

## Therapeutic Class Overview

### Angiotensin-Converting Enzyme (ACE) Inhibitors Single Entity Agents

#### Therapeutic Class

- Overview/Summary:** The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.<sup>1,2</sup> Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.<sup>3</sup> Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).<sup>1</sup> Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.<sup>1,3</sup> In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including ventricular hypertrophy, remodeling and myocyte apoptosis.<sup>1,2</sup> The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.<sup>4</sup> Evidence-based guidelines recognize the important role that ACE inhibitors play in the treatment of hypertension and other cardiovascular and renal diseases. With the exception of Epaned<sup>®</sup> (enalapril solution) and Qbrelis<sup>®</sup> (lisinopril solution), all of the ACE inhibitors are available generically.

**Table 1. Current Medications Available in Therapeutic Class<sup>5-19</sup>**

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Benazepril (Lotensin <sup>®*</sup> )	Hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✓
Captopril*	Diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 12.5 mg 25 mg 50 mg 100 mg	✓
Enalapril (Vasotec <sup>®*</sup> , Epaned <sup>®</sup> )	Asymptomatic left ventricular dysfunction, heart failure, hypertension	Solution: 1 mg/mL  Tablet: 2.5 mg 5 mg 10 mg 20 mg	✓
Enalaprilat*	Hypertension	Injection: 1.25 mg/mL	✓
Fosinopril*	Heart failure, hypertension	Tablet: 10 mg 20 mg 40 mg	✓
Lisinopril (Prinivil <sup>®*</sup> , Qbrelis <sup>®</sup> , Zestril <sup>®*</sup> )	Acute myocardial infarction to improve survival, heart failure, hypertension	Solution: 1 mg/mL  Tablet: 2.5 mg 5 mg 10 mg 20 mg	✓

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		30 mg 40 mg	
Moexipril*	Hypertension	Tablet: 7.5 mg 15 mg	✓
Perindopril (Aceon®*)	Hypertension, stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal myocardial infarction	Tablet: 2 mg 4 mg 8 mg	✓
Quinapril (Accupril®*)	Heart failure, hypertension	Tablet: 5 mg 10 mg 20 mg 40 mg	✓
Ramipril (Altace®*)	Heart failure post myocardial infarction, hypertension, reduce the risk of myocardial infarction, stroke and death from cardiovascular causes	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg	✓
Trandolapril (Mavik®*)	Heart failure post-myocardial infarction, hypertension, left ventricular dysfunction post-myocardial infarction	Tablet: 1 mg 2 mg 4 mg	✓

\*Generic available in at least one dosage form or strength.

### Evidence-based Medicine

- Angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective for coronary artery disease and to reduce the risk of cardiovascular mortality, myocardial infarction and stroke.<sup>19-30</sup>
- Clinical Trials have demonstrated the efficacy of ACE inhibitors in reducing mortality associated with congestive heart failure.<sup>31-47</sup>
- ACE inhibitors have demonstrated efficacy for the treatment for hypertension and for the use in diabetic nephropathy.<sup>48-79</sup>

### Key Points within the Medication Class

- According to Current Clinical Guidelines:<sup>80-97</sup>
  - Treatment guidelines for the management of stable angina recommend angiotensin-converting enzyme (ACE) inhibitors in patients with a left ventricular ejection fraction  $\leq 40\%$  and in those with hypertension, diabetes or chronic kidney disease. ACE inhibitors are also recommended in patients at lower risk (mildly reduced or normal left ventricular ejection fraction) in whom cardiovascular risk factors remain well controlled and revascularization has been performed.
  - Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommend the use of ACE inhibitors in the first 24 hours in patients with or without pulmonary congestion or left ventricular ejection fraction of  $\leq 40\%$ . ACE inhibitors are recommended in patients with heart failure, left ventricular dysfunction, diabetes or hypertension. In addition, ACE inhibitors are a reasonable for patients with heart failure and left ventricular ejection fraction  $>40\%$  and patients without hypertension or diabetes. The guidelines are similar for the management of ST-elevation myocardial infarction.
  - Treatment guidelines recommend ACE inhibitors in patients who are at risk for the development of heart failure. ACE inhibitors are recommended for the management of heart failure in patients who have cardiac structural abnormalities or remodeling who have not

- developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction.
- Treatment guidelines for hypertension recommend the use of ACE inhibitors as a first line option in all patients as well as in hypertensive patients with certain compelling indications including heart failure, post-myocardial infarction, left ventricular dysfunction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention.
  - Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including an ACE inhibitor. In patients with known cardiovascular disease, a regimen including an ACE inhibitor should be used to reduce the risk of cardiovascular events. In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension and microalbuminuria, ACE inhibitors have been shown to delay the progression to macroalbuminuria.
- Other Key Facts:
    - Clinical trials have not demonstrated significant differences when ACE inhibitors were compared to angiotensin II receptor blockers.
    - With the exception of Epaned<sup>®</sup> (enalapril solution) and Qbrelis<sup>®</sup> (lisinopril solution), all of the ACE inhibitors are available generically.

## References

1. Saseen JJ, Carter BL. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. 6<sup>th</sup> edition. New York (NY): McGraw-Hill; 2005. p. 185-217.
2. Parker RB, Patterson JH, Johnson JA. Heart failure. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. 6<sup>th</sup> edition. New York (NY): McGraw-Hill; 2005. p. 219-60.
3. Reid IA. Vasoactive peptides. In: Katzung BG, editor. *Basic and clinical pharmacology* [monograph on the Internet]. 11th ed. New York (NY): McGraw-Hill; 2009 [cited 2011 Mar 25]. Available from: <http://online.statref.com>.
4. Benowitz NL. Antihypertensive agents. In: Katzung BG, editor. *Basic and clinical pharmacology* [monograph on the Internet]. 11th ed. New York (NY): McGraw-Hill; 2009 [cited 2011 Mar 25]. Available from: <http://online.statref.com>.
5. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2014 [cited 2014 Apr 18]. Available from: <http://online.factsandcomparisons.com>.
6. Micromedex<sup>®</sup> Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2014 Apr 18]. Available from: <http://www.thomsonhc.com/>
7. Lotensin<sup>®</sup> [package insert]. Suffern (NY): Novartis Pharmaceuticals Corporation; 2015 Jul.
8. Captopril [package insert]. Morgantown (WV): Mylan Pharmaceuticals Inc.; 2015 Jun.
9. Epaned<sup>®</sup> [package insert]. Greenwood Village (CO): Silvergate Pharmaceuticals, Inc.; 2016 Jan.
10. Vasotec<sup>®</sup> [package insert]. Bridgewater (NJ): Valeant Pharmaceuticals North America, LLC; 2015 Aug.
11. Fosinopril [package insert]. Fort Lauderdale (FL): Andrx Pharmaceuticals, Inc.; 2004 Jan.
12. Prinivil<sup>®</sup> [package insert]. Whitehouse Station (NJ): Merck&Co., Inc.; 2015 Aug.
13. Qbrelis<sup>®</sup> [package insert]. Greenwood Village (CO): Silvergate Pharmaceuticals, Inc.; 2016 Jul.
14. Zestril<sup>®</sup> [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals, LP; 2014 Jun.
15. Moexipril [package insert]. Mahwah (NJ): Glenmark Pharmaceuticals, Inc.; 2014 Dec.
16. Perindopril [package insert]. Baltimore (MD): Lupin Pharmaceuticals, Inc.; 2010 Jan.
17. Accupril<sup>®</sup> [package insert]. New York (NY): Pfizer Inc; 2015 Sep.
18. Altace<sup>®</sup> [package insert]. Bristol (TN): King Pharmaceuticals; 2015 Sep.
19. Mavik<sup>®</sup> [package insert]. North Chicago (IL): AbbVie, Inc.; 2016 Jan.
20. Swedberg K, Held P, Kjeksus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction results of the cooperative New Scandinavian enalapril survival study II (CONSENSUS II). *N Engl J Med*. 1992 Sep 3;327(10):678-84.
21. Pitt B, Reichek N, Willenbrock R, Zannad F, Philips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation*. 2003;108(15):1831-8.
22. Fox KM, Bertrand M, Ferrari R, et al. EUROPA Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003 Sep 6;362:782-8.
23. PREAMI Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized perindopril and remodeling in elderly with acute myocardial infarction (PREAMI) study. *Arch Intern Med*. 2006 Mar 27;166:659-66.
24. PROGRESS Collaborative group. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. *Lancet*. 2001 Sep 29;358:1033-41.
25. 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 Jan 20;342:145-53.
26. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008 Apr 10;358(15):1547-59.

27. The PEACE Trial Investigators. Angiotensin-converting enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004 Nov 11;351(20):2058-68.
28. Pilote L, Abrahamowicz M, Rodrigues E, et al. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? *Ann Intern Med*. 2004 Jul 20;141(2):102-12.
29. Nissen SE, Tuzcu EM, Libby P, et al; for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004 Nov 10;292(18):2217-26.
30. Dahlof B, Sever PS, Poulter NR, et al; for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required vs atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*. 2005 Sep 10;366(9489):895-906.
31. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertens*. 2007 Jun;25(5):951-8.
32. Pfeffer MA, Braunwald E, Moye LA, et al; on behalf of the SAVE Investigators. 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 Sep 3;327(10):669-77.
33. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian enalapril survival study. *N Engl J Med*. 1987 Jun 4;316(23):1429-35.
34. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991 Aug 1;325(5):293-302.
35. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992 Sep 3;327(10):685-91.
36. Tu K, Mamdani M, Kopp A, Lee D. Comparison of angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure. *Am J Cardiol*. 2005 Jan 15;95:283-6.
37. Packer M, Poole-Wilson PA, Armstrong PW, et al; on behalf of the ATLAS Study Group. Comparative effects of low and high doses of angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*. 1999 Dec 7;100:2312-18.
38. 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;342:821-8.
39. Kober L, Torp-Pedersen C, Carlsen JE, et al; for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 1995 Dec 21;333(25):1670-6.
40. Pitt B, Segal R, Martinez FA, et al; on behalf of ELITE Study Investigators. Randomized trial of losartan vs captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997 Mar 15;349:747-52.
41. Pitt B, Poole-Wilson PA, Segal R, et al; on behalf of the ELITE II Investigators. Effect of losartan compared to captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study, ELITE II. *Lancet*. 2000 May 6;355:1582-7.
42. Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. *Lancet*. 2002 Sep 7;360:752-60.
43. Pfeffer MA, McMurray JJV, Velazquez EJ, et al; for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003 Nov 13;349:1893-906.
44. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: the RESOLVD Pilot Study Investigators. *Circulation*. 1999 Sep 7;100:1056-64.
45. Dobre D, van Veldhuisen DJ, Gouder MA, Krum H, Willenheimer R. Clinical effects of initial 6 months monotherapy with bisoprolol vs enalapril in the treatment of patients with mild to moderate chronic heart failure. Data from the CIBIS III Trial. *Cardiovasc Drugs Ther*. 2008 Oct;22(5):399-405.
46. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared to the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005 Oct 18;112(16):2426-35.
47. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991 Aug 1;325:303-10.
48. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med*. 2004 Nov 2;141(9):693-704.
49. Julien J, Dufoux MA, Prasquier R, Chatellier G, Menard D, Plouin PF, et al. Effects of captopril and minoxidil on left ventricular hypertrophy in resistant hypertensive patients: A 6 month double-blind comparison (abstract). *J Am Coll Cardiol*. 1990 Jul;16(1):137-42.
50. Williams GH, Burgess E, Kolloch RE, Ruilope LM, Neigowska J, Kipnes MS, et al. Efficacy of eplerenone vs enalapril as monotherapy in systemic hypertension. *Am J of Cardiol*. 2004;93(8):990-6.
51. Ruilope L, Jager B, Prichard B. Eprosartan vs enalapril in elderly patients with hypertension: a double-blind, randomized trial. *Blood Pressure*. 2001;10:223-9.
52. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared to enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med*. 1998 Mar 5;338(10):645-52.
53. Karlberg BE, Lins LE, Hermansson K. Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared to enalapril in elderly patients with primary hypertension. TEES Study Group. *J Hypertens*. 1999 Feb;17(2):293-302.

54. Wing LMH, Reid CM, Ryan P, et al; for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003 Feb 13;348(7):583-92.
55. ALLHAT Officers and Coordinators for ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium-channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002 Dec 18;288(23):2981-97.
56. Whelton A, Miller WE, Dunne, Jr B, et al. Once-daily lisinopril compared to twice-daily captopril in the treatment of mild-to-moderate hypertension: assessment of office and ambulatory blood pressure. *J Clin Pharmacol*. 1990 Dec;30(12):1074-80.
57. Rosei EA, Rizzoni D, Comini S, Boari G; Nebivolol-Lisinopril Study Group. Evaluation of the efficacy and tolerability of nebivolol vs lisinopril in the treatment of essential arterial hypertension: a randomized, multicentre, double-blind study. *Blood Press Suppl*. 2003 May;1:30-5.
58. Wald DS, Law M, Mills S, Bestwick JP, Morris JK, Wald NJ. A 16-week, randomized, double-blind, placebo-controlled, crossover trial to quantify the combined effect of an angiotensin-converting enzyme inhibitor and a beta-blocker on blood pressure reduction. *Clin Ther*. 2008 Nov;30(11):2030-9.
59. Karotsis AK, Symeonidis A, Mastorantonakis SE, Stergiou GS. Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. *Clin Exp Hypertens*. 2006;28(7):655-62.
60. Beckett NS, Peters R, Fletcher AE, et al; for the HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008 May 1;358(18):1887-98.
61. Williams B, Lacourcière Y, Schumacher H, Gosse P, Neutel JM. Antihypertensive efficacy of telmisartan vs ramipril over the 24-h dosing period, including the critical early morning hours: a pooled analysis of the PRISMA I and II randomized trials. *J Hum Hypertens*. 2009 Sep;23(9):610-9.
62. Tytus RH, Burgess ED, Assouline L, Vanjaka A. A 26-week, prospective, open-label, uncontrolled, multicenter study to evaluate the effect of an escalating-dose regimen of trandolapril on change in blood pressure in treatment-naïve and concurrently treated adult hypertensive subjects (TRAIL). *Clin Ther*. 2007 Feb;29(2):305-15.
63. Tytus RH, Assouline L, Vanjaka A. Blood pressure control rates with an antihypertensive regimen including trandolapril in a Canadian usual-care setting. *Adv Ther*. 2011;28(9):789-798.
64. Pauly NC, Safar ME; for the Investigator Study Group. Comparison of the efficacy and safety of trandolapril and captopril for 16 weeks in mild-to-moderate essential hypertension. *J Cardiovasc Pharmacol*. 1994;23 Suppl 4:s73-6.
65. Vaur L, Dutrey-Dupagne C, Boussac J, et al. Differential effects of a missed dose of trandolapril and enalapril on blood pressure control in hypertensive patients. *J Cardiovasc Pharmacol*. 1995;Jul;26(1):127-31.
66. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared to other antihypertensive drugs: a meta-analysis. *Am J Cardiovasc Drugs*. 2008;8(1):35-44.
67. Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD002003. doi: 10.1002/14651858.CD002003.pub2.
68. Hansson L, Lindholm LH, Ekblom T, Dahlöf B, Lanke J, Scherstén B, et al. Randomized trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 (STOP) study. *Lancet*. 1999 Nov 20;354(9192):1751-6.
69. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet*. 2005 Oct 29-Nov 4;366(9496):1545-53.
70. Baguet JP, Legallier B, Auquier P, Robitail S. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. *Clin Drug Investig*. 2007;27(11):735-53.
71. Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol*. 2007;18:1889-98.
72. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade vs converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*. 2004 Nov 4;351:1953-61.
73. Morgensen CE, Neldam S, Tikkanen I, et al. Randomized controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ*. 2000 Dec 9;321:1440-4.
74. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006 Oct 12;355(15):1551-62.
75. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*. 1997 Jun 28;349:1857-63.
76. Wright JT Jr, Bakris G, Greene T, et al. Effects of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002 Nov 20;288(19):2421-31.
77. Ruggenti P, Fassi A, Ilieva AP, et al; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med*. 2004 Nov 4;351(19):1941-51.
78. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005 Dec 10;366:2026-33.
79. Strippoli GFM, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ*. 2004 Sep 30;329:828-38.
80. Strippoli GFM, Bonifati C, Craig M, Navaneethan DS, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease (review). *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD006257.
81. Fraker T, Fihn S, Gibbons RJ, Abrams J, Chatterjee K, Daley J, et al. 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of chronic stable angina: a report of the American College of Cardiology/American Heart Association task force on practice guidelines writing group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation*. 2007 Dec 4;116(23):2762-72.

82. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;34:2949–3003; doi:10.1093/eurheartj/ehs296.
83. Amsterdam EA, Wenger NK, Brindis RG, Casey Jr DE, Ganiats TG, Holmes Jr DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, *Journal of the American College of Cardiology* (2014), doi: 10.1016/j.jacc.2014.09.017.
84. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2011;32:2999-3054.
85. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2012. doi:10.1016/j.jacc.2012.11.019.
86. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2012. doi:10.1016/j.jacc.2012.11.019.
87. Steg G, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569-2619.
88. National Institute for Health and Clinical Excellence. MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 May [cited 2014 Dec]. Available from: <http://www.nice.org.uk/guidance/cg172>.
89. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239. doi:10.1016/j.jacc.2013.05.019.
90. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail*. 2010 Jun;16(6):e1-194.
91. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J*. 2012;33:1787-1847.
92. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014 Feb 5;311(5):507-20. doi: 10.1001/jama.2013.284427.
93. Whitworth JA; World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003 Nov;21(11):1983-92.
94. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 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). *J Hypertens*. 2007 Jun;25(6):1105-87.
95. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield M, et al. Reappraisal of European guidelines on hypertension management: a European society of hypertension task force document. *Journal of Hypertension*. 2009;27(11):2121-58.
96. National Institute for Health and Clinical Excellence (NICE). Hypertension: the clinical management of primary hypertension in adults [guideline on the Internet]. London (UK): NICE; 2011 Aug [cited 2012 Dec]. Available from: <http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf>.
97. American Diabetes Association. Standards of medical care in diabetes-2012. *Diabetes Care*. 2012 Jan;35(Suppl 1):S11-S63.