REVIEW ARTICLE

A new paradigm in the treatment of the cardiovascular disease continuum: focus on prevention

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Abstract

The cardiovascular disease continuum (CVDC) is a sequence of cardiovascular events, which begins from a cluster of cardiovascular risk factors consisting of diabetes mellitus, dyslipidemia, hypertension, smoking and visceral obesity. If these factors are not intervened with early, they will, inexorably, progress to atherosclerosis, coronary artery disease, myocardial infarction, left ventricular hypertrophy, left ventricular dilatation leading to left ventricular diastolic or systolic dysfunction and eventually end stage heart failure and death. For this concise review, a Medline search of the English language literature between the years 2000 and 2009 was conducted and 33 pertinent publications were selected. Based on the evidence contained in these publications, it is possible that early intervention and treatment of the various cardiovascular risk factors, which initiate and perpetuate the CVDC, could prevent it or arrest its further progress. Therefore, this concise review will emphasize the early detection and treatment of the various cardiovascular risk factors, which initiate and perpetuate the CVDC. Hippokratia 2011; 15 (1): 7-11

Keywords: cardiovascular disease continuum, dyslipidemia, diabetes mellitus, obesity, hypertension, smoking, review

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The cardiovascular disease continuum (CVDC) is a chain of events precipitated by several cardiovascular risk factors, which if left untreated will, inexorably, culminate in end stage heart failure and death. The major cardiovascular risk factors that lead to CVDC are listed at the bottom of Figure 1 and consist of dyslipidemia, hypertension, diabetes, obesity and smoking[1]. Since its introduction, the CVDC has been validated by several clinical trials and epidemiologic studies, which have provided new insights into its underlying pathophysiology and the possible arrest of its progression by early intervention. Mounting evidence suggests that early intervention in managing the cardiovascular risk factors is more important than treating the cardiovascular disease (CVD) itself. Since CVD complications take years to develop, this affords ample time for early intervention and treatment of the various cardiovascular risk factors. A Medline search of publications in English language was conducted between the years 2000 and 2009 and 33 pertinent publications were selected and are included in this brief review. Based on the new evidence, the emphasis in this concise review will be on the early detection and treatment of the various cardiovascular risk factors that initiate and perpetuate the CVDC. The major CVD risk factor are listed in the table and will be, briefly, discussed.

Figure 1. The cardiovascular continuum.

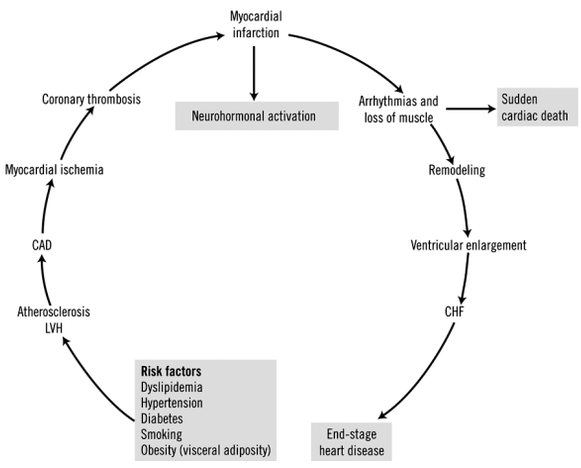

Figure 1: This figure shows the various stages of cardiovascular disease continuum and the different stages of intervention. Reprinted with permission[2].

Dyslipidemia

High cholesterol levels have long been considered an independent risk factor for CVD, and total cholesterol levels of 200mg/dl or higher and LDL-C levels of 130 mg/dl or higher have been found in 50.7% and 45.8% of adult subjects, respectively[2]. In addition, with the rising of obesity, total cholesterol levels above 200mg/dl have been found in 10% of children 12-19 years old and of those screened, only 28.6% knew that high cholesterol is a risk factor for CVD. Also, a recent analysis of data for the US, Finland and Australia[3] found that adolescents with dyslipidemia $\geq 95^{th}$ percentile had a higher incidence

Table 1: Incidence of major cardiovascular risk factors in the US population.

Risk Factor	Incidence
Cholesterol ≥ 200 mg/dl	50.7%
LDL-C > 130mg/dl	45.8%
Type 2 DM (FBG 100-125mg/dl)	6.0%
Increased Weight	64.0%
Obesity	30.5%
Smoking	19.8%
Hypertension	30.0%

FBG= Fasting Blood Glucose

of increased carotid intima-media thickness in adulthood, which is a progenitor of coronary artery disease in later life[4]. They suggest that obese adolescents with or without hypertension should be routinely screened for dyslipidemia and treated with lifestyle modification or treated more aggressively with cholesterol lowering drugs. Adults with dyslipidemia (Table 1) and preexisting coronary artery disease should also be aggressively treated according to ATP III guidelines to LDL-C < 130mg/dl for moderate CVD risk, to <100 mg/dl for high and to < 70 mg/dl for very high CVD risk[5]. Several recent outcomes trials have shown that aggressive treatment of LCL-C to <70 mg/dl with statins provides protection against recurrent CAD in high risk patients[6,7]. However, despite aggressive LDL-C lowering, CVD continues to increase. According to AHA statistics, the incidence of CVD increased by 12% from 70.1 million in 2005 to 79.4 million in 2007[8]. Therefore, besides LDL-C, other lipid subclasses have been considered as culprits for this increase in CVD, and recently, high non HDL-C levels have been the focus for this increase and suggest that dyslipidemia is a multifactorial disease and should be treated with a combination of statins and other drugs[9].

Diabetes Mellitus

Diabetes mellitus, especially type 2 accounts for over 97% of the adult diabetic population and its prevalence has increased from 5% in 1988 to 6.5% in 2002, and is in line with the 6% estimate of global prevalence[10]. This rise has been attributed to the increasing incidence of obesity and the aging of the population accounting for an annual incidence of 1.3 million Americans with new onset type 2 diabetes and for the 18.2 million Americans with type 2 diabetes in 2002[2]. Overt diabetes mellitus evolves from a pre-diabetic state characterized by insulin resistance, impaired glucose tolerance and fasting plasma glucose levels of 100 to 125 mg/dl. Several clinical trials have reported a significant improvement in the metabolic status, a delay in the progression of pre-diabetes to overt diabetes and a decrease in the incidence of cardiovascular events with a combination of diet, exercise and anti-diabetic drugs, if necessary[11,12]. Overt type 2 diabetes mellitus is a serious CVD risk factor and is presently considered a "cardiovascular risk equivalent" thus conferring to diabetic persons the same risk for future cardiovascular complications with those who have already, sustained a prior myocardial infarction[13]. It is therefore critical that type 2 diabetes mellitus be treated aggressively with a combination of diet, exercise and anti-diabetic drugs to a level of $H_bA_1c \leq 7\%$ and a BP < 130/80 mmHg in order to prevent cardiovascular and renal complications[14].

Overweight and Obesity

Body overweight and obesity start from an early age. A large epidemiologic study of 34 countries involving young persons 10-16 years old showed that overweight and obesity were directly related to TV viewing time, lack of exercise and increased consumption of sweets and soft drinks, and decreased consumption of fruits and vegetables[15]. Countries with the highest obesity rates were the United States, Canada, England and SW Europe[15]. Other epidemiologic studies have also shown that the percentage of Americans who are either overweight or obese has increased significantly over the past 25 years and accounts for 64% and 30.5% of subjects age 20 years or older, who are either overweight or obese, respectively[16]. Excess body weight, besides being an independent risk factor for cardiovascular disease, it also contributes to other risk factors such as type 2 diabetes mellitus, hypertension and dyslipidemia which further increase their prevalence and severity of CVD[16,17]. Central obesity has additionally been shown to be an independent risk factor for ischemic stroke, even after adjustments for body mass index and other risk factors[18]. Because of these alarming trends in obesity increase, major medical scientific societies have issued recent guidelines instructing the healthcare professionals about how to stem the rise of this epidemic by advising their patients about weight loss, diet, exercise, and pharmacologic treatment, if necessary[15,16,19,20] There is an urgent need to stem the rising tide of obesity and the metabolic syndrome and their consequences by stressing weight loss through diet and exercise,starting from childhood and continuing through adult life.

Smoking

Cigarette smoking is a well established risk factor for the CVDC[21,22], and is listed as one of the Framingham CVD risk factors[22]. Long-term prospective studies have clearly demonstrated the considerable mortality risk reduction associated with smoking cessation[21,23,24]. A 50 year follow up of 34,439 male British physicians has shown that quitting cigarette smoking at any age is associated with prolongation of life expectancy[21]. In this study,

physicians stopping cigarette smoking at age 60, 50, 40 or 30 years, gained about 3, 6, 9, or 10 years in life expectancy, respectively[21]. A recent study has also shown that subjects with CVD, improve their survival with smoking cessation[25]. In this study 1521 patients ≤ 65 years with a first myocardial infarction followed for a mean of 13.2 years the odds of dying were 0.57 for never smokers, 0.50 for pre-MI quitters compared to persistent smokers. In addition, of the persistent smokers, those who reduced the number of cigarettes smoked, there was an 18% decline in mortality for every 5 cigarette decrease in smoking[25]. The mechanism(s) by which cigarette smoking exerts its cardiovascular damaging effects is not clearly delineated. The most plausible mechanisms include, lipid oxidation, inflammation and thrombosis, with lipid oxidation being the most dominant[26]. Additional factors include vasospasm from nicotine and decreased O_2 delivery due to formation of carboxyhaemoglobin. Quitting cigarette smoking is very difficult and the recidivism is very high. According to a current US report, approximately 44% of smokers attempt to quit annually, but only 4% to 7% succeed[27]. The smoking cessation rate is a little higher in persons who suffer from CAD. It has been estimated that between 28% to 74% quit after an acute MI[28]. However, about 40% of the quitters will relapse and the major reason is post MI depression[28]. Medical intervention has resulted in higher percentage of patients who quit smoking, 61% versus 42% of controls[29]. Smoking cessation or abstinence altogether has been a major undertaking by many countries by either forbidding cigarette smoking in closed places or increasing the price of cigarettes. Family guidance and student education in schools about the health hazards of cigarette smoking will help young people from taking up cigarette smoking.

Hypertension

Hypertension is one of the major cardiovascular risk factors for the CVDC and its incidence continues to rise. It increased by 10% between 2005 and 2007, from 65 million to 72 million[8]. Like diabetes mellitus, hypertension evolves from a pre-hypertensive state, and this evolution can be delayed or prevented by treating pre-hypertension with exercise, diet, salt restriction or drugs[30,32]. There is a linear and continuous relationship between BP levels and cardiovascular morbidity and mortality regardless of age or sex[33], and its reduction is also directly related to the decreased incidence of cardiovascular and cerebrovascular complications[33,34]. In addition, hypertension is one of the most common conditions that predispose to heart failure. A recent meta-analysis of clinical trials including 193,424 patients found that 24,837 patients suffered major cardiovascular events[35]. Of these, 7,171 (28.9%) were cases of HF, 10,223 (41.1%) were cases of CAD, and 7,443 (30.0%) were stroke cases. The incidence of HF was similar with that of stroke and was more prevalent in older persons (> 65 years), in blacks, and in diabetics. Other investigators have also reported that hypertension is a major risk factor for HF[36,37]. In a meta-analysis by Moser and Hebert[36], of 13,342 subjects with hypertension, 1,493 (11.2%) from the control groups progressed from less severe to severe hypertension, compared with only 95 of 13,389 (0.17%) from the treated groups. The incidence of LVH and HF were higher in the control (placebo) than in the treated groups[36]. In the Framingham Heart Study, the association of baseline systolic, diastolic and pulse pressures were examined in 2040 subjects 50-79 years old who were free of HF at the baseline examination, and in whom HF developed in 11.8% after 24 years of observation[37]. All these studies point to a common pathophysiologic mechanism for the development of HF. Untreated or poorly treated hypertension either alone or in combination with obesity and diabetes mellitus, will eventually lead to cardiac remodeling, LVH, left ventricular dysfunction (LVDDF), heart failure and death. In addition, LVDDF may also lead to left ventricular systolic dysfunction (LSDF) which also could occur from a myocardial infarction, the result of hypertension, dyslipidemia and diabetes, which will lead to HF and death as depicted in Figure 2. It is, therefore, prudent that instead of focusing on treating the end stage disease, our attention should be directed in the early diagnosis and treatment of hypertension and the other comorbid conditions. There are several options for the treatment of hypertension including diet, exercise and salt restriction[32], or drug therapy with any class of antihypertensive drugs, but, preferably, with drugs that block the renin-angiotensin system (RAS), as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and direct renin inhibitors. These drugs are more effective in preventing or regressing cardiac remodeling and LVH[38-40].

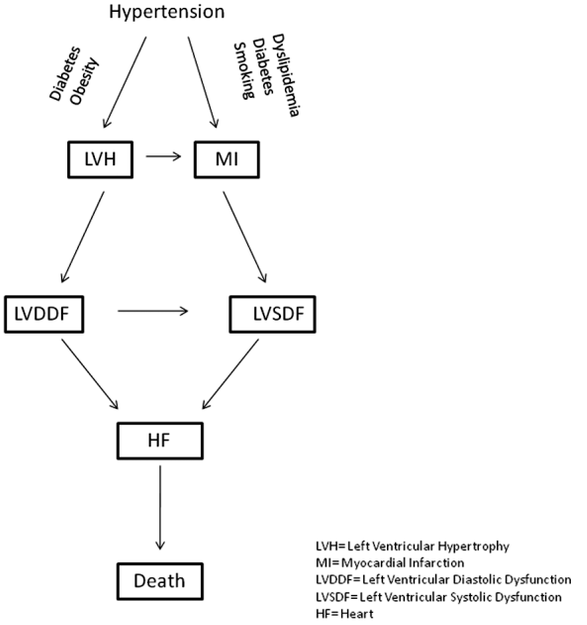

Figure 2: This figure depicts the pathophysiologic mechanisms leading to HF from hypertension.

Discussion

From the evidence presented, it appears that early detection and treatment of the risk factors which initiate the CVDC could arrest or greatly delay its further progression. The emphasis, therefore, should be based on preventing the disease, instead of waiting for it to develop and then treat it. The new treatment paradigm is, therefore, a shift to the left on the events that comprise the CVDC (Figure 1). On this theme there are several recent calls to practicing physicians by National Scientific Committees for proactive treatment of cardiovascular risk factors[17-19]. There is an urgent need to stem the rising tide of obesity and the metabolic syndrome and their consequences by stressing weight loss through diet and exercise, starting from childhood and continuing through adult life. Pre-diabetes should be recognized and treated early to prevent its progression to overt diabetes. High cholesterol should also be recognized and treated early, and cigarette smoking should be discouraged through parental guidance and school education about its serious health problems it will cause later in life. Above all, hypertension should be diagnosed and brought under control early, before it causes target organ damage which is difficult to repair. Whether to treat pre-hypertension pharmacologically, on a large scale, is a question that needs to be answered soon. Preliminary studies show that treatment of pre-hypertension can delay or stop its progression to overt hypertension. Non pharmacologic means such as weight loss, salt restriction and exercise should be tried first because they work. Aggressive control of uncomplicated hypertension is very important because it prevents target organ damage and prevents the incidence of strokes, heart failure and renal failure. There are several classes of antihypertensive drugs to choose from because they are all effective in lowering the BP pressure, but, individualization of treatment may be necessary. “Diuretics, although effective in lowering BP, may not be a good choice for hypertensive subjects with diabetes or the metabolic syndrome because they increase blood glucose which is associated with high incidence of cardiovascular morbidity and mortality”. Drugs that block the RAS are preferable in such cases, because they interfere with the action of ang II which is responsible for cardiovascular remodeling and the development of new onset diabetes mellitus[38]. Hypertension in association with comorbid conditions is a major risk factor for left ventricular remodeling and the development of HF (Figure 2). It is, therefore, possible that early detection and treatment of the various cardiovascular risk factors which initiate and perpetuate the CVDC, may result in its arrest or greatly delay its progression. In this respect, the role of physician is indispensable.

References

1. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, et al. The cardiovascular disease continuum validated. Clinical evidence of improved patient outcomes: Part 1: pathophysiology and clinical trial evidence. Circulation. 2006; 114: 2850-2870.
2. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, et al. Preventing cancer, cardiovascular disease, and diabetes: A common agenda for the American Cancer Society, the American Diabetes Association and the American Heart Association. Circulation. 2004; 109: 3244-3255.
3. Magnusen CG, Venn A, Thomson R, Juonala M, Srinivasan SR, Viikari JS, et al. The association of pediatric low and high density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood. J Am Coll Cardiol. 2009; 53: 860-869.
4. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation. 2007; 115: 459-467.
5. Grundy SM, Cleeman JI, Mertz CN, Brewer HB Jr, Clark LT. Implications of recent clinical trials for the National Cholesterol Education Program. Adult Treatment Panel III Guidelines. Circulation. 2004; 110: 227-239.
6. Tikkanen MJ, Szarek M, Fayyard R, Holme I, Cater NB, Faergeman O, et al. Total cardiovascular disease burden: Comparing intensive with moderate statin therapy: insights from the IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) trial. J Am Coll Cardiol. 2009; 54: 2353-2357.
7. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease, Treating to New Targets (TNT) Investigators. N Engl J Med. 2005; 352: 1425-1435.
8. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al. Heart disease and stroke statistics -2007 update. A report from the American Heart Association statistics committee and stroke statistics subcommittee. Circulation. 2007; 115: e69-e171.
9. Arsenault BJ, Rana JS, Stroes ES, Despres JP, Shah PK, Kastelein JJ, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high- density lipoprotein cholesterol levels, triglycerides and the total cholesterol/high density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2009; 55: 35-41.
10. Adeghate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. Ann NY Acad Sci. 2006; 1084: 1-29.
11. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: A Japanese trial in IGT males. Diabetes Res Clin Pract. 2005; 67: 152-162.
12. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomized trial. Lancet. 2002; 359: 2072-2077.
13. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339: 229-234.
14. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus. Diabetes Care. 2007; 30: 162-172.
15. Poirier P, Giles TD, Bray GA, Hong Y, Stera JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation and effect of weight loss. An update of 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity and metabolism. Circulation. 2006; 113: 898-918.
16. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002; 288: 1723-1727.
17. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk factor assessment equations: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation. 1999; 100: 1481-1492.
18. Suk SH, Sacco RL, Boden-Abala B, Cheun JF, Pitman JG, Elking MS, et al. Abdominal density and risk for ischemic stroke. The Northern Manhattan Stroke Study. Stroke. 2003; 34: 1586-1592.

19. Kumanyika SK, Obarzanek E, Stettler N, Bell R, Field AE, Fortmann SP, et al. Population based prevention of obesity: the need for comprehensive promotion of healthful eating, physical activity, and energy balance: a scientific statement for the American Heart Association Council on Epidemiology and Prevention. Interdisciplinary Committee for Prevention. Circulation. 2008; 118: 428-464.
20. Nilsson PM, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: The EVA syndrome. J Hypertens. 2008; 26: 1049-1057.
21. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004; 328: 1519-1528.
22. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol. 1976; 38: 46-51.
23. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: a meta-analysis of cohort studies. Arch Intern Med. 2000; 160: 939-944.
24. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003; 290: 86-97.
25. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y. Smoking status and long-term survival after first acute myocardial infarction. J Am Coll Cardiol. 2009; 54: 2382-2387.
26. Ambrose JA, Barua R S. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004; 43: 1731-1737.
27. Fiore MC, Jaen CR, Baker TB. Treating tobacco use and dependence: 2008 update. Clinical practice guideline Rockville, MD: US Department of Health and Human Services. Public Health Service. 2008.
28. Perez GH, Nicolau JC, Romano BW, Laranjeira R. Depression: a predictor of smoking relapse in a 6 month follow-up after hospitalization for acute coronary syndrome. Eur J Cardiovasc Prev Rehabil. 2008; 15: 89-94.
29. Van Berkel TF, Boersma H, Roos-Hesselink JW, Erdman RA, Simoons ML. Impact of smoking cessation and smoking interventions in patients with coronary heart disease. Eur Heart J. 1999; 20: 1773-1782.
30. Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, et al. Trial of preventing hypertension (TROPHY) investigators. Feasibility of treating pre-hypertension with an angiotensin receptor blocker. N Engl J Med. 2006; 354: 1685-1697.
31. Lóders S, Schrader J, Berger J, Unger T, Zidek W, Bohm M, et al. The PHARAO study: prevention of hypertension with the angiotensin converting enzyme inhibitor ramipril in patients with high normal blood pressure - a prospective, randomized, controlled prevention trial of the German Hypertension League. J Hypertens. 2008; 26: 1487-1496.
32. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. J Hum Hypertens. 2009; 23: 363-384.
33. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data from one million adults in 61 prospective studies. Lancet. 2002; 360: 1903-1913.
34. Staessen JA, Li Y, Thijs L, Wang JG. Blood pressure reduction and cardiovascular prevention: an update including the 2003-2004 secondary prevention trials. Hypertens Res. 2005; 28: 385-407.
35. Tocci G, Sciarretta S, Volpe M. Development of heart failure in recent hypertension trials. J Hypertens. 2008; 26: 1477-1486.
36. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. J Am Coll Cardiol. 1996; 27: 1214-1218.
37. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med. 2003; 138: 10-16.
38. Dahlof B, Devereaux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. For the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension. (LIFE): a randomized trial against atenolol. Lancet. 2002; 359: 995-1003.
39. Cuspidi C, Muiesan ML, Valagussa L, Salvetti M, Di Biagio C, Agabiti-Rosei E,et al. Comparative effects of candesartan and enalapril on left ventricular hypertrophy in patients with essential hypertension: The Candesartan Assessment in the Treatment of Cardiac Hypertrophy (CATCH) study. J Hypertens. 2002; 20: 2293-2300.
40. Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular hypertrophy. Circulation. 2009; 119: 530-537.