Original Article

Reverse J-Curve Relation between Diastolic Blood Pressure and Severity of Coronary Artery Lesion in Hypertensive Patients with Angina Pectoris

Naoyuki HASEBE, Shinsuke KIDO, Akira IDO, and Kenjiro KIKUCHI

for the Angiographical Study in Angina with Hypertension Induced Insults (ASAHI) Investigators

The existence of the J-curve in hypertension treatment remains controversial. The major question is whether the increase in mortality from coronary disease is induced by the lowering of blood pressure (BP) or by the severity of underlying coronary artery disease. We recruited patients with a history of hypertension (systolic BP (SBP) > 160 mmHg and/or diastolic BP (DBP) > 90 mmHg) and a diagnosis of angina pectoris with angiographically confirmed coronary artery lesion. The relationship among the treated levels of SBP and DBP, the severity of coronary artery lesion, and the clinical consequences were investigated. Among the 234 enrolled patients, 115 experienced further events, 19 of which were serious. There were no significant differences in the average BP of patients with and those without events, but the coronary severity indices (CSI) were significantly greater in patients with events. As a function of DBP from ≤ 74 to $105 \leq$ mmHg, there was a positive association with the incidence of serious events, and a reversed J-curve in CSI with a nadir at 95–104 mmHg. A similar relationship was observed in SBP, but a potentially unfavorable outcome was suggested in the lowest SBP range of ≤ 124 mmHg. In conclusion, there was no J-curve for DBP in hypertensive patients with angina pectoris; rather, the lower the DBP, the better was the prognosis. Interestingly, the severity of coronary lesion is in a reversed J-curve relation with DBP, suggesting that high BP plays a critical role in serious events in hypertensive patients with moderate coronary artery lesions. (*Hypertens Res* 2002; 25: 381–387)

Key Words: coronary disease, angiography, hypertension, prognosis, risk factors

Introduction

Lowering elevated blood pressure levels decreases cardiovascular morbidity and mortality. However, the optimal levels of blood pressure (BP) or treatment targets are still controversial. Cruickshank *et al.* reported a J-curve relationship between increased mortality and an achieved diastolic BP (DBP) of below 85 mmHg in patients with pre-existing ischemic heart disease (1). In contrast, the results of the Hypertension Optimal Treatment (HOT) study demonstrated the benefits of lowering DBP to 82.6 mmHg or lower (2).

Even this well-organized study, however, could not fully disprove the existence of a J-curve (3).

The J-curve phenomenon may explain why major clinical trials of hypertension treatment have not shown greater effects in reducing coronary events compared to cerebrovascular events. If lower DBP makes myocardial perfusion critical, the severity of coronary artery lesion is a crucial factor to be considered. The deleterious effect of lower DBP must be more critical for patients with serious coronary artery lesions. However, no clinical trials have investigated the J-curve phenomenon in regard to severity of coronary artery lesion.

From the First Department of Internal Medicine, Asahikawa Medical College, Asahikawa, Japan.

Address for Reprints: Naoyuki Hasebe, M.D., Ph.D., First Department of Internal Medicine, Asahikawa Medical College, 2-1-1 Midorigaoka Higashi, Asahikawa 078-8510, Japan. E-mail: haselove@asahikawa-med.ac.jp

Received December 7, 2001; Accepted in revised form February 5, 2002.

Importantly, the existence of a J-curve has been reported in untreated controls in several hypertension trials (4–7). Coope reported J-curves in both treated and control groups, with the curve in the treated patients being similar in shape but 10 mmHg lower than that in the controls (8). Thus, one of the major critical issues in regard to the J-curve phenomenon is whether the lower DBP is a result of anti-hypertensive treatment or simply due to the nature of complicated cardiovascular disease. Serious coronary artery disease may lower BP, and itself may be associated with a poor prognosis.

In the present study, we examined hypertensive patients with coronary artery lesions confirmed by coronary angiography who had been given a clinical diagnosis of angina pectoris. The specific question was whether there is a point beyond which BP reduction is no longer beneficial and possibly even deleterious in hypertension with coronary artery disease, and whether the severity of coronary artery lesions modifies the J-curve phenomenon.

Methods

Patients

The present study was approved by the Ethical Committee of Asahikawa Medical College. Patients were recruited from 11 hospitals based on their records from 1992 to 1997. The enrolled patients had history of hypertension (systolic BP (SBP) > 160 mmHg and/or DBP > 90 mmHg) and had been diagnosed with angina pectoris based on coronary angiography, but had no history of previous myocardial infarction. For all patients, the details of the clinical history and coronary angiographical findings in the hospital records were clinically confirmed upon enrollment. The patients' information, clinical history and clinical consequence were reported on data-record forms, as were the treated levels of blood pressure, and antihypertensive and antianginal drugs used. The listed cardiovascular events (Events) were hospitalization due to unstable condition, required coronary intervention such as percutaneous transluminal coronary angioplasty or coronary arterial bypass graft surgery, myocardial infarction and cardiovascular death. Myocardial infarction and cardiovascular death were additionally recorded as serious cardiovascular events (S-Events).

Assessment of Coronary Artery Lesions

The coronary artery lesions of eligible patients were evaluated by coronary angiography by referring to the anatomical severity of lesions, *i.e.*, the number of diseased vessels and the degree of narrowing of the coronary arterial lumen. The coronary angiographic findings were confirmed by more than two specialists at each hospital. The number of diseased major vessels exhibiting a more than 75% narrowing in luminal diameter was counted and used to divide the patients into four groups: a zero-, single-, double- and triple-vessel dis-

ease group. The coronary severity index (CSI) was calculated as the sum of the stenosis lesion grades for each coronary artery, with a grade of 1.0 being given for lesions with more than 90% narrowing in luminal diameter and a grade of 0.5 for lesions with 75–90% narrowing. Coronary spasm was diagnosed by typical anginal attack with ST elevation in ECG and positive provocation test with intracoronary acetylcholine or ergonovine administration in coronary angiography.

Statistics

All patients' data were reported on data-record forms at each hospital, and were sent to the coordinating center at Asahikawa Medical College. Questions about missing or inconsistent data were resolved directly by communication with doctors at each hospital. Comparisons between groups were made with χ^2 test or Fisher's exact test (discrete variables), and *t* test or Mann-Whitney test (continuous variables). Probability values were derived using a two-tailed significance test. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Patient Characteristics, Achieved Diastolic Blood Pressure and Cardiovascular Events

A total of 234 patients were enrolled, with a mean age of 64 ± 1 years. Eighty-two patients were women, and 79 (96.3%) of them were post-menopause. The average duration of clinical history, *i.e.*, the mean period over which a clinical history could be retrieved from the patients' records, was 11.2 ± 0.7 years for hypertension and 4.3 ± 0.3 years for angina pectoris. Patients were divided into two groups, a group with (Event(+); $n = 115$) and one without (Event(-); $n = 119$) cardiovascular events. The Event(+) group included a subgroup of 19 patients with serious events (S-Event(+)), 16 with acute myocardial infarction and 3 with cardiovascular death. No other cause of death was observed during the follow-up of this cohort. Thus, the cardiovascular events of the remaining 96 were hospitalization for unstable condition requiring coronary artery intervention. The average blood pressure on treatment in the Event(-) group, which was calculated by averaging the blood pressures retrieved for the 2 months prior to the start of the study, was $151 \pm 2/88 \pm 1$ mmHg. The average blood pressures in the Event(+) group and S-Event(+) group, which were determined by averaging the blood pressures retrieved for the 2 months prior to the onset of cardiovascular events, were $151 \pm 2/87 \pm 1$ and $153 \pm 4/93 \pm 3$ mmHg, respectively. There were no significant differences in the average blood pressure on treatment among the three groups (Table 1).

On entry to the study, 160 of 234 patients (68.4%) had been prescribed a calcium antagonist alone or in combina-

Table 1. Clinical Characteristics, Coronary Artery Lesion and Drug Therapy

	Event(-)	Event(+)	
		Total Event(+)	Serious Event(+)
<i>n</i>	119	115	19
Age (years)	64 ± 1	64 ± 1	64 ± 2
M:F	75:44	73:42	12:7
SBP (mmHg)	151 ± 2	151 ± 2	153 ± 4
DBP (mmHg)	88 ± 1	87 ± 1	93 ± 3
Angina type			
Organic	77	92	18
Vasospastic	32	17*	1*
Mixed	10	6	0
Coronary artery lesion			
CSI	0.97 ± 0.08	1.33 ± 0.08**	1.42 ± 0.20*
No. of VD	1.2 ± 0.1	1.5 ± 0.1**	1.6 ± 0.2
0 VD (%)	22.7	12.2*	10.5
1 VD (%)	42.0	40.9	36.8
2 VD (%)	25.2	27.0	31.6
3 VD (%)	10.1	20.0*	21.1
Risk factors			
Smoking (%)	55	40	32
DM (%)	27	29	37
T chol (mg/dl)	198 ± 4	207 ± 5	217 ± 12
SV ₁ + RV ₅ (mV)	3.0 ± 0.1	3.2 ± 0.1	3.4 ± 0.2
Drug therapy			
Diuretics (%)	5.9	3.5	10.5
β-Blockade (%)	10.1	11.3	5.3
Ca-antagonist (%)	68.1	68.7	63.2
ACEI (%)	15.1	11.3	5.3
Nitrate-D (%)	79.8	85.2	84.2
Aspirin (%)	12.6	7.8	10.5
LMA (%)	13.4	16.5	21.0

M:F, male : female; SBP, systolic blood pressure; DBP, diastolic blood pressure; CSI, coronary severity index; DM, diabetes mellitus; T chol, total cholesterol; No of VD, number of vessel disease; 0 VD–3 VD, zero- to triple-vessel disease; ACEI, angiotensin converting enzyme inhibitor; Nitrate-D, daily used nitrate; LMA, lipid-modifying agents. * $p < 0.05$, ** $p < 0.01$ vs. Event(-).

tion with other drugs: a β-blockade in 10.7%, an angiotensin converting enzyme (ACE) inhibitor in 13.2%, and a diuretic in 4.7%. The frequency of use of each drug was not significantly different between the Event(+) and Event(-) groups. The frequency of use of calcium antagonist was not significantly different among the three event subgroups: 68.1% in Event(-), 68.7% in Event(+) and 63.2% in S-Event(+). The incidence of Events was 48% in the patients treated with a calcium antagonist and 51% in the patients treated without a calcium antagonist, and the difference between groups was not statistically significant. Eighty-eight point five percent of the calcium antagonists used in the study were long acting.

The frequency of smoking was slightly higher in the Event(-) group; however, there were no significant differences in risk factors among groups (Table 1).

Angina Pectoris and Coronary Artery Lesions

The clinical forms of angina pectoris were classified in three groups: angina pectoris mainly due to organic coronary lesion ($n = 169$), angina pectoris mainly due to coronary spasm ($n = 49$), and mixed forms ($n = 16$). Angina pectoris with coronary spasm was more frequent in the Event(-) than in the Event(+) or S-Event(+) groups ($p < 0.05$). The incidence of triple vessel diseases was significantly higher in the Event(+) (20.0%) and S-Event(+) (21.1%) than in the Event(-) (11.5%) group ($p < 0.05$). In contrast, the incidence of zero vessel diseases was significantly higher in the Event(-) (22.7%) than in the Event(+) (12.2%) group ($p < 0.05$). The CSI in the Event(-) group was 0.97 ± 0.08 , which was significantly lower than that in the Event(+) (1.33 ± 0.08 ; $p < 0.01$) or S-Event(+) (1.42 ± 0.20 ; $p < 0.05$) groups (Table 1).

Table 2. Incidence of Cardiovascular Events (Events) and Coronary Severity Index (CSI) in Blood Pressure Subgroups

	<i>n</i>	Total Events		Serious Events	
		Incidence	CSI	Incidence	CSI
DBP (mmHg)					
74	38	21 (55.3%)	1.47 ± 0.12**	1 (2.6%)	2.00
75–84	56	29 (51.8%)	1.21 ± 0.13	4 (7.1%)	1.63 ± 0.47
85–94	78	31 (39.7%)	1.06 ± 0.10	7 (9.0%)	1.50 ± 0.39
95–104	46	26 (56.5%)	0.97 ± 0.12	5 (10.9%)	1.00 ± 0.35
105	16	8 (50.0%)	1.06 ± 0.20	2 (12.5%)	1.50 ± 0.50
SBP (mmHg)					
124	24	15 (62.5%)*	1.13 ± 0.17	2 (8.3%)	1.75 ± 0.25
125–139	36	18 (50.0%)	1.44 ± 0.16*	2 (5.6%)	1.00 ± 0.00
140–154	81	31 (38.3%)	1.09 ± 0.10	6 (7.4%)	1.42 ± 0.45
155–169	51	30 (58.8%)*	1.03 ± 0.12	4 (7.8%)	1.13 ± 0.43
170	42	21 (50.0%)	1.15 ± 0.12	5 (11.9%)	1.70 ± 0.44

DBP, diastolic blood pressure; SBP, systolic blood pressure. * $p < 0.05$, ** $p < 0.01$ vs. nadir of each column.

Fig. 1. The incidence of serious cardiovascular events including myocardial infarction and cardiovascular death (A) and the coronary severity index (CSI) (B) as a function of diastolic blood pressure (DBP). There was a positive association between DBP and the incidence of serious coronary events, and a reverse J-curve relationship between DBP and CSI in hypertensive patients with angina pectoris.

Incidence of Events and Levels of Blood Pressure

The incidence of Events as a function of SBP and DBP was compared among five subgroups divided according to the levels of DBP (≤ 74 , 75–84, 85–94, 95–104 and ≥ 105 mmHg) and SBP (≤ 124 , 125–139, 140–154, 155–169 and ≥ 170 mmHg) (Table 2). The relationship between the incidence of Events and BP levels was basically similar in shape in both SBP and DBP. However, the subgroup with significantly higher incidence of Events was observed only in SBP. The subgroups of SBP ≤ 124 and 155–169 mmHg showed significantly higher incidence of Events compared to the subgroup of 140–154 mmHg. In contrast, there were no significant dif-

ferences in the incidence of Events among the five subgroups of DBP.

Next, the incidence of S-Events as a function of SBP and DBP was compared among the five subgroups described above (Table 2). A positive correlation was observed between the incidence of S-Events and DBP, with the lowest incidence of 2.6% occurring in the lowest DBP subgroup of ≤ 74 mmHg and the highest incidence of 12.5% occurring in the highest DBP subgroup of ≥ 105 mmHg (Fig. 1). Similarly, the highest incidence of serious events was observed in the highest SBP subgroup of ≥ 170 mmHg. However, the relation assumed a J-shape. The incidence of S-Events gradually decreased with decreasing SBP, reached a nadir at

125–139 mmHg, and increased again at ≤ 124 mmHg.

Coronary Severity Index and Levels of Blood Pressure or Incidence of Events

The CSI was compared among five subgroups of DBP and SBP divided according to the levels of blood pressures as above (Table 2). There was a reversed J-shaped relation between the CSI and DBP: the highest CSI of 1.47 ± 0.12 was observed in the subgroup of DBP ≤ 74 mmHg and decreased stepwise as DBP increased with a nadir of 0.97 ± 0.12 at 95–104 mmHg, then increased again at ≥ 105 mmHg (Fig. 1). These relations between the CSI and DBP of patients with S-Events were similar in shape but the CSI component was shifted upward by approximately 0.5. There was a similar reversed J-shaped relation between the CSI and SBP: the highest CSI was observed in the subgroup of SBP 125–139 mmHg and decreased stepwise as SBP increased with the nadir at 155–169 mmHg, then increased again at the SBP subgroup of ≥ 170 mmHg. The CSI in the lowest SBP subgroup of ≤ 124 mmHg was a relatively low 1.13 ± 0.17 ; however, patients with S-Events had a significantly high CSI of 1.75 ± 0.25 .

The incidence of Events were compared among three subgroups of CSI: a Low (< 1.0), Middle (1.0 to < 2.0) and High (≥ 2.0) group. The incidence of Events in the Low CSI subgroup (32.5%) was significantly lower than those in the Middle (54.9%; $p < 0.01$) or High (60.6%; $p < 0.01$) CSI subgroups. In contrast, no statistically significant difference was observed in the incidence of S-Events (Low, 3.9%; Middle, 9.9%; High, 10.6%). There were no significant differences in SBP among the three groups (150 ± 2 , 152 ± 2 and 149 ± 3 mmHg, respectively). However, the DBP of the Low CSI subgroup (90 ± 1 mmHg) was somewhat higher than that of the Middle CSI subgroup (87 ± 1 mmHg), and significantly higher than that of the High CSI subgroup (85 ± 2 mmHg) ($p < 0.05$).

Discussion

This is the first report to investigate the impact of the severity of coronary artery lesions on the relationship between the incidence of cardiovascular events and the treated levels of blood pressure. Several previous reports have demonstrated a J-curve relation between cardiovascular events and DBP in hypertension treatment (1, 9–13); they have not, however, considered the severity of coronary artery lesions.

Cruickshank *et al.* reported a J-curve phenomenon with an increase in mortality for achieved DBP below 85 mmHg in hypertensive patients with pre-existing ischemic heart disease (1). However, their definition of ischemic heart disease was not based on the consideration of coronary artery lesions. In the present study, we investigated patients whose coronary lesions had been angiographically confirmed. We could not find a J-point in the vicinity of the DBP range of

85–90 mmHg. There were no significant differences in the incidence of total events among the DBP subgroups. The most important finding we observed was the positive correlation between DBP and the incidence of serious cardiovascular events in hypertensive patients with angina pectoris.

In contrast, the correlation between SBP and the incidence of serious cardiovascular events assumed a J-shape. The J-curve relation of SBP was reported in the Multiple Risk Factor Intervention Trial (MRFIT) in hypertensive patients with a history of myocardial infarction (9). This study suggested that low BP soon after myocardial infarction is potentially a consequence of myocardial damage, and predicts a poor prognosis. The possibility of a “reverse causality bias,” *i.e.*, the possibility that patients who have serious coronary artery disease and poor cardiac pump function cannot produce a high SBP, may explain the slight increase of events in the lowest subgroup of SBP. In fact, the patients who experienced serious events had high CSI scores in the subgroup of SBP ≤ 124 mmHg.

Although the major risk factors established in Caucasians are also risk factors for coronary arterial lesions in Japanese with hypertension (14), the severity of coronary artery stenosis and the number of diseased vessels are known determinants of morbidity and mortality in patients with coronary artery disease (15). As we expected, cardiovascular events were more frequently observed in patients with greater CSI. In other words, the CSI was significantly greater in patients either with total or serious events compared to event-free patients. More importantly, we found a reverse J-shaped curve relation between CSI and BP, particularly in DBP. These results indicate a potential high risk for cardiovascular events in patients with lower BP and greater CSI. However, it was surprising that the lower the DBP the better was the prognosis in terms of serious coronary events, and patients with an SBP of 125–139 mmHg had the greatest CSI but the lowest incidence of serious coronary events. We may speculate that the relatively high incidence of total events in patients with lower BP and greater CSI indicates a higher disease activity of coronary lesions, potentially requiring coronary intervention. However, the higher incidence did not necessarily mean that these patients were subject to serious events, such as myocardial infarction. One, and the most plausible, explanation for these discrepancies is the fact that coronary lesions responsible for acute ischemic events do not necessarily have severe stenosis, but often tend to have only mild-to-moderate stenosis (16). This conclusion was derived from either sequential angiograms (17, 18) or highly magnified cineangiographic views taken to speculate on the original lesions responsible for the infarction (19). These previous studies did not investigate hypertension as a specific factor for inducing an acute ischemic event. There is compelling evidence that high shear stress originating from high blood pressure may trigger acute plaque disruption on the coronary arterial wall (20, 21), which in turn may lead to acute coronary syndrome including unstable angina pectoris, acute myo-

cardial infarction and sudden cardiac death (22). We speculate that higher blood pressure plays a crucial role in inducing coronary events in the hypertensive patients with relatively lower CSI, *i.e.*, mild-to-moderate coronary stenotic lesion. Alterations in vessel-wall stresses on or within plaques are important in their disruption. The greater wall stresses on plaques make them more susceptible to rupture (16). The wall stress experienced by any blood vessel is directly proportional to intraluminal pressure and vessel radius (23). Therefore, the smaller wall stress in patients with lower DBP and smaller coronary diameter may contribute to the positive relationship between the level of DBP and the risk of serious events.

One more point that should be discussed is the antihypertensive drugs used in the present study. It is quite possible that the adverse effects of some drugs partly counterbalance any true cardioprotective effects of hypertension treatment. Calcium antagonists are the antihypertensive and antianginal drugs that have been used most frequently in Japan (24–26). More than two-thirds of patients were prescribed a calcium antagonist in the present study. Recently, the debate on the potential hazards of calcium antagonists in the treatment of ischemic heart disease and hypertension has been revived (27, 28). The debate was once concluded with a recommendation against the use of short-acting calcium antagonists, especially short-acting dihydropyridine compounds, in the treatment of ischemic heart disease and hypertension (29). In the present study, there were no significant differences in the frequency of use of calcium antagonists or any other types of antihypertensive drugs in patients with or without events. Fortunately, nearly 90% of the calcium antagonists used in the present study were long-acting. This may be the reason why the use of calcium antagonists did not affect the prognosis of the present cohort.

Our results are limited by several factors. Because the present study was a retrospective investigation, we could not intentionally control the treated levels of BP, the medication compliance of each patient or the application of coronary intervention. Since the application of coronary intervention was entrusted to doctors in each hospital, an inter-hospital difference in indication of coronary intervention may have affected the prognosis of the studied patients. Frequent coronary intervention may increase the risk of an advanced cardiovascular event. However, thanks to recent medical advancement in coronary intervention (30, 31), this risk has been greatly reduced. We believe the application of coronary intervention in our hospitals does not deviate from the recent medical standard of treatment of coronary artery disease (32, 33).

In conclusion, we found a reverse J-curve relationship between DBP and the severity of coronary artery lesion, and a positive association between DBP and serious coronary events in hypertensive patients with angina pectoris. Together with a similar relationship for SBP, this suggests that high BP plays a crucial role in the induction of serious events in

patients with moderate coronary artery lesion. Further investigation in a prospective randomized manner will be needed to confirm the optimal BP levels in antihypertensive treatment of hypertensive patients with coronary artery disease.

Appendix

ASAHI (Angiographical Study in Angina with Hypertension Induced Insults) Investigators

First Department of Medicine, Nayoro City Hospital: Akaishi T, Tanaka H, Fukuzawa J, Sasagawa Y, Makita Y; Division of Cardiovascular Medicine, Asahikawa Kosei Hospital: Kato J, Shiokoshi T, Okuyama J, Kitaoka T; Division of Cardiovascular Medicine, Hokkaido Junkanki Hospital: Fujiwara M, Tsuji S; Division of Cardiovascular Medicine, Megumino Hospital: Kataoka R, Hirayama T, Morihira M, Abe K; Division of Cardiovascular Medicine, National Sapporo Hospital: Takenaka T, Inoue H, Miyata S, Hamasakai S; Division of Cardiovascular Medicine, Asahikawa Red Cross Hospital: Nishimiya T, Ohtomo T, Tanno M, Sato S; Division of Cardiovascular Medicine, Asahikawa City Hospital: Takeuchi T, Kawasaki K, Goto D; Division of Cardiovascular Medicine, Engaru Kosei Hospital: Honda H, Matsusaka T, Sakuragi H; Division of Cardiovascular Medicine, Sapporo Higashi Tokushukai Hospital: Uekita K, Kanno M; Division of Cardiovascular Medicine, Shibetsu City Hospital: Tanazawa T, Yoshie H; First Department of Medicine, Asahikawa Medical College: Kikuchi K, Hasebe N, Ido A, Kido S, Kawamura Y, Sato N, Nakamura H, Natori S, Ohi S, Takahashi F, Saijo Y, Nakano A, Yoshida A, Sakamoto N, Saito M, Ohta H, Ito T, Makiguchi N, Takahashi K, Yao N.

References

1. Cruickshank JM, Thorp JM, Zacharias FJ: Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; **I**: 581–584.
2. Hansson L, Zanchetti A, Carruthers SG, *et al.* HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; **351**: 1755–1762.
3. Kaplan N: J-curve not burned off by HOT study: Hypertension Optimal Treatment. *Lancet* 1998; **351**: 1748–1749.
4. Anderson TW: Re-examination of some of the Framingham blood pressure data. *Lancet* 1978; **ii**: 1139–1141.
5. Lindholm L, Lanke J, Bengtsson B, Ejlerthsson G, Thulin T, Schersten B: Both high and low blood pressures risk indicators of death in middle aged males: isotonic regression of blood pressure on age applied to data from a 13-year prospective study. *Acta Med Scand* 1985; **218**: 473–480.
6. Coope J, Warrender TS: Randomized trial of treatment of hypertension in elderly patients in primary care. *Br Med J* 1986; **293**: 1145–1151.
7. Staessen J, Bulpitt C, Clement D, *et al.*: Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. *Br Med J* 1989; **298**: 1552–1556.

8. Coope J: Hypertension: the cause of the J-curve. *J Hum Hypertens* 1990; **4**: 1–4.
9. Flack JM, Neaton J, Grimm R Jr, et al for the Multiple Risk Factor Investigation Trial Research Group: Blood pressure and mortality among men with prior myocardial infarction. *Circulation* 1995; **92**: 2437–2445.
10. D'Agostino RB, Belanger AJ, Kannel WB, Cruickshank JM: Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *Br Med J* 1991; **303**: 385–389.
11. Samuelsson OG, Wilhelmsen LW, Pennert KM, Wedel H, Berglund GL: The J-shaped relationship between coronary heart disease and achieved blood pressure level in treated hypertension: further analyses of 12 years of follow-up of treated hypertensives in the Primary Prevention Trial in Gothenburg, Sweden. *J Hypertens* 1990; **8**: 547–555.
12. Fletcher AE, Bulpitt CJ: How far should blood pressure be lowered? *N Engl J Med* 1992; **326**: 251–254.
13. Alderman MH, Ooi WL, Madhavan S, Cohen H: Treatment-induced blood pressure: reductions and risk of myocardial infarction. *JAMA* 1989; **262**: 920–924.
14. Kato J, Aihara A, Kikuya M, et al: Risk factors and predictors of coronary arterial lesions in Japanese hypertensive patients. *Hypertens Res* 2001; **24**: 3–11.
15. Moise A, Lesperance J, Theroux P, Taeymans Y, Goulet C, Bourassa MG: Clinical and angiographic predictors of new total coronary occlusion in coronary artery disease: analysis of 313 nonoperated patients. *Am J Cardiol* 1984; **54**: 1176–1181.
16. Fuster V: Mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994; **90**: 2126–2146.
17. Ambrose J, Tannenbaum M, Alexopoulos D, et al: Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988; **12**: 56–62.
18. Little WC, Constantinescu M, Applegate RJ, et al: Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988; **78**: 1157–1166.
19. Brown BG, Gallery CA, Badger RS, et al: Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. *Circulation* 1986; **73**: 653–661.
20. Lee RT, Grodzinsky AJ, Frank EH, Kamm RD, Schoen FJ: Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. *Circulation* 1991; **83**: 1764–1770.
21. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT: Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. *Circulation* 1993; **87**: 1179–1187.
22. Fuster V, Badimon L, Badimon J, Chesebro J: The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992; **326**: 242–250.
23. MacIsaac AL, Thomas JD, Topol EJ: Toward the quiescent coronary plaque. *J Am Coll Cardiol* 1993; **22**: 1228–1241.
24. Saruta T: Current status of calcium antagonist in Japan. *Am J Cardiol* 1998; **82**: 32R–34R.
25. Hoshida S, Kario K, Mitsuhashi T, Ikeda U, Shimada K: Is there any difference between intermediate-acting and long-acting calcium antagonists in diurnal blood pressure and autonomic nervous activity in hypertensive coronary artery disease patients? *Hypertens Res* 2000; **23**: 7–14.
26. Sugawara H, Tobise K, Kikuchi K: Antioxidant effects of calcium antagonists on rat myocardial membrane lipid peroxidation. *Hypertens Res* 1996; **19**: 223–228.
27. Pahor M, Psaty BM, Alderman MH, et al: Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356**: 1949–1954.
28. 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; **355**: 1955–1964.
29. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organization and the International Society of Hypertension: Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *Hypertens Res* 1997; **20**: 61–73.
30. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffre PA: A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997; **336**: 817–822.
31. Weaver WD, Reisman MA, Griffin JJ, et al: Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomized trial. *Lancet* 2000; **355**: 2199–2203.
32. ACC/AHA/ACP-ASIM: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 1999; **33**: 2092–2197.
33. ACC/AHA: ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation* 2000; **102**: 1193–1209.