



Treatment of Hypertension in Patients With Coronary Artery Disease

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Abstract

Patients with coronary artery disease should have their modifiable coronary risk factors intensively treated. Dietary sodium should be reduced. Hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Long-acting nitrates are effective antianginal and antiischemic drugs. Calcium channel blockers may be added if angina persists despite beta blockers and long-acting nitrates... The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90 mm Hg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150 mm Hg if they are older than 80 years of age. Octogenarians should be checked for orthostatic changes with standing, and a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 65 mm Hg should be avoided. Caution is advised in causing a diastolic blood pressure less than 60 mm Hg in patients with diabetes mellitus or in patients older than 60 years of age. In addition to the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol, patients with hypertension and congestive heart failure should be treated with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and patients with persistent severe symptoms with aldosterone antagonists if not contraindicated.

Key Words

Myocardial infarction; coronary artery disease; hypertension; beta blockers; angiotensin-converting enzyme inhibitors; aldosterone antagonists; calcium channel blockers; nitrates.

Introduction

Hypertension is a major risk factor for cardiovascular disease [1–9]. These guidelines recommend lowering the blood pressure to less than 140/90 mm Hg in patients younger than age 80 years and to less than 150/90 mm Hg in patients aged 80 years and older if

tolerated [1–4, 7–9]. Hypertension is present in approximately 69% of patients with a first myocardial infarction [10], in approximately 77% of patients with a first stroke [10], in approximately 74% of patients with congestive heart failure [10], and in 60% of patients with peripheral arterial disease [11]. 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 [3]. This paper will discuss the management of patients with coronary artery disease recommended by the 2015 American Heart Association/American College of Cardiology/American Society of Hypertension guidelines on treatment of hypertension in patients with coronary artery disease [9].

Coronary Risk Factor Reduction

Modifiable coronary risk factors should be treated. Smokers should be strongly encouraged to stop smoking because it will reduce cardiovascular mortality and all-cause mortality in patients with coronary artery disease. A smoking cessation program should be recommended to smokers [12]. Nicotine replacement therapy [13], bupropion [14], and varenicline [15] are approved pharmacologic treatments for promoting smoking cessation.

Hypertension should be treated with sodium restriction to not exceed 1.5 grams daily, weight reduction if necessary, discontinuation of drugs that increase blood pressure, avoidance of caffeine and tobacco, limiting alcohol intake to no more than two drinks per day in men and one drink per day in women and light weight men, an increase in physical activity, a decrease of dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium, and magnesium intake [3].

Patients with coronary artery disease should consume a Step II American Heart Association (AHA) diet. Numerous double-blind, randomized, placebo-controlled trials have demonstrated that patients with coronary artery disease treated with statins have a reduction in cardiovascular events and in mortality [16–20]. High-dose statins (rosuvastatin 20–40 mg daily and atorvastatin 40–80 mg daily) lower serum low-density lipoprotein cholesterol 50% or more and should be administered to patients with coronary artery disease [21]. Addition of ezetimibe to high-dose statin therapy has been demonstrated to further reduce serum lipoprotein cholesterol and reduce coronary events in patients after an acute coronary syndrome [22].

Diabetics with coronary artery disease should be treated with dietary therapy, weight reduction if necessary, and appropriate drugs if needed to control hyperglycemia. Other coronary risk factors should

be controlled. Metformin should be the initial drug to treat hyperglycemia in most patients [23, 24]. The hemoglobin A1c level should be reduced to <7% in patients with diabetes mellitus [23].

Obese patients with coronary artery disease must undergo weight reduction [12]. Weight reduction is also a first approach to controlling hyperglycemia, mild hypertension, and dyslipidemia. Regular aerobic exercise should be added to diet in treating obesity. The body mass index should be reduced to 18.5 to 24.9 kg/m² [12]. Exercise training programs have been found to improve endurance and functional capacity in patients with coronary artery disease [25,26]. The goal to be achieved is at least 30 minutes of exercise daily for 7 days per week with a minimum of 5 days of physical exercise per week [12].

Target Blood Pressure

The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90 mm Hg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150 mm Hg if they are older than 80 years of age [9]. Consideration can be given to reduce the blood pressure to less than 130/80 mm Hg with a class IIb C indication [9]. Octogenarians should be checked for orthostatic changes with standing, and a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 65 mm Hg should be avoided [9]. Caution is advised in causing a diastolic blood pressure less than 60 mm Hg in patients with diabetes mellitus or in patients older than 60 years of age [9].

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial included 4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina pectoris) [27]. 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 [27].

Among 8,354 adults aged 60 years and older with coronary artery disease in the International Verapamil SR Trandolapril (INVEST) study, a baseline systolic blood pressure of 150 mm Hg and higher, and 22,308 patient years of follow-up, 57% had a systolic blood pressure less than 140 mm Hg, 21% had a systolic blood pressure of 140 to 149 mm Hg, and 22% had a

systolic blood pressure of 150 mm Hg and higher [6]. The primary outcome of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke occurred in 9.36% of adults with a systolic blood pressure of less than 140 mm Hg, in 12.71% of adults with a systolic blood pressure of 140–149 mm Hg, and in 21.3% of adults with a systolic blood pressure of 150 mm Hg and higher ($p < 0.0001$) [6]. Using propensity score analyses, compared with a systolic blood pressure of less than 140 mm Hg, a systolic blood pressure of 140 to 149 mm Hg increased cardiovascular mortality by 34% ($p = 0.04$), total stroke by 89% ($p = 0.002$), and nonfatal stroke by 70% ($p = 0.03$) [6]. Compared with a systolic blood pressure of less than 140 mm Hg, a systolic blood pressure of 150 mm Hg and higher increased the primary outcome by 82% ($p < 0.0001$), all-cause mortality by 60% ($p < 0.0001$), cardiovascular mortality by 218% ($p < 0.0001$), and total stroke by 283% ($p < 0.0001$) [6].

Antihypertensive Therapy

A meta-analysis of 147 randomized trials of 464,000 adults with hypertension reported 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, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers caused a similar decrease in coronary events and stroke for a given reduction in blood pressure [28]. The proportionate reduction in cardiovascular events was the same or similar regardless of pretreatment blood pressure and the presence or absence of cardiovascular events [28]. If beta blockers are used to treat adults with hypertension, atenolol should not be used [29-31].

Coronary Artery Disease

Coronary risk factors should be controlled including smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, and physical inactivity [9]. Dietary sodium should be reduced.

Beta blockers are the initial antihypertensive drugs to use in patients with coronary artery disease who have angina pectoris, who have had a myocardial infarction, and in those who have left ventricular systolic dysfunction unless contraindicated [9]. Patients with prior myocardial infarction and hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors [2-4, 8, 9, 28, 32-45]. Atenolol should be avoided [29-31]. If a third drug is

needed, aldosterone antagonists may be used based on the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trial [46]. Patients treated with aldosterone antagonists should not have significant renal dysfunction or hyperkalemia.

In addition to the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol, [9, 47-51], patients with hypertension and congestive heart failure should be treated with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [9, 47, 52-60], and patients with persistent severe symptoms with aldosterone antagonists [9, 46, 47, 61]. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should also be administered to patients with diabetes mellitus or chronic kidney disease [3, 4, 8, 62, 63].

Hydralazine plus isosorbide dinitrate should be added to African-American patients with New York Heart Association class III or IV heart failure with a reduced left ventricular ejection fraction already receiving diuretics, beta blockers, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [9, 47, 64]. Drugs to avoid in patients with hypertension and heart failure with a reduced left ventricular ejection fraction include verapamil, diltiazem, doxazosin, clonidine, moxonidine, hydralazine without a nitrate, and nonsteroidal anti-inflammatory drugs [9].

In patients with hypertension and heart failure with a preserved left ventricular ejection fraction, class I therapeutic indications include control of systolic and diastolic hypertension, control of the ventricular rate in patients with atrial fibrillation, and reduction of pulmonary congestion and peripheral edema with diuretics [9, 47]. Class IIb therapeutic indications include use of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or calcium channel blockers [9].

Stable Angina Pectoris

Patients with hypertension and chronic stable angina pectoris should be treated with beta blockers plus nitrates as antianginal agents [9]. The hypertension in these patients should be controlled with beta blockers plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with addition of a thiazide or thiazide-like diuretic if needed. If either the angina pectoris or the hypertension remains uncontrolled, a long-acting dihydropyridine calcium channel blocker can be added to the therapeutic regimen. Nondihydropyridine calcium channel blockers such

as verapamil and diltiazem cannot be used if there is left ventricular systolic dysfunction. Combining a beta blocker with either verapamil or diltiazem must be used with caution because of the increased risk of bradyarrhythmias and heart failure [9].

Acute Coronary Syndromes

In patients with an acute coronary syndrome, initial therapy of hypertension should include a short-acting beta₁ selective beta blocker without intrinsic sympathomimetic activity such as metoprolol tartrate or bisoprolol [9]. Treatment with beta blockers should be started initially within 24 hours of symptoms. In patients with severe hypertension or ongoing ischemia, intravenous esmolol may be considered [9]. In hemodynamically unstable patients or those with decompensated heart failure, treatment with beta blockers should be delayed until the patient is stabilized [9].

In patients with acute coronary syndromes with hypertension, nitrates can be used to reduce blood pressure or to reduce ongoing myocardial ischemia or pulmonary congestion [9]. However, nitrates should not be given to patients with suspected right ventricular infarction or in those with hemodynamic instability. Intravenous or sublingual nitroglycerin is preferred initially [9].

An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be given to patients with an acute coronary syndrome, especially in patients with an anterior myocardial infarction, if hypertension persists, if there is a reduced left ventricular ejection fraction, or if diabetes mellitus is present [9]. If hypertension persists after use of a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a long-acting dihydropyridine calcium channel blocker may be added [9]. Aldosterone antagonists are indicated in patients receiving 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 [9]. However, they should be avoided if the serum potassium is ≥ 5.0 mEq/L or if the serum creatinine is ≥ 2.5 mg/dL in men or ≥ 2.0 mg/dL in women [9]. Loop diuretics are preferred to thiazide and thiazide-type diuretics in patients with heart failure or in patients with chronic kidney disease and an estimated glomerular filtration rate less than 30 mL/minute [9].

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References

1. 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.
2. Rosendorff C, Black HR, Cannon CP, et al. 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
3. 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. *J Am Coll Cardiol* 2011; 57: 2037-2114
4. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013; 34: 2159-2219.
5. Banach M, Bromfield S, Howard G, et al. Association of systolic blood pressure levels with cardiovascular events and all-cause mortality among older adults taking antihypertensive medication. *Int J Cardiol* 2014; 176: 219-226.
6. Bangalore S, Gong Y, Cooper-DeHoff RM, et al. 2014 Eighth Joint National Committee Panel recommendation for blood pressure targets revisited: results from the INVEST study. *J Am Coll Cardiol* 2014; 64: 784-793.
7. Hackam DG, Quinn RR, Ravani P, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2013; 29: 528-542.
8. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. 2014; 16: 14-26.
9. 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.
10. 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.
11. 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.
12. 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.
 13. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996; 335: 1792-1798.
 14. Eisenberg MJ, Grandi SM, Gervais A, et al. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction. A randomized, placebo-controlled trial. *J Am Coll Cardiol* 2013; 61: 524-532.
 15. Rigotti NA, Pipe AL, Benowitz NL, et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease. A randomized trial. *Circulation* 2010; 121: 221-229.
 16. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris. Findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1997;96:4211-4218.
 17. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) Trial. *Ann Intern Med* 1998;129:681-689.
 18. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-1357.
 19. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
 20. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol \geq 125 mg/dL treated with statins versus no lipid-lowering drug. *Am J Cardiol* 2002;89:67-69.
 21. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2889-2934.
 22. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372: 2387-2397.
 23. American Diabetes Association. Position statement. Standards of Medical Care in Diabetes-2013. *Diabetes Care* 2013; 36 (supplement 1): S11-S-66
 24. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2012; 156: 218-231.
 25. Williams MA, Maresh CM, Aronow WS, et al. The value of early out-patient cardiac exercise programmes for the elderly in comparison with other selected age groups. *Eur Heart J* 1984;5(suppl E):113-115.
 26. Aronow WS. Exercise therapy for older persons with cardiovascular disease. *Am J Geriatr Cardiol* 2001;10:245-252.
 27. Bangalore S, Qin J, Sloan S, et al. 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.
 28. 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.
 29. Aronow WS. Might losartan reduce sudden cardiac death in diabetic patients with hypertension? *Lancet* 2003; 362: 591-592.
 30. Carlberg B, Samuelson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004; 364: 1684-1689.
 31. Aronow WS. Current role of beta blockers in the treatment of hypertension. *Expert Opin Pharmacotherap* 2010; 11:2599-2607.
 32. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA* 1993;270:1589-1595.
 33. Hansteen V. Beta blockade after myocardial infarction: The Norwegian Propranolol Study in high-risk patients. *Circulation* 1983;67(suppl I):I-57-I-60.
 34. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. *Lancet* 1981;2:823-827.
 35. Gundersen T, Abrahamsen AM, Kjekshus J, et al. Timolol-related reduction in mortality and reinfarction in patients ages 65-75 years surviving acute myocardial infarction. *Circulation* 1982; 66:1179-1184.
 36. Pedersen TR for the Norwegian Multicentre Study Group. Six-year follow-up of the Norwegian Multicentre Study on Timolol after acute myocardial infarction. *N Engl J Med* 1985;313:1055-1058.
 37. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982; 247:1707-1714.

38. 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.
39. Park KC, Forman DE, Wei JY. Utility of beta-blockade treatment for older postinfarction patients. *J Am Geriatr Soc* 1995;43:751-755.
40. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503-510.
41. The Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomised trials in post-infarction patients. *Eur Heart J* 1988;9:8-16.
42. 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.
43. 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.
44. 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
45. Aronow WS. Current role of beta blockers in the treatment of hypertension. *Expert Opin Pharmacotherap* 2010; 11: 2599-2607.
46. 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.
47. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guidelines for the management of heart failure: executive summary. A report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines . Developed in collaboration with the American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation. Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Am Coll Cardiol*. 2013;62:1495-1539.
48. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-1355.
49. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
50. 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.
51. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in chronic heart failure. *N Engl J Med* 2001;344:651-658.
52. 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
53. Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-1456.
54. 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.
55. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-828.
56. Ambrosioni E, Borghi C, Magnani B, for the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;332:80-85.
57. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-1676.
58. 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.
59. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-1906.
60. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772-776.
61. 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.

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62. American Diabetes Association. Position statement. Standards of Medical Care in Diabetes-2013. *Diabetes Care* 2013; 36 (supplement 1): S11-S-66.
63. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Chapter 3. Blood pressure management in CKD ND patients without diabetes mellitus. *Kidney Int Supplements* 2012; 2:357-362.
64. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049-2057