

# Treatment of Hypertension

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## Abstract

*Automated validated devices should be used to measure blood pressure (BP). A systolic BP between 120–129 mm Hg with a diastolic BP < 80 mm Hg should be treated by lifestyle measures. Treat with lifestyle measures plus BP 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 BP of  $\geq 130$  mm Hg or an average diastolic BP  $\geq 80$  mm Hg. Treat with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease  $\geq 10\%$  and an average systolic BP  $\geq 130$  mm Hg or an average diastolic BP  $\geq 80$  mm Hg. Treat with lifestyle measures plus BP lowering drugs for primary prevention of cardiovascular disease in patients with an estimated 10-year risk of atherosclerotic cardiovascular disease of < 10% and an average systolic BP  $\geq 140$  mm Hg or an average diastolic BP  $\geq 90$  mm Hg. Treat with antihypertensive drug therapy with 2 first-line drugs from different classes either as separate agents or in a fixed-dose combination in patients with a BP  $\geq 140/90$  mm Hg or with a BP > 20/10 mm Hg above their blood pressure target. White coat hypertension must be excluded before starting treatment with antihypertensive drugs in patients with hypertension at low risk for atherosclerotic cardiovascular disease. Antihypertensive drug therapy for different disorders is discussed.*

## Keywords

*Hypertension; systolic blood pressure; diastolic blood pressure; antihypertensive drugs; lifestyle measures*

## INTRODUCTION

Hypertension is the most common modifiable risk factor for cardiovascular events and mortality in the world. [1] The prevalence of hypertension is 69% in persons with a first myocardial infarction [2, 77% in persons with a first stroke [2, 74% in persons with

congestive heart failure [2, and 60% in persons with peripheral arterial disease. [3] Hypertension is also a major risk factor for sudden cardiac death, a dissecting aortic aneurysm, angina pectoris, left ventricular hypertrophy, thoracic and abdominal aortic aneurysms, chronic kidney disease, atrial fibrillation,

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diabetes mellitus, the metabolic syndrome, vascular dementia, Alzheimer's disease, and ophthalmologic disease [4]. A meta-analysis of 61 prospective studies with 1 million persons without prior cardiovascular disease demonstrated 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]. Numerous randomized prospective, double-blind, placebo-controlled studies have shown that antihypertensive drug treatment reduces cardiovascular events and mortality [4, 6, 10].

## **2017 ACC/AHA HYPERTENSION GUIDELINES**

The 2017 United States hypertension guidelines were written by members from 11 professional societies. [11] These guidelines stated that common modifiable risk factors present in persons who have hypertension are current cigarette smoking, passive smoking, diabetes mellitus, dyslipidemia/hypercholesterolemia, overweight/obesity, physical inactivity/low fitness, and unhealthy diet [11].

The new 2017 hypertension guidelines reported that a normal blood pressure is below 120/80 mm Hg. [11] An elevated blood pressure is 120–129/<80 mm Hg. Stage 1 hypertension is a systolic blood pressure of 130–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg. 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 [11]. Automated validated devices should be used to measure blood pressure. Using these new criteria, the prevalence of hypertension in the United States of America is 31% of men and 18% of women aged 20 to 44 years, 52% of men and 46% of women aged 45 to 54 years, 68% of men and 65% of women aged 55 to 64 years of age, 75% of men and 78% of women aged 65 to 74 years of age, and 83% of men 86% of women aged 75 years and older [11]. The overall prevalence of hypertension in the United States of America is 49% in non-Hispanic white men and 47% in non-Hispanic white women, 59% in non-Hispanic African-American men and 60% in non-Hispanic African-American women, and 46% in Hispanic men and 41% in Hispanic women [11].

These hypertension guidelines also reported that the absolute cardiovascular risk reduction caused by blood pressure lowering is greater at higher absolute levels of cardiovascular disease risk [11]. Antihypertensive drug therapy should be guided by

predicted cardiovascular disease risk in conjunction with blood pressure. [11–14] Hypertensive persons with a 10-year atherosclerotic cardiovascular risk less than 15% with a systolic blood pressure between 120–159 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 lowering [15].

A systolic blood pressure between 120–129 mm Hg with a diastolic blood pressure below 80 mm Hg should be managed by lifestyle measures. [11, 16] Persons with an untreated systolic blood pressure between 131–159 mm Hg or a diastolic blood pressure between 81–99 mm Hg, should be screened for white coat hypertension using either daytime ambulatory blood pressure monitoring or home blood pressure monitoring [11, 17].

The new hypertension guidelines recommended lifestyle measures plus blood pressure lowering drugs for secondary prevention of recurrent cardiovascular disease events in persons 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 [11, 18, 19]. These guidelines recommended 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  $\geq 10\%$  [20] and an average systolic blood pressure of 130 mm Hg and higher or an average diastolic blood pressure of 80 mm Hg and higher [11, 21]. These guidelines recommended 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 of  $< 10\%$  [20] 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, 11, 21]. These guidelines recommended treatment with antihypertensive drug therapy 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 [11, 22]. White coat hypertension must be excluded before using antihypertensive drugs in persons with hypertension at low risk for atherosclerotic cardiovascular disease. [11]

Secondary hypertension should be suspected if there is new onset or uncontrolled hypertension in

adults [11, 23]. 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, exacerbation of previously controlled hypertension, disproportionate target organ damage for the degree of hypertension, accelerated/malignant hypertension, onset of diastolic hypertension in older persons, or unprovoked or excessive hypokalemia [11, 23]. Common causes of secondary hypertension include renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, and drug- or alcohol-induced hypertension [11]. 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 [11].

The new hypertension guidelines recommended that the blood pressure should be lowered to less than 130/80 mm Hg in persons with ischemic heart disease [9–11, 19, 24] in persons with heart failure with a decreased left ventricular ejection fraction [11, 25], in persons with heart failure with a preserved left ventricular ejection fraction [11, 25], in persons with chronic kidney disease [11, 26], in persons after renal transplantation [11], in persons with lacunar stroke [11, 27], in persons with peripheral arterial disease [11, 18], in persons with diabetes mellitus [11, 28–31], in noninstitutionalized ambulatory community-dwelling persons older than 65 years of age. [9–11], and for secondary stroke prevention [11, 32].

## ANTIHYPERTENSIVE DRUG TREATMENT RECOMMENDED

The new hypertension guidelines recommended for white and other non-black persons younger than 60 years of age with primary hypertension, the first antihypertensive drug should be an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, the second drug a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker should be given [11]. For white and other non-black persons aged 60 years of age and older with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if

a third antihypertensive drug is required, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given [11]. For African-Americans with primary hypertension, the first antihypertensive drug should be a thiazide diuretic (preferably chlorthalidone) or a calcium channel blocker, and if a third antihypertensive drug is needed, a thiazide diuretic plus a calcium channel blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be administered [11].

Persons with stable ischemic heart disease and hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and if a third antihypertensive drug is needed, a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic or a calcium channel blocker should be administered. [8, 11, 33–44]. If a fourth antihypertensive drug is needed to adequately control hypertension, a mineralocorticoid receptor antagonist should be added [11]. In persons with stable ischemic heart disease who have angina pectoris despite beta blocker therapy and persistent uncontrolled hypertension, a dihydropyridine calcium channel blocker should be added [8, [11, 33, 45]. Beta blockers which should be administered in treating ischemic heart disease with hypertension include carvedilol, metoprolol tartrate, metoprolol succinate, bisoprolol, nadolol, propranolol, and timolol [11]. Atenolol should not be given [8, 11, 35, 46, 47]. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are contraindicated if there is left ventricular systolic dysfunction. [11] If there is left ventricular systolic dysfunction, the beta blockers that should be administered are carvedilol, metoprolol succinate, or bisoprolol [8, 11, 34].

If hypertension persists after treatment with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with an acute coronary syndrome, a long-acting dihydropyridine calcium channel blocker should be added to the therapeutic regimen [8, 11]. Aldosterone antagonists should be administered to patients treated with beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction 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 [8, 11, 48, 9].

Patients with hypertension who have heart failure with a decreased left ventricular ejection fraction should be treated with a beta blocker (carvedilol, metoprolol succinate, or bisoprolol) plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or preferably an angiotensin receptor–nephrolysin inhibitor plus a diuretic and if indicated with a mineralocorticoid receptor antagonist [11, 25, 35, 48, 49]. Nondihydropyridine calcium channel blockers are contraindicated in patients with heart failure and a decreased left ventricular ejection fraction. [11, 25, 50, 51].

Patients with hypertension and heart failure with a preserved left ventricular ejection fraction should have their volume overload treated with diuretics, their other comorbidities treated, and their hypertension treated with a beta blocker plus an angiotensin converting enzyme inhibitor or angiotensin blocker plus a mineralocorticoid receptor antagonist. [11, 25, 52, 53].

Patients with hypertension and chronic kidney disease stage 3 or higher or stage 1 or 2 chronic kidney disease with albuminuria  $\geq 300$  mg per day should be treated with an angiotensin-converting enzyme inhibitor to slow progression of chronic kidney disease [11, 26, 54–56]. If an angiotensin-converting enzyme inhibitor is not tolerated, these patients should be treated with an angiotensin receptor blocker [11]. Patients with stage 1 or 2 chronic kidney disease who do not have albuminuria may be treated with usual first-line antihypertensive drugs [11]. If 3 antihypertensive drugs are necessary, these patients should be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a thiazide diuretic plus a calcium channel blocker. After kidney transplantation, treat hypertension with a calcium channel blocker to improve glomerular filtration rate and kidney survival [11, 57].

Patients with hypertension and a prior stroke or transient ischemic attack should receive treatment with a thiazide diuretic or angiotensin-converting enzyme or angiotensin receptor blocker [11, 58–60]. If a third antihypertensive drug is needed, these patients should be treated with a thiazide diuretic plus an angiotensin-converting enzyme or angiotensin receptor blocker plus a calcium channel blocker.

Patients with hypertension and peripheral arterial disease should be treated with an angiotensin-converting enzyme or angiotensin receptor blocker or a calcium channel blocker or thiazide diuretic or beta blocker [11, 61]. There is no evidence that any

one class of antihypertensive drugs is superior to treat hypertension in patients with peripheral arterial disease [11, 61]. Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are effective antihypertensive drugs. In patients with hypertension and diabetes mellitus and may be used as initial therapy. [11, 62–64] Angiotensin-converting enzymes or angiotensin receptor blockers should be used for treating diabetics with hypertension and persistent albuminuria. [11, 65, 66]. Chlorthalidone was better than lisinopril, amlodipine, and doxazosin in reducing cardiovascular disease and renal outcomes in nondiabetic s with hypertension and the metabolic syndrome [11, 67].

Beta blockers are the preferred antihypertensive drugs in patients with hypertension and thoracic aortic aneurysm [11, 68]. Beta blockers also improve survival in adults with type A and with type B acute and chronic thoracic aortic dissection [11, 69, 70]. If thoracic aorta dissection develops, beta blockers are the initial drug of choice for reducing blood pressure, ventricular rate, dP/dt, and stress on the aorta [68, 71, 72]. Systolic blood pressure should be lowered to 100 to 120 mm Hg and the ventricular rate decreased to less than 60 beats/minute by intravenous propranolol, metoprolol, labetalol, or esmolol [68, 72].

Pregnant women with hypertension should not receive treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, or atenolol because these drugs are fetotoxic [11, 73–75]. Pregnant women with hypertension should be treated with methyldopa, nifedipine, and/or labetalol [11, 76, 77].

Resistant hypertension is diagnosed if the blood pressure is not controlled despite adequate doses of 3 first-line classes of antihypertensive drugs including a thiazide diuretic or if adequate blood pressure control needs 4 or more antihypertensive drugs from different classes [11, 78]. Therapy 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 [11, 16]. If a fourth antihypertensive drug is needed to control blood pressure in persons treated with adequate doses of antihypertensive drugs from different classes including a thiazide diuretic, a mineralocorticoid receptor antagonist should be added to the therapeutic regimen [11, 79].

Hypertensive emergencies are diagnosed if the systolic blood pressure is higher than 180 mm Hg or if

the diastolic blood pressure is higher than 120 mm Hg with the presence of acute target organ damage [11, 80]. Patients with a hypertensive emergency should be admitted to an intensive care unit for continuous monitoring of blood pressure and target organ damage and for intravenous administration of appropriate antihypertensive drugs. The drugs of choice for treating hypertensive emergencies caused by different disorders are extensively discussed elsewhere [11, 80].

In patients with hypertension, blood pressure lowering is reasonable to prevent cognitive decline and dementia [11, 81, 82]. We are awaiting the results from the Systolic Blood Pressure Intervention Trial (SPRINT) which is adequately powered to test whether intensive blood pressure control reduces dementia [11].

Patients with hypertension on beta blockers undergoing major surgery should continue treatment with beta blockers [11]. Beta blockers should not be started on the day of surgery in beta-blocker naive patients [11]. Abrupt preoperative discontinuation of beta blockers or clonidine is potentially harmful [11, 83, 84]. Patients undergoing major elective surgery should have their blood pressure controlled with a target blood pressure goal of less than 130/80 mm Hg [11]. Patients undergoing major elective surgery with a systolic blood pressure of  $\geq 180$  mm Hg or a diastolic blood pressure of  $\geq 110$  mm Hg should have their surgery deferred [11, 85]. Management of hypertension in patients undergoing surgery is discussed elsewhere. [86].

## REFERENCES

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224–2260.
2. Lloyd-Jones D, Adams R, Carnethon M, et al. 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.
3. Aronow WS, Ahmed MI, Ekundayo OJ, et al. A propensity-matched study of the association of PAD with cardiovascular outcomes in community-dwelling older adults. *Am J Cardiol* 2009; 103:130–135.
4. Aronow WS, Fleg JL, Pepine CJ, et al. 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.
5. Lewington S, Clarke R, Qizilbash N, et al. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
6. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Eng J Med* 2008; 358: 1887–1898.
7. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387: 957–967.
8. Rosendorff C, Lackland DT, Allison M, Aronow WS, et al. AHA/ACC/ASH scientific statement. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. *J Am Coll Cardiol* 2015; 65:1998–2038
9. Wright JT, Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373: 2103–2116.
10. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years. A randomized clinical trial. *JAMA* 2016; 315: 2673–2682.
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; 70: November 13 (Epub ahead of print)
12. Navar AM, Pencina MJ, Peterson ED. Assessing cardiovascular risk to guide hypertension diagnosis and treatment. *JAMA Cardiol* 2016; 1: 864–871.
13. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. *Hypertension* 2017; 69: e2–e9.
14. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. *J Am Coll Cardiol* 2017; 69: 2446–2456.
15. McEvoy JW, Martin SS, Dardari ZA, et al. Coronary artery calcium to guide a personalized risk-based approach to initiation and intensification of antihypertensive therapy. *Circulation* 2017; 135: 153–165.

16. Aronow WS. Lifestyle measures for treating hypertension. *Arch Med Sci* 2017; 13: 1241–1243.
17. Mancía G, Bombelli M, Brambilla G, et al. Long-term prognostic value of whitecoat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension* 2013; 62: 168–174.
18. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA* 2011; 305: 913–922.
19. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens* 2011; 29: 4–16.
20. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935–2959.
21. Blood Pressure-Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; 384: 591–598.
22. Chobanian AV, Bakris GL, Black HR, et al. 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.
23. Chiong JR, Aronow WS, Khan IA, et al. Secondary hypertension: current diagnosis and treatment. *Int J Cardiol* 2008; 124: 6–21.
24. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol* 2017; 2: 775–781.
25. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. A report of the American College of Cardiology /American Heart Association Task Force on clinical Practice Guidelines and the Heart Failure Society of America. Developed in collaboration with the American Academy of Family Physicians, the American College of Chest Physicians, and International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2017; 70: 776–803.
26. 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.
27. SPS3 Study Group, Benavente OR, Coffey CS, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; 382: 507–515.
28. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313: 603–615.
29. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 3 diabetes: The ACCORD randomized trial. *Diabetes Care* 2014; 37: 1721–1728.
30. Soliman EZ, Byington RP, Bigger JT, et al. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial. *Hypertension* 2015; 66: 1123–1129.
31. Aronow WS. Orthostatic hypotension in diabetics in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial. *Hypertension* 2016; 68: 851–852.
32. Wang WT, You LK, Chiang CE, et al. Comparative effectiveness of blood pressure-lowering drugs in patients who have already suffered from stroke: traditional and Bayesian network meta-analysis of randomized trials. *Medicine* 2016; 95: e3302. Law MR, Morris JK, Wald NJ. Use of BP 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.doi.10.1136/bmj.b1665.
33. Smith SC Jr, Benjamin EJ, Bonow RO, et al. 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. Endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011; 58: 2432–2446.
34. Aronow WS. Current role of beta blockers in the treatment of hypertension. *Expert Opin Pharmacotherap* 2010; 11:2599–2607.
35. Gundersen T, Abrahamsen AM, Kjekshus J, Ronnevik PK. Timolol-related reduction in mortality and reinfarction in patients ages 65–75 years surviving acute myocardial infarction. *Circulation* 1982; 66:1179–1184.
36. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982; 247:1707–1714.
37. 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.
38. 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
39. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; 357:1385–1390.
40. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318: 1730–1737.
41. HOPE (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.
42. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362: 782–788.
43. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669–677.
44. Leon MB, Rosing DR, Bonow RO, et al. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. *Am J Cardiol* 1981; 48: 131–139.
45. Aronow WS. Might losartan reduce sudden cardiac death in diabetic patients with hypertension? *Lancet* 2003; 362: 591–592.
46. Carlberg B, Samuelson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004; 364: 1684–1689.
47. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709–717.
48. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; 46:425–431.
49. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;82:1954–1961.
50. Goldstein RE, Bocuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. *Circulation* 1991;83:52–60.
51. 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 > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol* 1997; 80: 207–209.
52. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015; 131: 34–42.
53. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; 288: 2421–2431.
54. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252.
55. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010; 363: 918–929.
56. Cross NB, Webster AC, Masson P, et al. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. *Transplantation* 2009; 88: 7–18.
57. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6.105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033–1041.
58. Liu L, Wang Z, Gong L, Zhang Y, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. *Hypertens Res* 2009; 32: 1032–1040.
59. Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. *Int Arch Med* 2009; 2: 30.
60. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VERapamil-SR/Trandolapril STudy. *Hypertension* 2010; 55: 48–53.
61. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; 165: 1410–1419.
62. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313: 603–615.
63. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005; 165: 1401–1409.
64. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with

- diabetes and kidney disease: a network meta-analysis. *Lancet* 2015; 385: 2047–2056.
65. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; 369: 1208–1219.
66. Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Diabetes Care* 2008; 32: 353–360.
67. Hiratzka LF, Bakris GL, Beckman JA, et al. ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol* 2010; 55: e27–e12
68. Genoni M, Paul M, Jenni R, et al. Chronic beta-blocker therapy improves outcome and treatment costs in chronic type B aortic dissection. *Eur J Cardiothorac Surg* 2001; 19: 606–610.
69. Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2012; 109: 122–127.
70. Braverman AC. Acute aortic dissection. Clinician update. *Circulation* 2010; 122: 184–188.
71. Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. *Circulation* 2005; 112: 3802–3813.
72. Pucci M, Sarween N, Knox E, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. *Expert Rev Clin Pharmacol* 2015; 8: 221–231.
73. Ferrer RL, Sibai BM, Mulrow CD, et al. Management of mild chronic hypertension during pregnancy: a review. *Obstet Gynecol* 2000; 96 (Pt 2): 849–860.
74. Moretti ME, Caprara D, Drehuta I, et al. The fetal safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. *Obstet Gynecol Int* 2012; 2012: 658310.
75. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. *Heart* 2004; 90: 1499–1504.
76. Hypertension in pregnancy. Report of the American College of Obstetrics and Gynecologists' Task force on Hypertension in Pregnancy. *Obstetrics and Gynecology* 2013; 122: 1122–1131.
77. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117: e510–e526.
78. Tataru AP, Barry AR. A systematic review of add-on pharmacologic therapy in the treatment of resistant hypertension. *Am J Cardiovasc Drugs* 2017; 17: 311–318.
79. Aronow WS. Treatment of hypertensive emergencies. *Ann Translational Med* 2017; 5 (Suppl 1): S5. doi: 10.21037/atm.2017.03.34.
80. Forette F, Seux ML, Staessen JA, et al. 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.
81. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003; 163: 1069–1075.
82. Hart GR, Anderson RJ. Withdrawal syndromes and the cessation of antihypertensive therapy. *Arch Intern Med* 1981; 141: 1125–1127.
83. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J* 2001; 141: 148–153.
84. Fleisher LA. Preoperative evaluation of the patient with hypertension. *JAMA* 2002; 287: 2043–2046.
85. Aronow WS. Management of hypertension in patients undergoing surgery. *Ann Translational Med* 2017; 5 (10): 227. doi: 10.21037/atm.2017.03.54