# 2

# Vascular Response to Angiotensin II Predicts Long-Term Prognosis in Patients Undergoing Coronary Artery Bypass Grafting

Pim van der Harst[1,2], Meint Volbeda[1], Adriaan A. Voors[1], Hendrik Buikema[2], Sven Wassmann[3], Michael Böhm[3], Georg Nickenig[3], and Wiek H. van Gilst[2]

***Hypertension*** **2004;44(6):930-4**

[1]Department of Cardiology, [2]Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, and [3]Klinik für Innere Medizin III, Universitat des Saarlandes, Homburg, Germany

## Abstract

Persistent activation of the renin-angiotensin system leads to downregulation of the Angiotensin type 1 receptor, and consequently to a decreased response to exogenous angiotensin II. In the present study, we investigated the association of angiotensin II responsiveness to clinical outcome after coronary artery bypass grafting (CABG). We studied the responsiveness to exogenous angiotensin II in human thoracic artery preparations of 114 CABG patients. Mean duration of follow-up was 7.3±0.1 years during which 21 patients experienced a cardiovascular event. A diminished response to angiotensin II remained in multivariate cox-regression analysis, after adjustment for sex, age, blood pressure, and number of diseased coronary arteries, the strongest predictor for cardiovascular events (relative risk 3.37 [95% CI 1.20-9.51]; p=0.022). Furthermore, diminished response to angiotensin II was associated with an increased mean arterial pressure (102.85±1.38 versus 97.40±1.37; p=0.003) and a non-significant increase in Angiotensin-Converting Enzyme activity, suggestive for a persistently activated renin-angiotensin system. In conclusion, these results suggest that in patients undergoing CABG, a diminished vascular responsiveness of the thoracic artery to exogenous angiotensin II is related to an increased risk of future cardiovascular events.

# Introduction

An activated renin-angiotensin system (RAS) is characterized by increased serum levels of angiotensin II (Ang II), and is involved in hypertension, coronary heart disease, heart failure and other cardiovascular diseases. Increased plasma levels of Ang II, despite Angiotensin-Converting Enzyme (ACE) inhibition, is associated with increased mortality.[1] Although the knowledge of the pathophysiological role of the RAS continues to increase and treatment with ACE-inhibitors and angiotensin receptor blockers (ARBs) are well proven and accepted among clinicians worldwide, prognostic studies of direct assessment of vascular responsiveness to Ang II are lacking. Local or circulating Ang II can decrease the expression or the angiotensin type 1 ($AT_1$) receptor.[2-5] This agonist induced downregulation can subsequently result in relative resistance to Ang II.[2,3,6] It remains to be determined whether the response of the human vasculature to Ang II in patients with coronary heart disease can be related to an activated RAS and whether it is associated with future cardiovascular events. We undertook the present study to investigate whether or not the vascular responsiveness to Ang II in thoracic arteries from patients undergoing coronary artery bypass grafting (CABG) predicted long-term outcome for cardiovascular events, including death, myocardial infarction, stroke and vascular surgery. In this paper we present the prognostic significance of 7.3 years follow-up. Furthermore, we assessed the relation of vascular responsiveness to Ang II with blood pressure and ACE activity, as indicators of an activated RAS.

# Methods

## Study Population

Patients in the present study participated in the QUO VADIS study. A total of 187 patients were included into QUO VADIS, and methods and results of this study were published elsewhere.[7,8] We studied all 114 subjects undergoing CABG of whom Ang II responsiveness was assessed. The Institutional Review Board approved this study, and written, informed consent was obtained from each subject.

## In vitro vascular measurements

Measurements of vascular responsiveness to Ang II of human internal thoracic arteries performed in the QUO VADIS study has been described previously.[7] In brief, excess graft material as obtained during CABG was cut into several 2 mm rings and mounted in 15 mL organ chambers. Measurements of in vitro vascular function took place within 3 hours after harvesting. The rings were connected to an isotonic displacement transducer, where a preload of 1.4 g was given. The rings were allowed to equilibrate for 1 hour. All rings were primed and checked for viability by repeated stimulation with 10 μmol/L phenylephrine. The responses to Ang I and II (0.1 nmol/L to 1 μmol/L) were studied in parallel rings

**Table 1. Index of Cardiovascular Events During Follow-up**

| Outcome | | Response to Ang II | | |
|---|---|---|---|---|
| | All patients | Low | High | P-value |
| Cardiac Death | 2 | 2 | 0 | 0.165 |
| Myocardial infarction | 3 | 1 | 2 | 0.315 |
| PCI | 4 | 3 | 1 | 0.302 |
| Re-CABG | 1 | 1 | 0 | 0.313 |
| Stroke | 7 | 7 | 0 | 0.006 |
| Vascular Surgery | 6 | 4 | 2 | 0.334 |
| | | | | |
| Total Events | 23 | 18 | 5 | 0.007 |

P-value for Low versus High responsiveness to Angiotensin II.

under continuous presence of $N^G$-monomethyl-L-arginine (L-NMMA, 100 μmol/L) to avoid confounding Nitric Oxide (NO) release by endothelial NO Synthase (eNOS). At the end of the Ang measurements a control response was evoked with 10 μmol/L phenylephrine. Results are presented as percentage of the maximal phenylephrine induced response. To study the relationship between Ang II responsiveness and cardiovascular events, the study population was divided according to the median of maximal response to Ang II as decided before conducting follow-up. The lower half was considered to have relative resistance to Ang II (in parallel with relative resistance to insulin in diabetes mellitus).

### ACE activity determination

Plasma ACE activity was measured 1 day before CABG as described previously.[9] Briefly, using 35 times diluted plasma 10 minutes of incubation with 7 mmol/L hippuryl-L-histidyl-L-leucine (Hip-His-Leu) at 37°C the production of hippuric acid (nM His-Leu/min/mL) was measured spectrophotometricly. Local ACE activity was determined in arbitrary unites as the area between the Ang I and II dose-response curves, normalized for maximal response to Ang II, as described before.[10]

### Long-Term Follow-Up

Long-term follow up was performed by telephone contact. All cardiovascular events were validated by review of medical records. The outcome measure assessed was the time from CABG until the first occurrence of a component of the following: cardiovascular death, hospitalization for myocardial infarction, revascularization with percutaneous coronary intervention or re-CABG (if these procedures were performed at least 30 days after randomization), vascular surgery, and stroke.

### Statistical Analysis

Data are expressed as mean±SEM. Statistical significance of differences in baseline characteristics was assessed by unpaired Student's t test or $\chi^2$ test, when appropriate. Cardiovascular event rates were estimated by Kaplan-Meier survival curves and were compared by means of the log-rank method. Cox proportional hazards multivariate stepwise regression analysis was used to

determine the multivariate relationships between clinical variables and cardiovascular events during the follow-up period. Covariates entered in this regression model were Ang II resistance, number of diseased vessels, age, sex, smoking, hypertension, blood pressure, and LDL-cholesterol. Statistical analysis was performed with SPSS statistical software (SPSS Inc). All probability values were 2-tailed, and a value <0.05 was considered to indicate statistical significance.

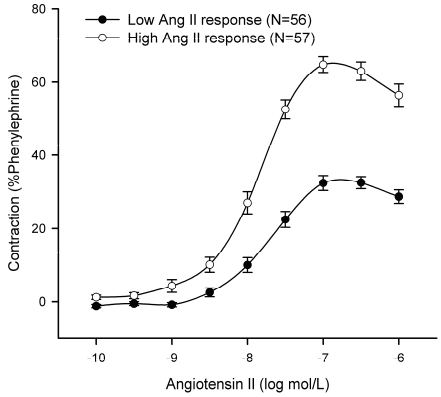
## Results

Of the 114 patients, one patient was lost to follow-up. Mean duration of follow-up was 7.3±0.12 years (median 7.4 years). During this period, 21 (18%) experienced a cardiovascular event, 2 of these subjects had 2 events (table 1). Baseline characteristics are presented in table 2. Their average age at baseline was 62.5±8.3 years, and 16 (14%) were women. Before CABG, 40% of patients had had a myocardial infarction and 15% had previously undergone a PCI. At baseline the total cholesterol level was 6.2±1.3 mmol/L (241 mg/dL), LDL-

**Table 2. Clinical Characteristics**

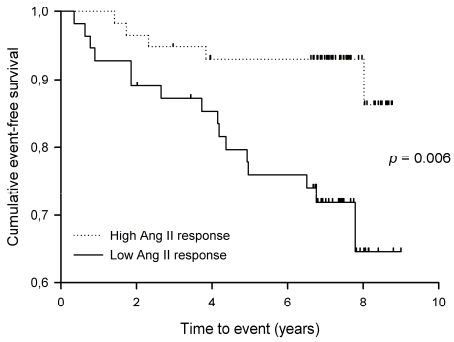
| Variables | Low Ang II response (N=56) | High Ang II response (N=57) |
|---|---|---|
| Age, years | 63.3±1.1 | 61.4±1.1 |
| Gender, male/female | 51/5 | 47/10 |
| Body Mass Index, kg/m$^2$ | 26.5±0.4 | 26.9±0.4 |
| Risk factors, n (%) | | |
| Hypertension | 31 (55) | 29 (51) |
| Smoking | | |
| Never smoked | 9 (16) | 9 (16) |
| Current smokers | 8 (14) | 6 (11) |
| CAD | | |
| 1-vessel disease | 1 | 1 |
| 2-vessel disease | 15 | 16 |
| 3-vessel disease | 40 | 40 |
| Ischemic NYHA (1-2/3-4) | 21/34 | 25/31 |
| History, n (%) | | |
| Angina (past/current) | 4/51 (7/91) | 4/53 (7/93) |
| Myocardial infarction | 25 (45) | 20 (35) |
| PTCA | 12 (21) | 5 (9) |
| Heart rate, bpm | 69.6±13.6 | 72.1±14.6 |
| Blood pressure, mmHg | | |
| Systolic | 144.2±3.0 | 136.2±2.6 |
| Diastolic | 82.2±1.0 | 80.0±1.0 |
| Lipid concentrations, mmol/l | | |
| Total cholesterol | 6.14 (0.16) | 6.37 (0.17) |
| LDL cholesterol | 4.20 (0.14) | 4.30 (0.15) |
| HDL cholesterol | 1.06 (0.04) | 1.13 (0.04) |
| Triglycerides | 1.90 (0.15) | 2.03 (0.18) |
| Medication (%) | | |
| Quinapril/Captopril/Placebo | 45/11/45 | 37/23/40 |
| Beta blocker | 78 | 91 |
| Nitrates | 74 | 82 |
| Lipid Lowering | 36 | 43 |
| Follow-up time (years) | 7.2 (0.1) | 7.3 (0.1) |

**Figure 1. Concentration-response curves of Angiotensin II (Ang II)-induced vasoconstriction.**




cholesterol 4.2±1.0 mmol/L (164 mg/dL), HDL-cholesterol 1.09±0.31 mmol/L (42 mg/dL), and triglycerides 1.96±1.25 mmol/L (174 mg/dL).
Median contraction to Ang II of the total population was 58.4% of the maximal response to phenylephrine. Maximal contraction to Ang II in the low responsive group was 38±2 (% phenylephrine) and in the high responsive group 74±2 (figure 1). Absolute contractions for phenylephrine was 346±23 and 444±34 μm (28% difference; p=0.02) and for Ang II 135±12 and 323±26 μm (139% difference; p<0.00001) in the low and high responsive group, respectively. Low responsiveness to Ang II was associated with an increased mean arterial blood pressure (102.9±1.4 versus 97.4±1.4; p=0.003). Both serum ACE activity (23.7±1.2 nM His-Leumin/mL versus 18.3±2.7; p=0.12) and local ACE activity (17.5±0.7 arbitrary units versus 16.3±0.5; p=0.19) were not significantly increased in patients with low responsiveness to Ang II.
For all patients, the Kaplan-Meier event rates of the primary end point was 29% in the low responsive group and 9% in the high responsive group. The high-responsive group was associated with 69% fewer events (p=0.0059; figure 2). In multivariate cox-regression analysis, after adjustment for sex, age, mean arterial blood pressure, and number of diseased coronary arteries, a diminished response to Ang II was the most significant predictor for cardiovascular events (relative risk 3.37 [95% CI 1.20-9.50]; p=0.022, table 3). When only the more objective events (cardiac death, myocardial infarction, and stroke) were combined, Ang II remained the most significant predictor (relative risk 5.0 [95% CI 1.06-23.62]). Response to phenylephrine was not associated with cardiovasular events. Among the individual components of the primary end point, there was a consistent pattern of benefit favoring the high-responsive Ang II over the low-responsive Ang II group, which included a significant association with fewer strokes (p=0.006; table 1).

**Figure 2. Kaplan-Meier curve for primary composite end point**




## Discussion

We are the first to report long-term follow-up data on in vitro assessment of vasomotor function. The present study demonstrated that in vitro resistance to exogenous Ang II independently predicts the long-term risk of cardiovascular events, including cardiac death, myocardial infarction, PCI, re-CABG, stroke, and vascular surgery after adjustment for blood pressure, and other cardiac risk factors. 78% of all cardiovascular events occurred in patients in the Ang II resistant group. In addition, Ang II resistance was associated with a higher blood pressure and a trend to an increased serum and local ACE activity.

Ang II is the principal mediator of the RAS. The $AT_1$ receptor mediates many of the known detrimental effects of Ang II, including vasoconstriction. Increased levels of endogenous Ang II have been associated with an increased mortality in chronic heart failure (CHF) patients.[1] Progression of CHF is associated with a progressive increase in cardiac Ang II formation, regardless of aetiology of CHF.[11] More importantly, in contrast to non-failing myocytes, myocytes from CHF patients are relatively resistant to Ang II since they are selectively unable to produce appreciable amounts of IGF-1 and ET-1 in response to Ang II stimulation.[11] In CHF, downregulation of $AT_1$ receptor has been reported by several studies.[12-14] Increased levels of endogenous Ang II itself diminish $AT_1$ receptor expression.[3-5] In our study, we demonstrated diminished responsiveness to Ang II, which might be explained as a reflection of chronic over activity of the RAS. This is supported by the increased blood pressure and trend to increased local and serum ACE activity. Despite chronic ACE inhibitor therapy, conversion of Ang I to Ang II may persist and Ang II levels may return to pre-treatment levels.[15,16] Non-ACE dependent pathways, like chymases[17-19], are thought to be involved. We assume that the observed diminished responsiveness to exogenous Ang II, relative resistance, in our population is due to downregulation of the vascular $AT_1$ receptor and can be explained by an increase in vivo endogenous Ang II levels. One could also speculate on changes in signaling of $AT_1$ receptor or differences in $AT_2$ receptor function. Nevertheless, effects mediated by eNOS by $AT_2$ receptor or otherwise are not

**Table 3. Clinical Predictors of Cardiovascular Events During Follow-up**

| Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | RR (95%CI) | P | RR (95%CI) | P |
| Age | 1.03 (0.98-1.09) | 0.24 | 1.01 (0.95-1.08) | 0.69 |
| Male Gender | 1.78 (0.41-7.66) | 0.44 | 1.24 (0.28-5.47) | 0.78 |
| Body Mass Index | 0.97 (0.84-1.13) | 0.73 | | |
| Hypertension | 0.99 (0.42-2.33) | 0.98 | | |
| Smoking | 2.10 (0.49-9.01) | 0.32 | | |
| Total cholesterol | 0.89 (0.61-1.29) | 0.54 | | |
| Blood pressure | | | | |
| Systolic | 1.02 (1.01-1.04) | 0.01 | 1.02 (0.99-1.04) | 0.14 |
| Diastolic | 1.01 (0.96-1.06) | 0.73 | | |
| Mean Arterial Pressure | 1.04 (0.99-1.09) | 0.06 | | |
| Three vessel disease | 4.99 (1.15-21.61) | 0.03 | 4.41 (1.00-19.41) | 0.05 |
| Phenylephrine contraction | 1.00 (0.99-1.01) | 0.69 | | |
| Low Ang II response | 3.74 (1.37-10.23) | 0.01 | 3.37 (1.20-9.51) | 0.02 |

likely, since vascular measurements were performed in the continuous presence of the eNOS inhibitor L-NMMA. The observed difference in stroke between groups is intriguing. Although blood pressure levels were different, our multivariate analysis suggests the Ang II responsiveness to be of greater importance. This suggestion is in good harmony with the Losartan Intervention For Endpoint reduction (LIFE) which demonstrated that the ARB losartan substantially reduced the rate of stroke, over and above blood pressure lowering therapy.[20,21] Potential interactions between medical treatment and Ang II response in the current study can not be excluded. Nevertheless, in our opinion, it is not feasible to obtain less confounded clinical data considering the current clinical guidelines.[22,23] Any future study would include even more confounding drug therapy regimes to make it unfeasible to assess the consequence of Ang II resistance.

Of note, we examined internal thoracic arteries. The response of these vessels does not represent the blood pressure increase as measured in humans since blood pressure increases are more dependent of resistance vessels. The local RAS might be differently regulated and is likely to be completely independent of the circulating system. Furthermore, we only assessed the internal thoracic artery, it is tempting to speculate $AT_1$ receptor upregulation in atherosclerotic coronary or cerebral arteries and downregulation $AT_1$ receptors in internal thoracic arteries in our patient population. The systemic or local increased Ang II levels might therefore be deleterious in the coronary and cerebral artery. The macroscopic non-atherosclerotic internal thoracic artery might have downregulated the $AT_1$ receptor rather than upregulated due to the increased circulating in vivo Ang II level.

### Study Limitations

This study was descriptive in nature, conducted retrospectively and will therefore require confirmation in a prospective investigation. Our results cannot be extended to conditions other than coronary artery disease, because we included only patients who underwent CABG. We were unable to rule out other factors (e.g. medication) known to influence the RAS and the $AT_1$ receptor expression. However, medical treatment was similar in both groups. Because

serum Ang II levels does not reflect local Ang II levels, the local ACE activity was assessed. Nevertheless, the present data is unique in its kind and provides important pathophysiological insight. We are not aware of a larger series of vascular assessment of Ang II responsiveness performed within one single, structured protocol, and the degree of Ang II resistance is an important predictor of outcome in these patients.

### Perspectives

We have demonstrated a strong association between Ang II resistance of the human thoracic artery and an adverse long-term cardiovascular prognosis. Although clinical value may be limited, assessment of Ang II resistance may provide a surrogate end point to evaluate therapy. Whether strategies that improve Ang II responsiveness will uniformly improve prognosis needs to be studied prospectively.

### Acknowledgment

Pim van der Harst is supported by Zon-MW (grand 920-03-236) of The Netherlands Organization for Health Research and Development.

### References

1. Roig E, Perez-Villa F, Morales M, Jimenez W, Orus J, Heras M, Sanz G. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J.* 2000;21:53-57.
2. Gunther S, Gimbrone MA, Jr., Alexander RW. Regulation by angiotensin II of its receptors in resistance blood vessels. *Nature.* 1980;287:230-232.
3. Lassegue B, Alexander RW, Nickenig G, Clark M, Murphy TJ, Griendling KK. Angiotensin II down-regulates the vascular smooth muscle AT1 receptor by transcriptional and post-transcriptional mechanisms: evidence for homologous and heterologous regulation. *Mol Pharmacol.* 1995;48:601-609.
4. Makita N, Iwai N, Inagami T, Badr KF. Two distinct pathways in the down-regulation of type-1 angiotension II receptor gene in rat glomerular mesangial cells. *Biochem Biophys Res Commun.* 1992;185:142-146.
5. Zeng C, Asico LD, Wang X, Hopfer U, Eisner GM, Felder RA, Jose PA. Angiotensin II Regulation of AT1 and D3 Dopamine Receptors in Renal Proximal Tubule Cells of SHR. *Hypertension.* 2003;41:724-729.
6. Wang DH, Yao A, Zhao H, DiPette DJ. Regulation of ANG II receptor in hypertension: role of ANG II. *Am J Physiol.* 1996;271:H120-H125.
7. Oosterga M, Voors AA, Buikema H, Pinto YM, Haber HE, Ebels T, Morshuis WJ, Kingma JH, Crijns HJ, van Gilst WH. Angiotensin II formation in human vasculature after chronic ACE inhibition: a prospective, randomized, placebo-controlled study. QUO VADIS Investigators. *Cardiovasc Drugs Ther.* 2000;14:55-60.
8. Oosterga M, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH, Crijns HJ, van Gilst WH. Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study). QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol.* 2001;87:542-546.
9. Santos RA, Krieger EM, Greene LJ. An improved fluorometric assay of rat serum and plasma converting enzyme. *Hypertension.* 1985;7:244-252.
10. Buikema H, Pinto YM, Rooks G, Grandjean JG, Schunkert H, van Gilst WH. The deletion polymorphism of the angiotensin-converting enzyme gene is related to phenotypic differences in human arteries. *Eur Heart J.* 1996;17:787-794.
11. Serneri GG, Boddi M, Cecioni I, Vanni S, Coppo M, Papa ML, Bandinelli B, Bertolozzi I, Polidori G, Toscano T, Maccherini M, Modesti PA. Cardiac angiotensin II formation in the clinical course of heart failure and its relationship with left ventricular function. *Circ Res.* 2001;88:961-968.
12. Asano K, Dutcher DL, Port JD, Minobe WA, Tremmel KD, Roden RL, Bohlmeyer TJ, Bush EW, Jenkin MJ, Abraham WT, Raynolds MV, Zisman LS, Perryman MB, Bristow MR. Selective downregulation of the angiotensin II AT1-receptor subtype in failing human ventricular myocardium. *Circulation.* 1997;95:1193-1200.
13. Regitz-Zagrosek V, Friedel N, Heymann A, Bauer P, Neu¯ M, Rolfs A, Steffen C, Hildebrandt A, Hetzer R, Fleck E. Regulation, Chamber Localization, and Subtype Distribution of Angiotensin II Receptors in Human Hearts. *Circulation.* 1995;91:1461-1471.
14. Regitz-Zagrosek V, Fielitz J, Dreysse R, Hildebrandt AG, Fleck E. Angiotensin receptor type 1 mRNA in human right ventricular endomyocardial biopsies: downregulation in heart failure. *Cardiovasc Res.* 1997;35:99-105.
15. Kokkonen JO, Saarinen J, Kovanen PT. Regulation of Local Angiotensin II Formation in the Human Heart in the Presence of Interstitial Fluid. Inhibition of Chymase by Protease Inhibitors of Interstitial Fluid and of Angiotensin-Converting Enzyme by Ang-(1-9) Formed by Heart Carboxypeptidase A-Like Activity. *Circulation.* 1997;95:1455-1463.

16. Petrie MC, Padmanabhan N, McDonald JE, Hillier C, Connell JMC, McMurray JJV. Angiotensin converting enzyme (ACE) and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. *J Am Coll Cardiol.* 2001;37:1056-1061.
17. Richard V, Hurel-Merle S, Scalbert E, Ferry G, Lallemand F, Bessou JP, Thuillez C. Functional Evidence for a Role of Vascular Chymase in the Production of Angiotensin II in Isolated Human Arteries. *Circulation.* 2001;104:750-752.
18. Urata H, Kinoshita A, Misono KS, Bumpus FM, Husain A. Identification of a highly specific chymase as the major angiotensin II- forming enzyme in the human heart [published erratum appears in J Biol Chem 1991 Jun 25;266(18):12114]. *J Biol Chem.* 1990;265:22348-22357.
19. Voors AA, Pinto YM, Buikema H, Urata H, Oosterga M, Rooks G, Grandjean JG, Ganten D, van Gilst WH. Dual pathway for angiotensin II formation in human internal mammary arteries. *Br J Pharmacol.* 1998;125:1028-1032.
20. Neal B, MacMahon S, Chapman N; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet.* 2000;356:1955-1964.
21. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire Ud, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:995-1003.
22. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger C, V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J.* 2003;24:1601-1610.
23. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Houston Miller N, Lauer RM, Ockene IS, Sacco RL, Sallis JF, Jr., Smith SC, Jr., Stone NJ, Taubert KA. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. *Circulation.* 2002;106:388-391.