Introduction

The age-adjusted prevalence of systemic hypertension in the United States is 64% of older men and 78% of older women according to the American Heart Association (AHA) Statistics Committee and Stroke Statistics Committee [1]. Patients with hypertension should be evaluated for other cardiovascular risk factors including smoking, dyslipidemia, diabetes mellitus, age older than 55 years for men and 65 years for women, body mass index $\geq 30$ kg/m$^2$, physical inactivity, microalbuminuria, an estimated glomerular filtration rate $<60$ ml/min/1.73 m$^2$, and for a family history of premature cardiovascular disease (younger than 55 years in fathers or brothers and younger than 65 years in mothers or sisters) [2]. Patients with hypertension should also be evaluated for target organ damage and clinical cardiovascular disease including left ventricular hypertrophy, prior myocardial infarction, angina pectoris, prior coronary revascularization, congestive heart failure, stroke or transient ischemic attack, peripheral arterial disease, nephropathy, and retinopathy [2].

The higher the systolic or diastolic blood pressure, the higher the risk of cardiovascular morbidity and mortality [3]. Increased systolic blood pressure and pulse pressure are stronger risk factors for cardiovascular morbidity and mortality in older persons than is increased diastolic blood pressure [4-6]. An increased pulse pressure found in older persons with isolated systolic hypertension indicates decreased vascular compliance in the large arteries and is even a better marker of risk than is systolic or diastolic blood pressure [4-6].

Systemic hypertension is a major risk factor for coronary events [2, 7-12], for stroke [2, 7, 8, 12-15], for congestive heart failure (CHF) [2, 7, 8, 16, 17], and for peripheral arterial disease [2, 18-22]. Hypertension is present in approximately 69% of patients with a first myocardial infarction [1], in approximately 77% of patients with a first stroke [1], in approximately 74% of patients with CHF [1], and in 60% of patients...
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with peripheral arterial disease [22]. Hypertension is also a major risk factor for a dissecting aortic aneurysm, sudden cardiac death, angina pectoris, atrial fibrillation, diabetes mellitus, the metabolic syndrome, chronic kidney disease, thoracic and abdominal aortic aneurysms, left ventricular hypertrophy, vascular dementia, Alzheimer's disease, and ophthalmologic disorders [2].

At 40-month follow-up of 664 men, mean age 80 years, and at 48-month follow-up of 1,488 women, mean age 82 years, hypertension increased the incidence of new coronary events in men (relative risk = 2.0, p = 0.0001) and in women (relative risk = 1.6, p = 0.0001) [9]. At 42-month follow-up of 664 men, mean age 80 years, and at 48-month follow-up of 1,488 women, mean age 82 years, hypertension increased the incidence of new stroke in men (relative risk = 2.2, p = 0.0001) and in women (relative risk = 2.4, p = 0.0001) [13]. Hypertension was an independent risk factor for peripheral arterial disease in 467 men, mean age 80 years, with an odds ratio of 2.2 (p = 0.023) and in 1,444 women, mean age 81 years, with an odds ratio of 2.8 (p = 0.001) [20]. Hypertension was an independent risk factor for CHF in 2,902 patients (926 men and 1,976 women), mean age 81 years, with a risk ratio of 2.5 (p = 0.0001) [16]. In 61 prospective studies of 1 million adults, coronary heart disease mortality increased with each decade from ages 40-49 to 80-89 and with each increase in systolic blood pressure from 120 to 140 to 180 mm Hg [23].

Older persons are more likely to have hypertension and isolated systolic hypertension, to have target organ damage and clinical cardiovascular disease, and to develop new cardiovascular events. Older persons also have the lowest rates of blood pressure control [2, 7, 24, 25]. Blood pressure is adequately controlled in 36% of men and 28% of women aged 60-79 years and in 38% of men and 23% of women aged 80 years and older [25]. Prevalent comorbidities, polypharmacy, an asymptomatic state, side effects from medications, and high cost of medications contribute to lower blood pressure control rates in older persons [2, 26]. A blood pressure of <140/90 mm Hg was achieved in 70% of 492 Medicaid or private insurance patients versus 38% of 122 patients who had to pay for their antihypertensive medications (p<0.001) [26].

Effect of antihypertensive therapy in reducing cardiovascular events

Numerous prospective, double-blind, randomized, placebo-controlled studies have shown that antihypertensive drug therapy reduces the development of new coronary events, stroke, and CHF [2, 7, 27-38]. Older patients with hypertension if treated appropriately will have a greater absolute reduction in cardiovascular events such as major coronary events, stroke, CHF, and renal insufficiency and a greater reduction in dementia [39] than in younger patients.

Therapy with antihypertensive drugs reduces the incidence of all strokes 38% in women, by 34% in men, by 36% in older persons, and by 34% in persons older than 80 years [14]. The overall data suggest that the decrease of stroke in older persons with hypertension is related more to a reduction in blood pressure than to the type of antihypertensive drugs used [14].

In the Perindopril Protection Against Recurrent Stroke Study [40], perindopril plus indapamide reduced stroke-related dementia by 34% and cognitive decline by 45%. In the Systolic Hypertension in Europe trial [41], nitrendipine reduced dementia by 55% at 3.9-year follow-up. In 1900 older African-Americans, antihypertensive drug treatment reduced cognitive impairment by 38% [42]. In the Rotterdam Study [43], antihypertensive drugs decreased vascular dementia by 70%.

At 1.8-year follow-up of 3, 845 patients aged 80 years and older (mean age 83.6 years) in the Hypertension in the Very Elderly Trial (HYVET) antihypertensive drug treatment reduced the incidence of the primary end point (fatal or non-fatal stroke) by 30% (p = 0.06) [38]. Antihypertensive drug treatment reduced fatal stroke by 39% (p = 0.05), all-cause mortality by 21% (p= 0.02), death from cardiovascular causes by 23% (p = 0.06), and heart failure by 64% (p<0.001).

Although the optimal blood pressure treatment goal has not been determined, a therapeutic target of less than 140/90 mm Hg in patients younger than 80 years and a systolic blood pressure of 140-145 mm Hg if tolerated in patients aged 80 years and older is reasonable [2]. We should also be careful to avoid intensive lowering of the blood pressure, especially in
patients with diabetes mellitus and coronary artery disease, as this might be poorly tolerated and might increase cardiovascular events (the J-curve phenomenon) [2, 44-48]. Until additional data from randomized controlled trials (including the Systolic Blood Pressure Intervention Trial-SPRINT) comparing various blood pressure targets in the elderly and younger 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 younger than 80 years and of 150 mm Hg of systolic blood pressure in adults 80 years of age and older [2].

**Lifestyle measures**

Lifestyle modification should be used to prevent mild hypertension and to decrease the dose levels of drugs needed to control hypertension. Weight reduction, consuming a diet rich in fruits, vegetables, and low-fat dairy products with a reduced amount of saturated fat and total fat, sodium reduction to not exceed 1.5 grams daily, smoking cessation, regular aerobic physical activity, avoidance of excessive alcohol intake, avoidance of excessive caffeine, and avoidance of drugs which can increase blood pressure including nonsteroidal antiinflammatory drugs, glucocorticoids, and sympathomimetics are recommended [2, 7]. Implementing a national salt reduction program is likely a simple and cost effective way of improving public health [49, 50].

Long-term observational follow-up was performed in 744 patients in the trial of hypertension prevention (TOHP) I (10 years after its end) and in 2,382 patients in TOHP II (5 years after its end) in which persons with prehypertension were randomized to sodium reduction or usual diet (25%-35% greater sodium intake) [51]. In these studies, sodium reduction decreased cardiovascular events by 25% (p =0.04) [51]. At 31-month follow-up of 1,981 Taiwanese veterans, mean age 75 years, living in a retirement home, those randomized to a potassium enriched diet with 50% less sodium had a 41% reduction in cardiovascular mortality (95% CI, 0.37, 0.95) compared with those randomized to a regular salt diet [52].

At 14.8-year follow-up of 12,267 adults in the Third National Health and Nutrition Examination Survey, a higher sodium intake was associated with a 20% increase in all-cause mortality per 1,000 mg of sodium intake per day (p = 0.02), whereas a higher potassium intake was associated with a 20% reduction in mortality per 1,000 mg of potassium intake per day (p = 0.01) [53]. For the sodium-potassium ratio, compared with the lowest quartile, the highest quartile increased all-cause mortality 46% (p<0.001), cardiovascular mortality 46% (P<0.001), and ischemic heart disease mortality 215% (p<0.001) [53]. Current guidelines suggest no more than 2,300 mg of sodium daily in the general population and no more than 1,500 mg of sodium daily in the elderly, in blacks, and in persons with hypertension, diabetes mellitus, chronic kidney disease, or CHF [54, 55].

**Use of antihypertensive drug therapy**

A meta-analysis of 147 randomized trials including 464,000 patients with hypertension showed that except for the extra protective effect of beta blockers given after myocardial infarction and a minor additional effect of calcium channel blockers in preventing stroke, use of beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, and calcium channel blockers cause a similar reduction in coronary events and stroke for a given decrease in blood pressure [56, 57]. The proportionate decrease in cardiovascular events was the same or similar regardless of pretreatment blood pressure and the presence or absence of cardiovascular events [56, 57]. Diuretics, ACE inhibitors, ARBs, calcium channel blockers, or beta blockers may be used as initial therapy in the treatment of primary hypertension in older and in younger patients. Atenolol should not be used [58-60]. Beta blockers such as carvedilol, nebivolol, and bisoprolol are preferred [60]. Centrally acting agents, such as clonidine, reserpine, and guanethidine, should not be used as monotherapy because they have been associated with a high incidence of significant side effects, including sedation, depression, and constipation.

Most patients with hypertension will need 2 or more antihypertensive drugs to control their blood pressure [2, 7]. If the blood pressure is more than 20/10 mm Hg above the goal blood pressure, drug therapy should be initiated with 2 antihypertensive drugs [2, 7].

The initial antihypertensive drug should be given to older patients at the lowest dose and gradually increased to the maximum dose. If the anti-
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hypertensive response to the initial drug is inadequate after reaching the full dose of drug, a second drug from another class should be given if the person is tolerating the initial drug. If there is no therapeutic response or if there are significant adverse effects, a drug from another class should be substituted. If the antihypertensive response is inadequate after reaching the full dose of two classes of drugs, a third drug from another class should be added.

Before adding new antihypertensive drugs, the physician should consider possible reasons for inadequate response to antihypertensive drug therapy, including nonadherence to therapy, volume overload, drug interactions (use of nonsteroidal antiinflammatory drugs, caffeine, antidepressants, nasal decongestants, sympathomimetics, etc.), and associated conditions such as increasing obesity, smoking, excessive ethanol intake, and insulin resistance [2, 7]. Causes of secondary hypertension should be identified and treated in accordance with current guidelines [2, 7, 61].

Older patients with hypertension have a very high prevalence of associated medical conditions [2, 7]. The selection of antihypertensive drug therapy in these patients depends on their associated medical conditions [2, 7].

Falls or syncope may be due to orthostatic or postprandial hypotension [62]. Management of orthostatic and postprandial hypotension is discussed in detail elsewhere [62]. The dose of antihypertensive drug may need to be decreased or another antihypertensive drug given. Elderly frail persons are most susceptible to orthostatic and postprandial hypotension [62]. Measurements of blood pressure in the upright position, especially after eating, are indicated in these persons.

Use of antihypertensive drugs with associated medical conditions

Patients with prior myocardial infarction should be treated with beta blockers and ACE inhibitor [2, 7, 63-68]. In an observational prospective study of 1,212 older men and women with prior myocardial infarction and hypertension treated with beta blockers, ACE inhibitors, diuretics, calcium channel blockers, or alpha blockers, at 40-month follow-up, the incidence of new coronary events in patients treated with 1 antihypertensive drug was lowest in those treated with beta blockers or ACE inhibitors [63]. In patients treated with 2 antihypertensive drugs, the incidence of new coronary events was lowest in those treated with beta blockers plus ACE inhibitors [63].

Beta blockers should be used to treat patients with complex ventricular arrhythmias with abnormal [69] or normal [70] left ventricular ejection fraction and with CHF with abnormal[71, 72] or normal [72, 73] left ventricular ejection fraction. Beta blockers should also be used to treat patients with hypertension who have angina pectoris [74], myocardial ischemia [75], supraventricular tachyarrhythmias such as atrial fibrillation with a rapid ventricular rate [76, 77], hyperthyroidism [78], preoperative hypertension [7], migraine [7], or essential tremor [7].

In addition to beta blockers, patients with CHF should be treated with diuretics and ACE inhibitors and with aldosterone antagonists if needed [79]. ACE inhibitors or ARBs should be administered to patients with diabetes mellitus, chronic renal disease, or proteinuria [2, 7, 65, 80, 81]. Diuretics and ACE inhibitors are recommended to prevent recurrent stroke in patients with hypertension [7, 40]. Thiazide diuretics should be used to treat patients with osteoporosis [7].

It is also very important to treat other cardiovascular risk factors in patients with hypertension to reduce cardiovascular events, and mortality [2]. Smoking must be stopped [82]. Dyslipidemia must be treated [44, 82, 83]. Diabetes mellitus must be controlled [84-87].

The more aggressive control of blood pressure among patients at high risk for coronary artery disease such as those with diabetes mellitus, chronic kidney disease, coronary artery disease or coronary artery risk equivalent, or a 10-year Framingham risk score ≥10% with maintenance of the blood pressure below 130/80 mm Hg and below 120/80 mm Hg in patients with left ventricular dysfunction recommended by the AHA Task Force scientific statement in 2007 [88] was based upon expert medical opinion at that time, not on prospective, randomized, adequately controlled trial data [45].

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trials enrolled
4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina pectoris) [89]. The lowest cardiovascular events rates occurred with a systolic blood pressure between 130 to 140 mm Hg and a diastolic blood pressure between 80 to 90 mm Hg with a nadir of 136/85 mm.

An observational subgroup analysis was performed in 6,400 of the 22,576 patients enrolled in the International Verapamil SR-Trandolapril Study (INVEST) [90]. The study participants had diabetes mellitus and coronary artery disease. Patients were categorized as having tight control of their blood pressure if they could maintain their systolic blood pressure below 130 mm Hg and their diastolic blood pressure below 85 mm Hg, usual control if they could maintain their systolic blood pressure between 130 to 139 mm Hg, and uncontrolled if their systolic blood pressure was 140 mm Hg or higher.

During 16,893 patient-years of follow-up, a cardiovascular event rate of 12.6% occurred in patients with usual control of blood pressure versus 19.8% in patients with uncontrolled hypertension, \( p < 0.001 \) [90]. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure versus 12.7% in patients with tight control of blood pressure (\( p \) not significant). The all-cause mortality rate was 11.0% with tight control of blood pressure versus 10.2% with usual control of blood pressure (\( p = 0.06 \)). When extended follow-up was included, the all-cause mortality rate was 22.8% with tight control of blood pressure versus 21.8% with usual control of blood pressure, \( p = 0.04 \).

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial randomized 4,733 patients with type 2 diabetes mellitus to intensive blood pressure control with a target systolic blood pressure of <120 mm Hg or to standard blood pressure control with a target systolic blood pressure < 140 mm Hg [91]. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive blood pressure control group versus 133.5 mm Hg in the standard blood pressure control group. The annual rate of the primary outcome was 1.87% in the intensive blood pressure control group versus 2.09% in the standard blood pressure control group (\( p \) not significant). The annual rate of death from any cause was 1.28% in the intensive blood pressure control group versus 1.19% in the standard blood pressure control group (\( p \) not significant). The annual rate of stroke, a prespecified secondary outcome, was 0.32% in the intensive blood pressure control group versus 0.53% in the standard blood pressure control group, \( p = 0.01 \). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive blood pressure control group versus 1.3% of the standard blood pressure control group (\( p < 0.001 \)) [91].

The impact of baseline systolic blood pressure on outcomes was investigated in 7,785 persons with mild to moderate chronic CHF in the Digitals Investigation Group trial [92]. A baseline systolic blood pressure \( \leq 120 \) mm Hg was associated during 5 years of follow-up with a 15% increase in cardiovascular mortality (\( p = 0.032 \), with a 30% increase in heart failure mortality (\( p = 0.006 \)), with a 13% increase in cardiovascular hospitalization (\( p = 0.008 \)), with a 10% increase in all-cause hospitalization (\( p = 0.017 \)), and with a 21% increase in heart failure hospitalization (\( p = 0.002 \)) [92].

In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), a progressive increase in the proportion of visits in which the blood pressure was decreased to <140/90 mm Hg or to <130/80 mm Hg was associated with a progressive decrease in stroke, new onset of microalbuminuria or macroalbuminuria, and return to normoalbuminuria in persons with albuminuria [93]. However, the adjusted risk of cardiovascular events was reduced by increasing the frequency of blood pressure control to <140/90 mm Hg but not to <130/80 mm Hg [93].

In ONTARGET, 9,603 of 25,584 patients had diabetes mellitus [94]. Diabetes mellitus increased the primary outcome of cardiovascular death, nonfatal myocardial infarction or stroke, or hospitalization for CHF by 48% (95% CI, 1.38 to 1.57). In both diabetics and nondiabetics, antihypertensive treatment reduced the primary outcome if baseline systolic blood pressure levels ranged from 143 to 155 mm Hg. Except for
stroke, there was no benefit in fatal or nonfatal outcomes by lowering systolic blood pressure below 130 mm Hg [94].

During >12 years of median follow-up in the Cardiovascular Health Study, isolated diastolic hypotension (a diastolic blood pressure <60 mm Hg with a systolic blood pressure ≥ 100 mm Hg) was associated with a 29% significant independent increase in incident CHF (p = 0.003) [95]. Therefore, isolated systolic hypertension and isolated diastolic hypotension are significant risk factors for CHF in community-dwelling older persons.

Three trials including 2,272 patients with chronic kidney disease and proteinuria without diabetes mellitus showed that a blood pressure target of <130/80 mm Hg did not improve clinical outcomes more than a blood pressure target of <140/90 mm Hg [96]. At 2.5-year follow-up of 20,330 patients with a recent noncardioembolic stroke, compared with a systolic blood pressure of 130-139 mm Hg, the incidence of the primary outcome of cardiovascular death, myocardial infarction, or stroke was increased 29% (95% CI, 1.07-1.56) by a systolic blood pressure <120 mm Hg, 23% (95% CI, 1.07-1.41) by a systolic blood pressure of 140-149 mm Hg, and 208% (95% CI, 1.07-1.56) by a systolic blood pressure ≥150 mm Hg [97].

Finally, although the optimal blood pressure treatment goal has not been determined a therapeutic target of <140/90 mm Hg in patients younger than 80 years and a systolic blood pressure of 140-145 mm Hg if tolerated in patients aged 80 years and older is reasonable [2, 44-48]. We should also be careful to avoid intensive lowering of the blood pressure, especially in those with diabetes and coronary artery disease, as this might be poorly tolerated and might increase cardiovascular events (the J-curve phenomenon).

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