Original Article

Left Ventricular Remodeling after Myocardial Infarction in Antecedent Hypertensive Patients

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Antecedent hypertension adversely affects mortality and heart failure after myocardial infarction (MI). In addition, accelerated ventricular remodeling is a contributor to the increased mortality observed after MI. The purpose of this study was to assess the relationship of antecedent hypertension to ventricular remodeling after MI. Ninety-four patients presenting with a first acute MI who were treated with reperfusion therapy within 12 h of their symptom onset were enrolled in this study. All of them underwent left ventriculography immediately after reperfusion therapy and again at 6 months after the occurrence of MI. Patients were divided into two groups: a hypertensive group and a normotensive group. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), and ejection fraction (EF) values in the acute phase were compared to those at 6 months after acute MI in either group. The hypertensive group showed a significant increase in both EDVI and ESVI after 6 months, whereas the normotensive group did not. In addition, there was no change in EF in the hypertensive group, whereas EF increased significantly after 6 months in the normotensive group. As a result, the percent changes in ESVI and EF were significantly different between the hypertensive group and normotensive group. The results demonstrated that antecedent hypertension interacts with ventricular cavity dilatation after MI. (*Hypertens Res* 2005; 28: 293–299)

***Key Words*: left ventricular remodeling, myocardial infarction, hypertension**

Introduction

Although antecedent hypertension is known to adversely affect mortality after acute myocardial infarction (MI) (*1–4*), whether (and in which patients) it also heightens the risk of developing heart failure is disputed (*5–7*). Furthermore, the potential interactions of antecedent hypertension with other predictors of postinfarction heart failure and poor prognosis are well known. Because hypertension induces structural changes within the left ventricle (*8–10*), we hypothesized that patients with antecedent hypertension would be more likely to develop left ventricular (LV) remodeling after MI. In the present study, therefore, we analyzed LV cavity and function by LV angiography after acute MI in patients with and without antecedent hypertension.

Methods

Patient Selection

Ninety-four patients presenting with a first acute MI who were treated with reperfusion therapy and attained a thrombolysis in myocardial infarction (TIMI) flow grade 3 within 12 h of their symptom onset were enrolled in this study. The diagnosis of acute MI was based on chest pain lasting >30 min, ST segment elevation of >0.2 mV in at least two contiguous ECG leads, and elevation of the serum creatine kinase (CK) level to greater than three times the upper limit of the normal range. Patients who had a history of previous MI, a

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Received September 9, 2004; Accepted in revised form January 25, 2005.

Table 1. Baseline, Clinical and Procedural Characteristics

	Normotensive group (n=48)	Hypertensive group (n=46)	p value
Age (years)	60.8±9.3	64.2±9.2	0.074
Male (%)	63.4	87.5	<0.01
Diabetes mellitus (%)	20.8	41.3	0.031
Hyperlipidemia (%)	43.8	34.8	0.37
Current smoker (%)	52.1	54.3	0.83
Blood pressure (at 6-month follow-up)			
Systolic	122±15	139±15	<0.001
Diastolic	71±11	81±11	<0.001
Lesion location			0.12
RCA (%)	29.1	39.1	
LAD (%)	66.7	47.8	
LCX (%)	4.2	13.0	
Interventions			0.72
PTCR (%)	2.1	0.0	
PTCR + balloon angioplasty (%)	25.0	26.1	
Balloon angioplasty (%)	22.9	28.3	
Stenting (%)	50.0	43.5	
Max serum CK (IU/l)	3,949±2,332	3,791±2,433	0.75
TIMI 3 time (h)	4.5±2.2	5.2±2.5	0.11
Medication			
ACE inhibitors (%)	47.9	63.0	0.14
β-Blockers (%)	12.5	10.9	0.81
Calcium channel blockers (%)	6.7	43.8	<0.01

RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PTCR, percutaneous transluminal coronary thrombolytic revascularization; CK, creatine kinase; TIMI, thrombolysis in myocardial infarction; ACE, angiotensin converting enzyme.

TIMI grade of 3 at the time of initial angiography, an occurrence of re-infarction within 6 months, or restenosis of target vessels at the 6-month follow-up, and those with significant valvular heart disease were excluded. In addition, patients with a maximum serum CK less than 1,000 IU/l were also excluded. The maximum serum CK was defined as the peak value among those measured every 3 h after reperfusion therapy. Patients were categorized as having antecedent hypertension if this diagnosis was known by the patients to have been made by their family physician or after specialist referral, if the acute admission note indicated a history of hypertension and/or they were receiving antihypertensive medication. All patients received conventional drug therapy according to individual need, and such therapy remained the responsibility of the attending physician. Patients with hypertension were started on antihypertensive drug treatment immediately after admission. In patients with hypertension, systolic blood pressure (SBP) was controlled to less than 120 mmHg during the acute phase. After that, in the chronic phase, we attempted to control SBP to less than 140 mmHg and diastolic blood pressure (DBP) to less than 90 mmHg.

All patients underwent coronary angiography immediately after admission. They received reperfusion therapy, including percutaneous transluminal coronary revascularization (PTCR), plain old balloon angioplasty (POBA), and percutaneous transluminal coronary stent implantation. Reperfusion therapy was considered successful when the coronary flow with the culprit lesion attained a TIMI flow grade of 3. After reperfusion therapy, all subjects underwent left ventriculography (LVG). Right anterior oblique 30° views of LVG were used for assessment of regional and global LV function. LV end-diastolic and LV end-systolic volumes (EDV, ESV), and LV ejection fraction (EF) were measured according to the area-length method. LVG was performed again 6 months after the occurrence of MI, and EDV, ESV, and EF were measured by the same method. None of the patients had residual ischemia after coronary intervention or before admission.

Clinical Data and Outcomes

Patients were divided into two groups on the basis of blood pressure at the examination before their MI. Normotensive patients (normotensive group) had an SBP less than 140 mmHg and a DBP less than 90 mmHg, and were not current users of antihypertensive drugs. Hypertensive patients (hypertensive group) had an SBP of 140 mmHg or more or a

Table 2. Comparison of EDVI, ESVI, and EF between Immediately after MI (Acute Phase) and 6 Months after MI in Each Group

	Normotensive group	Hypertensive group	*p* value
EDVI (ml/m^2)			
Acute phase	69.8±16.1	67.4±17.0	0.48
After 6 months	72.4±16.6	76.2±23.7	0.37
p value	0.27	<0.001	
Percent change (%)	6.1±21.7	14.9±25.4	0.08
ESVI (ml/m^2)			
Acute phase	30.3±12.2	26.3±12.5	0.12
After 6 months	28.6±16.4	32.0±18.7	0.60
p value	0.30	0.01	
Percent change (%)	−3.6±35.4	29.1±64.0	<0.01
EF (%)			
Acute phase	56.7±14.0	61.2±12.4	0.06
After 6 months	61.9±14.1	59.8±13.4	0.46
p value	<0.01	0.26	
Percent change (%)	11.9±23.4	−1.5±20.7	<0.01

EDVI, left ventricular end-diastolic volume index; ESVI, left ventricular end-systolic volume index; EF, left ventricular ejection fraction; MI, myocardial infarction. Percent change of a value A=100 × (value of A at 6 months after MI − value of A at acute phase) / value of A at acute phase.

DBP of 90 mmHg or more, or were current users of antihypertensive drugs. Patients with hypertension commenced treatment with antihypertensive drugs immediately after admission. End-diastolic volume index (EDVI), end-systolic volume index (ESVI), and EF were compared between the acute phase and 6 months after MI in each group. The percent changes in EDVI, ESVI, and EF were also compared between the two groups. The percent change of a value A was defined as: 100×(value of A at 6 months after MI − value of A at acute phase) / value of A at acute phase. An increase >15% in the LV EDVI or LV ESVI after revascularization was defined as ongoing LV remodeling (*11*).

Statistical Analysis

Values are expressed as the mean±SD. Categorical variables were analyzed by the χ^2 test. Continuous variables were analyzed by unpaired or paired *t*-test. All variables entered the multivariable stage, regardless of the results of univariable analyses. Multivariable regression was then performed by stepwise backward deletion. All variables with a probability value <0.25 remained in the final model. Values of $p<0.05$ were considered to indicate statistical significance.

Results

The study sample consisted of 94 patients who met all inclusion criteria. Baseline, clinical and procedural characteristics of the study group are listed in Table 1. Compared with the normotensive group, the hypertensive group had a higher percentage of males, higher incidence of diabetes mellitus, and greater frequency of use of calcium channel blockers.

LV parameters at acute phase and at the 6-month follow-up are summarized in Table 2. EDVI, ESVI, and EF were similar between the hypertensive group and the normotensive group both at the acute phase and the 6-month follow-up. However, changes in these parameters differed between the two groups over this 6-month period.

There were significant increases in both EDVI and ESVI in the hypertensive group after 6 months (67.4±17.0 to 76.2±23.7, $p<0.001$; and 26.3±12.5 to 32.0±8.7, $p=0.01$, respectively), whereas there were no significant increases in the normotensive group (69.8±16.1 to 72.4±16.6, p=NS; and 30.3±12.2 to 28.6±16.4, p=NS, respectively). In addition, EF in the hypertensive group did not change (61.2±12.4 to 59.8±13.4, p=NS), whereas EF in the normotensive group increased significantly after 6 months (56.7±14.0 to 61.9±14.1, $p<0.01$). As a result, there were significant differences in the percent change in ESVI and EF between the hypertensive group and the normotensive group, whereas there was no significant difference in the percent change in EDVI between the two groups.

In this study, the blood pressure was controlled at under 140/90 mmHg. For 1 week after acute MI, we kept the blood pressure under 120 mmHg because we had to prevent cardiac rupture. At 2 months after MI, the SBP values in antecedent patients and normotensive patients were 121±8 mmHg and 137±8 mmHg ($p<0.05$). At 2 months after MI, the DBP values in antecedent patients and normotensive patients were 71±8 mmHg and 87±7 mmHg ($p<0.05$). At 6 months after MI, the blood pressure in hypertensive patients was signifi - cantly higher than in normotensive patients. Heart rate was

Table 3. Logistic Regression Analysis of LV Remodeling

	Univariable analysis	Multivariable analysis		
	p value	*p* value	OR	95% CI
Age	0.597	0.0666	0.94	0.879–1.004
Male gender	0.187	0.1820	0.36	0.079–1.619
Hypertension	0.008	0.0159	5.08	1.355–19.07
Diabetes mellitus	0.482	0.9077	0.94	0.298–2.930
Hyperlipidemia	0.162	0.6532	1.28	0.432–3.820
Current smoker	0.283	0.0599	0.31	0.091–1.050
Anterior wall infarction (lesion located in LAD)	0.908	0.6588	0.76	0.225–2.567
Max serum CK	0.132	0.0539	1.00	1.000–1.001
Time interval (onset to TIMI 3)	0.711	0.4257	0.91	0.719–1.150
ACE inhibitors	0.006	0.0024	0.16	0.047–0.518
β-Blockers	0.242	0.5948	0.58	0.077–4.338
Calcium channel blockers	0.014	0.0496	5.32	1.003–28.20

LV, left ventricular; OR, odds ratio; CI, confidence interval; LAD, left anterior descending coronary artery; CK, creatine kinase; TIMI, thrombolysis in myocardial infarction; ACE, angiotensin converting enzyme.

Table 4. Baseline Characteristics Comparison with BP-Matched Patients

	Normotensive group (n=48)	BP-mathched patients (hypertensive group) (n=24)	*p* value
Age (years)	60.8±9.3	62.8±9.9	0.41
Male (%)	87.5	66.7	0.035
Diabetes mellitus (%)	20.8	33.3	0.25
Hyperlipidemia (%)	43.8	87.5	0.12
Current smoker (%)	52.1	54.2	0.87
Blood pressure (at 6-month follow-up)			
Systolic	122±15	128±11	0.08
Diastolic	71±11	76±10	0.11
Lesion location			0.47
RCA (%)	29.1	25.0	
LAD (%)	66.7	62.5	
LCX (%)	4.2	12.5	
Max serum CK (IU/l)	3,949±2,332	3,715±2,377	0.69
TIMI 3 time (h)	4.5±2.2	5.6±2.9	0.11
Medication			
ACE inhibitors (%)	47.9	66.7	0.13
β-Blockers (%)	12.5	12.5	1.00
Calcium channel blockers (%)	6.7	29.2	0.008

BP, blood pressure; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PTCR, percutaneous transluminal coronary thrombolytic revascularization; CK, creatine kinase; TIMI, thrombolysis in myocardial infarction; ACE, angiotensin converting enzyme.

not different between the two groups.

Table 3 shows the predictors of LV remodeling after revascularization. Hypertension was both a univariable (p=0.008) and a multivariable predictor of LV remodeling (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.879 to 1.004; p=0.0159). ACE inhibitors and calcium channel blockers were also both univariable and multivariable predictors of LV remodeling.

The baseline, clinical and procedural characteristics of the study group with blood pressure-matched patients are listed in Table 4. LV parameters at acute phase and at the 6-month follow-up are summarized in Table 5. EDVI, ESVI, and EF were similar between the hypertensive group and the normotensive group both at the acute phase and at 6 months of follow-up.

Table 5. Comparison of EDVI, ESVI, and EF between Baseline and 6-Month Follow-Up with BP-Matched Patients

	Normotensive group (n=48)	BP-matched patients (hypertensive group) (n=24)	p value
EDVI (ml/m^2)			
Acute phase	69.8±16.1	68.2±17.8	0.70
After 6 months	72.4±16.6	78.4±28.4	0.26
p value	0.27	0.02	
Percent change (%)	6.1±21.7	15.1±27.9	0.17
ESVI (ml/m^2)			
Acute phase	30.3±12.2	26.8±11.0	0.23
After 6 months	28.6±16.4	34.1±21.7	0.28
p value	0.30	0.055	
Percent change (%)	−3.6±35.4	30.7±63.7	0.02
EF (%)			
Acute phase	56.7±14.0	61.3±10.8	0.12
After 6 months	61.9±14.1	58.2±13.6	0.29
p value	<0.01	0.21	
Percent change (%)	11.9±23.4	−4.3±19.9	0.005

EDVI, left ventricular end-diastolic volume index; ESVI, left ventricular end-systolic volume index; EF, left ventricular ejection fraction; MI, myocardial infarction. Percent change of a value $A = 100 \times$ (value of A at 6 months after MI − value of A at acute phase) / value of A at acute phase.

As a result, there were no significant differences between the hypertensive group with blood pressure-matched patients and the normotensive group.

Discussion

Hypertension is a well-established risk factor for coronary artery disease and acute MI (*12*, *13*). Effects of chronic hypertension, which may negatively affect outcomes after acute MI, include increased coronary vascular resistance, decreased coronary reserve, pre-existing muscle fiber hyperplasia and augmented interstitial collagen together with possible alterations in the responsiveness of the coronary vasculature to vasoactive transmitters (*14*, *15*). Hypertension is also a common substrate for heart failure (*16*, *17*), which has a high mortality (*18*). In those with antecedent hypertension, we found increased LV cavity after MI. Our most important finding is that hypertension was both a univariable predictor and a multivariable predictor of LV remodeling. We suppose that the antecedent hypertension may play an important role in stimulating the LV remodeling after MI.

LV remodeling is a process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors (*19–21*). Remodeling may be physiological and adaptive during normal growth or pathological due to MI, cardiomyopathy, hypertension, or valvular heart disease. The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote noninfarcted myocardium. Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar. This balance is determined by the size, location, and transmurality of the infarct, the extent of myocardial stunning, the patency of the infarct-related artery, local tropic factors and mechanical stress (*19*, *20*). In this study, the blood pressure was controlled at under 140/90 mmHg. For 1 week after acute MI, we kept the blood pressure under 120 mmHg because we had to prevent cardiac rupture. After discharge, the blood pressure in antecedent hypertensive patients might have been higher than that in normotensive patients. This difference may affect the LV remodeling after MI.

Recent outcome trials have examined and continued to investigate the benefits associated with different levels of blood pressure control or have compared several of the "newer" classes of antihypertensive drugs (*22–24*). Staessen *et al*. performed a meta-regression analysis of 30 clinical trials that included a total of 149,407 patients (*25*). They based their analysis on summary statistics reported in the literature, and showed that blood pressure gradients accounted for most, if not all, of the differences in outcome in patients with hypertension or patients at high cardiovascular risk. They conducted a study in patients with isolated systolic hypertension and showed that antihypertensive drug treatment reduced the risk of stroke and all cardiovascular complications. They emphasized the desirability of tight blood pressure control. Thus, to achieve risk reduction in hypertensive patients, we may have to decrease blood pressure more strictly after MI.

In 1992, with the publication of the Survival and Ventricular Enlargement (SAVE) trial, angiotensin converting

enzyme (ACE) inhibitors were established as an important addition to the list of treatments for ST elevation myocardial infarction (STEMI) (*26*). The rationale for their use includes experimental and clinical evidence of a favorable impact on ventricular remodeling, improvement in hemodynamics, and reductions in congestive heart failure (*27*). There is now unequivocal evidence from randomized, placebo-controlled mortality trials that ACE inhibitors reduce the rate of mortality from STEMI. These trials can be grouped into two categories. The first consists of trials that included only selected myocardial patients who showed features indicative of increased mortality, such as LV EF of less than 40%, clinical signs and symptoms of congestive heart failure (*28*), anterior location of infarction (*29*), and abnormal wall motion score index (*30*). The second group consists of unselective trials that randomized all patients with MI provided they had a minimum systolic pressure of approximately 100 mmHg (ISIS-4 (*31*) , GISSI-3 (*28*), and CONSENSUS II (*32*)). A consistent survival benefit was observed in ISIS-4 and GISSI-3, but not in CONSENSUS II. In our study, EF was about 60% and the myocardial damage was small. In this ISIS-4 study, no benefit was observed in patients without ST elevation. Short-term ACE inhibition does not appear to confer any benefit for patients with non-ST elevation myocardial infarction (NSTEMI). On the other hand, long-term use of ACE inhibition is beneficial in preventing recurrent ischemic events and mortality in a broad population of patients now including those with any evidence of coronary artery disease (*33*, *34*). It is of note that recurrent MI and the need for revascularization were reduced with captopril and enalapril in the SAVE (*26*) and Studies of Left Ventricular Dysfunction (SOLVD) trials (*35*), which has now been confirmed using ramioril and perindopril in the Heart Outcomes Prevention Evaluation (HOPE) (*33*) and European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) (*34*), suggesting an antiischemic effect of this entire class of agents. However, the PEACE study recently reached a different conclusion (*36*). In patients with stable coronary artery disease and preserved LV function who are receiving current standard therapy, there is no evidence that the addition of an ACE inhibitor provides further benefit in terms of preventing death from cardiovascular causes, MI, or coronary revascularization. Therefore, it remains a matter of controversy whether ACE inhibitors should be administered to patients with acute MI with minimal myocardial damage.

Study Limitations

Because echocardiographic follow-up was not performed after revascularization, cardiac hypertrophy and cardiac weights could not be estimated. Both of these parameters are important in LV remodeling, and echocardiographic examination is an excellent method to determine the cardiac morphology and function non-invasively and repeatedly. In a future study, we will try to use echocardiography to examine the remodeling process more precisely.

In summary, our results showed that antecedent hypertension may have a deleterious effect on LV remodeling after MI.

References

1. Gustafsson F, Kober L, Torp-Pedersen C, *et al*: Long-term prognosis after acute myocardial infarction in patients with a history of arterial hypertension. *Eur Heart J* 1998; **19**: 588–594.
2. Njolstad I, Arnesen E: Preinfarction blood pressure and smoking are determinants for a fatal outcome of myocardial infarction: a prospective analysis from the Finnmark Study. *Arch Intern Med* 1998; **158**: 1326–1332.
3. Herlitz J, Bang A, Karlson BW: Five-year prognosis after acute myocardial infarction in relation to a history of hypertension. *Am J Hypertens* 1996; **9**: 70–76.
4. Rutherford JD, Pfeffer MA, Moye LA, *et al*: Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. *Circulation* 1994; **90**: 1731–1738.
5. Berton G, Cordiano R, Mbaso S, De Toni R, Mormino P, Palatini P: Prognostic significance of hypertension and albuminuria for early mortality after acute myocardial infarction. *J Hypertens* 1998; **16**: 525–530.
6. Kober L, Torp-Pedersen C, Pedersen OD, Hoiberg S, Camm AJ: Importance of congestive heart failure and interaction of congestive heart failure and left ventricular systolic function on prognosis in patients with acute myocardial infarction. *Am J Cardiol* 1996; **78**: 1124–1128.
7. Spencer FA, Meyer TE, Goldberg RJ, *et al*: Twenty year trends (1975–1995) in the incidence, in-hospital and long-term death rates associated with heart failure complicating acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol* 1999; **34**: 1378–1387.
8. Vogt M, Strauer BE: Systolic ventricular dysfunction and heart failure due to coronary microangiopathy in hypertensive heart disease. *Am J Cardiol* 1995; **76**: 48D–53D.
9. Schwartzkopff B, Strauer BE: Squeezing tubes: a case of remodeling and regulation: coronary reserve in hypertensive heart disease. *Cardiovasc Res* 1998; **40**: 4–8.
10. Rossi MA: Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. *J Hypertens* 1998; **16**: 1031–1041.
11. Rizzello V, Poldermans D, Boersma E, *et al*: Opposite patterns of left ventricular remodeling after coronary revascularization in patients with ischemic cardiomyopathy: role of myocardial viability. *Circulation* 2004; **110**: 2383–2388.
12. MacMahon S, Peto R, Cutler J, *et al*: Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.
13. Neaton JD, Wentworth D: Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992; **152**: 56–64.
14. Strauer BE: Ventricular function and coronary hemodynamics in hypertensive heart disease. *Am J Cardiol* 1979; **44**:

999–1006.
15. Strauer BE: Significance of coronary circulation in hypertensive heart disease for development and prevention of heart failure. *Am J Cardiol* 1990; **65**: 34G–41G.
16. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK: The progression from hypertension to congestive heart failure. *JAMA* 1996; **275**: 1557–1562.
17. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D: Profile for estimating risk of heart failure. *Arch Intern Med* 1999; **159**: 1197–1204.
18. Ho KK, Pinsky JL, Kannel WB, Levy D: The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993; **22**: 6A–13A.
19. Pfeffer MA, Braunwald E: Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 1990; **81**: 1161–1172.
20. Warren SE, Royal HD, Markis JE, Grossman W, McKay RG: Time course of left ventricular dilation after myocardial infarction: influence of infarct-related artery and success of coronary thrombolysis. *J Am Coll Cardiol* 1988; **11**: 12–19.
21. Takano H, Zou Y, Akazawa H, *et al*: Inhibitory molecules in signal transduction pathways of cardiac hypertrophy. *Hypertens Res* 2002; **25**: 491–498.
22. Julius S, Kjeldsen SE, Weber M, *et al*: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.
23. Yui Y, Sumiyoshi T, Kodama K, *et al*: Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004; **27**: 181–191.
24. Fukui T, Rahman M, Hayashi K, *et al*: Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. *Hypertens Res* 2003; **26**: 979–990.
25. Staessen JA, Wang JG, Thijs L: Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. *J Hypertens* 2003; **21**: 1055–1076.
26. 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.
27. Pfeffer MA: Left ventricular remodeling after acute myocardial infarction. *Annu Rev Med* 1995; **46**: 455–466.
28. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico: GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343**: 1115–1122.
29. Ambrosioni E, Borghi C, Magnani B: The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 1995; **332**: 80–85.
30. 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. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995; **333**: 1670–1676.
31. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group: ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345**: 669–685.
32. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H: 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; **327**: 678–684.
33. HOPE Study Investigators: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145.
34. Fox KM: 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.
35. 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; **325**: 293–302.
36. Braunwald E, Domanski MJ, Fowler SE, *et al*: Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004; **351**: 2058–2068.