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State-of-the-Art Review

Managing Hypertension in the elderly: What's new?

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ABSTRACT

Hypertension is the leading modifiable risk factor for cardiovascular events and mortality in the world. Hypertension is a major risk factor for cardiovascular events and mortality in the elderly. The 2017 American College of Cardiology/American Heart Association hypertension guidelines recommend treatment of noninstitutionalized ambulatory community-dwelling persons aged 65 years and older with an average systolic blood pressure of 130 mm Hg or higher or a diastolic blood pressure of 80 mm Hg or higher with lifestyle measures plus antihypertensive drug to lower the blood pressure to less than 130/80 mm Hg For elderly adults with hypertension and a high burden of comorbidities and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions about the intensity of SBP lowering and the choice of antihypertensive drugs to use for treatment. Randomized clinical trials need to be performed in frail elderly patients with hypertension living in nursing homes. Elderly frail persons with prevalent and frequent falls, marked cognitive impairment, and multiple comorbidities requiring multiple antihypertensive drugs also need to be included in randomized clinical trials. Data on patients older than 85 years treated for hypertension are also sparse. These patients need clinical trial data. Finally, the effect of different antihypertensive drugs on clinical outcomes including serious adverse events needs to be investigated in elderly frail patients with hypertension and different comorbidities.

1. Introduction

Hypertension is the leading modifiable risk factor for cardiovascular events and mortality in the world [1]. Hypertension is a major risk factor for cardiovascular events and mortality in the elderly [2]. Hypertension is present in 69% of persons with a first myocardial infarction [3], in 77% of persons with a first stroke [3], in 74% of persons with congestive heart failure [3], and in 60% of elderly persons with peripheral arterial disease [4]. Hypertension is also a major risk factor for developing sudden cardiac death, a dissecting aortic aneurysm, angina pectoris, left ventricular hypertrophy, thoracic and abdominal aortic aneurysms, chronic kidney disease, atrial fibrillation, diabetes mellitus, the metabolic syndrome, vascular dementia, Alzheimer's disease, and ophthalmologic disease [2]. A meta-analysis of 61 prospective studies including data from 1 million adults without prior cardiovascular disease found that cardiovascular risk increases progressively from a blood pressure level of 115/75 mm Hg with a doubling of the incidence of coronary heart disease and of stroke for every 20/10 mm Hg increase [5]. This review article will discuss management of the elderly patient with hypertension.

1.1. Clinical trials on treating hypertension in the elderly

Numerous randomized, placebo-controlled trials have demonstrated that antihypertensive drug treatment decreased cardiovascular events in the elderly with hypertension [2,6–11]. At 4.5-year follow-up of elderly patients with isolated systolic hypertension in the Systolic Hypertension in the Elderly Program (SHEP), antihypertensive drug therapy reduced stroke by 36%, major cardiovascular events by 32%, and all-cause mortality by 13% [6]. In this study, antihypertensive drug therapy reduced ischemic stroke by 37% and hemorrhagic stroke by 54% [7]. The SHEP study also showed that antihypertensive drug therapy reduced heart failure by 49% and by 80% in patients with prior myocardial infarction [8]. The target systolic blood pressure was higher than 140 mm Hg in both the interventional and control groups in SHEP [6–8].

The Systolic Hypertension in Europe trial showed in 4695 elderly patients with isolated systolic hypertension that antihypertensive treatment of 1000 patients for 5 years will prevent 29 strokes and 53 major cardiovascular events [9]. The Systolic Hypertension In China study showed in 2506 elderly patients with isolated systolic hypertension that antihypertensive treatment of 1000 patients for 5 years would prevent 55 deaths, 39 strokes, or 59 major cardiovascular events [10]. A

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meta-analysis of 8 trials of 15,693 persons aged 60 years and older with treated and untreated isolated systolic hypertension followed for 3–8 years showed that antihypertensive drug therapy decreased all-cause mortality by 13%, cardiovascular death by 18%, cardiovascular events by 26%, stroke by 30%, and coronary events by 23% [11]. The number needed to treat for 5 years to prevent 1 major cardiovascular event was 18 men versus 38 women, 19 persons aged 70 years and older versus 39 persons younger than 70 years, and 16 persons with prior cardiovascular disease versus 37 persons without prior cardiovascular disease [11]. The target systolic blood pressure was higher than 140 mm Hg in both the interventional and control groups in these studies [9–11].

Aronow recommended in an editorial that unless the Hypertension in the Very Elderly (HYVET) trial showed that antihypertensive drug therapy was not beneficial for persons aged 80 years and older, these adults should be treated with antihypertensive drug treatment [12]. Goodwin [13] disagreed with this recommendation, and his response to Aronow's editorial [12] was accompanied by 8 commentaries, some of which supported the treatment of very old persons with hypertension and some of which did not.

The HYVET trial.randomized 3845 persons aged 80 years and older (mean age 83.6 years; 60.5% women) with a systolic blood pressure of 160 mm Hg or higher to antihypertensive drug therapy or to double-blind placebo [14]. The target blood pressure was 150/80 mm Hg, and the lowest systolic blood pressure achieved was 143 mm Hg. The median follow-up was 1.8 years. Elderly persons randomized to antihypertensive drug therapy had a 30% decrease in fatal or nonfatal stroke, a 39% decrease in fatal stroke, a 21% decrease in all-cause mortality, a 23% decrease in cardiovascular mortality, and a 64% decrease in heart failure [14].

The REasons for Geographic and Racial Differences in Stroke (REGARDS) study is an observational study of the incidence of stroke in persons living in the stroke belt and stroke buckle regions of the United States [15]. In this study, 4181 adults were aged 55–64 years, 3737 adults were aged 65–74 years, and 1839 adults were aged 75 years and older (mean age 79.3 years) being treated with antihypertensive drugs. The median follow-up was 4.5 years for cardiovascular disease (coronary heart disease or stroke) and coronary heart disease, 5.7 years for stroke, and 6.0 years for all-cause mortality. This study showed that in adults aged 55 years and older treated with antihypertensive drugs, a systolic blood pressure between 120 and 139 mm Hg was significantly associated with a reduced risk for cardiovascular events and for all-cause mortality [15]. The optimal diastolic blood pressure in this study was 70–90 mm Hg [16].

A post hoc analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial investigated the effects of a systolic blood pressure target of less than 130 mm Hg versus 130–149 mm Hg in 3020 adults, mean age 63 years, with a recent lacunar stroke [17]. After 1 year, the mean systolic blood pressure was 138 mm Hg in 1519 adults and 127 mm Hg in 1501 adults. Compared to a systolic blood pressure of 138 mm Hg, a systolic blood pressure of 127 mm Hg reduced at 3.7-year follow-up all stroke by 19%, disabling or fatal stroke by 19%, myocardial infarction or vascular death by 16%, and intracerebral hemorrhage by 63%. These data support a systolic blood pressure target of less than 130 mm Hg in adults with a lacunar stroke [17,18].

The Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 adults with a systolic blood pressure of 130 mm Hg–180 mm Hg and an increased cardiovascular risk but without diabetes mellitus, history of stroke, symptomatic heart failure within the past 6 months, a left ventricular ejection fraction below 35%, and an estimated glomerular filtration rate below 20 ml/min/1.73 m^2 to a systolic blood pressure target of less than 120 mm Hg or to a systolic blood pressure target of less than 140 mm Hg [19]. The participants were aged 50 years and older with a mean age of 67.9 years. Of the 9361 participants, 2636 (28.2%) were aged 75 years and older, 3332 (35.6%) were women, 5399 (57.7%) were non-Hispanic whites, 2947 (31.5%) were blacks, and 984 (10.6%) were Hispanics. Cardiovascular disease was present in 1877 participants (20.1%), and the Framingham 10-year cardiovascular disease risk score was 15% and higher in 5, 737 participants (61.3%).

At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive treatment group and 136.2 mm Hg in the standard treatment group. The study was stopped after a median follow-up of 3.26 years [19].

The primary composite outcome was myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes and was decreased 25% by intensive blood pressure treatment [19]. (Table 1). Intensive blood pressure therapy decreased all-cause mortality by 27%, heart failure by 38%, death from cardiovascular causes by 43%, myocardial infarction by 17%, stroke by 11%, and the primary composite outcome or death by 22% [19]. Intensive blood pressure therapy reduced the primary outcome by 33% in participants aged 75 years and older and reduced the primary outcome by 20% in participants aged 50–74 years [19].

Serious adverse events were similar in both treatment groups [19]. However, intensive blood pressure therapy caused more hypotension (2.4% versus 1.4%), more syncope (2.3% versus 1.7%), more electrolyte abnormality (3.1% versus 2.3%), and more acute kidney injury or acute renal failure (4.1% versus 2.5%). The incidence of bradycardia, injurious falls, and orthostatic hypotension with dizziness was similar in both treatment groups [19].

Of the 2636 persons aged 75 years and older, mean age 79.9 years, in SPRINT, 33.4% of persons randomized to a systolic blood pressure target of less than 120 mm Hg and 28.4% of persons randomized to a systolic blood pressure target of less than 140 mm Hg were frail [20]. At 3.14-year median follow-up, compared with a systolic blood pressure target of less than 140 mm Hg, a systolic blood pressure target of less than 120 mm Hg decreased the primary endpoint of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or cardiovascular death by 34%, all-cause mortality by 33%, heart failure by 38%, and the primary outcome or death by 32% (Table 1). Absolute cardiovascular event rates were lower for the intensive treatment group within each frailty stratum. The incidence of serious adverse events was similar in both treatment groups. However, intensive blood pressure lowering nonsignificantly increased hypotension, syncope, electrolyte abnormalities, and acute kidney injury. Serious adverse events were higher with greater frailty or slower walking speed in both treatment groups [20]. The number needed to treat to prevent 1 primary outcome event with intensive systolic blood pressure control was 27 in the patients aged 75 years and older group in SPRINT and 61 in the entire SPRINT group aged 50 years and older [19,20]. The number needed to treat to prevent 1 death t with intensive systolic blood pressure control was 41 in the patients aged 75 years and older group in SPRINT and 90 in the entire SPRINT group aged 50 years and older [19,20].

Overall, 16.8 million United States adults and 8.2 million United States adults with treated hypertension meet the Sprint eligibility criteria

Table 1
Clinical outcomes in SPRINT.

1. For the entire group of 9361 adults, mean age 67.9 years, intensive lowering of systolic blood pressure to less than 120 mm Hg reduced the primary composite outcome of myocardial infarction, other acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes by 25%, all-cause mortality by 27%, heart failure by 38%, death from cardiovascular causes by 43%, myocardial infarction by 17%, stroke by 11%, and the primary composite outcome or death by 22% [19].
2. Of the 2636 persons aged 75 years and older, mean age 79.9 years, in SPRINT, 33.4% of persons randomized to a systolic blood pressure target of less than 120 mm Hg and 28.4% of persons randomized to a systolic blood pressure target of less than 140 mm Hg were frail. Intensive lowering of systolic blood decreased the primary outcome by 34%, all-cause mortality by 33%, heart failure by 38%, and the primary outcome or death by 32%. Absolute cardiovascular event rates were lower for the intensive treatment group within each frailty stratum [20].
3. Intensive lowering of systolic blood pressure in SPRINT-MIND insignificantly reduced probable dementia by 17%, reduced mild cognitive impairment by 19%, and reduced mild cognitive impairment plus probable dementia by 15% [27].

[21]. The SPRINT eligibility criteria were applied to the 1999 to 2006 National Health and Nutrition Examination Survey and linked with the National Death Index through December 2011 [22]. This study found that intensive lowering of systolic blood pressure of all eligible United States adults could prevent 107,500 deaths per year and 46,100 cases of heart failure per year but cause an increase in serious adverse events [22].

The Heart Outcomes Prevention Evaluation (HOPE)-3 trial randomized 12,705 participants (49% Asians, 20% whites, 27% Hispanics, and 2% blacks), mean age 65.7 years, without cardiovascular disease and at intermediate risk to treatment with candesartan 16 mg plus hydrochlorothiazide 12.5 mg daily or to placebo [23]. The baseline mean blood pressure was 138.1/81.9 mm Hg. The reduction in blood pressure in the drug treatment group was 6.0/3.0 mm Hg. At 5.6-year median follow-up, there was no significant decrease in the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. In the subgroup of patients with a systolic blood pressure higher than143.5 mm Hg, antihypertensive drug therapy decreased the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 27% [23].

Less than 40% of the participants in the HOPE-3 trial had hypertension, and the risk for cardiovascular disease was much lower in the HOPE-3 trial than in SPRINT [24]. The systolic blood pressure decrease in SPRINT was 14.8 mm Hg lower with intensive treatment than with standard treatment, whereas the systolic blood pressure was reduced only 6 mm Hg by antihypertensive drug therapy in the HOPE-3 trial [24]. Chlorthalidone was used in SPRINT and has been shown to decrease cardiovascular events in clinical trials, whereas hydrochlorothiazide 12.5 mg daily used in the HOPE-3 trial has not been found to reduce cardiovascular events [24].

A systematic review and meta-analysis was performed in 123 studies of randomized studies of use of antihypertensive drugs which included 613, 815 participants [25]. This study demonstrated that every 10 mm Hg reduction in systolic blood pressure significantly reduced major cardiovascular events by 20%, coronary heart disease by 17%, stroke by 27%, and heart failure by 28%, which in the populations studied reduced all-cause mortality by 13% [25].

Subcortical microvascular disease is associated with hypertension in older persons [26].

Of the 9361 participants in SPRINT, 8563 (91.5%) completed at least 1 cognitive assessment [27]. During a median follow-up of 5.11 years, compared with reducing the systolic blood pressure to less than 140 mm Hg, reducing the systolic blood pressure to less than 120 mm Hg insignificantly reduced probable dementia by 17%, reduced mild cognitive impairment by 19%, and reduced mild cognitive impairment plus probable dementia by 15% [27]. (Table 1).

A prospective, randomized, blinded end-points study was performed in 199 patients, mean age 80.5 years, with systolic hypertension and magnetic resonance imaging evidence of white matter hyperintensity lesions [28]. Compared to a mean 24-h systolic blood pressure treatment achieved of 144.0 mm Hg, a mean 24-h systolic blood pressure treatment achieved of 127.7 mm Hg at 3 years did not affect mobility outcomes but reduced accrual of subcortical white matter disease by 0.29% [28].

Elderly persons with hypertension and left ventricular hypertrophy have a higher incidence of congestive heart failure, coronary events, and stroke than elderly persons with hypertension who do not have left ventricular hypertrophy [29]. Among 7, 559 SPRINT participants without baseline electrocardiographic left ventricular hypertrophy, intensive blood pressure lowering to a systolic blood pressure less than 120 mm Hg was associated with a 46% lower risk of developing left ventricular hypertrophy than lowering the systolic blood pressure to less than 140 mm Hg [30]. Among 605 SPRINT partcipants with baseline electrocardiographic hypertrophy, those treated with intensive blood pressure lowering were 66% more likely to regress/improve their left ventricular hypertrophy than lowering the systolic blood pressure to less than 140 mm Hg [30].

SPRINT showed that the benefit of intensive systolic blood pressure lowering was not affected by baseline diastolic blood pressure [31] or by baseline pulse pressure [32]. SPRINT showed that patient-reported outcomes were similar in patients treated to a systolic blood pressure target of less than 120 mm Hg as in patients treated to a systolic blood pressure target less than 140 mm Hg including in those with decreased physical or cognitive function [33]. A microsimulation model applying SPRINT treatment effects and health care costs also showed that intensive systolic blood pressure control prevented cardiovascular events and prolonged life at levels below common willingness-to pay thresholds per quality-adjusted life-year [34]. This model showed that the quality-adjusted life-years (QALY) would be 0.27 higher among patients with intensive systolic blood pressure control than among the patients who received standard systolic blood pressure control and would cost about $47,000 more per QALY gained if there was a decrease in adherence and treatment effects after 5 years [34]. The cost would be about $28,000 more per QALY gained if the treatment effects persisted for the remaining lifetime of the patient [34].

1.2. 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines

The 2017 ACC/AHA hypertension guidelines state that stage 1 hypertension is a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg [35]. Stage 2 hypertension is a systolic blood pressure of 140 mm Hg and higher or a diastolic blood pressure of 90 mm Hg and higher [35]. Automated validated devices should be used for measuring blood pressure. Using these new criteria, the prevalence of hypertension is 68% of men and 65% of women aged 55–64 years of age, 75% of men and 78% of women aged 65–74 years of age, and 83% of men 86% of women aged 75 years and older [35].

The 2017 ACC/AHA hypertension guidelines recommend that the absolute cardiovascular risk reduc6tion caused by blood pressure lowering is greater at higher absolute levels of cardiovascular disease risk [35]. Antihypertensive drug therapy should be guided by predicted cardiovascular disease risk in reduction in blood pressure [35–38]. Hypertensive persons with a 10-year atherosclerotic cardiovascular risk below 15% with a systolic blood pressure between 120 and 159 mm Hg and a coronary artery calcium score greater than 100 also have an increased risk for cardiovascular events and should be considered for intensive blood pressure reduction [39].

A systolic blood pressure between 120 and 129 mm Hg with a diastolic blood pressure less than 80 mm Hg should be treated by lifestyle measures [35,40]. (Table 2). In elderly persons with an untreated systolic

Table 2
Treatment of blood pressure in elderly patients.

1. A systolic blood pressure between 120 and 129 mm Hg with a diastolic blood pressure less than 80 mm Hg should be treated by lifestyle measures [35,40].
2. The 2017 ACC/AHA hypertension guidelines recommend therapy with lifestyle measures plus blood pressure lowering drugs for secondary prevention of recurrent cardiovascular disease events in patients with clinical cardiovascular disease and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher [31,35,42,43].
3. These guidelines recommend therapy with lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease greater than or equal to 10% [44]. and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher/[17,18,35,45]
4. These guidelines recommend treatment with lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease below 10% [44] and an average systolic blood pressure of 140 mm Hg and higher or an average diastolic blood pressure of 90 mm Hg and higher [5,35,45]. 5. These guidelines recommend initiation of antihypertensive drug treatment with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in persons with a blood pressure of 140/90 mm Hg and higher or with a blood pressure more than 20/10 mm Hg above their blood pressure target [2,35,46].

blood pressure between 131 and 159 mm Hg or a diastolic blood pressure between 81 and 99 mm Hg, it is reasonable to screen for white coat hypertension using either daytime ambulatory blood pressure monitoring or home blood pressure monitoring [35,41].

The 2017 ACC/AHA hypertension guidelines recommend therapy with lifestyle measures plus blood pressure lowering drugs for secondary prevention of recurrent cardiovascular disease events in patients with clinical cardiovascular disease (coronary heart disease, congestive heart failure, and stroke) and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher [31,35,42,43]. (Table 2). These guidelines recommend therapy with lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease greater than or equal to 10% [44]. and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher/[17,18,35,45] (Table 2). These guidelines recommend treatment with lifestyle measures plus blood pressure lowering drugs for primary prevention of cardiovascular disease in persons with an estimated 10-year risk of atherosclerotic cardiovascular disease below 10% [44] and an average systolic blood pressure of 140 mm Hg and higher or an average diastolic blood pressure of 90 mm Hg and higher [5,35,45]. (Table 2). Most elderly patients will have an estimated 10-year risk of atherosclerotic cardiovascular disease of 10% and higher and would need to be treated with lifestyle measures plus blood pressure lowering drugs to lower the blood pressure to less than 130/80 mm Hg. However, the treatment of hypertension in elderly patients needs to be individualized.

These guidelines recommend initiation of antihypertensive drug treatment with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in persons with a blood pressure of 140/90 mm Hg and higher or with a blood pressure more than 20/10 mm Hg above their blood pressure target [2,35,46]. (Table 2). White coat hypertension must be excluded before initiating therapy with antihypertensive drugs in persons with hypertension at low risk for atherosclerotic cardiovascular disease [35].

Secondary hypertension should be suspected if there is new onset or uncontrolled hypertension in adults [35,47]. Screen for secondary hypertension if there is drug-resistant/induced hypertension, abrupt onset of hypertension, onset of hypertension in a person younger than 30 years of age, exacerbation of previously controlled hypertension, disproportionate target organ damage for the degree of hypertension, accelerated/malignant hypertension, onset of diastolic hypertension in elderly persons, or unprovoked or excessive hypokalemia [35,47]. Common causes of secondary hypertension include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug-or alcohol-induced hypertension [35]. Uncommon causes of secondary hypertension include pheochromocytoma/paraganglioma, Cushing's syndrome, hypothyroidism, hyperthyroidism, aortic coarctation, primary hyperparathyroidism, congenital adrenal hyperplasia, mineralocorticoid excess syndromes, and acromegaly [35].

The 2017 ACC/AHA hypertension guidelines recommend lowering the blood pressure to less than 130/80 mm Hg in patients with ischemic heart disease [19,20,35,43,48], in patients with heart failure with a reduced left ventricular ejection fraction [35,49], in patients with heart failure with a preserved left ventricular ejection fraction [35,49], in patients with chronic kidney disease [35,50], in patients after renal transplantation [35], in patients with lacunar stroke [17,35], in patients with peripheral arterial disease, [35,42] in patients with diabetes mellitus,[35, 51−54]] and in noninstitutional ambulatory community-dwelling persons older than 65 years of age [19,20,27,35]. For secondary stroke prevention, these guidelines recommend reducing the blood pressure to less than 140/90 to 130/80 mm Hg [35,55].

It should be pointed out that automated blood pressures were obtained in the SPRINT study. Because the systolic blood pressure may be 10 mm Hg higher when measured in a physician's office than when an automated systolic blood pressure is measured, the 2017 ACC/AHA hypertension guidelines committee decided it would be safer to reduce the systolic blood pressure to less than 130 mm Hg rather than to less than 120 mm Hg [35].

1.3. 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines

The 2018 ESC/ESH hypertension guidelines recommend that the blood pressure should be decreased to less than 140/90 mm Hg in all patients provided that the treatment is well tolerated [56]. Antihypertensive therapy should be targeted to a blood pressure goal of 120–129 mm Hg in most patients. These guidelines recommend in patients aged 65–80 years and in patients older than 80 years a systolic blood pressure of 130–139 mm Hg if tolerated. These guidelines recommend in all patients with hypertension a diastolic blood pressure of less than 80 mm Hg independent of the level of risk and comorbidities [56]. On the basis of the available data discussed in this paper, especially from SPRINT [19,20, 27], this author favors the recommendations made by the 2017 ACC/AHA hypertension guidelines [35] for the management of hypertension in elderly patients.

1.4. Antihypertensive drug management of elderly patients with hypertension

A meta-analysis of 147 randomized trials of 464, 000 participants with hypertension found that except for the major effect of beta blockers given after myocardial infarction in decreasing coronary events and a minor additional effect of calcium channel blockers in decreasing stroke, all major antihypertensive drug classes diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and calcium channel blockers caused a similar decrease in coronary events and stroke for a given decrease in blood pressure [57]. The choice of specific antihypertensive drugs such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers in the management of elderly patients with hypertension depends on efficacy, tolerability, presence of specific comorbidities and cost [2,35].

For elderly patients with hypertension and a high burden of comorbidities and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions about the intensity of systolic blood pressure lowering and the choice of antihypertensive drugs to use for treatment [35]. Elderly adults who live in nursing homes and assisted living facilities have not been included in randomized clinical trials [35]. All elderly adults with hypertension should be treated with lifestyle measures.[2,35 40]

For white and other non-black elderly adults with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker [35]. (Table 3). The first and if needed second antihypertensive drug should be a thiazide diuretic plus a calcium channel blocker [35]. (Table 3). If a third antihypertensive drug is needed, the patient should be treated with the thiazide diuretic plus a calcium channel blocker plus an

Table 3
Antihypertensive drug management of elderly patients with hypertension.

1. For elderly patients with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker [35].
2. The first and if needed second antihypertensive drug should be a thiazide diuretic plus a calcium channel blocker.
3. If a third antihypertensive drug is needed, the patient should be treated with the thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [35].
4. If a fourth antihypertensive drug is needed to control hypertension in elderly patients, it should be a mineralocorticoid antagonist [35].
5. The choice of antihypertensive drug treatment would be modified depending on comorbidity, as discussed in the paper [35]

angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [35]. (Table 3). For black elderly adults with primary hypertension, these recommendations are identical [35]. (Table 3). A thiazide diuretic and a calcium channel blocker are considered to be more efficacious than an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker as initial antihypertensive therapy for elderly adults with primary hypertension [35]. If a fourth antihypertensive drug is needed to control hypertension in elderly adults, it should be a mineralocorticoid antagonist [35]. The choice of antihypertensive drug treatment would be modified depending on comorbidity, as discussed below and in greater detail in the 2017 ACC/AHA guidelines [35].

Elderly patients with stable ischemic heart disease and hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [2,35,57–65]. If a third antihypertensive drug is indicated, a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker should be given. If a fourth antihypertensive drug is indicated to control hypertension despite use of a thiazide diuretic, a mineralocorticoid antagonist should be given [2,35,58]. In elderly adults with stable ischemic heart disease who have angina pectoris despite therapy with a beta blocker and persistent uncontrolled hypertension, a dihydropyridine calcium channel blocker such as amlodipine or felodipine should be added to the therapeutic regimen [2,35,58]. Beta blockers that may be used in treating hypertension in elderly adults with ischemic heart disease include carvedilol, metoprolol succinate, bisoprolol, metoprolol tartrate, nadolol, propranolol, and timolol. Atenolol should not be used [2,35,58,59,66,67]. If the left ventricular ejection fraction is reduced, carvedilol, metoprolol succinate, or bisoprolol should be administered [2,35,58,59]. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are contraindicated if the left ventricular ejection fraction is decreased [2,35,58].

If hypertension persists after therapy with a beta blocker or angiotensin -converting enzyme inhibitor or angiotensin receptor blocker in elderly adults with an acute coronary syndrome, a long-acting dihydropyridine calcium channel blocker should be added [2,58]. An aldosterone antagonist should be administered to elderly adults treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker after myocardial infarction if they have a left ventricular ejection fraction $\leq$40% and either heart failure or diabetes mellitus if their serum potassium is less than 5.0 meq/L and if their serum creatinine is $\leq$ 2.5 mg/dL in men and $\leq$2.0 mg/dL in women [2,35,68,69].

Elderly persons with heart failure and a reduced left ventricular ejection fraction with hypertension should be treated with a beta blocker (carvedilol, metoprolol tartrate or bisoprolol) plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or preferably an angiotensin receptor-neprolysin inhibitor plus a diuretic and if indicated with an aldosterone antagonist [2,35,58,68,69]. Nondihydropyridine calcium channel blockers are contraindicated in patients with heart failure and reduced left ventricular ejection fraction [2,35,49,58,70].

Elderly persons with heart failure and a preserved left ventricular ejection fraction and hypertension should have their volume overload treated with diuretics and their other comorbidities treated [2,35,49,58]. Their hypertension should also be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus an aldosterone antagonist [2,35,49,58,71,72].

Elderly persons with hypertension and a prior stroke or transient ischemic attack should be treated with a thiazide diuretic or angiotensin -converting enzyme inhibitor or angiotensin receptor blocker [2,35,73,74]. If a third antihypertensive drug is indicated, it should be a calcium channel blocker [2,35].

Elderly persons with hypertension and chronic kidney disease stage 3 or higher or stage 1 or 2 chronic kidney disease with albuminuria $\geq$300 mg/day should be treated with an angiotensin-converting enzyme inhibitor to slow progression of chronic kidney disease [2,35,75,76]. If the person is intolerant to an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker should be administered [2,35]. Elderly persons with stage 1 or 2 chronic kidney disease without albuminuria may be treated with either an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, thiazide diuretic, or calcium channel blocker [2,35]. If 3 antihypertensive drugs are necesaary, they should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker [2,35]. After renal transplantation, it is reasonable to treat patients with hypertension with a calcium channel blocker [35].

An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, thiazide diuretic, or calcium channel blocker may be used initially to treat elderly diabetics with hypertension [2,35,51,77,78]. However, an angiotensin -converting enzyme inhibitor or angiotensin receptor blocker should be used to treat elderly diabetics with hypertension who have hypertension and persistent albuminuria [2,35,79]. Chlorthalidone should be used to treat elderly nondiabetics with hypertension who have the metabolic syndrome [35,80].

Elderly persons with peripheral arterial disease and hypertension may be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a thiazide diuretic, a calcium channel blocker, or a beta blocker [2,35,81]. Beta blockers are the antihypertensive drugs of choice in elderly persons with a thoracic aortic aneurysm and improve survival in elderly patients with type A and with type B acute and chronic thoracic aortic dissection [2,35,82–84]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may prevent development of atrial fibrillation in patients with hypertension with reduced left ventricular ejection fraction or left ventricular hypertrophy [35,85].

1.5. *Drug management of resistant hypertension*

Management of resistant hypertension includes improving compliance with use of medication, detection and treatment of secondary hypertension, use of lifestyle measures, and treatment of obesity and other comorbidities [35,40]. If a fourth antihypertensive drug is necessary to control blood pressure in patients treated with adequate doses of antihypertensive drugs from different classes including a thiazide-type diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen [2,35,86].

Patients with resistant hypertension should be treated with appropriate antihypertensive drugs for their comorbidities as discussed in this review. Drug therapy of resistant hypertension should maximize diuretic therapy [2,35]. Excess sodium and fluid retention is an important cause of resistant hypertension [86–88].. Switching the patient from hydrochlorothiazide to a longer acting thiazide-type diuretic such as chlorthalidone may improve blood pressure control [35,89]. The beneficial effects of thiazide diuretics are less when the glomerular filtration rate is decreased to less than 40 ml/min/1.73 m^2 [2,35,87,90,91]. These patients should be treated with a loop diuretic such as furosemide every 12 h [2,35,90].

Increased activation of the renin-angiotensin-aldosterone system plays an important role in the development of treatment-resistant hypertension [88,90,92]. Low dose eplerenone has also been shown to reduce aortic stiffness in patents with resistant hypertension [93]. The available data support the use of a mineralocorticoid receptor antagonist such as spironolactone or eplerenone as the fourth antihypertensive drug to prescribe in patients with treatment-resistant hypertension [2,35,88,90,92–100].

Sacubitril/valsartan was shown in a double-blind, randomized controlled trial to be superior to olmesartan in decreasing clinic and ambulatory central aortic and brachial pressures in 454 patients, mean age 67.7 years, with systolic hypertension and stiff arteries [101]. A meta-analysis of 11 randomized controlled trial in 6028 persons demonstrated that sacubitril/valsartan was more effective than angiotensin receptor antagonists for the treatment of patients with hypertension [102]. Sacubitril/valsartan merits investigation of management of resistant hypertension [101–103].

A phase 2, open-label, multicenter, dose-titrating study in 256 overweight or obese hypertensive patients (56% black or Hispanic) found that firibastat, a first-in-class brain aminopeptidase A inhibitor was effective in lowering blood pressure [104]. Firibastat should also be investigated for the management of resistant hypertension.

1.6. Target blood pressure in diabetics with hypertension

Patients with diabetes mellitus were excluded from SPRINT [19,20,27]. In The ACTION to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial, reducing the systolic blood pressure to less than 120 mm Hg in 4733 participants insignificantly reduced the composite primary outcome of myocardial infarction, stroke, or cardiovascular death by 12% but significantly lowered the incidence of stroke (a prespecified secondary outcome) by 41% [105]. The participants in SPRINT were older (mean age 67.9 years) than in ACCORD BP (mean age 62.2 years). The participants in ACCORD BP were at lower risk than the participants in SPRINT. Participants with dyslipidemia were assigned to the lipid arm and excluded from the blood pressure arm in ACCORD BP. Participants with a serum creatinine above 1.5 mg/dL were also excluded from ACCORD BP. In addition, the use of diuretics was different in these trials. ACCORD BP often used hydrochlorothiazide, whereas SPRINT primarily used chlorthalidone (my preference) [19,20,27,105].

A post-hoc analysis of the results from ACCORD BP showed that the primary cardiovascular disease outcome was decreased 26% in participants randomized to intensive blood pressure treatment and standard glycemia goals than in participants randomized to standard blood pressure therapy and standard glycemia goals [52]. Targeting a systolic blood pressure of less than 120 mm Hg in ACCORD BP was associated with a 39% lower risk of electrocardiographic left ventricular hypertrophy [53]. The ACCORD BP trial also showed that hypertensive diabetics treated to a systolic blood pressure goal of less than 120 mm Hg had a tendency to a reduced incidence of orthostatic hypotension than those randomized to a systolic blood pressure goal of less than 140 mm Hg [54,106]. On the basis of the available data, I recommend lowering the blood pressure to less than 130/80 mm Hg in elderly diabetics with hypertension [107].

1.7. Future research

There are observational data not supporting reducing the systolic blood pressure to less than 120 mm Hg in patients with heart failure with a preserved left ventricular ejection fraction [108,109] and to less than 120 mm Hg [108] or to less than 13° mm Hg[110] in patients with heart failure with a reduced left ventricular ejection fraction. Randomized clinical trial data are needed to investigate the effects of a systolic blood pressure less than 120 mm Hg versus less than 140 mm Hg on clinical outcomes in elderly patients with heart failure and a reduced left ventricular ejection fraction, in elderly patients with heart failure and a preserved left ventricular ejection fraction, and in elderly patients with a left ventricular ejection fraction below 35% since these patients were excluded from SPRINT [19,20]. SPRINT showed that reducing the systolic blood pressure to less than 120 mm Hg reduced the development of heart failure by 38% [19,20]. Until randomized trial data are available, I favor treating elderly patients with heart failure to a blood pressure goal of less than 130/80 mm Hg [35,49].

Patients with a prior stroke and patients with an estimated glomerularfiltration rate less than 20 ml/min/1.73 m^2 were also excluded from SPRINT. Until randomized clinical trial data are available for the optimal blood pressure in these elderly patients, I recommend that the target blood pressure in these elderly patients should be less than 130/80 mm Hg.

Randomized clinical trials need to be performed in frail elderly patients with hypertension living in nursing homes. Elderly frail persons with prevalent and frequent falls, marked cognitive impairment, and multiple comorbidities requiring multiple antihypertensive drugs also need to be included in randomized clinical trials. Data on patients older than 85 years of age treated for hypertension are also sparse. These patients need clinical trial data. Finally, the effect of different antihypertensive drugs on clinical outcomes including serious adverse events needs to be investigated in elderly frail patients with hypertension and different comorbidities.

2. Conclusion

The 2017 ACC/AHA hypertension guidelines recommend treatment of noninstitutionalized ambulatory community-dwelling persons aged 65 years and older with an average systolic blood pressure of 130 mm Hg or higher or a diastolic blood pressure of 80 mm Hg or higher with lifestyle measures plus antihypertensive drug to lower the blood pressure to less than 130/80 mm Hg For elderly patients with hypertension and a high burden of comorbidities and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions about the intensity of systolic blood pressure lowering and the choice of antihypertensive drugs to use for treatment. Randomized clinical trials need to be performed in frail elderly patients with hypertension living in nursing homes. Elderly frail persons with prevalent and frequent falls, marked cognitive impairment, and multiple comorbidities requiring multiple antihypertensive drugs also need to be included in randomized clinical trials. Data on patients older than 85 years treated for hypertension are also sparse. These patients need clinical trial data. Finally, the effect of different antihypertensive drugs on clinical outcomes including serious adverse events needs to be investigated in elderly frail patients with hypertension and different comorbidities.

Declaration of competing interest

Dr. Wilbert S. Aronow has no conflicts of interest to disclose for submission of his manuscript titled Managing Hypertension in the Elderly-What's new to the American Journal opf preventive Cardiology.

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