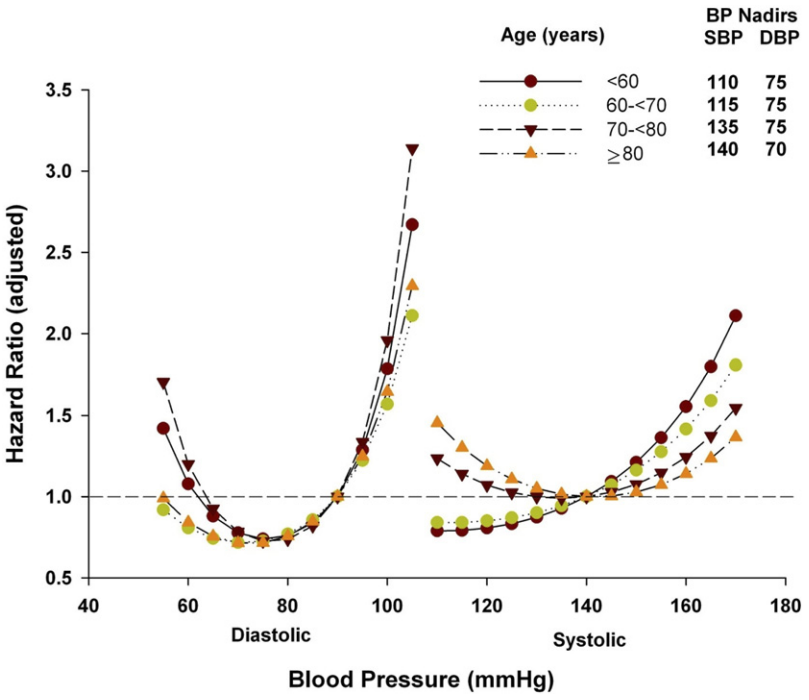

Figure 9. Risk of Adverse Outcomes by Age and Blood Pressure

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
Reprinted from Denardo et al. (13).

to both genetic and lifestyle factors as well as pharmacotherapy (263) and survivor bias.

Hypertension precedes MI and angina in a large majority of the elderly with these conditions. In the case of angina, hypertension may play a causal role (as a risk factor for underlying CAD and as a precipitating factor by increasing myocardial oxygen demand). For persons 60 to 69 years of age, a 20 mm Hg SBP increase doubles CAD risk, and the absolute risk difference for a given BP difference increases with age (42). However, the positive relationship between absolute risk increase and SBP increase becomes less steep with each decade increase in age (42), so the absolute benefit for a given SBP reduction would be expected to decrease among the very elderly. Benefits of BP lowering on incidence of angina and MI are generally similar with different antihypertensive drug classes, and overall, better BP control is associated with better outcomes; effects were not different among older individuals (251,264). A more detailed analysis of the influence of age from INVEST (265) compared patients <60 years of age (n=6,668), 60 to 69 years of age (n=7,602), 70 to 79 years of age (n=6,126), and ≥80 years of age (n=2,180), and showed that for 70 to 79 and ≥80 years of age, higher SBP (135 and 140 mm Hg, respectively) was associated with less risk for death, MI, or stroke than SBP <130 mm Hg (Figure 9). The oldest patients appeared to tolerate a higher SBP better and a lower SBP worse compared with younger patients, and patients <70 years of age had a relatively narrow range of optimal DBP.

Another study in >12,000 patients (mean age 66 years) suggested that hypertension recorded during admission for acute MI is not independently associated with higher mortality (266). Although crude hospital mortality in this study was higher in patients with hypertension (14.4% versus 12.4%, p<0.001), hypertension was not an independent predictor of mortality on multivariate analysis. Of note, patients with hypertension had a 17% lower risk of ventricular fibrillation but a 26% greater risk of AF in this analysis.

Hypertension is an established risk factor for sudden cardiac death among the elderly, and both ECG and echo evidence for LVH are also predictors (267). Treatment for hypertension reduces the risk of sudden cardiac death in the elderly (14).

The optimal BP level in hypertension patients with prior MI is not definitely established. In INVEST, a J-curve between BP and all-cause mortality, MI, or stroke, as well as total MI, was observed with a nadir of 119/84 mm Hg (268). Results were particularly strong for DBP and were the same for those above and below the mean age of 65 years. Interestingly, this relationship was not observed for total stroke (fatal and nonfatal) and was not present among patients who had undergone coronary revascularization. Because there were no differences in BP control (>70% with <140/<90 mm Hg) comparing the randomized CA versus beta-blocker treatment strategies, the entire cohort was analyzed. After 61,835 patient-years, 2,269 patients suffered an adverse outcome (as death, or stroke). The adjusted hazard ratios for these events were related to

on-treatment SBP and DBP as a "J-shaped" curve for each age group (Figure 9). But the optimal BP level for these very elderly post-MI individuals is unknown and may be >140/90 mm Hg.

Our understanding of the growing population of elderly patients with hypertension with prior coronary revascularization is limited. An analysis of patients with prior revascularization from INVEST found that they were older (mean age 67 years) and had higher frequencies of prior MI, HF, stroke/transient ischemic attack, PAD, and diabetes mellitus compared with those who were not revascularized (269). They also had worse outcomes: death, MI, or stroke, 14.2% versus 8.5% among those without prior revascularization. Interestingly, both SBP and DBP were more difficult to control among those with prior revascularization, suggesting more severe vascular disease, and again the J-curve between BP and mortality, MI, or stroke was observed even with propensity score adjustment.

1.6.3. Disorders of Left Ventricular Function

1.6.3.1. HEART FAILURE

Aging and hypertension are both strongly associated with development of HF (270). In 1 study, approximately 82% of incident HF occurred among individuals ≥65 years of age and 55% among those ≥75 years of age. Hypertension may lead to HF through different but frequently overlapping pathways. These include development of LVH, impaired LV filling, and increased wall thickness as discussed in the preceding text, especially when coexistent with diabetes mellitus (see Section 2.3), obesity, AF, and/or CAD with MI. After MI, neurohormonal activation results in LV remodeling, systolic dysfunction, and elevated filling pressures. In addition to hypertension and CAD, HF with depressed ejection fraction may occur in dilated cardiomyopathies of alcoholic and other etiologies.

Aging and hypertension result in decreased arterial compliance, initially with impaired systolic and diastolic CV reserve and impaired responsiveness to catecholamines. At a later stage, LV dilation occurs. Thus, development of HF among patients with hypertension occurs in the presence of decreased LV systolic function (e.g., LV ejection fraction <45% or 50%), as well as with preserved LV systolic function, where it is attributed to impairment of diastolic function (e.g., from LVH) as described previously. HF with preserved systolic function is important in the elderly and probably related to progressive fibrosis and myocardial stiffening associated with CAD, diabetes mellitus, and age per se plus LVH attributable to hypertension.

In a cross-sectional study of patients with hypertension ≥65 years of age with LV ejection fraction ≥45%, HF was observed in 22.6% and diastolic dysfunction in 25.8% (271). In ALLHAT, persons >55 years of age developing HF with preserved systolic function were more likely to be women and to have higher BMI, SBP, and high-density lipoprotein cholesterol than those who developed HF with impaired LV systolic function (272). In this study, HF symptoms and signs were similar among those with and without impaired LV systolic function. Ankle edema was present in a higher percentage of patients with preserved ejection fraction, whereas S3 gallop, hepatomegaly, and paroxysmal nocturnal dyspnea were present in a smaller percentage in this group compared with those with impaired LV systolic function (272). Patients with HF and preserved ejection fraction are in general less likely to have CAD and more likely to have diabetes mellitus than patients with HF and depressed ejection fraction (273).

Although hospital mortality of elderly patients (≥65 years of age) with first MI has declined in the last decade, HF developed in over three fourths of them over 5 years of follow-up (274). In addition, new-onset HF significantly increased the mortality of MI survivors (274). In a population study from Scotland, mean age at first discharge increased from 70.7 years in 1986 to 72.4 years in 2003 for men and from 76 to 77.3 years for women, whereas the age-standardized rate decreased after 1994 in both sexes (275). Also, case fatality rates decreased in parallel with an increase in HF therapies. In another study of patients with hypertension or at high CV risk, the rate of HF was 8.5 events per 1,000 and the rate for stroke was 9.1 events per 1,000 patients, because HF was more likely to occur in patients >65 years of age and those with diabetes mellitus (OR: 4.91; 95% CI: 4.40 to 5.43) (276).

1.6.3.2. LEFT VENTRICULAR HYPERTROPHY

As discussed previously, aging and hypertension-related aortic and conduit artery stiffening (Figure 7) increase LV loading and promote LVH. Among the older population included in the Cardiovascular Health Study, LV mass index was an independent predictor of incident HF not related to prevalent or incident MI (277). LVH is associated with adverse outcomes, including CAD, stroke, and especially HF (277). The association of LVH with CV events is especially strong in the elderly (278,279). After a 36-year follow-up in FHS, the relative risk related to LVH in those 65 to 94 years of age for CVD in general was 2.82 for men and 4.13 for women. The risk imposed by LVH is not totally explained by development of CAD, but regression of LVH with BP control is associated with reduced risk of CVD, especially development of HF (280). ECG LVH was present in 23.4% of 782 patients (mean age 66 years, BMI 28.2 kg/m^2, baseline BP 155.7±17.7/90.8±10.6 mm Hg), and predictors of LVH were age, male sex, and grade II hypertension (281).

Myocardial fibrosis and diastolic dysfunction precede LVH development in hypertension (282). In the LIFE study, regression of LVH was associated with a 36% reduction in the rate of new HF (283), and BP lowering improved diastolic function (284). In the same study, regression of LVH during therapy was related to reduced risk for sudden cardiac death after adjustment for BP reduction, CAD, antihypertensive treatment modality, and other cardiovascular risk factors (285).

1.6.4. Atrial Fibrillation

AF is primarily a disorder of older age, with a prevalence as high as 10% in octogenarians (286–288); hypertension is a major risk factor for AF. Aging of the population, more sensitive diagnostic modalities such as ambulatory electrocardiography, and increased prevalence of hypertension, obesity, and HF have contributed to a growing number of elderly persons diagnosed with AF. In those ≥65 years of age, the risk for new onset of AF is approximately 2% per year (289). In the Cardiovascular Health Study, among patients ≥65 years of age, incidence of a first episode of AF during average follow-up of 3.28 years, was 19.2 per thousand person-years (277). This was associated with age, male sex, and the presence of CVD. For men 75 to 84 years of age, the incidence of AF was 42.7 per thousand patient years. Use of diuretics, older age, higher SBP, glucose, left atrial size, height, and history of valvular or CAD increased the risk (290). In the elderly, the pathophysiology of AF is related to increased arterial stiffness and reduced LV compliance, findings often predicted by elevated pulse pressure, a surrogate for increased proximal aortic stiffness, higher BMI, and prevalent diabetes mellitus (291). Occurrence of AF is associated with increased mortality, cardiac sudden death, HF, embolic stroke, and reduced QoL.

Control of BP is associated with reduced occurrence or recurrence of AF in patients with hypertension. In SHEP (average age 72 years), AF increased CV mortality risk at 4.7 and 14.3 years (292). In the STOP-Hypertension-2 trial (Swedish Trial in Old Patients with Hypertension) (mean age 76 years, range was 72 to 84 years with ISH), AF was present in approximately 5% at baseline. During follow up, "newer" antihypertensive therapy (ACEI, CA) was significantly better than "conventional" (diuretic/beta blockers) in preventing stroke. However, there were more new cases of AF in patients randomized to newer agents, especially CAs (RR: 1.53; 95% CI: 1.05 to 2.21) (293). The conventional agents were associated with less new AF. Others, however, have reported lower AF recurrence rates with agents affecting the RAAS. A meta-analysis of 22 studies including 56,309 patients showed that ACEI and ARBs significantly reduced the risk of AF by 28%, with a 44% significant reduction in AF in patients with congestive HF (294). This benefit was limited to patients with reduced LV ejection fraction or LVH. In patients with diabetes mellitus, hypertension, and paroxysmal AF, combination valsartan and amlodipine was associated with a lower rate of recurrence than combination amlodipine and atenolol with similar BP reductions (295). However, in the GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation) trial, symptomatic AF patients (average age 68 years) with diabetes mellitus, CVD, or enlarged left atrium, valsartan did not prevent AF recurrence compared with placebo. This secondary prevention trial addresses a different population than the earlier prevention studies (296). Regardless of treatment, survival is worse for those ≥65 years of age as well as for patients with history of CAD, HF, or abnormal ejection fraction (297).

1.6.5. Abdominal Aortic Aneurysm and Peripheral Arterial Disease

1.6.5.1. ABDOMINAL AORTIC ANEURYSM

AAAs, defined as dilation of the aorta with a minimum anteroposterior diameter of ≥30 mm, occur with increasing frequency with increasing age. The prevalence of AAAs is 12.5% among men 75 to 84 years of age (298). Usually AAAs are due to aortic medial degeneration associated with abnormalities in tissue metalloproteinases, metalloproteinase inhibitors, elastase, and other proteinases. Risk factors for asymptomatic AAAs resemble those for obstructive PAD and include older age, male sex, smoking, hypertension, diabetes mellitus, family history of AAA, history of MI, and PAD.

1.6.5.2. THORACIC AORTIC DISEASE

Thoracic aortic aneurysm is increasingly prevalent in the elderly and, although the pathology is denegation of the aortic wall, hypertension is a major risk factor for development along with smoking, chronic obstructive pulmonary disease, and several genetic syndromes (299). Acute aortic dissection (acute aortic syndrome) is a catastrophic complication in the elderly patient. Chest and or back pain are the classic symptoms, although older patients can present without chest or back pain. The incidence varies from 5 to 30 cases per million persons per year, but hypertension and age are major risk factors (300). Surgery is indicated for type A dissections (those involving the ascending aorta). Control of BP, including beta blockade, is needed for both type A and B (not involving the ascending aorta) dissection. Endovascular techniques may be used in patients with high operative risk (301).

1.6.5.3. PERIPHERAL ARTERIAL DISEASE

PAD, or occlusive arterial disease distal to the aortic arch and including arterial narrowing usually caused by atherosclerotic disease as well as aneurysmal dilation with or without dissection, may lead to intermittent claudication, rest pain, critical limb ischemia, and amputation. PAD is usually not limited to the peripheral arterial system, but often associated with CAD as well as cerebrovascular disease. It is estimated that >10 million persons have PAD in the United States, the prevalence among persons ≥75 years of age is approximately 20% and is >50% in persons >85 years of age (302,303).

PAD is associated with a 4-fold increase in MI risk and a 3-fold increase in stroke or transient ischemic attack risk (304,305). Among persons with PAD, average age 66 years, the 5-year mortality risk approaches 25% and the 10-year risk approaches 48% (305). Mortality adjusted for age, sex, and CVD risk factors is 2 to 3 times higher than that of persons without PAD. Although about 1 of 3 persons with symptomatic PAD has typical claudication, >50% have leg

pain on exertion, and about 5% to 10% have critical limb ischemia (306).

Age and hypertension, along with risk factors for atherosclerosis, are also associated with PAD. In addition, hyperhomocysteinemia (307–309), high plasma lipoprotein (a), and AAAs are associated with increased risk of PAD (310,311). In persons screened for AAAs, increasing age, male sex, and PAD were independent predictors. The prevalence in persons >60 years of age was 4% for men and 1.2% in women (311). Patients with combined CAD and PAD in the REACH (REduction of Atherothrombosis for Continued Health) registry (German cohort, mean age 67.3 years) were older and more likely to be treated with antithrombotic agents, statins, and ACEIs (312).

Hypertension is associated with more rapid progression of PAD (313). Therefore, elderly patients with hypertension and exertional limitation involving lower extremity muscles, non- or poorly healing lower extremity wounds should be screened for PAD (298) by comprehensive examination of the pulses, measurement of the ankle-brachial index, and careful examination of the feet. A clinical prediction model (PREVALENT) giving 1 point per 5 years of age starting at age 55 years, 2 points for smoking history, 7 for current smoking, and 3 for hypertension identifies a subset of individuals in whom PAD is highly prevalent and who may benefit from ankle-brachial index measurement (314). The risk of PAD increased from 7% in patients with a score of 0 to 3 to 41% in those with a score of ≥13. A strategy to screen for cerebrovascular disease and CAD, as well as limb preservation and claudication relief, needs to be included in the evaluation.

1.6.6. Chronic Kidney Disease

Hypertension and aging both impact renal function. Elderly patients are more likely to have CKD, usually defined by a measured eGFR <60 mL/min/1.73 m^2. Multiple studies over the past 2 decades have shown that CKD is a powerful CVD risk factor. Unless GFR is eGFR, CKD is often unrecognized in elderly patients. Patients >75 years of age have more than a 2-fold risk of CKD versus younger patients, and a 60% risk for further loss of kidney function independent of baseline function (315). Prevalence of CKD ranges from 11% to 14% in the United States, and 75% of the CKD population is ≥65 years of age (316). However, it should be noted that the equation for eGFR has not been validated in this age group (317). Thus, although this group is more vulnerable to renal injury as a result of surgical or diagnostic procedures, the actual estimation of CKD in the population may be inaccurate.

In the elderly, CKD is an independent risk factor for congestive HF (318). CV outcomes increase in patients with hypertension as GFR decreases (319). Moreover, SBP is a strong independent predictor of decline in kidney function among older persons with ISH (151). Reduced kidney function in elderly people is a marker for adverse outcomes (318,320–322). Substantial proteinuria is associated with a rapid decline in kidney function. A progressive decline in kidney function is more prevalent in elderly patients with diabetic nephropathy (323). Hypertension and HF are associated with a more pronounced decline in renal function in older age (324).

1.6.7. Ophthalmologic Impairment

1.6.7.1. AGE-ASSOCIATED RETINAL CHANGES

The major cause of vision limitation in patients with hypertension of all ages is retinopathy, defined as arteriolar narrowing (generalized and focal), arteriovenous nicking, flame and blot hemorrhages, cotton-wool spots, and optic disk edema (325,326). Based on population studies, markers of hypertensive retinopathy (e.g., arteriovenous nicking, focal arteriolar narrowing) were found in 3% to 14% of those ≥40 years of age (327). Retinal lesion prevalence increased with higher SBP, but not necessarily with DBP. The specificity of retinal changes, however, decreases with age: Arteriolar narrowing is common in normotensive elders, and focal arteriolar sclerosis has been reported in 2% to 15% of normotensive patients ≥40 years of age (326,328).

In a study of people with nonmalignant hypertension of at least 10 years duration, 33% had no fundoscopic changes, 37% had slight arteriolar narrowing (especially in older patients), and 6% had hemorrhages or lipid deposits (329). In older patients, retinal vessel changes are less reliable indicators of the presence or duration of hypertension. For individual patients with hypertension, retinal findings may be reasonable indicators of organ damage. Significant retinal damage (e.g., hemorrhages, exudates, or disc edema) is more significantly associated with stroke and warrants prompt evaluation and treatment of elevated BP.

1.6.7.2. PATHOPHYSIOLOGY

A series of retinal changes in response to increased BP includes generalized arteriolar narrowing due to alterations in local auto-regulatory vasoconstrictive responses (some mediated by nitric oxide). Persistent BP elevation produces intimal thickening, medial hyperplasia, and hyaline degeneration (sclerosis). These later changes are associated with focal narrowing, disturbed arteriovenous nicking, and widening of the arteriolar light reflex ("copper wiring"). Aging itself is also associated with most of these "early" changes, which makes grading of retinal pathology in older patients less reliable versus younger patients. The final stages of retinal disease are caused by disruption of the retinal/blood barrier and lead to hemorrhages and lipid exudates. Optic disk swelling usually indicates severely elevated BP (330) and can be associated with visual impairment, and this is extremely serious in a patient of any age. Papillidema associated with hypertension is an extremely serious condition.

Hypertension is also associated with retinal artery occlusion and nonarteritic anterior ischemic optic neuropathy (331). Other than a general increase in prevalence with age, information is limited about age-related changes in these 2

conditions. Little to no correlation of hypertension with the prevalence of glaucoma is reported (332). Older population-based studies failed to show consistent association of hypertension and age-related macular degeneration (333), but more recent studies have linked neovascular age-related macular degeneration with moderate to severe hypertension, particularly among elderly patients (median age 72 years) receiving antihypertensive treatment (334,335). In addition to SBP, pulse pressure is also a strong predictor of neovascular age-related macular degeneration (334). These findings support the hypotheses that neovascular and non-neovascular age-related macular degeneration have a different pathogenesis, and that neovascular age-related macular degeneration and hypertensive vascular disease have a similar underlying systemic process. Age-related macular degeneration is the most common cause of blindness in the Western world.

1.6.8. Quality of Life Issues

Hypertension is often portrayed as a "silent killer" because patients with mild or moderate hypertension are often asymptomatic. When symptoms appear as a result of organ damage, therapeutic options are limited. Although the symptoms produced by these organ complications (MI, HF, stroke, or chronic renal failure) are associated with decreased QoL, possible alterations in QoL in patients with mild to moderate hypertension who do not have such complications remain controversial. Declines in QoL seen in aging populations complicate the analysis of a potential relationship between "asymptomatic" hypertension and QoL in older patients.

The INVEST study examined a measure of subjective well-being, which was validated in a substudy (336,337), in 22,576 CAD patients >50 years of age (mean age 66±10 years) with hypertension (338). Patients were asked a single question rating their overall feeling of well-being in the prior 4 weeks. Data were collected at baseline and at each follow-up visit before BP was measured. Measures of subjective well-being were highly negatively correlated with SBP measured during treatment. Age had minimal effect on measured subjective well-being, but the presence of angina was also a predictor.

QoL alterations were examined in hypertensive patients from hospital-based clinics in China using a standard QoL instrument focusing on self-report of symptoms across several domains (339); 2,331 were >65 years of age. Whereas hypertension prevalence was highest in those >65 years of age (65%), as expected, decreases in QoL with age were seen in almost all domains, with older hypertensive subjects reporting more stress, worries about health, and difficulties with coping. Although contributions to QoL changes by other comorbid conditions were not assessed, treatment of hypertension resulted in modest improvement in these scales. Two additional studies reported decreases in QoL scores with hypertension. In another study, although older hypertensive patients had more comorbid conditions, subanalysis showed small decreases in selected physical health QoL measures (340). Yet another study found increasing prevalence of hypertension and comorbid conditions in older patients but the presence of any illness was correlated with decreased QoL. Conversely, a study of community-based Finns found no correlation between QoL symptoms and hypertension (341), and 2 additional studies found QoL changes correlated with age, more so than with hypertension (342,343).

Some question the effects of labeling a patient with the diagnosis of hypertension, and the effects of that diagnostic label on QoL (340,342). Although small changes in QoL scales in younger patients with the solitary diagnosis of hypertension might be measurable, the additional effect of a diagnosis of hypertension on the lower QoL scores seen in older patients is likely minimal. In "younger old" patients in the seventh decade, control of systolic hypertension has been associated with modest improvement in QoL scores, a conclusion also supported by previously discussed findings from INVEST (344).

Finally, excessive reduction in BP is an important cause of symptoms that impair QoL and is linked to adverse outcomes among the elderly. In older persons, orthostatic hypotension (decrease of SBP >20 mm Hg after 3 minutes of standing) is common and is associated with increased CV risk. In the Honolulu Heart Program, orthostatic hypotension was present in 6.9% of 3,522 Japanese-American men 71 to 93 years of age and was a significant independent predictor of 4-year all-cause mortality (137). Postprandial hypotension, defined as a fall in SBP of ≥20 mm Hg 1 hour after a meal while sitting, was associated with advanced age, higher baseline BP, and use of vasodilating antihypertensive drugs (345), as well as with increased overall total mortality (RR: 1.79; 95% CI: 1.19 to 2.68) among elderly individuals (346).

2. Interactions Between Aging and Other CV Risk Conditions Associated With Hypertension

2.1. Family History of Premature Coronary Artery Disease

Premature coronary disease is defined as a first-degree male relative with established CAD at <55 years of age or a first-degree female relative with established CAD at age <65 years (347). Although several studies have shown that the presence of a family history of premature coronary events increases an individual's risk for CV events anywhere from 2- to 12-fold (348,349), data on this relationship in older adults are sparse. In the FHS, history of parental premature CAD in persons ≥60 years of age was associated with a doubling of CAD risk compared with a 3-fold risk increase in persons 30 to 59 years of age (350). Of note, this increased risk in older persons was seen only in women. Thus, the limited data available suggest an attenuated risk

associated with a family history of premature CAD in older adults.

2.2. Dyslipidemia

Concordance of dyslipidemia and hypertension is common; both increase with aging and hence are management targets (351–354). The specific approach to management of dyslipidemia in the elderly, however, has rarely been consolidated with that for hypertension (355). In the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial, 60% of subjects (mean age >75 years) had elevated low-density lipoprotein cholesterol. In HYVET, the mean total cholesterol was 205 mg/dL (4). Given the independent CVD risk associated with both conditions and proven benefits of treatment across age (356), it is reasonable to be aggressive with lipid lowering in elderly patients with hypertension.

Elderly persons with hypertension are often treated with statins because of concomitant hypercholesterolemia. The CAFÉ-LLA (Conduit Artery Function Evaluation-Lipid-Lowering Arm) substudy of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) included 891 patients, mean age 63 years, randomized to atorvastatin or placebo, with central aortic pressures and hemodynamic indices (radial artery applanation tonometry) repeated over 3.5 years (357). Statin therapy, sufficient to significantly decrease CV events in treated patients with hypertension in ASCOT, did not influence central aortic BP or hemodynamics (357).

However, in the UCSD (University of California, San Diego) Statin Study, simvastatin and pravastatin significantly lowered SBP by 2.2 mm Hg and DBP by 2.4 mm Hg in 973 adults without known CVD (358). A meta-analysis of 12 trials including 69,984 patients, mean ages 55 to 75 years, treated for at least 2 years, found that statin therapy significantly reduced CV morbidity and mortality to the same extent in patients with hypertension (by 22%) and nonhypertensive patients (by 24%) (359). Meta-regression also showed that the efficacy of statins on reducing adverse outcomes was not moderated by presence of hypertension at baseline (359).

2.3. Diabetes Mellitus

Cumulative life-time risk for diabetes mellitus in the United States increases exponentially between about 35 and 70 years of age but then plateaus (360). Overall risk of diabetes mellitus ranges from approximately 25% to 45% in men and approximately 30% to 55% in women and is frequently associated with hypertension. Risk of diabetes mellitus is higher in Hispanics and non-Hispanic blacks versus non-Hispanic whites. Elderly patients with hypertension and diabetes mellitus have a higher mortality risk than similarly aged controls without diabetes mellitus (361,362).

Hypertension is well recognized as an insulin-resistant state. Among patients with hypertension, SBP level, fasting glucose level, and thiazide diuretic and/or beta-blocker use are independent risk factors for incident diabetes mellitus (363–365). Although several of the previously referenced hypertension trials were comprised mostly of elderly patients, increasing age was associated with less incident diabetes mellitus (365,366).

Diabetes mellitus is a risk factor for development of HF among those >65 years of age (367). The ONTARGET/TRANSEND (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease) trials of 31,546 high-risk subjects (mean age 67 years, about 70% with hypertension, coronary, peripheral, or cerebrovascular disease or diabetes mellitus with organ damage) found fasting plasma glucose level was an independent predictor of HF hospitalization (598). These data provide theoretical support for potential direct beneficial effects of lowering blood glucose in reducing HF risk and suggest need for specific studies targeted at this issue (368).

Elderly patients with diabetes mellitus have a higher prevalence and incidence of microvascular and macrovascular complications (369), as well as excess mortality risk compared to age-matched controls without diabetes mellitus (370). Albuminuria is a predictor of higher mortality risk among those with diabetes mellitus (371). In older patients with type 2 diabetes mellitus, both high-office SBP and high-awake ambulatory SBP independently predict albuminuria (372).

2.4. Obesity and Weight Issues

Obesity and its clinical consequences have been described for centuries (373), and obesity has reached epidemic proportions worldwide (374). In the United States, the prevalence of obesity, defined as a BMI >30 kg/m^2 in adults, has doubled from 15% to 32.9% in the last 24 years, and 66.6% of adults are now overweight (BMI 25 to <30 kg/m^2) or obese (375). When ORs were calculated to determine the prevalence of hypertension in the period from 1999 to 2004 before and after adjustments for BMI, the increases in BMI adjusted for age accounted for nearly all the increases in hypertension in men and much of the increase in women (33). Thus, in overweight or obese elderly, including those with metabolic syndrome, obesity-related health risks add to the pathophysiologic changes of aging. These changes ultimately affect the structure of the heart, blood vessels, and the kidneys and may adversely affect CV and renal morbidity and mortality (376).

2.4.1. Structural and Hemodynamic Changes

Obesity may be associated with increases in LV wall thickness, volume, and mass independent of a patient's BP (377). Pressure overload leads to thickening of the LV wall without increasing cavity size. Myocyte thickening then leads to concentric hypertrophy, and volume overload causes cavity dilation, fiber elongation, and eccentric hypertrophy. Each of these factors leads to elevated stroke work (377).

Patients with obesity-related hypertension have high intravascular volume, high cardiac output, and a normal total peripheral resistance when compared with lean patients with hypertension. The high stroke volume in obese subjects is caused by increased intravascular volume in the context of normal heart rate (378). Obese patients with hypertension are also characterized by a circadian rhythm that does not show the expected BP drop during sleep time (nondipping), and they respond to mental stress with a higher increase in total peripheral resistance and smaller increase in heart rate, stroke volume, and cardiac output than lean patients with hypertension (379).

In the LIFE study, the association of Cornell ECG voltage criteria with greater body mass supported the known association of anatomic LVH with obesity (380) and showed obese, elderly patients with hypertension had similar cardiac changes previously described in younger patients: LVH with a high prevalence of geometric abnormalities, especially eccentric hypertrophy (381).

2.4.2. Vascular Changes

Several metabolic and hormonal changes that occur in obesity–hypertension are associated with impaired endothelial function and premature atherosclerosis (382). Metabolic syndrome and obesity have been linked to altered vasodilation. Other markers such as arterial stiffness or intima-media thickness increase in overweight or obese subjects and in aging individuals. However, the contribution of obesity to adverse outcome among elderly hypertensive patients is unclear.

An analysis from INVEST showed that in a well-treated cohort with hypertension with CAD, increased BMI in the elderly population was associated with decreased morbidity and mortality compared with normal BMI (383).

2.4.3. Role of the Sympathetic Nervous System

Increased sympathetic activity in obese subjects is associated with an increased incidence of hypertension, arrhythmias, and angina pectoris (384). This mechanism may also be important in overweight or obese elderly subjects, as studies have shown an age-dependent increase in plasma norepinephine levels in individuals >50 years old (385) and an increase in renal norepinephine spillover in obese individuals (386). Plasma epinephrine levels, by the contrary, tended to decrease with age (385). Furthermore, the reduction in baroreflex sensitivity in aging may further stimulate norepinephrine production (387).

This increased sympathetic nervous system activity in obese subjects may be explained by dysregulation of the hypothalamic-pituitary-adrenal axis and inappropriate response to cortisol (388). Another mechanism that may increase sympathetic nervous system activity in obese and elderly subjects might be sleep apnea and resultant hypoxia and hypercapnia (389). Sympathetic hyperactivity increases BP, heart rate, cardiac output, and renal tubular sodium reabsorption, changes that occur as a consequence of increased alpha- and beta-adrenergic receptor stimulation with a consequent increase in RAAS activity (390).

2.4.4. Role of the Renin-Angiotensin-Aldosterone System

In obesity, adipose tissue may contribute to RAAS activation (391), and a positive correlation has been found between plasma angiotensin levels, plasma renin activity, angiotensin-converting enzyme activity, and BMI (392). Adipose tissue produces all components of the RAAS locally and may play an autocrine, paracrine, and/or endocrine role in the development of obesity–hypertension. Angiotensin II may also contribute to the development of insulin resistance through its effect on glucose metabolism (393).

The RAAS may also contribute to systolic hypertension in the elderly (394). Activation of the RAAS system at the tissue levels contributes to the vascular inflammation and fibrosis triggered by AII; renin and aldosterone may also contribute. These changes eventually induce vascular atherosclerosis and organ failure (395).

Recent studies have explored the genes that encode components of the RAAS. Homozygosity for the D allele of the ACE gene was found to be associated with abdominal adiposity, obesity, and BP in individuals ≥54 years of age (396). In TONE (Trial of Nonpharmacological Intervention in the Elderly), obese subjects with DD genotype had a significant decrease in BP after weight loss, suggesting that this genotype may be linked with obesity–hypertension in the elderly through an increase in AII activity and aldosterone production (397). These findings reinforce the concept that obesity within genetically susceptible individuals will cause hypertension.

2.5. Microalbuminuria

Microalbuminuria, or urinary albumin excretion expressed as an albumin-to-creatinine ratio >30 and <300 mg albumin/g creatinine (398), on 2 separate first–morning-voided collections, is a marker for heightened CVD risk (399–402) and may be a marker for abnormal endothelial function. In people 60 to 74 years of age, an association between urinary albumin excretion rate and mortality has been described (403). In elderly subjects who did not have diabetes mellitus and were followed for 3.5 years, microalbuminuria was a strong predictor of CAD events (404,405). A separate prospective study of 70-year-old men in the community support the observation that microalbuminuria is a marker of subclinical CV damage that predisposes to future HF (406). Specific prevalence data for albuminuria focused on the elderly are lacking (407,408). Screening for albuminuria is recommended for all patients with hypertension and concomitant diabetes mellitus and for those with early CKD (23,409).

2.6. Hyperhomocysteinemia

Hyperhomocysteinemia is a risk factor for endothelial dysfunction (410). Investigators have reported a positive association between homocysteine levels and both SBP and DBP (411,412), including a possible causal relationship to ISH in older individuals (413). Mechanisms that could

explain the relationship between homocysteine and BP include homocysteine-induced arteriolar constriction, renal dysfunction and increased sodium reabsorption, and increased arterial stiffness (414). More research is needed to confirm these mechanisms and to establish whether lowering homocysteine with folic acid is an effective treatment for older patients with hypertension.

2.7. Gout

Gout incidence rates are 3 times higher for hypertensive patients than for normotensive patients ($p<0.01$) (415). Thiazide diuretics, often the preferred initial agent for treatment of hypertension, increase serum uric acid levels and may provoke gout (22,416,417). Both hypertension and diuretic use are independent risk factors for gout (418). Serum uric acid independently predicts CV events in older persons with ISH (419–421); therefore, monitoring serum uric acid change during diuretic treatment is reasonable. Diuretics should be used cautiously in elderly patients with hypertension with gout (22).

2.8. Osteoarthritis and Rheumatoid Arthritis

Arthritis is a common problem in the elderly with important implications for hypertension. Osteoarthritis affects approximately 10% of men and 20% of women >60 years of age, and they may need medications to reduce pain and inflammation (422). These medications usually include NSAIDs, which are implicated in BP elevation that is proportional to the level of BP prior to starting medication. Individuals with rheumatoid arthritis have excess risk for morbidity and mortality from CVD, which in part may be due to hypertension (423), with prevalence ranging between 52% and 73% (424–426). In rheumatoid arthritis, the chronic inflammatory burden may lead to increased arterial stiffness, a physical cause of elevated SBP (427). Drugs commonly administered to patients with rheumatoid arthritis, such as NSAIDS, cyclo-oxygenase-2 inhibitors (234), oral steroids (236), and some disease-modifying antirheumatic drugs (e.g., cyclosporine, leflunomide) may also raise BP levels (428,429). Additionally, insulin resistance and dyslipidemia are common comorbidities in rheumatoid arthritis and are also associated with hypertension (430,431). Hypertension may be poorly controlled in older patients with rheumatoid arthritis compared with younger patients, possibly because of suboptimal therapy or noncompliance (426). Thus, hypertension cannot be addressed in isolation in the elderly arthritis patient but must be considered in the context of other CV risk factors and arthritis treatment.

3. Clinical Assessment and Diagnosis

3.1. Measurement of Blood Pressure

BP should be accurately and reliably measured and documented. The diagnosis of hypertension should be based on at least 3 different BP measurements, taken on ≥2 separate office visits to account for the natural variability of BP and other factors that can affect BP. To confirm the validity and reliability of the measurement, at least 2 measurements should be obtained once the patient is comfortable and settled for at least 5 minutes. BP should be measured in the sitting position with the back supported, feet on the floor, arm supported in the horizontal position, and the BP cuff at heart level. The BP should also be measured with the patient standing for 1 to 3 minutes to evaluate for postural hypotension or hypertension. This is particularly important in the elderly because of stiff large arteries, age-related decreases in baroreflex buffering, and autonomic dysregulation (22) (see Section 1.5.2.2). In the initial evaluation, BP should be measured in each arm, and the arm with the highest BP used for future BP monitoring. It is important to use an appropriately sized cuff with a bladder that encircles at least 80% of the upper arm circumference. An auscultatory gap, as defined by the period during which sounds indicating true systolic pressure fade away and reappear at a lower pressure point, is more common in the elderly and is associated with vascular disease. This is a common source of underestimating SBP in the elderly. Elderly patients should also be evaluated for post-prandial hypotension (345,432), which is especially common in frail elderly patients on multiple antihypertensive and psychotropic drugs (433). Pseudohypertension, discussed in detail in the following section, is another source of inaccurate BP measurement in the elderly.

3.1.1. Pseudohypertension

Pseudohypertension refers to a falsely increased SBP that results from markedly sclerotic arteries that do not collapse during inflation of the BP cuff. Pseudohypertension occurs in 1.7% to 70% of the elderly (434–438), and this extreme range in prevalence is likely due to methodological differences between studies. Thus, the actual prevalence is unclear. In the elderly, the brachial arteries may become very thickened and stiff due to arterial medial sclerosis and calcification (434,439). The BP reading measured with indirect techniques may be falsely high if the artery is excessively thickened and therefore noncompressible (439). Although the Osler maneuver (i.e., the presence of a radial artery pulse that is still palpable after the cuff is inflated above the systolic pressure) has been recommended as a means to screen for pseudohypertension, investigators have reported it to have questionable accuracy and usefulness (438,439). Correct identification of pseudohypertension is necessary to avoid overtreating high BP and should be suspected in elders with refractory hypertension, no organ damage, and/or symptoms of overmedication (440). Confirmation of pseudohypertension requires direct intra-arterial measurement of BP (441).

3.1.2. White-Coat Effect and White-Coat Hypertension

When assessing BP in the elderly, both the white-coat effect and white-coat hypertension need to be considered, with

prevalence rates between 15% and 25% (442,443). Elderly individuals tend to exhibit more white-coat effect (i.e., transient BP elevations when in a medical environment) than younger individuals (444,445). *White-coat hypertension,* a term reserved for those not on antihypertensive medication but with persistently elevated office BP (>140/90 mm Hg) together with a normal daytime ambulatory BP (<135/85 mm Hg), is also more common in the elderly and is more frequent among centenarians (446,447). Ambulatory BP monitoring is recommended to confirm a diagnosis of white-coat hypertension in patients with office hypertension but no organ damage (22).

3.1.3. Ankle Blood Pressure

Ankle BPs measure subclinical atherosclerosis (448). In healthy individuals, ankle SBPs are slightly higher than the arm, but as occlusive disease develops in the lower extremities, the systolic pressure at the level of the ankle decreases (448,449). The finding of a reduced ankle-to-brachial artery BP ratio (ankle-brachial index) indicates atherosclerosis of the lower extremity arteries. The prevalence of an abnormal ankle-brachial index (<0.9) increases dramatically with age. In 1 study, this prevalence increased from 5.6% in persons 38 to 59 years of age, to 15.9% in persons 60 to 69 years of age, and to 33.8% in persons 70 to 82 years of age (303). The prevalence of PAD, defined by an ankle-brachial index <0.9, was 29% in 6,979 men and women (mean age 69 years) screened because they were ≥70 years of age or were 50 to 69 years of age with either a history of cigarette smoking or diabetes mellitus. Among these patients with PAD, classic claudication was present in only 11% (450). An ankle-brachial index of ≤0.9 is associated with a significantly increased risk of CVDs (in particular MI and stroke) that is independent of other risk factors (449,451). At 10-year follow-up of 565 men and women (mean age 66 years), PAD significantly increased the risk of all-cause mortality (RR: 3.1), CV mortality (RR: 5.9), and mortality from CAD (RR: 6.6) (305). High values of an ankle-brachial index also carry risk for mortality in adults, including the elderly (451,452). An ankle-brachial index >1.30 suggests a noncompressible, calcified vessel (306). Among older adults, low and high ankle-brachial index values carry elevated risk for CV events (coronary heart disease, stroke, and congestive HF) (451). Noncompressible leg arteries carry elevated risk for stroke and congestive HF specifically (451).

3.2. Ambulatory Blood Pressure Monitoring

Application and feasibility of automated ambulatory BP monitoring in the elderly are comparable to younger age groups (443). Major side effects are sleep disturbances and pain during cuff inflation (443). Main indications for ambulatory BP monitoring are for patients in whom the diagnosis of hypertension or response to therapy is unclear from office visits. Further indications include suspected syncope or hypotensive disorders, evaluation of vertigo, and dizziness (443). Ambulatory BP monitoring is also important for avoiding overtreatment in the elderly with white-coat hypertension and also to ensure diagnosis and treatment of those with masked hypertension (453).

Ambulatory BP is a better predictor of risk than clinic or office BP measurement in older patients with ISH (454,455). After adjustment for clinical BP measurements, ambulatory day time, night time, and 24-hour SBP all independently predict CV mortality (454). For each 10 mm Hg increase in daytime SBP and nighttime SBP, CV death increased 10% and 18% respectively, but the same increase in clinic SBP was not associated with a significant mortality increase (455). Elevated SBPs, while awake and/or asleep, by ambulatory BP monitoring, in subjects (mean age 70.4±9.9 years) over 50±23 months predicted increased risk of CVD more accurately than clinic BP in those with or without diabetes mellitus (456), and others have confirmed these findings (454). Heart rate dipping ratios, and an ambulatory arterial stiffness index using ambulatory BP monitoring may add significantly to prediction of mortality in the elderly population who do not have diabetes mellitus (457).

3.3. Out-of-Office Blood Pressure Recordings

The case for using out-of-office BP readings with the elderly, particularly home BP measurements, is strong due to the potential hazards of excessive BP reduction in older people (458). Home BP monitoring alone may be as useful as clinic measurements for treatment decisions in the elderly (459). Others have suggested that home BP measurement has a better prognostic accuracy than office BP measurement (460). The difference between the office and home BP (the white-coat effect) increases progressively with age, so that the office BP tends to overestimate the out-of-office BP more in older than younger people; variability of systolic home BP also increases with age (461). Monitors that measure BP with an upper arm cuff are the most reliable (458). Wrist monitors provide convenience and the potential advantage of use with elderly patients who are obese in whom putting on an upper arm cuff is difficult (458), but these monitors must be held at the level of the heart when a reading is taken. If this does not occur, there is an increased possibility of erroneous readings. Additionally, most wrist monitors that have been tested have failed validation studies; thus, they are not usually recommended for routine clinical use (458).

Home BP measurement has disadvantages that need to be considered before advising elderly patients to purchase and take their BPs at home. Individuals with cognitive and physical disabilities are potentially unable to operate a home BP monitor (462). Although automatic electronic devices are more convenient and easier to use, aneroid manometers with a stethoscope require manual dexterity and good hearing. Additionally, the automated devices available for self-measurement all use the oscillometric technique where small oscillations in cuff pressure are used to identify SBP,

mean, and DBP (463,464). Unfortunately, oscillometric techniques cannot measure BP in all patients, especially patients with arrhythmias, such as rapid ventricular rate in a patient with AF, an arrhythmia common among the elderly patients with hypertension (463).

Finally, there can be substantial observer error in reporting of self-measured BP values (465). Diaries completed by patients recording BP over time lack reliability. Erroneous reporting occurs more often in cases of uncontrolled BP and heart rate, conditions more common in the elderly (466). Memory-equipped devices and/or telemonitoring are strategies to overcome unreliable reporting, but both strategies add to nonreimbursable costs of providing care for elderly patients.

3.4. Clinical Evaluation

There is limited evidence to provide evidence-based recommendations on history, physical examination, or testing for evaluating elderly patients with hypertension (22,23,467,468). As such, the following recommendations are based on expert opinion, rather than evidence, but we believe they provide a reasonable clinical approach.

Typical evaluation includes a history and physical examination and ordering laboratory or other diagnostic or prognostic tests. A good history and examination are the starting point for the clinical evaluation (468). However, given the time constraints of a typical outpatient encounter, often in the range of 10 to 15 minutes, it is most important to hone in on aspects of the history and examination that relate to hypertension. These include historical issues such as duration and severity of high BP, causes or exacerbations of high BP, current and previous treatments (including adverse effects of medications or other interventions), target organ damage, other CVD risk factors and overall CVD risk, and comorbidities that can affect hypertension management and prognosis. Because high BP is a risk factor for CV, peripheral vascular, cerebrovascular, renal, and ophthalmologic disease, the history and examination should look for evidence of organ damage in these systems. The examination, in addition to the organ systems noted above, should include the patient's weight and waist circumference at the level just above the anterior superior iliac crests.

Many guidelines advocate "routine laboratory testing" in evaluation of patients with high BP. Despite such recommendations, there is little evidence to support routine laboratory testing, and clinicians should take a more deliberative and reasoned approach to ordering tests. Routine testing increases costs and may have adverse effects such as anxiety, pain/discomfort, additional testing, complications from such testing, and time and travel burden. In elderly patients, the burden of getting to appointments is often greater, and the elderly may suffer more discomfort during testing. Many elderly patients also will have had laboratory tests performed recently for other reasons, so obtaining copies of these tests is more cost-effective than repeating them. In general, tests should only be ordered if they will help the clinician make a diagnosis or establish a prognosis and if the result is likely to affect decisions regarding management.

The most important role for testing in an elderly patient with hypertension is to assess for organ damage and modifiable CVD risk factors, including tobacco smoking, hypercholesterolemia, diabetes mellitus, and excessive alcohol intake (469–472). Information on the following laboratory tests should be available:

1. Urinalysis to look for any evidence of renal damage, especially albuminuria/microalbuminuria
2. Blood chemistry to assess electrolytes and renal function, especially potassium and creatinine with eGFR
3. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides, preferably fasting levels
4. Fasting blood sugar and, if there are concerns about diabetes mellitus, hemoglobin A1c
5. ECG

At this time, we cannot routinely recommend other laboratory tests unless there are other indications for such testing. In selected elderly persons, 2-dimensional echocardiography should be considered because it is more sensitive and more specific in diagnosing LVH than is ECG and has a greater prognostic value. In addition, echocardiography may detect abnormalities in LV function that would warrant additional therapy (i.e., ACEIs, beta blockers). Future studies could lead to additional tests being recommended if evidence becomes available that such testing leads to improvements in important health outcomes.

A 12-lead ECG is recommended to assess for evidence of underlying cardiac abnormalities or previous cardiac damage and to provide a baseline for future comparison. However, many elderly patients will have had a recent ECG performed for a variety of reasons, so obtaining a copy of a recent ECG, especially if it is less than a year old, should at least be attempted before ordering another ECG. Additional testing to identify specific causes of high BP are generally not indicated unless the history, physical examination, or testing reveals an abnormality that arouses suspicion or if BP is not well controlled despite adequate dosing of multiple medications and good patient compliance.

4. Recommendations for Management

4.1. General Considerations

4.1.1. Blood Pressure Measurement and Goal

Reliable, calibrated BP measurement equipment is critical for hypertension management in any age group, and these considerations are detailed in Section 3.1. As discussed, the general recommended goal BP in persons with uncomplicated hypertension is <140/90 mm Hg. However, this tar-

get for elderly patients with hypertension is based on expert opinion rather than on data from RCTs, and it is unclear whether the target SBP should be the same in 65 to 79 year olds versus older patients.

4.1.2. Quality of Life and Cognitive Function

The decision to initiate antihypertensive therapy in the elderly should include consideration of potential impact on QoL. Although the high rate of comorbid conditions and need for polypharmacy influence compliance, these factors also have QoL and economical impacts for patients and their families. Because symptomatic well-being, cognitive function, activity, and sexual function have already been diminished by aging and disease, it is important to give particular attention to these QoL areas when making therapy decisions (473). In general, trials confirm long-term antihypertensive treatment does not necessarily negatively impact QoL; however, some specific drug classes may do so. The TONE study (474) found benefits were similar among hypertension patients treated with diuretics, beta blockers, CAs, and ACEIs, but beta blockers increased depressive symptoms. Conversely, other antihypertensive medications may be associated with beneficial effects on QoL. For example, among elderly patients with hypertension with mild cognitive impairment (Mini-Mental State Exam score 24 to 28), SCOPE (475) found no difference in cognitive outcomes between treatment groups overall, with evidence suggesting that candesartan may prevent cognitive decline. However, BP reduction was greater (2.5/1.9 mm Hg) with candesartan, also suggesting that better BP control may delay cognitive decline (259). A SCOPE substudy reported that "good" health-related QoL was preserved in the presence of substantial BP reduction with an advantage among candesartan-treated patients in 4 health-related QoL variables (476). Existing data do not associate hypertension treatment in the elderly with significant impairment in QoL, but there is potential for differences in adverse and beneficial effects among drug classes (336).

4.1.3. Nonpharmacological Treatment: Lifestyle Modification

Lifestyle modifications may be the only treatment necessary for preventing or even treating milder forms of hypertension in the elderly (Table 5) (469). Smoking cessation, reduction in excess body weight and mental stress, modification of sodium and alcohol intake, and increased physical activity may also reduce antihypertensive drug doses needed for BP control (470,471,477–479). Unfortunately, national surveys indicate that nutrition and exercise counseling are provided at only 35% and 26% of visits, respectively, in hypertension patients, and patients >75 years of age are least likely to receive such counseling (480).

Smokers >65 years of age benefit greatly from abstinence (202,481–484). Older smokers who quit reduce their risk of death from CAD, chronic obstructive pulmonary disease, lung cancer, and osteoporosis (485–487). Age does not appear to diminish the desire to quit (488) or the benefits of quitting (489,490). Treatments shown effective in the U.S. Department of Health and Human Service's Guideline have also been shown to be effective in older smokers (481). Medicare has expanded benefits for tobacco cessation counseling and prescription medications for treating tobacco dependence (491). However, smokers >65 years of age are less likely to be prescribed smoking cessation medications (492). Because of issues common in the elderly, such as difficulty with mobility and travel, use of interventions such as telephone counseling may be particularly applicable.

Weight reduction lowers BP in overweight individuals: A meta-analysis of 18 trials concluded that loss of 3% to 9% of body weight reduces systolic and DBP about 3 mm Hg each (493). In the TONE study, a diet that reduced weight by a 3.5 kg lowered BP by 4.0/1.1 mm Hg among 60- to 80-year-old patients with hypertension (494). Combining weight reduction with sodium restriction in TONE resulted in greater benefit.

Dietary sodium restriction is perhaps the best-studied lifestyle intervention for BP reduction. A meta-analysis of 56 RCTs found mean BP reduction of 3.7/0.9 mm Hg for

Table 5. Lifestyle Modifications to Manage Hypertension

Lifestyle Modifications to Manage Hypertension*		
Modification	**Recommendation**	**Approximate Systolic BP Reduction, Range**
Weight reduction	Maintain normal body weight (BMI, 18.5–24.9 kg/m^2)	5–20 mm Hg/10-kg weight loss (160,514,515)
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg (516,517)
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mEq/L (2.4 g sodium or 6 g sodium chloride	2–8 mm Hg (160,516–518)
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)	4–9 mm Hg (477,511,519)
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks/d (1 oz or 30 mL ethanol [e.g., 24-oz beer, 10-oz wine, or 3-oz 80-proof whiskey]) in most men and no more than 1 drink/d in women and lighter-weight persons	2–4 mm Hg (478)

*For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be higher for some individuals.
BMI indicates body mass index calculated as weight in kilograms divided by the square of height in meters; BP, blood pressure; and DASH, Dietary Approaches to Stop Hypertension.
Modified from Chobanian et al. (22).

a 100 mmol/day decrease in sodium excretion; BP declines were generally larger in older adults (495). Strongest evidence for sodium restriction in older persons comes from TONE (160). In patients 60 to 80 years of age with BP <145/85 mm Hg while taking 1 antihypertensive drug, mean BP reduction of 4.3/2.0 mm Hg occurred after 3 months of sodium restriction to 80 mmol/d coupled with medication withdrawal and 30 to 45 minutes brisk walking most days (494). However, BP and adverse outcome reductions did not achieve statistical significance in 70 to 80 year olds. Other studies have confirmed benefits of lifestyle modification in older subjects for BP control (496–501).

Increased potassium intake, either by fruits and vegetables or pills, reduces BP. In a meta-analysis of 33 RCTs, potassium supplements significantly lowered BP by 3.1/2.0 mm Hg, and this effect was enhanced in persons with higher sodium intake (502). Two trials in this meta-analysis confirmed significant BP reductions (4.3/1.7 mm Hg and 10.0/6.0 mm Hg, respectively [503,504]) among elderly patients with hypertension. The DASH diet showed a mean BP decrease of 11.4/5.5 mm Hg in patients with hypertension (mean age 47 years) with a diet enriched with fruits and vegetables and low in saturated and total fat (505). Similar BP reductions were seen in those >45 years of age (506). The DASH combination diet lowered SBP more in African Americans (6.8 mm Hg) than in whites (3.0 mm Hg) ($p<0.05$) and in persons with hypertension (11.4 mm Hg) than in persons without hypertension (3.4 mm Hg) ($p<0.05$). Potassium supplementation (>90 mmol [3,500 mg] daily) reduces BP in individuals with and without hypertension (502,507), and effects are greater in individuals with higher dietary sodium levels (469). In elderly patients with substantially impaired renal function, serum potassium should be monitored when supplementation is given.

Calcium and magnesium supplementation results in minimal to no change in BP. However, it is prudent to include adequate calcium in the diet (469,508). There is no evidence that vitamin, fiber, or herbal supplements influence BP in the elderly (469,470,509).

Consumption of >2 alcohol drinks per day is strongly associated with BP elevations in epidemiologic studies. Although several small RCTs demonstrate significant BP declines after reduced alcohol intake, few older patients are included. In the multicenter PATHS (Prevention and Treatment of Hypertension Study), reduction of alcohol intake by a mean of 1.3 drinks/d in patients (mean age 57 years) resulted in a nonsignificant BP decrease of 1.2/0.7 mm Hg; similar BP reductions of 1.9/0.6 mm Hg occurred in hypertension patients (510). Thus, evidence for meaningful BP reduction from lowering alcohol intake is limited in older adults.

Among the benefits of aerobic exercise training is BP reduction. A meta-analysis of 54 RCTs found aerobic exercise programs reduced BP about 3.8/2.6 mm Hg among 21 to 79 year olds, but an analysis by age was not provided (477). Exercise modality, frequency, intensity, and presence or absence of hypertension did not significantly affect the magnitude of BP decline. Trials in older patients with hypertension show BP reductions from aerobic training. In 33 such individuals 60 to 69 years of age, 9 months of training 3 times weekly at either 53% or 73% peak aerobic capacity elicited BP reductions averaging 7/3 mm Hg and 6/9 mm Hg, respectively (511). In 70 to 79 year old patients with hypertension, BP reductions of 8/9 mm Hg occurred after 6 months training at 75% to 85% peak aerobic capacity (512). In sedentary men (mean age 59 years) with prehypertension, 9 months of aerobic training 3 days per week elicited a BP reduction of 9/7 mm Hg; men who combined exercise and a weight loss diet had a 11/9 mm Hg decline (513). Thus, aerobic exercise alone or combined with a weight reduction diet reduces BP in older adults with hypertension. The finding that exercise at moderate intensities elicits BP reductions similar to those of more intensive regimens is especially meaningful for the elderly.

4.1.4. Management of Associated Risk Factors and Team Approach

Most guidelines for treatment of hypertension or dyslipidemia emphasize risk estimates obtained from an overall or global instrument such as the Framingham Risk Score for predicting MI, stroke, or CVD in general (520) or its modifications such as the Reynolds score (521) or scores developed in other countries, including Q-risk derived from practices in the United Kingdom (522). These algorithms emphasize age and classify all persons >70 or 75 years of age as high risk (i.e., ≥10% risk of CAD in next 10 years), thus deserving therapy. Therefore, older patients with hypertension may be classified at high or very high risk (e.g., those with diabetes mellitus). Patient preferences and values are also important in deciding on the advisability and mode of therapy, especially in older individuals where QoL sometimes becomes more important than duration.

Several trials including some subjects with hypertension (351,353,355,523–525) have evaluated multiple risk interventions. Subgroup post hoc analyses have not suggested that elderly subgroups differed from younger subgroups in response to risk factor management. This management is fostered by behavioral interventions that focus on re-enforcement techniques to enhance engagement of elderly individuals in their own care employing a team. The team should ideally be composed of clinical pharmacists, nurses, physician assistants, clinical psychologists, and others (as necessary). Communication with and compliance by elderly patients might be facilitated by interactions at group visits with caregivers or counselors. Technology enhancements to achieve these goals span the spectrum from simple printed prompts and reminders through complex systems of telemedicine and text messaging.

4.2. Pharmacological Management

4.2.1. Considerations for Drug Therapy

4.2.1.1. EVIDENCE BEFORE HYVET

In the mid-1980s, the EWPHE (European Working Party on High Blood Pressure in the Elderly) (526) demonstrated

that, among patients ≥60 years of age with BPs ≥160 mm Hg systolic and/or 90 mm Hg diastolic, drug treatment reduced CV events. Other studies extended beneficial effects of antihypertensive drugs to patients >70 years of age (11,15,18,527) and elderly patients with ISH (i.e., SBP ≥160 mm Hg but DBP <95 or 90 mm Hg) (20,528,529). Meta-analyses (45,249) are the basis on which to recommend drug treatment for elderly patients with hypertension (22,23,530,531). A greater degree of caution is required in older patients because of alterations in mechanisms responsible for drug disposal as well as changes that occur in homeostatic CV control (532) as well as QoL factors discussed in the preceding text.

Most patients recruited in antihypertensive trials in the elderly were <80 years old, thus limiting information about octogenarians. Pooling the limited number (n=1,670) of patients ≥80 years of age from trials mainly composed of younger patients (249) provided data difficult to interpret. Compared with controls, treated patients showed a reduction in the incidence of both stroke and CV morbidity but a trend toward increased all-cause mortality. So the overall benefits of treating a cohort >80 years old seemed questionable. Thus, despite epidemiologic evidence that hypertension remains a risk factor in 80 to 89 year olds (533,534), guidelines avoided firm recommendations on drug treatment in octogenarians with statements like "in subjects aged 80 years or over, evidence for benefits of antihypertensive treatment is as yet inconclusive." However, they added that "there is no reason for interrupting successful and well-tolerated therapy when a patient reaches 80 years" (23, p. 1497).

4.2.1.2. EVIDENCE AFTER HYVET

Results of HYVET (4) modify previous recommendations for patients >80 years of age. In HYVET, 3,845 patients ≥80 years of age with SBP ≥160 mm Hg were randomly assigned to placebo or drug therapy. The latter included a non-thiazide sulphonamide diuretic (indapamide) supplemented by an ACEI (perindopril) when needed for target SBP of 150 mm Hg. After 2 years, with about one fourth of the patients using monotherapy and three fourths combination therapy, the trial was stopped because drug treatment, although decreasing BP compared with the placebo group (144/78 mm Hg versus 161/84 mm Hg), reduced adverse outcomes. This consisted of reductions in the incidence of stroke (−30%), congestive HF (−64%), and CV morbid and fatal events (−23%). Most impressively, there was a significant reduction (−21%) in the incidence of all-cause death. Of importance, drug treatment was well tolerated. The reduction in BP in the standing position was similar to that in the sitting position. Furthermore, serum electrolyte and biochemical values were similar in drug- and placebo-treated groups. In fact, fewer serious adverse events were reported in the drug-treated than in placebo-treated patients (4).

The HYVET results provide clear evidence that BP lowering by drugs is associated with definite CV benefits in patients ≥80 years of age. They not only refute concern that this may lead to an increase, rather than a decrease in mortality, but also show that in this stratum of the population, there is a prolongation of life. This finding is highly relevant for public health because subjects ≥80 years of age represent the fastest growing fraction of the population; the prediction is that by 2050, they will account for more than one fifth of all elderly individuals (535).

However, HYVET has some limitations that should be taken into account when considering antihypertensive treatment in very elderly patients. Patients with stage 1 hypertension were not included. Patients on whom HYVET results are based are not representative of the general very elderly population. First, to limit dropouts, recruitment focused on patients in relatively good physical and mental condition and with a low rate of previous CVD. This is at variance from the high rate of frail and medically compromised patients typical in this very old age range. Second, because identifying appropriate subjects was difficult, recruitment required about 6 years and was only possible through participation of Eastern European countries and China, which together accounted for 98% of the patients. Furthermore, premature interruption of the trial (because of mortality benefit) made average follow-up relatively short (median 1.8 years). It remains unknown whether benefits of antihypertensive treatment persist or diminish after 2 or 3 years. Also, the mean age was 83 years, and only a small fraction was >85 years of age, which leaves open the question whether the benefit extends to ages much older than those investigated in previous trials. Compared with placebo, drug treatment was not accompanied by significant improvement in the incidence of dementia or cognitive dysfunction (260). Finally, the optimal BP goal for reducing CV events and mortality was not investigated.

4.2.2. Initiation of Drug Therapy

The initial antihypertensive drug should be started at the lowest dose and gradually increased depending on the BP response to the maximum tolerated dose. If the antihypertensive response to the initial drug is inadequate after reaching full dose (not necessarily maximum recommended dose), a second drug from another class should be added, provided the initial drug is tolerated. If the person is having no therapeutic response or significant adverse effects, a drug from another class should be substituted. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching the full dose of 2 classes of drugs, a third drug from another class should be added. When the BP is >20/10 mm Hg above goal, drug therapy should generally be initiated with 2 antihypertensive drugs, 1 of which should be a thiazide diuretic; however, in the elderly, treatment must be individualized (22).

Before adding new antihypertensive drugs, possible reasons for inadequate BP response should be examined. These include noncompliance, volume overload, drug interactions (e.g., use of

NSAIDs, caffeine, antidepressants, nasal decongestants containing sympathomimetics), and associated conditions such as obesity, smoking, excessive intake of alcohol, insulin resistance, and pseudoresistance (22). Pseudoresistance (536) is an inadequate response to antihypertensive therapy because the BPs measured in the physician's office are falsely high compared with those measured at home or by 24-hour ambulatory BP monitoring. Causes of secondary hypertension should be identified and treated (22,537).

Polypharmacy and potential drug interactions are a greater concern in the elderly than in younger patients. The average elderly patient is taking >6 prescription drugs. Medications likely to be used in the elderly that increase BP include NSAIDS, corticosteroids, erythropoietin, amphetamines, ergotamine, and anabolic steroids. Agents that increase the antihypertensive effect of beta blockers and CAs include cimetidine, antifungal azolides, and grapefruit juice (538,539). A detailed list of drug interactions is included (Table 6).

Table 6. Drug Interactions

Drug Class/Drug	Interacting Drug	Mechanism	Consequence	Prophylaxis
Beta blockers				
All beta blockers (hemodynamic interactions)	Calcium antagonists, especially nifedipine	Added hypotension	Risk of myocardial ischemia	BP control, adjust doses
	Verapamil or diltiazem; flecainide; most anesthetics	Added negative inotropic effect	Risk of myocardial failure; hypotension	Check for CHF; adjust doses; flecainide levels
(electrophysiologic interactions)	Verapamil; diltiazem	Added inhibition of SA, AV nodes; added negative inotropic effect	Bradycardia, systole, complete HB, hypotension	Exclude "sick-sinus" syndrome; AV nodal disease, LV failure
	Amiodarone	Added nodal inhibition	Bradycardia, HB	Exclude nodal disease
All lipid-soluble beta blockers (hepatic interactions): carvedilol, labetalol, metoprolol, propranolol, probably timolol	Inhibitors of hepatic CYP2D6; cimetidine, ritonavir, quinidine	Decreased hepatic breakdown of the lipid-soluble beta blocker	Excess beta-blocking effects	Avoid interaction or reduce beta-blocker dose
Calcium antagonists				
Verapamil (V)	Beta blockers	SA and AV nodal inhibition; myocardial failure	Added nodal and negative inotropic effects	Care during cotherapy; check ECG, BP, heart size
	Digitalis poisoning	Added SA and AV nodal inhibition	Asystole; complete HB after IV V	Avoid IV V
	Digoxin (D)	Decreased D clearance; inhibition of P-glycoprotein	Risk of D toxicity	Halve D dose; blood D level
	Disopyramide	Pharmacodynamic	Hypotension, constipation	Check BP, LV, and gut
	Flecainide (F)	Added negative inotropic	Hypotension	Check LV; F levels
	Prazosin and other alpha blockers	Hepatic interaction	Excess hypotension	Check BP during cotherapy
	Quinidine (Q)	Added alpha receptor inhibition; V decreased Q clearance	Hypotension; increased Q levels	Check Q levels and BP
	Beta blockers	Added SA nodal inhibition; negative inotropism	Bradycardia	Check ECG and LV function
Diltiazem	Digoxin (D)	Some fall in D clearance	Only in renal failure	Check D levels
	Flecainide (F)	Added negative inotropic effects	Hypotension	Check LV; F levels
Nicardipine (see also nifedipine)	Digoxin (D)	Decreased D clearance	Blood D doubles	Decrease; check D levels
	Beta blockers; propranolol (P)	Added negative inotropism N and P have opposite effects on blood liver flow	Excess hypotension N decreased P levels; P increases N levels	Check BP, use low initial dose; readjust P and N doses if needed
	Digoxin (D)	Minor/modest changes in D	Increased D levels	Check D levels
Nifedipine (N)	Prazosin (PZ), other alpha blockers	PZ blocks alpha-reflex to N	Postural hypotension	Low initial dose of N or PZ or other alpha blockers
	Quinidine (Q)	N improves poor LV function; Q clearance faster	Decreased Q effect	Check Q levels

Table 6. Continued

Drug Class/Drug	Interacting Drug	Mechanism	Consequence	Prophylaxis
Diuretics				
Loop and thiazide	NSAIDs	Pharmacodynamic	Decreased anti-hypertensive effect	Adjust diuretic dose or add another agent
	Probenecid	Decreased intratubular secretion of diuretic	Decreased diuretic effect	Increased diuretic dose
	ACEI, ARBs	Excess diuretics, high renins	Excess hypotension; prerenal uremia	Lower diuretic dose; initial low-dose ACEI or ARB
	Captopril	Possible interference with tubular secretion	Loss of diuretic efficacy of furosemide	Change to another ACEI
Loop	Aspirin	Inhibition of acute vasodilator response	Presumed less efficacy in HF	Delay aspirin when initiating acute therapy for HF
Potassium sparing	ACEI, ARBs	Both retain potassium	Hyperkalemia	Monitor potassium, reduce ACEI dose
Aldosterone receptor antagonist				
Eplerenone	ACEI	Retains potassium	Hyperkalemia	Monitor potassium, reduce ACEI dose
Direct renin inhibitors				
Aliskiren	ACEI, ARB, potassium-sparing diuretics	Retain potassium	Hyperkalemia	Monitor potassium, reduce or eliminate ACEI, ARB, or potassium-sparing diuretic
Angiotensin-converting enzyme inhibitor				
ACEI class effect	Excess diuretics; rare in hypertension	High renin levels in overdiuresed patients; volume depletion	First-dose hypotension; risk of renal failure	Reduce diuretic dose; correct volume depletion
	Potassium-sparing diuretics; spironolactone	Added potassium retention	Hyperkalemia	Avoid combination or use with care
	NSAIDs	Less vasodilation	Less BP and ↓ less antifailure effect	Avoid if possible
	Aspirin	Less vasodilation	Less HF effects	Low-dose aspirin
	Loop diuretics	Possible interference with tubular secretion	Lessened diuretic effect of furosemide	Consider alternate ACEI
Captopril (C)	Immunosuppressive drugs, procainamide–hydralazine	Added immune effects	Increased risk of neutropenia	Avoid combination; check neutrophils
	Probenecid (P)	P inhibits tubular secretion of C	Small rise in C levels	Decrease C dose
Angiotensin receptor blockers				
ARB class effect	Excess diuretics; rare in hypertension	High renin levels in overdiuresed patients; volume depletion	First-dose hypotension; risk of renal failure	Reduce diuretic dose; correct volume depletion
Vasodilators	Beta blockers (hepatically metabolized)	Hepatic shunting	Beta-blocker metabolism ↓; blood levels ↑	Propranolol; metoprolol dose ↓
Hydralizine	Nitrates (N)	Renal blood flow ↑; added vasodilation; free radicals scavenged	Less N tolerance (benefit); risk of excess hypotension	Start with low dose of an alpha blocker or dihydropyridine; calcium blocker
	Verapamil	Hepatic metabolism	Synergistic antihypertensive effect	Adjust doses
Cilostazol (C)	Inhibition of P450 3A4; diltiazem, verapamil, erythromycin, ketoconazole, cyclosporine	↓ hepatic interaction	↑ C levels, risk of increased mortality in HF	Lessen C dose or avoid

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CHF, congestive heart failure; CYP2D6, cytochrome P450 2 D6; ECG, electrocardiogram; HB, heart block; HF, heart failure; IV, intravenous; LV, left ventricle; NSAIDs, nonsteroidal anti-inflammatory drugs; SA, sinoatrial; ↑, increase; and ↓, decrease.
Modified from Opie and Frishman (540).

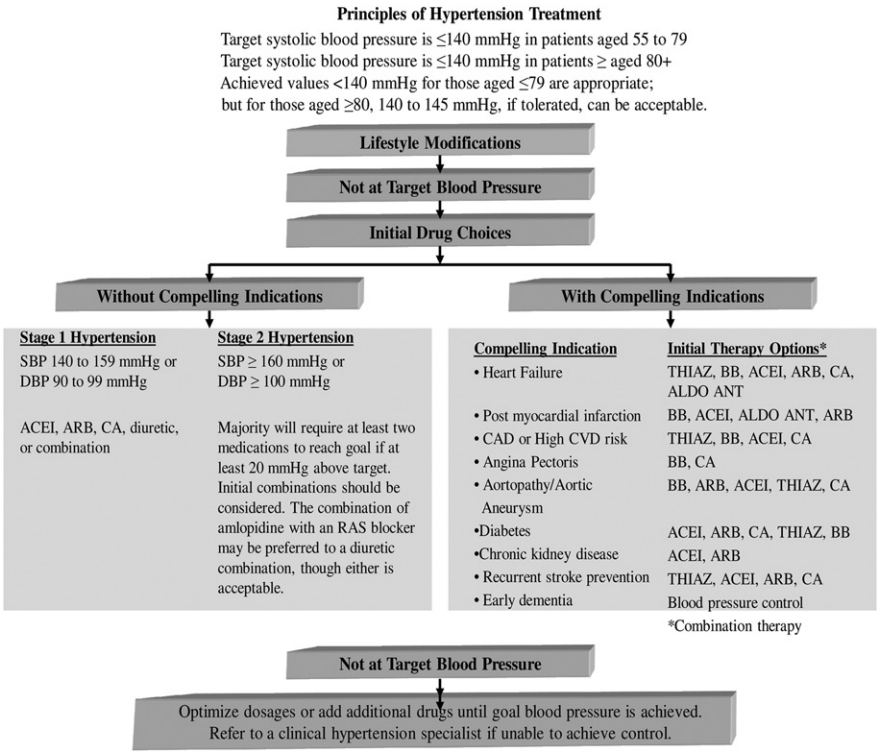

Figure 10. Algorithm for Treatment of Hypertension in the Elderly

ACEI indicates angiotensin-converting enzyme inhibitor; ALDO ANT, aldosterone antagonist; ARB, aldosterone receptor blocker; BB, beta blocker; CA, calcium antagonist; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; RAS, renin-angiotensin system; SBP, systolic blood pressure; and THIAZ, thiazide diuretic. Modified from Chobanian et al. (22).

4.2.2.1. SPECIFIC DRUG CLASSES

This section reviews the rationale for pharmacological treatments in elderly subjects, some general considerations, and experiences with specific drug classes. There is strong clinical trial–based evidence that elderly patients with hypertension benefit greatly from pharmacological BP reduction (541–546). This evidence shows that treatment reduces both CV and cerebrovascular morbidity and mortality. A meta-analysis (31 trials with 190,606 participants) showed that BP reduction produces benefits in older adults with no strong evidence that protection against major CV events afforded by different drug classes varies substantially with age (251). Individual drug classes are reviewed in the following text, and their suggested use in treating hypertension is summarized in Figure 10.

Age-related physiologic changes that may affect absorption include reduced gastric acid secretion and emptying rate, reduced splanchnic blood flow, and decreased mucosal absorptive surface area (Table 7). Yet, oral absorption of CV drugs is not significantly affected by aging, probably because most drugs are absorbed passively (547). Drug distribution may be altered in the elderly secondary to decreased lean body mass and relative increased body fat. Age-related declines in renal or hepatic function alter drug disposition in elderly patients, mostly as a result of declines in first-pass metabolism. This decline decreases total body clearance and increases elimination half-life. Individualized dose adjustments or dosing schedules help to decrease adverse effects (548). Pharmacokinetic changes, route of elimination, and dosage adjustment for antihypertensive drugs used among the elderly, are summarized in Table 8.

4.2.2.1.1. DIURETICS

4.2.2.1.1.1. Thiazides. Thiazide diuretics, such as HCTZ, chlorthalidone, and bendrofluazide (bendroflumethiazide), a mainstay of antihypertensive treatment in the elderly, are recommended for initiating therapy (22). Chlorthalidone differs from HCTZ by its longer duration of action and greater potency, and for this reason, may be associated with a higher risk of metabolic adverse effects. Diuretics cause an initial reduction in intravascular volume, peripheral vascular resistance (551–553), BP in >50% of patients, and are generally well tolerated and inexpensive. Several trials demonstrate their ability to also reduce CV, cerebrovascular, and renal adverse outcomes in the elderly.

Aging-related, physiological changes can be exacerbated with diuretics. The elderly have contracted intravascular volumes with impaired baroreflexes, and diuretics cause sodium and water depletion (hypovolemia) and orthostatic hypotension. Older people have a high prevalence of LVH, which predisposes to ventricular ectopy and sudden death. Diuretics can cause hypokalemia, hypomagnesemia, and hyponatremia, which can increase arrhythmias. Hypokalemia and hypomagnesemia can develop within the first few days of treatment. However, after that, the body can achieve

Table 7. Physiologic Changes With Aging Potentially Affecting the Pharmacokinetics of Antihypertensive Drugs

Process	Physiological Change	Result	Drugs Affected
Absorption	Reduced gastric acid production	Reduced tablet dissolution and decreased solubility of basic drugs	...
	Reduced gastric emptying rate	Decreased absorption for acidic drugs	...
	Reduced GI motility, GI blood flow, and absorptive surface	Less opportunity for drug absorption	...
Distribution	Decreased total body mass; increased proportion of body fat	Increased V_d of highly lipid-soluble drugs	Beta blockers, central alpha agonists
	Decreased proportion of body water	Decreased V_d of hydrophilic drugs	ACE inhibitors
	Decreased plasma albumin, disease-related increased α_1-acid glycoprotein, and altered relative tissue perfusion	Changed percent of free drug, V_d, and measured levels of bound drugs	Propranolol
Metabolism	Reduced liver mass, liver blood flow, and hepatic metabolic capacity	Accumulation of metabolized drugs	Propranolol, diltiazem, labetalol, verapamil
Excretion	Reduced glomerular filtration, renal tubular function, and renal blood flow	Accumulation of renally cleared drugs	ACE inhibitors, atenolol, sotalol, nadolol

Ellipses indicate no drugs affected. ACE indicates angiotensin-converting enzyme; GI, gastrointestinal; and V_d, volume of distribution. Modified from Hui (549).

a new homeostatic balance, and loss of these ions is lessened. Nevertheless, these agents are not advised in patients with baseline electrolyte abnormalities, and when they are used, serum potassium levels should be monitored and supplementation given if needed (554). With aging, renal blood flow and GFR decrease; diuretics can further decrease renal blood flow, creatinine clearance, and GFR. The elderly have a tendency toward hyperuricemia and glucose intolerance. The latter is a particular concern for hypertension patients because many have insulin resistance and related coronary vascular dysfunction (555,556). Diuretics can increase uric acid levels and need for antigout therapy in patients ≥65 years of age with hypertension (364,417), as well as glucose intolerance, and dyslipidemia (557). However, their long-term use has been associated with an overall decrease in serum cholesterol levels. Because of side effects, about 3.6% of patients withdrew from the MRC (Medical Research Council) trial (less than the beta-blocker group) (15) and 15% (comparable to other drug groups) withdrew from ALLHAT (9). In SHEP, the most frequent adverse event was abnormal serum electrolyte levels (16). Despite these side effects, diuretics have reduced CV events in the elderly to a similar extent as other drug classes, except for findings in ACCOMPLISH (8), when combined with an ACEI discussed elsewhere.

4.2.2.1.1.2. Other Diuretics. Indapamide, a non-thiazide sulfonamide diuretic, was used in several hypertension trials that included elderly patients (HYVET, PROGRESS, etc.). This drug also increases blood glucose but not uric acid and may cause hyponatremia. Because indapamide reduces the renal clearance of lithium, caution is advised in using this combination. Furosemide and its analogs (bumetanide or torsemide) are loop diuretics used for hypertension (AASK [African American Study of Kidney Disease]) (558) when complicated by HF or CKD. They also increase blood sugar levels, and may cause headaches, fever, anemia, and/or electrolyte disturbances.

Potassium-sparing diuretics, mineralocorticoid antagonists (spironolactone and eplerenone), and epithelial sodium transport channel antagonists (amiloride and triamterene) are useful in hypertension when combined with other agents. Because vascular stiffness and endothelial nitric oxide production are influenced by sodium ion under control of the mineralocorticoid receptor, these agents reduce vascular stiffness and SBP (559). Alternately, an increase in potassium softens vascular endothelium and increases nitric oxide release. These drugs are also useful for patients with hypertension with HF or primary aldosteronism. Gynecomastia and sexual dysfunction are limiting adverse reactions for men treated with spironolactone, but these are less frequent with eplerenone (189). The epithelial sodium transport channel inhibitors have minimal effects on BP as monotherapy and are most useful for their potassium-sparing effects when combined with another diuretic. The combination of a HCTZ and amiloride was equivalent to nifedipine gastrointestinal therapeutic system in preventing CV adverse outcomes in INSIGHT (Intervention as a Goal in Hypertension Treatment) (560) among patients 55 to 80 years of age with hypertension.

4.2.2.1.2. BETA-ADRENERGIC BLOCKERS. Although beta blockers have been used for hypertension in the elderly for years, evidence for benefit has not been convincing (14–16,18,327). A meta-analysis of 10 studies comparing beta blockers and diuretics in patients ≥60 years of age showed two thirds of the patients assigned diuretics were well controlled on monotherapy (561). Diuretics were superior to beta blockade with regard to all clinical outcomes, and were more effective in preventing CV adverse outcomes.

Therefore, clinical benefits of beta blockers as monotherapy in the uncomplicated elderly patient are poorly documented, although they may have a role in combination therapy, especially with diuretics. Beta blockers have an established role in the treatment of elderly patients with hypertension complicated by certain arrhythmias, migraine

Table 8. Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Antihypertensive Drugs in the Elderly

Drug Class/Drug	Half–Life	Volume of Distribution	Clearance	Primary Route(s) of Elimination	Dosage Adjustment
Alpha-adrenergic agonists, centrally acting					
Guanfacine	↑	...	↓	Hepatic/renal	Initiate at lowest dose; titrate to response
Alpha$_1$ selective adrenergic antagonists, peripherally acting					
Doxazosin	↑	↑	*	Hepatic	Initiate at lowest dose; titrate to response
Prazosin	↑	...	...	Hepatic	Initiate at lowest dose; titrate to response
Terazosin	↑	...	...	Hepatic	Initiate at lowest dose; titrate to response
Angiotensin-converting enzyme inhibitors					
Benazepril	↑	...	↓	Renal	No adjustment needed
Captopril	NS	...	↓	Renal	Initiate at lowest dose; titrate to response
Fosinopril	...	...	...	Hepatic/renal	No adjustment needed
Lisinopril	↑	...	↓	Renal	Initiate at lowest dose; titrate to response
Perindopril	...	...	↓	Renal	Initiate at lowest dose; titrate to response
Ramipril	...	...	...	Renal	Initiate at lowest dose; titrate to response
Angiotensin II receptor blockers					
Candesartan	...	...	...	Hepatic/renal	No adjustment needed
Eprosartan	...	...	↓	Hepatic/biliary/renal	No adjustment needed
Irbesartan	NS	...	...	Hepatic	No adjustment needed
Losartan	...	...	...	Hepatic	No adjustment needed
Valsartan	↑	...	...	Hepatic	No adjustment needed
Beta-adrenergic blockers					
Nonselective without ISA					
Nadolol	NS	...	...	Renal	Initiate at lowest dose; titrate to response
Propranolol	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Beta$_1$ selective without ISA					
Atenolol	↑	NS	↓	Renal	Initiate at lowest dose; titrate to response
Metoprolol	NS	NS	NS	Hepatic	Initiate at lowest dose; titrate to response
Beta$_1$ selective with ISA					
Acebutolol	↑	↓	...	Hepatic/biliary	Initiate at lowest dose; titrate to response
Dual acting					
Carvedilol	...	...	...	Hepatic/biliary	Initiate at lowest dose; titrate to response
Labetalol	...	...	NS	Hepatic	Initiate at lowest dose; titrate to response
Nebivolol	...	...	...	Hepatic/renal	No adjustment needed
Calcium antagonists					
Amlodipine	↑	...	↓	Hepatic	Initiate at lowest dose; titrate to response
Diltiazem	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Felodipine	...	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Nicardipine	NS	...	...	Hepatic	No initial adjustment needed
Nifedipine	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Verapamil	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Diuretics					
Loop					
Bumetanide	...	NS	...	Renal/hepatic	No initial adjustment needed
Furosemide	↑	NS	↓	Renal	No initial adjustment needed
Torsemide	...	...	...	Hepatic	No initial adjustment needed
Potassium sparing					
Eplerenone	...	...	...	Hepatic	No initial adjustment needed
Triamterene	↑	...	...	Hepatic/renal	Initiate at lowest dose; titrate to response
Spironolactone	...	...	...	Hepatic/biliary/renal	No initial adjustment needed

Ellipses indicate no information is available. NS indicates nonsignificant; ↑, increase; and ↓, decrease. Reprinted from Frishman (550).

headaches, senile tremor, CAD, or HF. Consideration should be given to adding beta blockers in patients with hypertension and these comorbid conditions (562–566). In older patients with ISH, a clinic heart rate >79 bpm was a significant predictor for an increase in all-cause, CV, and non-CV mortality, suggesting a role for beta blockers and

rate-lowering CAs in this population (567). But in the INVEST, with more than 11,000 CAD patients >66 years of age with hypertension, those randomized to a beta-blocker strategy had lower on-treatment heart rates, but there was no difference in death, MI, or stroke compared with a verapamil strategy (568). Although earlier generation beta blockers have been associated with depression, sexual dysfunction, dyslipidemia, and dysglycemia, no such associations were found with nebivolol (569). Nebivolol also produced favorable outcomes in SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) ≥70 years of age with HF, the majority of whom also had hypertension (570).

4.2.2.1.3. ALPHA-ADRENERGIC BLOCKING AGENTS. In comparative trials, the efficacy and safety of alpha blockers have been documented (562), but their usefulness is limited. Doxazosin 2 mg to 8 mg daily in the ALLHAT showed 25% excess CV events compared with chlorthalidone, largely driven by a 204% increase in HF (571) and a 19% increase in stroke. Based on this study, alpha blockers should not be considered as first-line therapy for hypertension in older adults. These drugs are used for urinary symptoms related to prostate hypertrophy, and caution should always be exercised for orthostatic hypotension. In addition, alpha-beta blockers are important in hypertensive urgencies (labetalol) and congestive HF (carvedilol). However, due to concern for orthostatic hypotension in the elderly, their use is discouraged.

4.2.2.1.4. CALCIUM ANTAGONISTS. CAs are a heterogeneous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular conduction, peripheral arteries, and coronary circulation (572–575). Chemically, they can be divided into phenylalkylamines (verapamil); benzothiazepines (diltiazem); and dihydropyridines (nifedipine, nicardipine, nimodipine, amlodipine, felodipine, isradipine, nitrendipine). Despite their heterogeneity, they all block influx of calcium ions into the cells of vascular smooth muscle and myocardial tissue (576), and are significantly more effective inhibiting contraction in coronary and peripheral arterial smooth muscle than in cardiac and skeletal muscle. Vascular smooth muscle is more dependent on external calcium (577) entry for contraction, whereas cardiac and skeletal muscle rely on a recirculating internal pool of calcium. Because CAs are membrane active, they reduce calcium entry into cells and therefore exert a much greater effect on vascular tissue. This preferential effect allows CAs to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility or skeletal muscle (573).

CAs appear well suited for elderly patients whose hypertensive profile is based on increasing arterial stiffness and diastolic dysfunction secondary to decreased atrial and ventricular compliance (578–580). Because they have multiple clinical applications, including treatment of angina and supraventricular arrhythmias, CAs hold promise for treatment of elderly patients with hypertension and comorbid CV conditions.

In general, CAs appear well tolerated by the elderly. Most adverse effects of the dihydropyridines relate to vasodilation (e.g., ankle edema, headache, and postural hypotension). Postural hypotension is associated with an increased risk of dizziness and falls; thus, a serious concern for elderly patients. Peripheral edema also may be confused with HF (581). Verapamil, which may be useful for LV diastolic dysfunction, may increase constipation (582). Verapamil and diltiazem can precipitate heart block in elderly patients with underlying conduction defects. Results of controlled trials have demonstrated the safety and efficacy of CAs in elderly patients with hypertension (9,17,19,20,583,584). First-generation CAs (nifedipine, verapamil, and diltiazem) should be avoided in patients with LV systolic dysfunction.

4.2.2.1.5. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. ACEIs block conversion of angiotensin-I to angiotensin-II both systemically and locally in multiple tissues as well as plasma. The latter lowers total peripheral vascular resistance, and BP is reduced without reflex stimulation of heart rate and cardiac output. As aging occurs, angiotensin levels are lower, and theoretically, ACEI should not be as effective as other therapies, but multiple studies have shown otherwise. Additional benefits of ACEI are reduction in morbidity and mortality in patients with MI, reduced systolic function HF (585–588), progression of diabetic renal disease (589), and progression of hypertensive nephrosclerosis (558).

In the HOPE (Heart Outcomes Prevention and Evaluation) study, ramipril significantly reduced CV death 26%, all-cause mortality 16%, stroke 32%, and HF 23% in high-risk older patients with pre-existing CVD or diabetes mellitus (524). In PROGRESS, perindopril plus indapamide reduced stroke-related dementia 34% and cognitive decline 45% in patients with prior stroke or transient ischemic attack (mean age 64 years, 64% with prior hypertension) (246). Available data indicate ACEIs should be considered drugs of choice in elderly patients with hypertension with HF and/or diabetes mellitus or CKD (22). The main adverse effects of ACEIs include hypotension, chronic dry cough, and, rarely, angioedema or rash. Renal failure can develop in those with RAS. Hyperkalemia can occur in patients with renal insufficiency or those taking potassium supplements or potassium-sparing diuretics. Therefore, these agents must be used carefully in patients with renal impairment. Rarely, neutropenia or agranulocytosis can occur; therefore, close monitoring is suggested during the first months of therapy.

4.2.2.1.6. ANGIOTENSIN RECEPTOR BLOCKERS. ARBs selectively block the AT1-receptor subtype that mediates all known physiological effects of angiotensin-II believed relevant to CV and cardiorenal homeostasis (590,591). Overall, ARBs are similar to other agents in reducing BP and are well tolerated. ARBs protect the kidney in type 2 diabetes mellitus (592), both in established diabetic nephropathy

with proteinuria and in patients with microalbuminuria (593). ARBs also reduce mortality and morbidity in patients with HF (593,594). In elderly patients with hypertension with diabetes mellitus, ARBs are considered first-line treatment and as an alternative to ACEI in patients with hypertension and HF who cannot tolerate ACEI (594). In patients with HF with an ejection fraction >40%, candesartan reduced HF hospitalizations but did not significantly impact mortality (595).

The LIFE study compared losartan with atenolol in patients (age 55 to 80 years) with hypertension and LVH (592), showing reduced stroke rate in the losartan-treated group despite comparable BP reduction in both treatment groups. The first occurrence of death, stroke, or CV mortality was reduced in favor of losartan and there was also a greater effect on LVH regression versus atenolol. In SCOPE, candesartan reduced nonfatal stroke by 28% and showed a trend for reduction of fatal stroke among patients 70 to 89 years of age. In the MOSES (Morbidity and Mortality After Stroke–Eprosartan Compared With Nitrindipine in Secondary Prevention) study, eprosartan reduced stroke by 25% in patients with mean age 68 years (596). The ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) study was stopped early because of reduction in death, CV event, or cerebrovascular event (OR: 0.475; 95% CI: 0.252 to 0.895; p=0.026) (597). ONTARGET showed similar efficacy between telmisartan and ramipril in a large (n=25,620) elderly (mean age 66 years) population (598), the majority of whom had hypertension.

4.2.2.1.7. DIRECT RENIN INHIBITORS. Aliskiren is an orally active direct renin inhibitor approved for hypertension; 150 mg to 300 mg once daily appears as effective as ARBs and ACEIs for BP management (599–601) for 24-hour BP lowering with no evidence of dose-related increases in adverse events in elderly patients (602). In another group of elderly patients with systolic hypertension, aliskiren, with optional add-on HCTZ (12.5 mg/d to 25 mg/d) and amlodipine (5 mg/d to 10 mg/d), appeared more effective and better tolerated overall versus ramipril (603). Combining aliskiren with HCTZ, ramipril, or amlodipine causes greater BP lowering than with either agent alone (601,604). Evidence is lacking with combination aliskiren and beta blockers, or with maximal dose ACEIs, and only limited data are available in black patients with hypertension (605).

In patients >75 years of age, including those with renal disease with a GFR ≥30 mL/min/1.73 m^2, aliskiren appears well tolerated with no dose adjustment necessary (602). The major side effect is a low incidence of mild diarrhea, which usually does not lead to discontinuation (606). There are no data on treating patients with a creatinine level <30 mL/min/1.73 m^2. There are no outcome data available at this time, but the AGELESS (Aliskiren for Geriatric Lowering of Systolic Hypertension), and APPOLO (Aliskiren in Prevention of Later Life Outcomes) studies, as well as the ALOFT-Age substudy (Aliskiren Observation of Heart Failure Treatment) (HF trial and the majority have history of hypertension) (603) have a large number of elderly patients and are in progress.

4.2.2.1.8. NONSPECIFIC VASODILATORS. Hydralazine and minoxidil are potent vasodilators, but due to unfavorable side effects, they are fourth-line drugs as part of a combination drug regimen. Hydralazine as a monotherapy causes tachycardia, and minoxidil causes fluid accumulation and atrial arrhythmias. Nitrates, which are a mainstay of antianginal treatment in the elderly, have no role in chronic hypertension management because of tolerance.

4.2.2.1.9. CENTRALLY ACTING AGENTS. Centrally acting agents (e.g., clonidine) are not first-line treatments in the elderly because many patients experience troublesome sedation or bradycardia, and abrupt discontinuation leads to increased BP and heart rate, which aggravates ischemia and/or HF. These agents should not be considered in patients who may be noncompliant. They can be used as part of a combination regimen to maximize BP control after other agents have been deployed.

4.2.3. Combination Therapy

Combination therapy provides more opportunity for creative solutions to a number of problems. Five issues in combined therapy—some practical, some speculative—are listed in Table 9 (607). The most obvious benefit of drug combinations is enhanced efficacy. Theoretically, some drug combinations might produce synergistic effects that are greater than predicted by summing efficacies of component drugs. More commonly, combination therapy achieves a little less than the sum of its component drug efficacies. In contrast, some combinations of drugs produce offsetting interactions that may weaken rather than strengthen antihypertensive effects. A second benefit concerns avoidance of adverse effects because each drug can be administered in a lower dose. A third issue concerns convenience although a combination regimen could be confusing and distracting to elderly patients, and could lead to poor treatment compliance. Conversely, a well-designed, combination pill that incorporates logical doses of 2 agents enhances convenience and compliance. Further potential value may result from the reciprocal pharmacokinetic effects that 2 drugs have on each other. Although this has not been well studied, there may be situations where the duration of action of the drugs becomes longer when used in combination. Finally, it is interesting to

Table 9. Rationale for Combination Drug Therapy for Hypertension

- Increased antihypertensive efficacy
  - Additive effects
  - Synergistic effects
- Reduced adverse events
  - Low-dose strategy
  - Drugs with offsetting actions
- Enhanced convenience and compliance
- Prolonged duration of action
- Potential for additive target organ protection

Reprinted from Weber et al. (607).

consider the attributes of ACEIs, ARBs, and CAs, which exhibit antimitotic or antiatherosclerotic actions in addition to BP lowering. Some combinations of these newer agents may provide even more protective effects on the CV system (Figure 10). The ACCOMPLISH trial of high-risk hypertension patients (mean age 67 years) compared combination therapy with benazepril plus either HCTZ (12 mg to 25 mg daily) or amlodipine and found clear superiority for the ACEI-CA combination in terms of reduction in morbidity and mortality (8). Both combinations had the same effect on 24-hour mean daytime and nighttime BPs, and surges in BP. Thus, the greater reduction in clinical events with the benazepril-amlodipine combination could not be explained by a greater reduction in BP. Although multiple combinations of diuretics with other antihypertensive drugs have been used to reduce BP, outcome data from RCTs in elderly patients are lacking. The beneficial effect on outcomes was only present for patients with an eGFR >60 mL/min; for those with reduced renal function there was no difference in CV outcomes between the 2 combinations (607a). Multiple RCTs, including HYVET, EWPHE, MRC, and STOP-HTN (Swedish Trial in Old Patients with Hypertension), have shown combination therapy with a diuretic to be efficacious in the elderly (4,12,15,18).

4.2.4. Uncomplicated Hypertension

The 2009 updated ESH guidelines recommend initiating therapy in the elderly with either thiazide diuretics, CAs, ACEIs, ARBs, or beta blockers based on a meta-analysis of major hypertension trials (608,609). When BP is >20/10 mm Hg above goal, consideration should be given to starting with 2 drugs (22). Most elderly persons with hypertension will need ≥2 drugs to control their hypertension (22,610).

4.2.5. Complicated Hypertension

When additional comorbidities complicate hypertension, at least 2 drugs should generally be used. In elderly patients with hypertension at high risk for CV events, a benazepril–amlodipine combination was more effective in reducing CV events than a benazepril–HCTZ combination with a 2.2% absolute risk reduction in CV events by the former combination (8). Recommended antihypertensive agents for specific comorbidities are detailed in the following text.

4.2.5.1. CORONARY ARTERY DISEASE

In elderly patients with hypertension and stable angina and/or prior MI, the initial choice is a beta blocker (22,26,611). A long-acting dihydropyridine CA should be administered in addition to the beta blocker when the BP remains elevated or if angina persists. An ACEI should also be given, particularly if LV ejection fraction is reduced (22,524,588,612–614) and/or if HF is present where an aldosterone antagonist should be added in the absence of hyperkalemia or significant renal dysfunction (22,615). The INVEST demonstrated that a verapamil SR–trandolapril-based strategy was as clinically effective in terms of BP control and adverse outcomes as an atenolol–HCTZ-based strategy in elderly patients with hypertension with CAD, including those with prior MI (584). Angina was better controlled with the verapamil SR–trandolapril strategy. Elderly patients with hypertension at high risk for coronary events should be treated with beta blockers plus ACEI (22,26,524,612–614).

In elderly patients with acute coronary syndromes, hypertension should be treated with beta blockers and ACEI, with additional drugs added as needed for BP control (22,26,616). Verapamil and diltiazem should not be used if there is significant LV systolic dysfunction (26,616).

Some (26) recommend reducing BP to <130/80 mm Hg in CAD patients, yet there is limited evidence to support this lower target in elderly patients with CAD (584). In INVEST, the nadir BP for risk was 135/75 mm Hg among 6,126 patients 70 to 80 years of age, and 140/70 mm Hg for 2,180 patients ≥80 years of age (13). Beta blockers with intrinsic sympathomimetic activity must not be used after MI. The hydrophilic beta blocker atenolol may not be as efficacious as propranolol, timolol, metoprolol, or carvedilol in treating hypertension (617,618), but in most of the patients in these studies (e.g., LIFE), it was used only once daily.

4.2.5.2. LEFT VENTRICULAR HYPERTROPHY

LVH associated with hypertension is an independent risk factor for coronary events, stroke, PAD, and HF. LVH can regress with antihypertensive therapy except for the direct vasodilators hydralazine and minoxidil (22). A meta-analysis of 109 treatment studies found that ACEI was more effective than other antihypertensive drugs in decreasing LV mass (619). Losartan was superior to atenolol in reducing first occurrence of CV death, stroke, or MI in elderly patients with ISH and electrocardiographic LVH (620). Thus, antihypertensive therapy with ACEI or ARBs should generally be used in elderly persons with hypertension and LVH. However, all antihypertensive agents except for direct-acting vasodilators will reduce LV mass if BP is controlled.

4.2.5.3. HEART FAILURE

Elderly patients with hypertension and systolic HF should be treated with diuretics, beta blockers, ACEI, and an aldosterone antagonist if necessary (22,585,615,621–627). If a patient cannot tolerate an ACEI because of cough, rash, or angioedema, an ARB should be used (594,621). Elderly black patients with hypertension and HF may benefit from isosorbide dinitrate plus hydralazine (628). Based on expert opinion, the BP should be reduced to <130/80 mm Hg in HF patients with CAD (26). Elderly patients with hypertension and asymptomatic LV systolic dysfunction should be treated with ACEI and beta blockers (22,26,588,629). Because HF may improve in elderly patients with hypertension and RAS after renal revascularization, a search for RAS should be considered when HF is refractory or recurs with conventional management (630). Diastolic HF is very

common in the elderly (625,631). Fluid retention should be treated with diuretics, hypertension should be adequately controlled, and when possible, comorbidities should be treated.

4.2.5.4. CEREBROVASCULAR DISEASE

Elderly patients with hypertension with prior stroke or transient ischemic attack should be treated with a diuretic plus an ACEI (22,246). Despite this, recommendation by "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," the overall data suggest that reduction of stroke risk among elderly persons with hypertension is related more to reduction in BP than to type of antihypertensive drugs (632). Ischemic stroke was reduced 37% (18% to 52%), and hemorrhagic stroke reduced 54% (−2% to 79%) (95% CI: 0.21 to 1.02).

4.2.5.5. DISEASES OF THE AORTA AND PERIPHERAL ARTERIES

The presence of aortic aneurysm requires very intense BP control to the lowest tolerated level, and therapy should include an ACEI or ARB plus a beta blocker, because in addition to lowering BP, beta blockers decrease peak LV ejection rate (633,634).

In acute aortic dissection (acute aortic syndrome), control of BP, with multiple drugs including beta blockade, is needed for both type A and B (not involving the ascending aorta) dissection. Surgery is indicated for type A dissections (those involving the ascending aorta), and endovascular techniques may be used in elderly patients with high operative risk (301).

For PAD patients, lifestyle interventions including smoking cessation, weight loss, a structured walking program, and management of hypertension, as well as coexistent CAD and HF, are essential, as is control of blood glucose and lipids. ACEIs or ARBs, as well as antiplatelet therapy, are required (635). Patients with critical limb ischemia, (defined as PAD resulting in ischemic pain at rest), ulceration, or gangrene should be evaluated for revascularization. In the HOPE study, compared with placebo, the ACEI ramipril 10 mg daily significantly reduced CV events in persons with symptomatic and asymptomatic PAD, most of whom had increased BP and were elderly (636,637). The absolute reduction in CV events was 50 events per 1,000 patients with an ankle-brachial index <0.9 compared with 24 events per 1,000 patients with an ankle-brachial index of ≥0.9. Multiple professional societies suggest the BP target should be below 130/80 mm Hg in patients with PAD. But in the INVEST, elderly patients with CAD and hypertension with PAD (n=2,699, mean age 69 years, 44% >70 years old), followed for a mean of 2.7 years (6,970 patient-years), showed a J-shaped relationship with BP treatment. Adverse outcomes (22,26,28,29,608) (death, MI, or stroke) occurred least frequently on treatment with SPB 135 to 145 mm Hg and DBP 60 to 90 mm Hg (638), suggesting that PAD patients may require a different BP (638). Specific data in very elderly patients with PAD regarding benefits of treatment and optimal BP target are sparse.

4.2.5.6. DIABETES MELLITUS

In the absence of RCT data, guidelines recommend that patients with diabetes mellitus should have BPs <130/80 mm Hg, if tolerated (22,28,29,613,639), and often multiple drugs are required to meet this goal. However, recent RCT data from the ACCORD BP (see Section 1.4) found no benefit of a SBP goal of 120 mm Hg compared with 140 mm Hg on CV endpoints in 4,733 patients (mean age 62 years) with type 2 diabetes mellitus (32). Observational data from extended follow-up of the 6,400 INVEST diabetes mellitus cohort of mostly elderly patients (mean age 66 years) showed an increase in mortality when on treatment; SBP was <115 mm Hg or DBP <65 mm Hg (640). Based on available data, reduction of macrovascular and microvascular complications in elderly diabetics with hypertension depends more on reducing the BP than on the type of drugs used: drug choice depends on associated comorbidities (22,28). However, thiazide diuretics will increase hyperglycemia and risk for incident diabetes mellitus. Incident diabetes mellitus has been associated with increased HF hospitalizations and other CV events in elderly patients with hypertension (556,641). In ALLHAT, patients with pre-existing diabetes mellitus appeared to receive the same benefit on future coronary events from diuretics as patients without diabetes mellitus (9) over an intermediate follow-up period. Elderly persons with diabetes, hypertension, and nephropathy should be treated initially with ACEIs or ARBs (22,642–645). In ACCOMPLISH, over the background of ACEI, patients with diabetes mellitus who were treated with amlodipine had a 21% relative risk reduction and 2.2% absolute risk reduction in CV events (8) compared with HCTZ plus the ACEI.

4.2.5.7. METABOLIC SYNDROME

Initially attempts should be made to reduce BP in elderly persons with metabolic syndrome and prehypertension using lifestyle modification (646). In those who are hypertensive, drug therapy should be used if needed to achieve BP <140/90 mm Hg (646).

4.2.5.8. CHRONIC KIDNEY DISEASE AND RENAL ARTERY STENOSIS

4.2.5.8.1. CHRONIC KIDNEY DISEASE. Based solely on expert opinion and observational data, elderly patients with hypertension and CKD should have BP <130/80 mm Hg, if tolerated (22,29,409). Drug regimens that include ACEIs or ARBs are more effective than regimens without them in slowing progression of advanced proteinuric nondiabetic CKD (647). ACEI therapy is also indicated in patients with nondiabetic nephropathy. It should be noted, however, that there are no data on outcomes with any class of antihypertensive agents among elderly patients with hypertension with CKD. In the absence of proteinuria (i.e., >300 mg/d), there are no data that ACEIs or ARBs are better than BP control alone with any agent that is well tolerated (648,649).

ACEIs or ARBs should be administered to elderly hypertension persons with CKD if proteinuria is present (22,29,409,642–645,647,650).

Hypertension and HF are associated with a more pronounced decline in renal function in older age (324). With the recognition of early renal dysfunction, more patients should benefit from aggressive therapy. A retrospective cohort of elderly individuals with CKD and acute MI found benefit from combination cardioprotective therapy with aspirin, beta blockers, and ACEI (651). In an observational study of elderly (mean age 79 years) hospitalized patients with acute systolic HF and advanced CKD (mean serum creatinine 2.9 mg/dL), ACEI use was associated with a 31% absolute mortality reduction (652).

4.2.5.8.2. RENAL ARTERY STENOSIS

4.2.5.8.2.1. Surgical Revascularization. Revascularization has been used to treat hypertension, preserve renal function, and treat HF and unstable angina in patients with RAS and ischemic nephropathy. Techniques range from aortorenal bypass with graft of autogenous hypogastric artery or saphenous vein, to aortorenal endoarterectomy (298). Nephrectomy is used only in select patients after revascularization failure or when benefit in BP control or decrease in CV morbidity is expected after kidney removal (298,653).

Surgical results in patients with atherosclerotic RAS (age 69±9 years, mean serum creatinine 2.6 mg/dL) showed that at discharge, renal function remained unchanged in 41%, declined in 16%, and improved in 43%, including 7 patients removed from dialysis (654). At 1 year, renal function was improved or unchanged in 72%. Aortorenal bypass was used in 38%, endoarterectomy in 24%, combined aortic and renal artery revascularization in 24%, and bilateral renal artery revascularization in 27%, with perioperative death in 4.1%. Predictors of worsened excretory function included decline of renal function at hospital discharge, unilateral RAS, and elevated baseline creatinine level. In another study, mean age 66±8 years with RAS who underwent repair, 83/232 underwent unilateral and 149 bilateral renal artery repair, including 17 with repair to a solitary kidney (655). A total of 332 renal arteries were reconstructed and 32 nephrectomies performed; 58% of patients had improved renal function after surgery, including 27 removed from dialysis. Renal function was unchanged in 35% and worsened in 7%. Death within 30 days of surgery occurred in 7.3% of the patients, and advanced age and HF were independent predictors of mortality.

In patients 66±9 years of age, the Nationwide Inpatient Sample of all hospital discharges in the United States reported a 73% decrease in combined aortic and renal surgical revascularization; and in patients aged 63±12 years, a 56% decline in surgical renal revascularization between 1988 and 2001 (656). However, catheter-based renal revascularization procedures increased 173% in patients aged 67±12 years during the same period.

4.2.5.8.2.2. Catheter-Based Interventions

4.2.5.8.2.2.1. PERCUTANEOUS TRANSLUMINAL RENAL ARTERY BALLOON ANGIOPLASTY. Risks of surgical renal revascularization and relatively good results with catheter-based interventions have shifted therapy toward more percutaneous catheter-based interventions. In 1 study, patients with hypertension and RAS (stenosis ≥50% and serum creatinine ≤2.3 mg/dL) were assigned to percutaneous balloon angioplasty (BA) or medical treatment and followed for a total of 12 months (657). Average ages were 59±10 years and 61±10 years for the angioplasty and drug therapy groups, respectively. At 12 months, there were no significant differences between groups in BP, daily antihypertensive drug doses, or renal function. However, >40% of patients assigned medical treatment crossed over to BA after 3 months. Other studies (658–660) confirmed that BA is associated with low procedural success and high restenosis rates in RAS, the most common pathology in the elderly. BA stent placement has consistently proven superior when compared to BA alone. Based on these results, stenting with BA has replaced BA alone.

4.2.5.8.2.2.2. PERCUTANEOUS RENAL ARTERY STENTING. Because atherosclerotic RAS usually involves narrowing of the ostium by aortic plaques extending into proximal vessels, BA results in recoil, and stent use better maintains patency (661). A study of patients (average age 65 years) found that angioplasty with stent placement was more effective than BA for ostial atherosclerotic stenosis (662). Primary patency rate at 6 months was 79% in the stent versus 28% in the BA group and in patients with restenosis, secondary patency was also higher in the stent than in the BA group: 82% versus 46%, respectively. No differences occurred between groups in the distribution of patients with improved BP or improved, unchanged, or worse renal function; the number of antihypertensive medications did not change in either group after revascularization. Complications, including bleeding, femoral artery aneurysm, renal artery injury, and cholesterol embolism, were similar in both groups. This prospective study concluded that stenting provides improved vessel patency in the elderly population with ostial atherosclerotic RAS; however, it does not prove that the clinical evolution of the disease will change following revascularization.

One study summarized experience with angioplasty and stenting in 39 patients (mean age 69.9 years) with recurrent episodes of HF and flash pulmonary edema (630). Following the procedure, 77% of patients had no hospitalization for HF over 21 months, and 9 patients died. In another study, the presence of HF was examined in a cohort (mean age 73 years) of patients with significant hypertension and RAS. Approximately one third (31%) of the patients referred for BA with stenting presented with HF. Outcomes in HF and BP control were improved by revascularization compared with outcomes of patients who underwent medical management, but mortality was not affected (663).

Investigators from the ASPIRE II (renal Artery Stenting After Unsuccessful Balloon Angioplasty) study analyzed

safety and durability of renal stenting after suboptimal or failed renal artery BA in patients, average age 69±9.9 years. Stenting was immediately successful in 80.2% lesions treated, and at 9 months, the restenosis rate was 17.4%. The SBP/DBP decrease was significant, but creatinine was unchanged after 24 months, as adverse events occurred in 19.7% (664). Others (665) found patients <75 years of age have similar findings in follow-up after BA; however, patients who are ≥75 years of age have a higher mortality at 2 years.

Uncertainty regarding the effect of stenting on BP control and progression of kidney failure continues. Some suggest that stenting for atherosclerotic RAS can stabilize declining kidney function; however, for patients with stable renal function, the benefit is less clear (666). Others advise caution in performing percutaneous revascularization in patients with CKD (667).

Early acute functional renal injury related to renal interventions in patients with atherosclerotic RAS was analyzed in a prospective study of patients who averaged >70 years of age (668). Indications for the procedure were poorly controlled hypertension, associated CKD (creatinine >1.5 mg/dL), diabetes mellitus, and hyperlipidemia. Acute functional parenchymal renal injury occurred in 20%. In the injury group, there were more current smokers with non–insulin-dependent diabetes mellitus and presence of AAA. The CKD was more advanced (GFR <20 mL/min), and contralateral renal artery disease was more frequent in patients who suffered acute kidney injury after the procedure. Acute kidney injury was associated with more kidney morbidity 3 months after the procedure and decreased survival at 5 years; in addition, 3 times more patients progressed to hemodialysis as compared with those without acute kidney injury. It seems that patients with unrepaired AAA, diabetes mellitus, and persistent renal disease are more predisposed to acute functional injury following RAS. Medical therapy or use of a distal renal protective device may be beneficial until results of prospective trials (e.g., CORAL) help to address appropriate use of renal interventions.

The ASTRAL trial (669) recruited 806 patients with RAS (mean age 70 years, range 42 to 88 years) including patients who quit smoking and those with a history of diabetes, PAD, CVD, and stroke. Eighty percent were treated with statins, 90% with antiplatelet drugs, and 90% with antihypertensive agents. Participants were randomized between renal artery revascularization (BA-S) plus medical therapy versus medical therapy alone, and the primary outcome was rate of decline of renal function; the secondary outcomes were BP control, renal events (acute renal failure, dialysis), serious vascular events, or mortality. At 12 months, there were no differences between groups in renal function, SBP or DBP, combined renal events, and CV events, inducing death. During 4-year follow-up, there was slight benefit in favor of revascularization for creatinine (10 mmol/L difference), SBP, combined renal (17% versus 23%), and CV events (34% versus 41%), but the study was underpowered. Serious complications associated with revascularization occurred in 23 patients (6%), including 2 deaths and 3 amputations of toes or limbs. Based on this definitive trial, there is no evidence for benefit of BA-S for RAS. The authors concluded that in patients with a range of radiologically significant RAS lesions, there was no benefit in any outcome measure but significant risk from additional revascularization when both groups were treated with optimal medical therapy (669). The ongoing CORAL study (670) will analyze response to medical treatment versus revascularization and might also provide evidence about diagnostic tests that may predict the best treatment.

Technical improvements in percutaneous renal artery interventions have evolved. These include polyurethane filter and basket (Angioguard XP emboli capture guide wire system) (671) to decrease the number of microembolic particles introduced into the renal artery. Analysis of a retrospective cohort of consecutive patients undergoing with and without distal embolic protection, ages 69±7 years and 75±6 years, respectively, did not show a difference between groups in renal function or SBP changes. The authors concluded that renal artery stenting improves GFR and SBP, however distal embolic protection did not enhance this effect (672).

4.2.5.9. OTHER CONDITIONS/SITUATIONS/SPECIAL POPULATIONS

Resistant hypertension: *Resistant hypertension* is defined as BP that remains above goal when a patient adheres to lifestyle measures (23) and maximum tolerated doses of 3 complementary antihypertensive agents including a diuretic (673), has an unknown prevalence in the elderly. Data from NHANES (2003 to 2004), show hypertension prevalence progressively increases with age, reaching 77% in people >77 years of age (674), so increasing age, particularly >65 years of age, is associated with a higher prevalence of resistant hypertension (675,676).

There are no studies specifically powered to address prognosis of older patients with resistant hypertension. In adults 40 to 69 years of age with no previous vascular disease, each difference of 20 mm Hg in SBP or 10 mm Hg in DBP was associated with more than a 2-fold difference in the stroke death rate (Figure 8), and with 2-fold differences in the death rates from vascular causes (Figure 11). This association was consistent for the entire range of BP studied, about 115/75 to 180/110 mm Hg. Differences in vascular mortality were about half as extreme at 80 to 89 years of age versus 40 to 49 years of age, but the annual absolute differences in risk were greater in old age. Age-specific associations were similar for men and women, and for cerebral hemorrhage and cerebral ischemia (42).

Increasing age was the characteristic that was most significantly associated with lack of SBP control among treated subjects. The FHS showed that subjects >75 years of age are 4 times less likely to achieve SBP control compared with those ≥60 years of age (677). This was confirmed in another study where BP control gradually

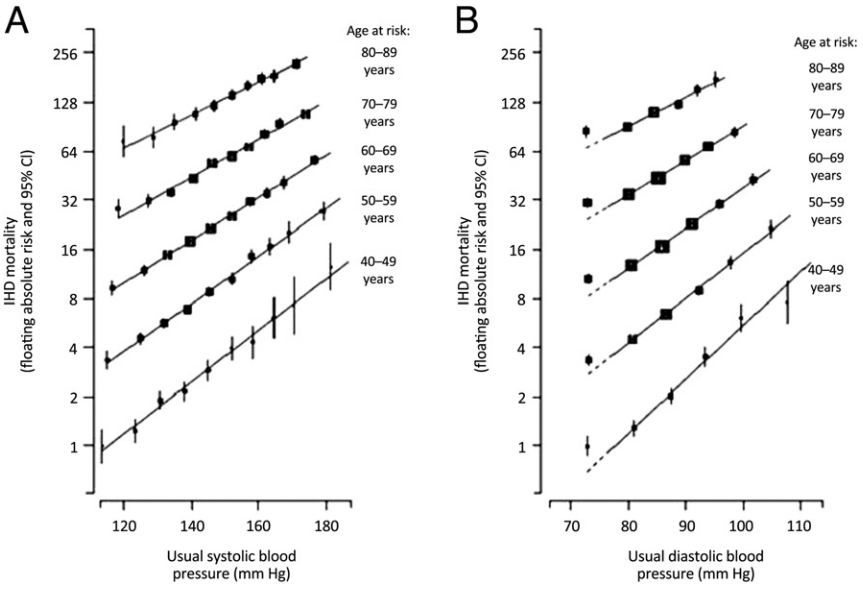

Figure 11. Absolute Risk of Ischemic Heart Disease Mortality in Relation to Blood Pressure

(A) Systolic blood pressure. **(B)** Diastolic blood pressure. The Y axis is logarithmic.
CI indicates confidence interval; IHD, ischemic heart disease. Reprinted from Lewington et al. (42).

declined with age, from 74% among those <40 years of age to 33% for those ≥70 years of age (674). Reasons for resistant hypertension in the elderly include excess dietary salt intake, weight, alcohol, and nicotine; decrease in efficacy of antihypertensive medication with higher baseline BP; higher incidence of organ damage comorbidities (e.g., dyslipidemia, metabolic syndrome, diabetes mellitus, CKD, stroke, HF, PAD, CAD [674]); poor adherence to drug treatment; volume overload; pseudohypertension; and use of pain medications such as NSAIDs. NSAIDs inhibit prostaglandin production, followed by sodium and fluid retention (215) and volume overload, especially in elderly patients with organ damage (675).

Elderly subjects with higher baseline SBP typically have a more severe or longer duration of hypertension that makes it more difficult to treat. Higher baseline SBP is also often associated with dysfunction or damage of organs that play a key role in BP regulation. In elderly patients, volume overload is a common finding because of excessive salt intake, inadequate kidney function, or insufficient diuretic therapy. Physicians are less aggressive in treating elderly patients, as 25% of physicians believe that hypertension treatment in an 85 year old has more risks than benefits (678).

Pseudohypertension represents another reason for resistant hypertension in the elderly population. Increased arterial stiffness and the presence of heavily calcified arteries that cannot fully compress makes BP readings falsely higher than the intra-arterial BP (679). Managing resistant hypertension in the elderly requires a careful medical history, followed by BP measurements in seated and in erect posture because of the increase risk of postural hypotension. Complete investigation of comorbidities and concomitant medications, as well as suboptimal compliance and dietary indiscretions may help explain the difficulties in BP control.

Recommendations for modification and intensification of antihypertensive regiments for elderly patients taking ≥3 drugs are based on pharmacological principles, underlying pathology, clinical experience, and comorbidities. We wish to reinforce the importance of dietary sodium restriction, reduction in alcohol intake, and the DASH diet in resistant hypertension. Most patients should receive a RAAS blocker along with a CA and an appropriately dosed diuretic. It is extremely important that the agents be given in adequate dosages and at appropriate time intervals. An appropriate diuretic to decrease volume expansion remains the cornerstone of therapy in elderly patients. Thiazides can be selected if the eGFR is >30 mL/min/1.73 m^2; if hypoalbuminemia or hyperkalemia is not present. If eGFR is below 30 mL/min/1.73 m^2, a loop diuretic is recommended (675). Next, add either a CA or vasodilating beta blocker if pulse rate is not <50 bpm. Blockade of aldosterone should be considered especially in certain settings, (i.e., those with HF, obesity, or sleep apnea) (680). Peripheral alpha blockers may be considered, especially in older men with coexistent symptoms from benign prostatic hypertrophy, but these will increase orthostatic hypotension and are associated with excess HF and stroke (Section 4.2.2.1.3, Alpha-Adrenergic Blocking Agents).

As discussed previously, RAS and other secondary causes of hypertension should be considered in elderly patients with resistant hypertension. A key point in the management of BP in this cohort of patients is that volume depletion with diuretics, especially during summer months, is to be avoided. Hence, CAs become useful agents as they are efficacious for pressure reduction and avoid increases in serum creatinine and volume depletion.

Osteoporosis: Thiazide diuretics preserve hip and spine bone mineral density in older patients (681–683), so those with hypertension and osteoporosis should generally receive a thiazide (22), which can increase blood calcium levels. Loop diuretics (such as furosemide and bumetanide) can decrease calcium levels. Amiloride (a potassium-sparing diuretic) may decrease the amount of calcium excreted in the urine (thus increasing blood calcium levels), and may also be considered for people with calcium oxalate kidney stones.

Arrhythmias: Beta blockers, verapamil, or diltiazem should be used for ventricular rate control with supraventricular tachyarrhythmias such as AF in elderly persons with hypertension (22,286). Beta blockers should also be considered in treatment of elderly persons with complex ventricular arrhythmias with abnormal (684) or normal (685) ejection fraction. Beta blockers are also useful to treat elderly persons with hypertension who have hyperthyroidism, preoperative hypertension, migraine, or essential tremor (22). CAs are useful in patients with Raynaud's disease, asthma, or chronic obstructive lung disease, in whom beta blockers are relatively contraindicated.

Blacks: In general, treatment of hypertension is similar for all racial/ethnic groups (22) including blacks (686). Blacks have reduced BP responses to monotherapy with beta blockers, ACEIs, ARBs, and some CAs compared with diuretics, but this is eliminated by including a diuretic in combination (22). RAAS (686) inhibitors appear less effective than other classes in decreasing BP in elderly blacks, unless combined with diuretics or CAs. ACEIs prevent adverse outcomes such as decline of renal function in those with hypertensive nephropathy (558). The SHEP demonstrated benefit in an older black cohort with chlorthalidone-based treatment versus placebo (16). Patients were >60 years of age with SBP 160 to 219 mm Hg, and DBP <90 mm Hg. Over 4.5 years, stroke was reduced in black women (RR: 0.36; 95% CI: 0.16 to 0.83), but not in black men. In LIFE, black patients aged 55 to 80 years with stage 2 hypertension and LVH showed greater benefit with atenolol plus diuretics versus losartan plus diuretics in protection against stroke and CAD (687).

The initial agent in blacks with uncomplicated hypertension should be a thiazide diuretic. In ALLHAT, chlorthalidone was unsurpassed in blacks decreasing BP and major CV events versus regimens based on lisinopril, amlodipine, and doxazosin (9,688). CAs effectively lowered BP in blacks and decreased CV event, especially stroke (688). Amlodipine in ALLHAT was effective with similar protection against CAD and stroke, although less effective for new onset HF when compared with chlorthalidone (688). Because ALLHAT compared those agents with diuretics and CAs, patients randomized to chlorthalidone or amlodipine-based therapies could not additionally take lisinopril, despite the fact that a diuretic or CA combination with an ACEI would be a reasonable combination in blacks. In ALLHAT, a 40% higher incidence of stroke in blacks with lisinopril-based therapy was noted versus the diuretic (68). This occurred, to a large extent, related to 4 to 5 mm Hg less SBP reduction in the lisinopril-based versus chlorthalidone-based cohort, although BP reductions did not fully explain outcome differences.

In the AASK, ramipril-based therapy versus metoprolol succinate and amlodipine was renoprotective in those with hypertensive nephropathy, especially with proteinuria. The AASK results confirm benefit of ACEI when needed in blacks, such as protection against progression of renal disease in concert with diuretics (558); however, the diuretic used was furosemide.

Although ACEIs and ARBs may be less efficacious for BP reduction in blacks, at higher doses or combined with a diuretic or long-acting CA, blacks benefit from these agents. ACEIs are associated with a higher rate of cough and angioedema among blacks versus whites (688). Nevertheless, in blacks, socioeconomic status, dietary, and other lifestyle considerations must be examined and addressed, because, to a large extent, these non-drug aspects of elevated BP are of primary significance. Blacks, many of whom have more severe and complicated hypertension, usually will not reach control with monotherapy. Aldosterone antagonists, spironolactone, and eplerenone are beneficial in patients with resistant hypertension, including blacks (689).

Hispanics: Recommendations for pharmacological management of elderly Hispanic patients are the same as for elderly patients in general. In INVEST, elderly Hispanic patients with CAD had better BP responses to combination therapy with either a CA plus ACEI or beta blocker plus HCTZ versus white patients (76,77).

Women: There is no evidence that elderly women respond differently than elderly men to antihypertensive drugs (690,691). Recent studies have shown that multidrug therapy is needed for elderly high-risk men and women with hypertension (691). A recent meta-analysis of randomized trials showed that different antihypertensive drug classes protected similarly against major CV events in persons >65 years of age and persons <65 years of age (251).

Octogenarians: Successful treatment of hypertension in octogenarians may be expected to substantially reduce CV risk and mortality based on available data. Benefits on cognitive function and appearance of dementia are less certain. Although a BP <140/90 mm Hg was recommended for all patients by "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (22), except for a lower level in special populations, randomized trial evidence to support this BP level in the very elderly is not robust. Nevertheless, data available from RCTs, which included patients over the age of 80 years, come largely from subpopulations, which in some trials and collectively are larger than HYVET. These trials (e.g., ACCOMPLISH, INVEST) noted no difference in the effects on outcomes among those ≥80 years of age versus <80 years of age (8,584). Based on these results and limitations, the follow-

ing recommendations can be offered for persons ≥80 years of age. Those with SBP >150 mm Hg are candidates for antihypertensive drugs with target SBP 140 to 145 mm Hg if tolerated (i.e., somewhat more conservative target than in individuals <80 years of age).

Initiate treatment with a single drug followed by addition of a second drug if needed. Low-dose thiazides, CAs, and RAAS blockers are preferred. Concomitant conditions will often dictate which drugs are appropriate, as detailed in the preceding text. Indeed, because of the evidence that the benefits of antihypertensive treatment largely depend on BP lowering per se (22), all drugs (alone or in rational combinations) may be used provided that they have a suitable safety profile and no excessive effect on orthostatic BP.

In starting or continuing treatment, use precautions even more stringent than those employed in younger patients. Octogenarians should be seen frequently and the medical history accurately updated at each visit. Standing BP should always be checked for excessive orthostatic decline. Although BP values below which vital organ perfusion is impaired are not known, SBPs lower than 130 mm Hg and DBP <60 mm Hg should generally be avoided, if possible. Drug treatments for concomitant diseases should be carefully monitored to prevent adverse interactions with antihypertensive drugs.

Drug treatment should not indiscriminately involve all patients with hypertension who are >80 years of age. In deciding whether to initiate treatment, physicians should consider the general health condition of their patients. Treatment may be withheld in more frail or medically compromised patients, and there is less evidence of benefit in patients approaching 90 years of age or who are >90 years of age.

4.2.5.10. COMPLIANCE WITH PHARMACOLOGICAL THERAPY

Compliance may be defined as the extent to which a patient takes medication as prescribed. The term *compliance* is often used interchangeably with *adherence,* but *compliance* is preferred because it implies a responsibility shared by both patient and physician (692,693). Compliance rates are often reported as percentage of prescribed dose of medication actually taken over a period of time. Measurements of blood or urine drug metabolites or serum drug concentrations can also be used (694), but these have limited applications in a primary care setting as they are invasive and potentially costly. Clinicians are more inclined to evaluate compliance by questioning the patient, taking pill count assessments at checkup, and using electronic medication caps that record when a bottle is opened (694,695). Unfortunately, patients do not always report nonadherent behavior, and such indirect measures can mislead providers to overestimate compliance (694).

Definition and Predictors: Unfortunately, a large proportion of elderly patients will discontinue or take the drugs inappropriately (692,696,697). This noncompliance often results in failing to reach guideline-recommended BP targets and impacts outcomes; patients are much more likely to be hospitalized and have greater healthcare costs than those who follow their prescriptions (22). About 1 in 3 patients remain highly adherent to antihypertensive medication after 12 months, and after that, adherent patients are much less likely to discontinue medication. Older age, in addition to previous noncompliance, low risk for CV events, competing health problems, nonwhite race, low socioeconomic status, complexity (e.g., multiple dosing, pill burden), side effects, and cost of medication regimen predict noncompliance (698,699).

Compliance Barriers: The asymptomatic state associated with hypertension appears to be a common barrier (692,697,700). A prospective study found that only 37% of patients surveyed reported consistent compliance to antihypertensive regimen (701). In a cross-sectional study, 21% of patients with hypertension stopped treatment without being advised to do so. A factor most commonly found to distinguish nonadherent patients from those adherent to medication regimens was perception of health status (700). The poorer the patients perceived their health, the more likely they were to adhere to prescribed treatment; the reason given most often for discontinuation was that they felt well without the medication. Although the mean age of this cohort was only 58, elderly patients with hypertension are likely to be asymptomatic with a variety of serious comorbidities (e.g., AF, CAD, diabetes mellitus, HF) (700). Prevalent comorbidities, polypharmacy, and high cost of medications also contribute to lower BP control rates in the elderly (610).

Some patients with hypertension are more likely to adhere to their medication regimen. Patients who viewed hypertension as a symptomatic disease and believed treatment had beneficial effects on symptoms were more adherent and had better BP control (702).

Side Effects: Side effects are another common reason for therapy discontinuation in the elderly (703–705) and may be more apparent in patients with hypertension. This because the illness is often asymptomatic, which may increase awareness of side effects associated with therapy. A drug's side-effect profile has been demonstrated to contribute to poor compliance by affecting a patient's QoL (701,706). In patients with hypertension, approximately 10% of poor compliance was due to adverse effects of prescribed medication (707). In addition to side effects, new symptoms that may be unrelated to the medication regimen can also impact compliance. It is therefore important to advise patients of side effects that may be related to medications, as patients tend to blame their drugs for any new symptoms they experience (Table 10) (708).

Pill Burden and Dosing Complexity: Complexity of a drug regimen influences compliance (709) and is especially problematic for hypertension and HF, as dosing complexity and number of medications increases with disease severity. This problem has been growing as the number of medications and evidence-based guidelines have increased (710).

Table 10. Adverse Effects of Antihypertensive Therapy in the Elderly

Drug Class	Adverse Effect
Thiazide and loop diuretics	Hypokalemia, hyponatremia, hypomagnesemia, volume-depletion hypotension, renal impairment, hyperuricemia, gout, hyperglycemia
Potassium-sparing diuretics	Hyperkalemia, hypotension
Beta-adrenergic blockers	Sinus bradycardia, fatigue, AV nodal heart block, bronchospasm, intermittent claudication, confusion, aggravation of acute heart failure, hyperglycemia
Alpha-beta adrenergic blockers (vasodilator-beta adrenergic blockers)	Hypotension, heart block, sinus bradycardia, bronchospasm
$Alpha_1$-adrenergic antagonists	Orthostatic hypotension
Angiotensin-converting enzyme inhibitors	Cough, hyperkalemia (only with eGFR <50 mL/min), angioneurotic edema, rash, altered taste sensation, renal impairment
Angiotensin receptor blockers	Hyperkalemia, renal impairment
Central-acting drugs	Sedation, constipation, dry mouth
Calcium antagonists (non-dihydropyridines)	Rash, exacerbation of GERD symptoms, sinus bradycardia, heart block, heart failure, constipation (verapamil), gingival hyperplasia
(dihydropyridines)	Peripheral edema, heart failure, tachycardia, aggravation of angina pectoris (short-acting agents)
Direct vasodilators	Tachycardia, fluid retention, angina pectoris

AV indicates atrioventricular; eGFR, estimated glomerular filtration rate; and GERD, gastroesophageal reflux disease.

An average of 2 to 4 antihypertensive medications are required for BP control in most high-risk patients with hypertension and comorbid conditions such as renal disease or diabetes mellitus (711). As seen in Figure 12, ≥2 antihypertensive agents were needed to achieve target BP goals in the majority of patients (712). As new treatment strategies are added, the increased pill burden may contribute to problems with compliance.

There is an inverse relationship between the number of daily drug doses and the adherence rate (692,699). A meta-analysis for chronic conditions including CVD showed that mean dose-taking compliance was 79% for 1 dose, 69% for 2 doses, 65% for 3 doses, and 51% for 4 doses ($p<0.001$ among dose schedules) (699). Thus, it is important to prescribe therapies that will help to alleviate pill burden. Reduction in dose frequency through selection of once-daily agents improves medication compliance (713), particularly in hypertension treatment (698). Once-daily dosing was shown to have the highest compliance rate among dosing schedules for a range of CV disorders: as the number of doses per day increased, compliance rates declined (699,714). Although these data are from cohorts that included few elderly patients, reducing daily dose frequency was found to produce a significant improvement in compliance. The average compliance rate was significantly higher for once-daily dosing compared with multiple-daily dosing (91.4% versus 83.2%, $p<0.001$). Average compliance was higher for once-daily (92.7%) versus twice-daily dosing (87.1%, $p=0.026$).

One concern regarding once-daily formulations is that when patients are not adherent, they miss an entire day of medication as opposed to missing half a day or less with multiple dosing. Although this is an important consideration, the properties of long-acting oral formulations may help to provide protection from adverse events even when compliance is not perfect. Although BP control was significantly reduced in patients who were only partially adherent (<80% of prescribed pills taken) to short-acting, twice-daily diltiazem, this was not the case in patients who were only

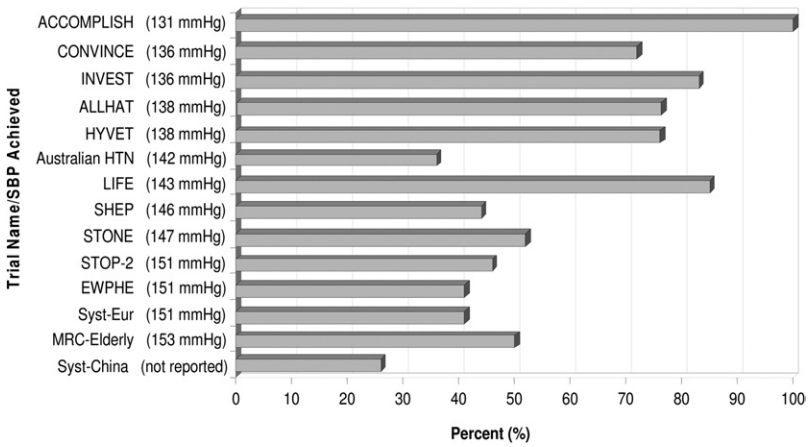

Figure 12. Percentage of People in Outcomes Trials of the Elderly Taking 2 or More Antihypertensive Medications

ACCOMPLISH (8) indicates Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension; ALLHAT (9), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; Australian HTN (718), Australian Hypertension Study; CONVINCE (719), Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial; EWPHE (12), European Working Party on High Blood Pressure in the Elderly; HYVET (4), Hypertension in the Very Elderly Trial; INVEST (584), International Verapamil-Trandolapril Study; LIFE (14), Losartan Intervention For Endpoint Trial; MRC-Elderly (15), Medical Research Council Trial of treatment of hypertension in older adults; SBP, systolic blood pressure; SHEP (16), Systolic Hypertension in the Elderly Program; STONE (17), Shanghai Trial of Hypertension in the Elderly; STOP-2 (720), Swedish Trial in Old Patients with Hypertension; Syst-China (19), Systolic Hypertension in China Trial; and Syst-Eur (20), Systolic Hypertension in Europe Trial.

partially adherent to the once-daily amlodipine formulation (715). This suggests that the negative consequences of partial compliance for BP control may be offset by selecting agents with a longer duration of action beyond the dosing intervals. Overall, use of once-daily drug formulations provide a significant improvement in compliance to a prescribed regimen and may improve outcomes.

Cost Considerations: Although higher out-of-pocket medication costs are associated with reduced compliance in the overall population, this is a particular concern in the elderly because of their generally lower incomes. Clinicians should use generic and formulary drugs when possible. Conversely, an impact on overall healthcare costs is also observed with poor compliance. An analysis of the association between interruption or termination of therapy and total healthcare costs (716) using paid claims data (California Medicaid) found each patient with interrupted antihypertensive drug therapy accumulated an additional $873 in healthcare costs during the first year. These costs were primarily the result of increased hospital expenditures (716). These findings were confirmed in a patient primary database in the United Kingdom (717).

5. Future Considerations

5.1. Prevention of Hypertension

Most consideration of preventing hypertension has been targeted at young people, and little information is available about preventive strategies in the elderly. Increases in SBP occur with aging in most societies around the world. Unfortunately, there are no clear explanations for these exceptions and thus no clinical guidance (721). It is likely that patterns of decreasing physical activity and weight gain with age in industrialized societies partially explain this trend for increasing SBP with age.

Usual recommendations for hypertension prevention are based on the following lifestyle changes: reduced sodium intake; weight loss; moderation of alcohol use; diets centered on fresh produce; and physical activity (722). Excess weight is common in older people, so weight loss represents an opportunity for slowing progression to hypertension. Likewise, use of the DASH diet, based on increased intake of fresh produce and discussed elsewhere in this report, has a BP-lowering effect. Although dietary strategies are not easy to achieve or sustain in younger people, it is possible that elderly people might be more acutely sensitive to the CV consequences of rising BPs and thus more motivated to make lifestyle changes, including the assumption of increased physical activity such as walking.

Perhaps the best documented of these approaches in elderly people is reduced dietary sodium. A study in China demonstrated that switching to sodium intake at the lower end of the usual dietary range produced meaningful BP reductions in older persons (723). A possible explanation for this is that the reactive increase in activity of the RAAS that blunts antihypertensive efficacy of salt restriction is less active in the elderly (724,725). From a mechanistic point of view, sodium and the RAAS have synergistic effects accelerating arterial disease, including arterial stiffening that leads to systolic hypertension of the elderly (726). Indeed, it has been suggested that aging may increase sensitivity of arteries to sodium (727). Integrity of endothelium, vascular smooth muscle cells, and connective tissue are all compromised by sodium so as to reduce vascular compliance, particularly in concert with effects of AII and aldosterone. Evidence implicates the role of the high vascular tissue concentrations of AII found in the elderly in amplifying adverse changes in extracellular tissues, so increasing rigidity of the wall structure (727).

These considerations would support the dual strategies of dietary salt restriction and RAAS blockade for preventing or modifying the appearance of hypertension in older people. One trial, albeit in a young-to-middle-aged cohort, showed 2-year intervention with an ARB in patients with prehypertension modestly but significantly reduced progression to overt hypertension (728). It is not known whether this strategy would be effective in an older group. On theoretical grounds, addition of a CA to a RAAS blocker might provide additional inhibition of adverse vascular proliferative changes (729).

At present, prevention of hypertension in the elderly should be based primarily on a strategy of dietary salt restriction, weight control, and physical activity. This could be augmented by relatively early introduction of RAAS blockade in stage 1 hypertension with the intent of limiting further progression of hypertensive disease.

5.2. Unanswered Questions

There remain many important but unresolved issues regarding hypertension treatment in the elderly. One is to agree on a working definition of the term *elderly.* Another is to establish BP values for making the diagnosis of hypertension as well as setting targets for treatment. A third is to identify, for those patients in whom pharmacological therapy is indicated, which drugs will be most effective for reducing CV events. A final question is whether there is a subgroup of elderly patients with hypertension in whom treatment is not beneficial.

Defining elderly is a difficult task, as discussed earlier in this document. Because of the great heterogeneity among individuals in the aging process, it is not possible to readily assign an overall chronological value that establishes the state of being elderly. Some octogenarians can be fully active in the work environment or elsewhere on a daily basis, but others are not so fortunate. Given this marked heterogeneity of health and physiological function in older adults, it is more important to focus on defining the extent of these age-associated conditions than on using chronologic age to define and treat the elderly patient with hypertension.

Ongoing and future research will further explore the causes and mechanisms of age-related development and

progression of vascular disease. It is clear that age, apparently independent of other CV risk factors, is a powerful predictor of events. In the future, it should be possible to apply objective measurements of vascular or other clinical properties to better define hypertension and to tailor therapy.

The most practical definition of hypertension in the elderly should describe a BP level above which medical intervention—lifestyle changes or drugs—could be expected to provide clinical benefits. Although several clinical trials have reported beneficial results of treating hypertension in the elderly, these studies have not provided clear guidance for selecting a specific BP value that could be used to diagnose hypertension or to use as a target for treatment. A report from INVEST found that patients who had BP <140/90 mm/Hg at ≥75% of their follow-up visits had the lowest risk for adverse outcomes (730). As a simple generalization, it could be stated that pretreatment SBP >160 mm Hg would fit the profile of most of these studies, including HYVET (4), as would a target SBP <150 mm Hg. These studies have shown clinical benefits with achieved SBP values averaging in the 140s, 150s, and 160s. Thus, unlike previous guidelines that addressed the full spectrum of adults (22,23), there is limited evidence in the elderly to support a value of 140 mm Hg as a diagnostic and therapeutic threshold. There are also limited data as to whether patients with initial SBP between 150 and 159 mm Hg would benefit from treatment (731). Nevertheless, achieved values <140 mm Hg for those ≤79 years of age are appropriate; but for those ≥80 years of age, 140 to 145 mm Hg, if tolerated, can be acceptable.

Until recently, no randomized trials had compared effects on clinical outcomes of achieving different BP values in older adults. However, in 2009, the Cardio-Sis (Studio Italiano Sugli Cardiovascolari del Controllo della Pressione Arteriosa Sistolica) trial, in 1,111 nondiabetic patients (mean age 67 years) with baseline SBP ≥150 mm Hg reported a reduction in the primary outcome, the rate of ECG LVH at 2 years median follow-up in patients randomized to a SBP goal <130 mm Hg versus a goal of 140 mm Hg using open-label drugs (11.4% versus 17%, OR: 0.63; 95% CI: 0.43 to 0.91; p=0.013). In addition, a composite CV endpoint occurred in 9.4% in the usual control group versus 4.8% in the tight-control group (HR: 0.50; 95% CI: 0.31 to 0.79; p=0.003) (732). Although the age–treatment group interaction was nonsignificant, the greatest reduction in the primary outcome was seen in the subgroup >70 years of age (732). Other than Cardio-Sis, comparisons of different BP treatment targets in the elderly are limited to post hoc interpretations of previously conducted studies comparing different achieved BP levels (4,11,15,16,18,20,526,529). However, as discussed earlier in this report, these studies varied, not only in their target BPs, but also in patient selection, drug choices, and duration of therapy. Furthermore, they were all based primarily on SBPs and generally did not attempt to reach the aggressive BP goals used in more contemporary hypertension trials in younger cohorts (8,9,21).

Until additional data from RCTs comparing various BP targets in the elderly become available, existing epidemiologic and clinical trial data suggest a diagnostic and therapeutic threshold for hypertension of 140/90 mm Hg remains reasonable in adults 65 to 79 years of age. As mentioned previously (see Section 1.4), the ACCORD BP, although limited to high-risk persons with type 2 diabetes mellitus, found no additional benefit from an intense BP-lowering strategy targeting SBP of 120 mm Hg, with an increase in adverse experiences related to antihypertensive drugs in the cohort ≥65 years of age. The soon-to-be-launched SPRINT (Systolic Blood PRessure INtervention Trial) should provide additional information about the optimal BP treatment goal in older adults. Among individuals >80 years of age, HYVET data suggest a SBP of 150 mm Hg as the diagnostic criterion for hypertension and the treatment target in octogenarians and beyond. Should SBP fall readily to lower levels, it would be reasonable to maintain this level of control, provided treatment is well tolerated. Yet it is the low DBP that concerns many clinicians from the J-curves reported (268). Clinicians, however, should consider 2 exceptions to this recommendation. First, in those elderly patients in whom a SBP <150 mm Hg is readily and safely obtained with just 1 or 2 drugs, a further modest intensification of treatment to achieve a value <140 mm Hg could be considered, even though there is no firm evidence to support this target. The second exception to the recommendation applies to patients whose SBP remain ≥150 mm Hg under the following 3 circumstances that: 1) despite taking a regimen of 4 well-selected and appropriately dosed drugs, this goal has not been achieved; 2) prescribed therapy is causing unacceptable side effects, particularly postural changes that could result in the potentially disastrous consequences of physical injury; and 3) in attempting to reach the SBP target, the DBP is being reduced to a potentially dangerous level <65 mm Hg. Under any of these circumstances, the lowest safely achieved SBP ≥150 mm Hg is acceptable.

Finally, there is no evidence in older people to support the use of lower BP targets in patients at high risk because of conditions such as diabetes mellitus, CKD, or CAD.

Drug choice to treat the elderly is often dictated by concomitant conditions (e.g., CAD, HF, diabetes mellitus, and kidney insufficiency). Diuretics, CAs, and RAAS blockers have all been effective in reducing events in the elderly. There are no authoritative comparison trials that would indicate superiority of monotherapy with 1 class over the other. As discussed elsewhere, most patients will require combination drug therapy (Table 9). Diuretic-based regimens were effective in earlier studies, although a large hypertension trial that included mostly elderly patients indicated that amlodipine is preferable to a thiazide in combination treatment for reducing fatal and nonfatal CV outcomes (579).

5.3. Future Research

Future research should include both fundamental and clinical investigation directed toward defining the pathogenesis

of increased vascular and LV stiffness, characteristic of elderly patients with hypertension. The goal of this research should be to develop strategies to both prevent and reverse this form of vascular pathology, which is the cornerstone of systolic hypertension in the elderly. Another direction should be well-designed randomized controlled outcome trials to define appropriate thresholds and goals for antihypertensive treatment in the elderly. These might include randomizing persons with SBP >160 mm Hg to SBP goals of either 150 mm Hg or 140 mm Hg. Safety considerations would be important in these trials. Finally, comparative effectiveness trials are needed to test various treatment strategies (i.e., different drug regimens and different intensities of lifestyle modification) and to assess the relative safety and efficacy of these approaches in the prevention of CV mortality and morbidity and total mortality. Strategies using non-physician providers (nurses, pharmacists, and trained laypersons) should be tested, given the increasing demands of an expanding elderly population and the growing shortage of physicians.

Potential New Therapeutic Strategies: Because several efficacious and well-tolerated antihypertensive drug classes are now available, there are relatively few new classes in development. It is likely that advances for the foreseeable future will focus primarily on innovative strategies for selecting and combining available drugs. Thiazide diuretics and dihydropyridine CAs have been the best-studied drugs in older cohorts. However, there is growing evidence both of the fundamental role of RAAS mechanisms in the genesis of vascular pathology and hypertension in the elderly and of the benefits of pharmacologically blocking this system.

As emphasized elsewhere in this document, a limiting factor for therapy in older people is uncertainty about appropriate BP targets. Whereas the general BP goal in adults has been <140/90 mm Hg, HYVET results in octogenarians showed meaningful event reduction with SBP in the mid-150s (4). However, the Cardio-Sis trial showed lower event rates in "younger" elderly hypertensive patients with a goal of SBP <130 mm Hg versus <140 mm Hg (732). Yet the results of ACCORD BP (Section 1.4), found no benefit targeting 120 mm Hg versus 140 mm Hg in high-risk patients with an increase in drug-related adverse experiences. A trial now underway in Japan is comparing event rates in elderly patients whose SBPs are reduced to <140 mm Hg versus 140 to 160 mm Hg (733). The SPRINT trial, sponsored by NHLBI, is comparing SBP targets of 120 mm Hg versus 140 mm Hg in higher-risk adults, and oversampling elderly patients. These trials and others will hopefully cast more light on 1 key treatment objective in older patients: avoidance of cognitive dysfunction, perhaps most readily accomplished by effective BP control (260).

Future treatment strategies should evaluate sodium restriction together with therapeutic blockade of the RAAS. In fact, RAAS blockers are all effective in elderly patients with hypertension (602,734). Further research with bradykinin and related targets, including newly developed angiotensin immunotherapy (735), may also be warranted. Innovative combinations of CAs with RAAS blockers have demonstrated benefit in high-risk patients and could be especially useful for the elderly (8).

Endothelin antagonists could also be valuable in older patients. Endothelin antagonists provide efficacy in resistant hypertension, and their main drawback, teratogenicity, is not an issue in elderly patients (736). Likewise, increased use of aldosterone antagonists could be anticipated, for in low doses, they can also be effective for adjunctive therapy (737). Moreover, a new progestogen, drospirenone, has exhibited antialdosterone activity and BP-lowering effects in post-menopausal women and may represent a novel strategy (738).

There is limited information on non-drug substances for hypertension treatment in the elderly. Soy nuts, for instance, reduce BP in elderly women, though it is not clear whether soy proteins or other components produce this effect (739,740). Studies with calcium and vitamin D supplements or vitamin C have not demonstrated useful BP effects (241).

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Key Words: ACCF/AHA Expert Consensus Documents ■ antihypertensive agents ■ elderly ■ risk assessment ■ hypertension comorbidities ■ hypertension pathophysiology ■ hypertension therapy.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHERS—ACCF/AHA 2011 EXPERT CONSENSUS DOCUMENT ON HYPERTENSION IN THE ELDERLY

Name	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Wilbert S. Aronow	New York Medical College—Clinical Professor of Medicine	None	None	None	None	None	None
Jerome L. Fleg	National Heart, Lung, and Blood Institute—Medical Officer	None	None	• Bristol-Myers Squibb	None	None	None
Carl J. Pepine	University of Florida, Division of Cardiovascular Medicine—Professor of Medicine	• Angioblast–DSMB member • Boehringer Ingleheim • CV Therapeutics • DCRI/The Medicines Company–Interim Analysis Review Committee • Forest Pharmaceuticals • Indigo • NicOx • Novartis/Cleveland Clinic DSMB Chair • Pfizer	None	None	• Abbott* • Baxter* • Bioheart* • Cardium* • NIH/NHLBI* • Pfizer* • Viron*	• AstraZeneca* • AtCore* • Baxter* • Boehringer Ingelheim* • CV Therapeutics* • Cardionet* • Daiichi Sankyo* • GlaxoSmithKline* • Merck* • Pfizer* • Sanofi-aventis* • Schering-Plough* • The Medicines Company* • Wyeth*	None
Nancy T. Artinian	Wayne State University College of Nursing—Professor; Associate Dean for Research; Director of the Center for Health Research	None	None	None	None	None	None
George Bakris	University of Chicago Pritzker School of Medicine—Professor of Medicine; Director, Hypertensive Diseases Unit	• Abbott • Boehringer Ingelheim • Daichii Sankyo • Forest Pharmaceuticals • Gilead • GlaxoSmithKline • Merck • Novartis • Takeda • Walgreens	• Forest Pharmaceuticals • Novartis	None	• Forest Pharmaceuticals • GlaxoSmithKline • Juvenile Diabetes Research Foundation • National Institutes of Health (NIDDK)	None	None
Alan Brown	Midwest Heart Specialists—Medical Director, Midwest Heart Disease Prevention Center	• Abbott • Merck • Sanofi-aventis	• Abbott • AstraZeneca* • GlaxoSmithKline • Merck* • Merck Schering-Plough • Novartis • Pfizer	None	None	None	None
Keith C. Ferdinand	Association of Black Cardiologists—Chief Science Officer	• AstraZeneca • Merck • Pfizer • Roche	• AstraZeneca	None	• Novartis	None	None
Mary Ann Forciea	University of Pennsylvania Health System—Clinical Associate Professor of Medicine	• National Board of Medical Examiners	None	None	None	None	None
William Frishman	New York Medical College/Westchester Medical Center—Rosenthal Professor; Chairman of Medicine	• Forest Pharmaceuticals • GlaxoSmithKline • Pfizer	• Bristol-Myers Squibb • Forest Pharmaceuticals • Novartis • Pfizer	• Merck*	None	None	None

Name	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Cheryl Jaigobin	University Health Network, University of Toronto—Doctor	None	• Boehringer Ingelheim • Sanofi-aventis	None	None	None	None
John B. Kostis	UMDNJ–Robert Wood Johnson Medical School—Professor of Medicine and Pharmacology; Chairman, Department of Medicine	• Novartis • Pfizer • Pharmacopeia • Sankyo	• Forest* • Pfizer	None	None	None	• Arent Fox (legal firm)*
Guiseppe Mancia	University of Milano at Bicocca—Professor of Medicine	• Boehringer Ingelheim • Merck • Novartis	• Bayer • Boehringer Ingelheim • Novartis • Servier	None	None	None	None
Suzanne Oparil	University of Alabama at Birmingham—Professor Medicine, Physiology and Biophysics; Director, Vascular Biology and Hypertension Program	• Bristol-Myers Squibb* • Daiichi Sankyo* • Merck* • Novartis* • Pfizer* • Sanofi-aventis* • The Salt Institute*	• Boehringer Ingelheim • Bristol-Myers Squibb • Daiichi Sankyo • Merck	None	• Daiichi Sankyo • Eisai • Forest Laboratories • GlaxoSmithKline • Merck • Novartis • Sanofi-aventis	None	None
Eduardo Ortiz	National Heart, Lung, and Blood Institute—Senior Medical Officer	None	None	None	None	None	None
Efrain Reisin	LSUHSC, New Orleans—Professor of Medicine; Chief, Section of Nephrology and Hypertension	• Forest Research Institute • Mission Pharmacal • AstraZeneca	None	None	• AstraZeneca*	None	None
Michael W. Rich	Washington University School of Medicine—Professor of Medicine	None	None	None	• Astellas Pharma • Bristol-Myers Squibb • Sanofi-aventis	None	None
Douglas D. Schocken	Duke University School of Medicine—Professor of Medicine	• ARCAS Biopharma	• AstraZeneca	None	• Boehringer Ingelheim • Novartis • Sanofi-aventis	None	None
Michael A. Weber	State University of New York Downstate College of Medicine—Professor of Medicine	• Boehringer Ingelheim • Bristol-Myers Squibb • Daiichi Sankyo • Forest Pharmaceuticals • Gilead • Novartis • Takeda Pharmaceuticals	• Boehringer Ingelheim • Bristol-Myers Squibb • Daiichi Sankyo • Forest Pharmaceuticals • GlaxoSmithKline • Novartis • Sanofi-aventis	None	None	None	None
Deborah J. Wesley	Wake Forest University Health Sciences—Cardiology Nurse Manager	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. ACCF indicates American College of Cardiology Foundation; DSMB, Data and Safety Monitoring Board; NIDDK, National Institute of Diabetes & Digestive & Kidney Diseases; NIH, National Institutes of Health; and NHLBI, National Heart, Lung, and Blood Institute.

*Indicates significant relationship.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHERS—ACCF/AHA 2011 EXPERT CONSENSUS DOCUMENT ON HYPERTENSION IN THE ELDERLY

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Emaad M. Abdel-Rahman	Official Reviewer—American Society of Nephrology	None	None	None	None	None	None
John Bisognano	Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Ellen D. Burgess	Official Reviewer—American Society of Nephrology	• Bristol-Myers Squibb • Schering-Plough	• Boehringer Ingelheim • Bristol-Myers Squibb* • Merck Frosst* • Novartis Pharmaceuticals • Sanofi-aventis* • Schering-Plough	None	• Steering Committee for trial that is now "dead" —Bayer	None	None
Richard Cannon, III	Official Reviewer—National Heart, Lung and Blood Institute	None	None	None	None	None	None
William Cushman	Official Reviewer—American Heart Association and American Society of Preventive Cardiology	• Bristol-Myers Squibb • Novartis Pharmaceuticals* • Sanofi-aventis • Takeda Pharmaceuticals • Theravance	None	None	• NHLBI* • Novartis Pharmaceuticals	None	None
Richard M. Dubinsky	Official Reviewer—American Academy of Neurology	• Allergan Pharmaceuticals, physician training	• Allergan Pharmaceuticals	None	• Site investigator for the following through subcontracts with the University of Rochester and Massachusetts General Hospital: • Allergan Pharmaceuticals • Merz Pharmaceuticals • NIH	• American Academy of Neurology: Chair, Practice Improvement Subcommittee; Member, Practice Committee • Outgoing member, Huntington's Study Group Executive Committee	• Defense deposition testimony, stroke in a young person 2008 • Defense deposition and trial testimony, alleged traumatic brain injury 2009
Victor Ferrari	Official Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	None	None	None	None	None	None
Lawrence Fine	Official Reviewer—National Heart, Lung and Blood Institute	None	None	None	None	None	None
Sverre Kjeldsen	Official Reviewer—European Society of Hypertension	None	• AstraZeneca LP • Boehringer Ingelheim • Novartis Pharmaceuticals • Sanofi-aventis • Takeda Pharmaceuticals	None	• Norwegian Government	None	None
Robert Palmer	Official Reviewer—American Geriatrics Society	None	None	None	None	None	None
Robert A. Phillips	Official Reviewer—American Society of Hypertension	None	None	None	• Monarch Pharmaceuticals*	None	None
Joseph Redon	Official Reviewer—European Society of Hypertension	None	• Boehringer Ingelheim • Merck Shark & Dohme • Novartis Pharmaceuticals • Pfizer	None	None	None	None

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Elijah Saunders	Official Reviewer—Association of Black Cardiologists	• Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership • Forest • Novartis Pharmaceuticals • Pfizer	• Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership • Forest Laboratories • Novartis Pharmaceuticals • Pfizer	None	• Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership • Forest Laboratories • Novartis Pharmaceuticals • Pfizer	None	None
Pushpendra Sharma	Official Reviewer—American Geriatrics Society	None	None	None	None	None	None
Vincenza Snow	Official Reviewer—American College of Physicians	None	None	None	• Boehringer Ingelheim • Bristol-Myers Squibb • Centers for Disease Control and Prevention • Merck Vaccines • Novo Nordisk • Sanofi Pasteur • Wyeth Pharmaceuticals	None	None
Sandra J. Taler	Official Reviewer—American Society of Hypertension	None	None	None	None	None	None
Carole Warnes	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Paul Whelton	Official Reviewer—American Heart Association	None	None	None	None	None	None
Jackson Wright	Official Reviewer—Association of Black Cardiologists	• Daiichi Sankyo • Novartis Pharmaceuticals • Sanofi-aventis • Take Care Health Systems • Wyeth Pharmaceuticals	None	None	• CVRx	None	None
Nathan Wong	Official Reviewer—American Society of Preventive Cardiology	None	None	None	None	None	None
Daniel Forman	Content Reviewer—Geriatric	None	None	None	None	None	None
Stanley Franklin	Content Reviewer—Hypertension	None	None	None	None	None	None
Andrew P. Miller	Content Reviewer—Hypertension	None	• AstraZeneca LP • Boehringer Ingelheim • Pfizer	None	• Novartis	• John A. Hartford Foundation	None
Nanette Wenger	Content Reviewer—Geriatrics	• Abbott Laboratories • AstraZeneca LP • Boston Scientific • Genzyme • Gilead Sciences* • Medtronic • Merck • Pfizer • Schering-Plough*	None	None	• Abbott Laboratories* • Eli Lilly* • Gilead Sciences* • Merck* • NHLBI* • Pfizer* • Sanofi-aventis*	None	None

This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. ACCF indicates American College of Cardiology Foundation; NIH, National Institutes of Health; and NHLBI, National Heart, Lung, and Blood Institute.

*Significant relationship.

APPENDIX 3. ABBREVIATION LIST

ACEI = angiotensin-converting enzyme inhibitors
AF = atrial fibrillation
AMD = age-related macular degeneration
ARB = angiotensin receptor blocker
BA = balloon angioplasty
BP = blood pressure
CA = calcium antagonist
CHD = coronary heart disease
CKD = chronic kidney disease
CV = cardiovascular
CVD = cardiovascular disease
DBP = diastolic blood pressure
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate
HCTZ = hydrocholorothiazide
ISH = isolated systolic hypertension
LV = left ventricular
LVH = left ventricular hypertrophy
NSAIDs = nonsteroidal anti-inflammatory drugs
QoL = quality of life
RAAS = renin-angiotensin-aldosterone system
RAS = renal artery stenosis
RCT = randomized control trial
SBP = systolic blood pressure
TSH = thyroid stimulating hormone

ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly

American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association ofBlack Cardiologists, European Society of Hypertension, Wilbert S. Aronow, Jerome L. Fleg, Carl J. Pepine, Nancy T. Artinian, George Bakris, Alan S. Brown, Keith C. Ferdinand, Mary Ann Forciea, William H. Frishman, Cheryl Jaigobin, John B. Kostis, Giuseppi Mancia, Suzanne Oparil, Eduardo Ortiz, Efrain Reisin, Michael W. Rich, Douglas D. Schocken, Michael A. Weber, and Deborah J. Wesley

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