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Review Article

Treatment of systemic hypertension

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Abstract: Systemic hypertension is a major risk factor for cardiovascular disease and is present in 69% of patients with a first myocardial infarction, in 77% of patients with a first stroke, in 74% of patients with chronic heart failure, and in 60% of patients with peripheral arterial disease. Double-blind, randomized, placebo-controlled trials have found that antihypertensive drug therapy reduces cardiovascular events in patients aged younger than 80 years and in patients aged 80 years and older in the Hypertension in the Very Elderly Trial. Although the optimal blood pressure treatment goal has not been determined, existing epidemiologic and clinical trial data suggest that a reasonable therapeutic blood pressure goal should be <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. Non-pharmacologic lifestyle measures should be encouraged both to prevent development of hypertension and as adjunctive therapy in patients with hypertension. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and diuretics have all reduced cardiovascular events in randomized trials. The choice of specific drugs depends on efficacy, tolerability, presence of specific comorbidities, and cost.

Keywords: Hypertension, diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers

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 ≥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

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 160 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 nonfatal 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-

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 nonadherance 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 Digitalis Investigation Group trial [92]. A baseline systolic blood pressure ≤ 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 by a systolic blood pressure of ≥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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References

[1] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Halpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommitttee. Heart disease and stroke statistics-2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119: e21-e181.

[2] Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, Ferdinand KC, Forciea MA, Frishman WH, Jaigobin C, Kostis JB, Mancia G, Oparil S, Ortiz E, Reisin E, Rich MW, Schocken DD, Weber MA, Wesley DJ. 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. J Am Coll Cardiol 2011; 57: 2037-2114.

[3] National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program working group report on hypertension in the elderly. Hypertens 1994; 23: 275-285.

[4] Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertens 1994; 23: 395-401.

[5] Rigaud A-S, Forette B. Hypertension in older adults. J Gerontol Med Sci 2001; 56A: M217-M225.

[6] Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart study. Circulation 1999; 100: 354-360.

[7] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. National Heart, Lung, and Blood institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA 2003; 289: 2560-2572.

[8] Aronow WS, Ahn C, Kronzon I, Koenigsberg M. Congestive heart failure, coronary events and atherothrombotic brain infarction in elderly blacks and whites with systemic hypertension and with and without echocardiographic and

electrocardiographic evidence of left ventricular hypertrophy. Am J Cardiol 1991; 67: 295-299.
[9] Aronow WS, Ahn C. Risk factors for new coronary events in a large cohort of very elderly patients with and without coronary artery disease. Am J Cardiol 1996; 77: 864-866.
[10] Vokonas PS, Kannel WB. Epidemiology of coronary heart disease in the elderly. In Aronow WS, Fleg JL, Rich MW (eds): Cardiovascular Disease in the Elderly, fourth edition, New York City, Informa Healthcare 2008; pp: 215-241.
[11] Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001; 103: 1245-1249.
[12] Psaty BM, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, O'Leary DH, Bryan RN, Anderson M, Lumley T. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. Arch Intern Med 2001; 161: 1183-1192.
[13] Aronow WS, Ahn C, Gutstein H. Risk factors for new atherothrombotic brain infarction in 664 older men and 1,488 older women. Am J Cardiol 1996; 77: 1381-1383.
[14] Aronow WS, Frishman WH. Treatment of hypertension and prevention of ischemic stroke. Current Cardiology Reports 2004; 6: 124-129.
[15] Wolf PA. Cerebrovascular disease in the elderly. In: Tresch DD, Aronow WS, eds. Cardiovascular Disease in the Elderly Patient. New York City: Marcel Dekker, Inc. 1994: 125-147.
[16] Aronow WS, Ahn C, Kronzon I. Comparison of incidences of congestive heart failure in older African-Americans, Hispanics, and whites. Am J Cardiol 1999; 84: 611-612.
[17] Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. JAMA 1996; 275: 1557-1562.
[18] Stokes J III, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. Circulation 1987; 75 (suppl V): V-65-V-73.
[19] Aronow WS, Sales FF, Etienne F, Lee NH. Prevalence of peripheral arterial disease and its correlation with risk factors for peripheral arterial disease in elderly patients in a long-term health care facility. Am J Cardiol 1988; 62: 644-646.
[20] Ness J, Aronow WS, Ahn C. Risk factors for peripheral arterial disease in an academic hospital-based geriatrics practice. J Am Geriatr Soc 2000; 48: 312-314.
[21] Ness J, Aronow WS, Newkirk E, McDanel D. Prevalence of symptomatic peripheral arterial disease, modifiable risk factors, and appropriate use of drugs in the treatment of peripheral arterial disease in older persons seen in a university general medicine clinic. J Gerontol Med Sci 2005; 60A: M255-M257.
[22] Aronow WS, Ahmed MI, Ekundayo OJ, Allman RM, Ahmed A. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomes in community-dwelling older adults. Am J Cardiol 2009; 103: 130-135.
[23] Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 6 prospective studies. Lancet 2002; 360: 1903-1913.
[24] Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001; 345: 479-486.
[25] Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA 2005; 294: 466-472.
[26] Gandelman G, Aronow WS, Varma R. Prevalence of adequate blood pressure control in self -pay or Medicare patients versus Medicaid or private insurance patients with systemic hypertension followed in a university cardiology or general medicine clinic. Am J Cardiol 2004; 94: 815-816.
[27] Report by the Management Committee: The Australian Therapeutic Trial in Mild Hypertension. Lancet 1980; 1: 1261-1267.
[28] Medical Research Council Working Party. MRC trial of mild hypertension: principal results. Br Med J 1985; 291: 97-104.
[29] MRC Working Party. Medical Research Council Trial of treatment of hypertension in older adults: Principal results. Br Med J 1992; 304: 405-412.
[30] Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De Schaepdryver A, Dollery C, Fagard R, Forette F, Forte J, Hamdy R, Henry JF, Joossens JV, Leonetti G, Lund-Johansen P, O'malley K, Petrie J, Strasser T, Tuomilehto J, Williams B. Morbidity and mortality results from the European Working Party on High Blood Pressure in the Elderly Trial. Lancet 1985; 1: 1349-1354.
[31] Coope J, Warrender TS. Randomised trial of the treatment of hypertension in elderly patients in primary care. Br Med J 1986; 293: 1145-1151.
[32] Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients With Hypertension (STOP Hypertension). Lancet 1991; 338: 1281-1285.
[33] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;

265: 3255-3264.
[34] Kostis JB, Davis BR, Cutler J, Grimm RH Jr, Berge KG, Cohen JD, Lacy CR, Perry HM Jr, Blaufox MD, Wassertheil-Smoller S, Black HR, Schron E, Berkson DM, Curb JD, Smith WM, McDonald R, Applegate WB. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1997; 278: 212-216.
[35] Perry HM Jr, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probstfield JL. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke. The Systolic Hypertension in the Elderly Program (SHEP). JAMA 2000; 284: 465-471.
[36] Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350: 757-764.
[37] Wang J-G, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Arch Intern Med 2000; 160: 211-220.
[38] Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Eng J Med 2008; 358: 1887-1898.
[39] Aronow WS, Frishman WH. Effect of antihypertensive drug treatment on cognitive function. Clin Geriatr 2006; 14: 25-28.
[40] Progress Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358: 1033-1041.
[41] Forette F, Seux M-L, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, Bossini A, Fagard R, Gil-Extremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Wbster J, Yodfat Y, Birkenhager WH; Systolic Hypertension in Europe Investigators. The prevention of dementia with antihypertensive treatment. New evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002; 162: 2046-2052.
[42] Murray MD, Lane KA, Gao S, Evans RM, Unverzagt FW, Hall KS, Hendrie H. Preservation of cognitive function with antihypertensive medications. A longitudinal analysis of a community-based sample of African Americans. Arch Intern Med 2002; 162: 2090-2096.
[43] Veld BA, Ruitenberg A, Hofman A, Stricker BH, Breteler MM. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001; 22: 407-412.
[44] Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly. Nat Rev Cardiol 2011; 8: 13-28.
[45] Aronow WS. Hypertension guidelines. Hypertension 2011; 58: 347-348.
[46] Banach M, Aronow WS. Should we have any doubts about hypertension therapy in elderly patients. ACCF/AHA 2011 expert consensus document on hypertension in the elderly. Pol Arch Med Wewn 2011; 121: 253-258.
[47] Aronow WS, Banach M. Ten most important things to learn from the ACCF/AHA 2011 expert consensus document on hypertension in the elderly. Blood Pressure 2012; 21: 3-5.
[48] Banach M, Aronow WS. Hypertension therapy in the elderly-do we know the answers to all the questions? The status after publication of the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly. J Hum Hypertens In press.
[49] Webster JL, Dunford EK, Hawkes C, Neal BC. Salt reduction initiatives around the world. J Hypertens 2011; 29: 1043-1050.
[50] Frohlich ED, Susic D. Sodium and its multiorgan targets. Circulation 2011; 124: 1882-1885.
[51] Cook NR, Cutler JA, Obarzanek E, Burng JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). B M J 2007; 334: 885-888.
[52] Chang HY, Hu YVV, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr 2006; 83: 1289-1296.
[53] Yang Q, Liu T, Kuklina EV, Flanders WD, Hong Y, Gillespie C, Chang MH, Gwinn M, Dowling N, Khoury MJ, Hu FB. Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2011; 171: 1183-1191.
[54] US Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans, 2010. 7th ed. Washington, DC: US Government Printing Office; January 2011.
[55] Whelton PK. Urinary sodium and cardiovascular disease risk. Informing guidelines for sodium consumption. JAMA 2011; 306: 2262-2264.
[56] Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clement D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, Van Zwieten PA, Viigimaa M, Zanchetti A. Reappraisal of European guidelines on hypertension

management: a European Society of Hypertension Task Force document. Blood Press 2009; 18: 308-347.
[57] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009; 338: b1665.
[58] Aronow WS. Might losartan reduce sudden cardiac death in diabetic patients with hypertension? Lancet 2003; 362: 591-592.
[59] Carlberg B, Samuelson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet 2004; 364: 1684-1689.
[60] Aronow WS. Current role of beta blockers in the treatment of hypertension. Expert Opin Pharmacotherap 2010; 11: 2599-2607.
[61] Chiong JR, Aronow WS, Khan IA, Nair CK, Vijayaraghavan K, Dart RA, Behrenbeck TR, Geraci SA. Secondary hypertension: current diagnosis and treatment. International J Cardiol 2008; 124: 6-21.
[62] Aronow WS. Dizziness and syncope. In: Hazzard WR, Blass JP, Ettinger WH Jr, Halter JB, Ouslander JG, eds. Principles of Geriatric Medicine and Gerontology, 4th edition New York City: McGraw-Hill, Inc, 1998, 1519-1534.
[63] Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and systemic hypertension treated with beta blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium antagonists, and alpha blockers. Am J Cardiol 2002; 89: 1207-1209.
[64] Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE 3rd, Weaver WD, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Smith SC Jr. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999; 100: 1016-1030.
[65] The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-153.
[66] Aronow WS, Ahn C, Kronzon I. Effect of beta blockers alone, of angiotensin-converting enzyme inhibitors alone, and of beta blockers plus angiotensin-converting enzyme inhibitors on new coronary events and on congestive heart failure in older persons with healed myocardial infarcts and asymptomatic left ventricular systolic dysfunction. Am J Cardiol 2001; 88: 1298-1300.
[67] Aronow WS, Ahn C. Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and diabetes mellitus. Am J Cardiol 2001; 87: 780-781.
[68] Aronow WS, Ahn C. Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and symptomatic peripheral arterial disease. Am J Cardiol 2001; 87: 1284-1286.
[69] Kennedy HL, Brooks MM, Barker AH, Bergstrand R, Huther ML, Beanlands DS, Bigger JT, Goldstein S. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. Am J Cardiol 1994; 74: 674-680.
[70] Aronow WS, Ahn C, Mercando AD, Epstein S, Kronzon I. Effect of propranolol versus no antiarrhythmic drug on sudden cardiac death, total cardiac death, and total death in patients ³62 years of age with heart disease, complex ventricular arrhythmias, and left ventricular ejection fraction ³40%. Am J Cardiol 1994; 74: 267-270.
[71] MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001-2007.
[72] Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, anker SD, Thompson SG, Poolw-Wilson PA; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005; 26: 215-225.
[73] Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction ³40% treated with diuretics plus angiotensin-converting-enzyme inhibitors. Am J Cardiol 1997; 80: 207-209.
[74] Aronow WS, Frishman WH. Angina in the elderly. In: Aronow WS, Fleg JL, Rich MW, eds. Cardiovascular Disease in the Elderly, fourth edition. New York City: Informa Healthcare 2008, 269-292.
[75] Aronow WS, Ahn C, Mercando AD, Epstein S, Kronzon I. Decrease of mortality by propranolol in patients with heart disease and complex ventricular arrhythmias is more an antiischemic than an antiarrhythmic effect. Am J Cardiol 1994; 74: 613-615.
[76] Aronow WS. Treatment of atrial fibrillation. Part 1. Cardiology in Review 2008; 16: 181-188.
[77] Aronow WS. Treatment of atrial fibrillation and atrial flutter Part 2. Cardiology in Review 2008; 16: 230-239.
[78] Aronow WS. The heart and thyroid disease. In:

Gambert SR, ed. Clinics in Geriatric Medicine. Thyroid Disease. Philadelphia: W. B. Saunders Co 1995; 219-229.

[79] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr; American College of Cardiology/American Heart Association. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the International Society for Heart and Lung Transplantation. Endorsed by the Heart Failure Society of America. J Am Coll Cardiol 2001; 38: 2101-2113.

[80] Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, Charleston J, Cheek D, Cleveland W, Douglas JG, Douglas M, Dowie D, Faulkner M, Gabriel A, Gassman J, Greene T, Hall Y, Hebert L, Hiremath L, Jamerson K, Johnson CJ, Kopple J, Kusek J, Lash J, Lea J, Lewis JB, Lipkowiotz M, Massry S, Miller ER 3rd, Norris K, O' Connor D, Ojo A, Phillips RA, Pogue V, Rahman M, Randall OS, Rostand S, Schulman G, Smith W, Thornley-Brown D, Tisher CC, Toto RD, Wright JT Jr, Xu S; African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril versus amlodipine on renal outcomes in hypertensive nephrosclerosis. A randomized controlled trial. JAMA. 2001; 285: 2719-2728.

[81] Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345: 861-869.

[82] Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. A guideline from the American Heart Association and American College of Cardiology Foundation. J Am Coll Cardiol 2011; 58: 2432-2446.

[83] Grundy SM, Cleeman JI, Merz CNB, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-239.

[84] American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2003; 26 (supplement 1): 533-550.

[85] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Brit Med J 2000; 321: 405-412.

[86] Ravipati G, Aronow WS, Ahn C, Sujata K, Saulle LN, Weiss MB. Association of hemoglobin A_{1c} level with the severity of coronary artery disease in patients with diabetes mellitus. Am J Cardiol 2006; 97: 968-969.

[87] Aronow WS, Ahn C, Weiss MB, Babu S. Relation of hemoglobin A_{1c} levels to severity of peripheral arterial disease in patients with diabetes mellitus. Am J Cardiol 2007; 99: 1468-1469.

[88] Rosendorff C, Black HR, Cannon CP, Gersh BJ, Izzo JL Jr, Kaplan NM, O'Connor CM, O'Gara PT, Oparil S; American Heart Association council for High Blood Pressure Research; American Heart Association Council on Epidemiology and Prevention; Veterans Health Administration, USA. Treatment of hypertension in the prevention and management of ischemic heart disease. A scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007; 115: 2761-2788.

[89] Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP, PROVE-IT -TIMI 22 Trial Investigators. What is the optimal blood pressure in patients after acute coronary syndromes? Relationship of blood pressure and cardiovascular events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation 2010; 122: 2142-2151.

[90] Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010; 304: 61-68.

[91] The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1575-1585.

[92] Banach M, Bhatia V, Feller MA, Mujib M, Desai RV, Ahmed MI, Guichard JL, Aban I, Love TE, Aronow WS, White M, Deedwania P, Fonarow G, Ahmed A. Relation of baseline systolic blood pressure and long-term outcomes in ambulatory patients with chronic mild to moderate heart failure. Am J Cardiol 2011; 107: 1208-1214.

[93] Mancia G, Schumacher H, Redon J, Verdecchia

P, Schmieder R, Jennings G, Yusoff K, Ryden L, Liu GL, Teo K, Sleight P, Yusuf S. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation 2011; 124: 1727-1736.

[94] Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J, Fagard R, Verdecchia P, Weber M, Bohm M, Willioams B, Yusoff K, Teo K, Yusuf S; ONTARGET Investigators. Safety and efficacy of low blood pressures among patients with diabetes. Subgroup analyses from the ONTARGET (ONgoing Telmisartan and in combination with Ramipril Endpoint trial). J Am Coll Cardiol 2012; 59: 74-83.

[95] Guichard JL, Desai RV, Ahmed MI, Mujib M, Fonarow GC, Feller MA, Ekundayo OJ, Bittner V, Aban IB, White M, Aronow WS, Love TE, Bakris GL, Zieman SJ, Ahmed A. Isolated diastolic hypotension and incident heart failure in older adults. Hypertension 2011; 58: 895-901.

[96] Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann intern Med 2011; 154: 541-548.

[97] Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM; PROFESS Investigators. Level of systolic blood pressure within the normal range and risk of recurrent stroke. JAMA 2011; 306: 2137-2144.