Low Diastolic Blood Pressure and Atherosclerosis in Elderly Subjects

The Rotterdam Study

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Background: A low diastolic blood pressure has been associated with increased cardiovascular risk. The following proposed mechanisms underlie this phenomenon: a low diastolic pressure that compromises coronary blood flow, a low diastolic pressure that is due to deteriorating health, and a low diastolic pressure that is a consequence of stiffening of the large arteries. Atherosclerosis may be the link between stiffening of the arteries, a low diastolic pressure, and an increased cardiovascular risk.

Objective: To study whether a low diastolic blood pressure in older subjects is a reflection of atherosclerosis.

Methods: The Rotterdam (the Netherlands) Study is a population-based follow-up study of 7983 subjects (age, ≥ 55 years) who are living in the suburb of Ommoord of Rotterdam. Baseline measurements included ultrasonographic evaluation of the carotid arteries, measurement of blood pressure, and determination of other cardiovascular risk factors. The main cross-sectional analyses were

performed among 930 subjects who currently were not using blood pressure-lowering drugs.

Results: A J-shaped association of the intima-media thickness of the common carotid artery with diastolic blood pressure was found with a nadir from 60 to 69 mm Hg. The intima-media thickness was increased in subjects with a diastolic pressure that was less than 60 mm Hg compared with that in subjects with a diastolic pressure that was between 60 and 69 mm Hg (a difference of 0.033 mm [95% confidence limits: 0.001, 0.065]). Beyond a diastolic pressure of 70 mm Hg, a gradual increase in the intima-media thickness was observed. The association was most pronounced among subjects with relatively high pulse pressures.

Conclusions: Results of the present study indicate the existence of a J-shaped association between carotid atherosclerosis and diastolic pressure. These findings support the hypothesis that in elderly subjects, a low diastolic pressure may be a reflection of widespread atherosclerosis.

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IN STUDIES THAT have been performed among elderly people¹⁻⁶ and among hypertensive middle-aged subjects,⁷⁻¹¹ a low diastolic blood pressure was associated with an increased risk of cardiovascular disease and all-cause mortality. With some exceptions,^{12,13} this J-shaped association was not observed in studies among middle-aged subjects who were at low risk of cardiovascular disease.¹⁴ Although a low diastolic blood pressure is generally regarded as a favorable sign, this may not apply to elderly persons. To understand the nature of blood pressure in elderly subjects, it is important to study which factors relate to a low diastolic blood pressure and may, at least in part, explain the J-shaped association.

One hypothesis is that a low diastolic blood pressure compromises coronary blood flow and subsequently increases the risk of coronary heart dis-

ease.¹⁵ In particular, subjects with coronary heart disease would be at increased risk.^{16,17} Indeed, in some studies, a J-shaped association between diastolic blood pressure and cardiovascular risk was mainly confined to subjects with preexisting symptomatic coronary heart disease.^{8,13} However, other investigators could not confirm this finding,⁹ although a J-shaped association was also found in subjects without coronary heart disease.^{5,6,10,11,18}

A second hypothesis is that a low diastolic blood pressure is a consequence of deteriorating health, which is associated with increased mortality.⁶ Some investigators have reported results in favor of this

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See Subjects and Methods
on next page

SUBJECTS AND METHODS

POPULATION

The Rotterdam (the Netherlands) Study is a population-based prospective cohort study of 7983 subjects (age, ≥ 55 years). The principal objective of the study is to investigate the incidence of and risk factors for chronic disabling diseases (ie, cardiovascular, locomotor, neurogeriatric, and ophthalmologic diseases).²⁴ The study was approved by the Medical Ethics Committee of Erasmus University Medical School, Rotterdam, and written informed consent was obtained from all participants. The baseline data collection comprised a home interview and two visits at the research center. Baseline measurements were performed from March 1990 to July 1993.

All subjects (age, ≥ 55 years) who were living in a geographically well-defined area (ie, the suburb of Ommoord of Rotterdam were invited to participate). Of all subjects ($N=10\,275$), 7983 (78%) decided to participate. This included 897 subjects who were residing in homes for elderly people. Baseline data collection included an extensive structured and computerized interview at home. Information was collected with regard to medical history, smoking, alcohol consumption, physical activity, dietary habits, family history, socioeconomic status, and disability. During two visits at the research center, information was obtained on cognition (Mini-Mental State Examination), fractures (x-ray film), and bone mass (dual energy x-ray absorptiometry). A comprehensive ophthalmologic examination was performed that included fundus photography. With respect to cardiovascular risk factors, blood pressure was measured (with the subjects in the sitting and supine positions), an electrocardiogram was recorded, and several indicators of atherosclerosis were assessed noninvasively (ie, intima-media thickness of the carotid arteries, ankle-arm index, and calcifications and lumen diameter of the abdominal aorta). A venous blood sample was taken, and a nonfasting glucose tolerance test was performed.

ULTRASONOGRAPHY OF THE CAROTID ARTERIES

To assess the intima-media thickness of the carotid arteries, ultrasonography of both carotid arteries was performed with a 7.5-MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories Inc, Bothell, Wash). On a longitudinal two-dimensional ultrasound image of the carotid artery, the near and far walls of the carotid artery are displayed as two bright white lines that are separated by a hypoechogenic space (**Figure 1**).²⁵ The distance of the leading edge of the first bright line of the far wall (the lumen-intima interface) and the leading edge of the second bright line (the media-adventitia interface) indicates the intima-media thickness. Studies that compared the ultrasound intima-media thickness with morphological features have indicated that the intima-media thickness of the far wall, as seen with ultrasound, truly reflects the anatomic intima-media layer.²⁵

The Rotterdam Study ultrasound protocol demanded a careful examination of the lumen-intima interface and the media-adventitia interface on the far wall of the distal common carotid artery.²⁶ When an optimal longitudinal image was obtained, it was frozen on the R wave of the electrocardiogram and stored on videotape. This procedure was repeated three times for each left and right side. The actual measurements of the intima-media thickness were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer by using additional dedicated software.²⁵ From the average of the three frozen images per carotid artery, a mean intima-media thickness ($[\text{left} + \text{right}]/2$) of the common carotid artery was calculated as a measurement for current thickness of the far wall of the distal common carotid artery. Findings of a study among 80 participants in the Rotterdam Study on the reproducibility of the intima-media thickness measurements have been reported elsewhere.²⁷ In short, the mean difference (SD) in the intima-media thickness between repeated measurements that were obtained by two ultrasonographers and by two off-line ultrasound image readers were -0.005 mm (0.09 mm) and 0.06 mm (0.05 mm), respectively. The mean difference in the intima-media thickness between measurements at the first and

hypothesis,⁴ whereas it could not be confirmed by others.^{13,19}

Sleight²⁰ proposed that in elderly persons, stiffening of the large arteries may lead to a high systolic and a low diastolic blood pressure and that stiffer arteries are associated with an increased risk of coronary heart disease. Widespread atherosclerosis may be the link between stiffening of the large arteries,^{21,22} a low diastolic blood pressure, and an increased risk of cardiovascular disease. Recently, Witteman et al²³ reported on a J-shaped association between the decline of diastolic blood pressure and the progression of atherosclerosis of the abdominal aorta in postmenopausal women. The results suggested that a decline in low diastolic blood pressure is owing to stiffening of the vessel wall, as indicated by progression of aortic atherosclerosis.

To explore the hypothesis of Sleight²⁰ further, we set out to evaluate the association between carotid atherosclerosis and diastolic blood pressure in a random

sample of 1500 participants in the Rotterdam Study; these participants underwent an ultrasound examination of the carotid artery. The main analyses were restricted to 930 subjects who currently were not using blood pressure-lowering drugs.

RESULTS

In the **Table**, general characteristics of the study subjects are presented. The male-female ratio (1:2) in our study population reflects the actual distribution in the suburb of Ommoord. Most differences in cardiovascular risk factors between men and women were as expected. Among men, smoking and a history of cardiovascular disease were more common, and men had higher levels of systolic blood pressures. In women, higher mean levels of total serum cholesterol and higher body mass indexes were observed. The intima-media thickness of

second visits was -0.033 mm (0.12 mm). The intraclass correlation coefficient was .74.

CARDIOVASCULAR RISK FACTORS

In the Rotterdam Study, baseline information on current health status, drug use, and medical history was obtained by using a computerized questionnaire that included a Dutch version of the cardiovascular questionnaire of Rose et al²⁸ for assessment of prevalent angina pectoris. A history of myocardial infarction and stroke was based on two questions: (1) "Did you ever suffer from a myocardial infarction for which you were hospitalized?" (2) "Did you ever suffer from a stroke, diagnosed by a physician?" For the purpose of the present analysis, subjects were classified as having symptomatic cardiovascular disease when responses to questions with regard to angina pectoris, myocardial infarction, or stroke were confirmative.

Subjects were categorized as current or former smokers or persons who never smoked.

Information on drug use was obtained by having all participants bring their regularly used drugs to the visits at the Rotterdam Study research center. All drugs were coded according to the criteria of the Anatomical Therapeutic Chemical classification.²⁹ The Anatomical Therapeutic Chemical codes C02 (antihypertensive drugs), C03 (diuretics), and C07 (β -blocking agents) were used to identify subjects who currently were taking blood pressure-lowering drugs, irrespective of the indication for use.

Blood pressure was measured during the second visit at the research center. Subjects were measured after a 5-minute rest while they were in a sitting position; a random-zero sphygmomanometer was used on the right upper extremity. Measurements were performed by trained nurses. Sphygmomanometers were regularly checked and calibrated. The average of two measurements, obtained at one occasion and separated by a count of the pulse rate, was used in the present analysis. Diastolic blood pressure was measured at the fifth Korotkoff sound. Hypertension was defined as a systolic blood pressure of 160 mm Hg or greater, a diastolic blood pressure of 95 mm Hg or greater, or current use of antihypertensive drugs for the indication of hypertension. Height and weight were measured, and the body

mass index (weight in kilograms divided by height in meters squared) was calculated. A nonfasting venous blood sample was taken. The total serum cholesterol level was determined by using an automated enzymatic procedure. The high-density lipoprotein cholesterol level was measured similarly, after precipitation of the non-high-density lipoprotein fraction with phosphotungstate-magnesium.

DATA ANALYSIS

The present study was based on vascular measurements in 1500 participants of the Rotterdam Study. In six subjects, measurement of the intima-media thickness could not be performed from the videotape because of poor quality of the recorded images. In 52 subjects, measurement of the intima-media thickness at either the left or right carotid artery could not be performed from the stored images because of poor visualization. For these subjects, the estimate of the intima-media thickness was based on the measurement of the side for which a value was available.

No information was present on the use of blood pressure-lowering drugs or on history of cardiovascular disease in 31 subjects. Analyses were performed separately for the 930 subjects who currently were not using blood pressure-lowering drugs and for the 539 subjects who currently were using blood pressure-lowering drugs.

Five categories of diastolic blood pressure were made with cutoff values at 60, 70, 80, and 90 mm Hg. Inspection of the data by categories of blood pressure showed that the nadir of the association between diastolic blood pressure and the intima-media thickness of the common carotid artery was in the second category, which was therefore used as the reference group (ie, 60 to 69 mm Hg). Separate analyses were performed in the strata of pulse pressure (tertiles). Dummy variables were used to assess differences in the intima-media thickness of the common carotid artery between the reference category and the other categories of diastolic blood pressure by using linear regression. All results were adjusted for differences in age and gender and additionally for differences in smoking, body mass index, and serum lipid levels.

the common carotid artery was higher in men compared with that in women.

The systolic blood pressure was clearly related to the intima-media thickness of the common carotid artery. An increase of 10 mm Hg in systolic blood pressure was associated with an increase in the intima-media thickness of the common carotid artery, namely, 0.02 mm (95% confidence limits [CL]: 0.015, 0.025), without any indication of a J shape.

The intima-media thickness of the common carotid artery was significantly thicker in subjects with a diastolic blood pressure less than 60 mm Hg compared with that in subjects with a diastolic blood pressure between 60 and 69 mm Hg, with a mean difference of 0.033 mm (95% CL: 0.001, 0.065) for all subjects and of 0.035 mm (95% CL: 0.002, 0.068) for subjects who were free from symptomatic cardiovascular disease (**Figure 2**). Beyond a diastolic pressure of 70 mm Hg, a significant gradual increase in the intima-media thickness of the com-

mon carotid artery was observed. Adjustment for differences in smoking, the high-density lipoprotein cholesterol level, and the body mass index did not alter the direction or magnitude of the difference in the intima-media thickness of the common carotid artery between subjects with a diastolic blood pressure less than 60 mm Hg and those with a diastolic blood pressure between 60 and 69 mm Hg. The difference in the intima-media thickness between subjects with a diastolic blood pressure less than 60 mm Hg compared with that in subjects with a diastolic blood pressure between 60 and 69 mm Hg was most pronounced among subjects with relatively high pulse pressures (**Figure 3**).

Analyses among subjects who were taking blood pressure-lowering drugs ($n=539$) similarly showed that in subjects with a low diastolic blood pressure, the intima-media thickness of the common carotid artery was increased compared with the reference category, with a mean difference of 0.042 mm (95% CL: -0.018 , 0.102). Be-

Figure 1. Characteristic longitudinal two-dimensional ultrasound image of the distal common carotid artery. AW indicates the near wall of the carotid artery; PW, the far wall of the carotid artery; arrows from top to bottom, the leading edge of the intima-lumen interface at the near wall, the lumen-intima interfaces, and the media-adventitia interface at the far wall, respectively.

General Characteristics of the Study Population*

Characteristic	Women	Men
No. of subjects	560	372
Mean (SD) age, y	70.0 (9.1)	69.6 (8.3)
Mean (SD) body mass index, kg/m ²	26.1 (4.0)	25.5 (3.3)
Smoking, %		
Current	22.0	35.5
Former	28.7	56.9
Mean (SD) blood pressure, mm Hg		
Systolic	135 (21)	136 (19)
Diastolic	70 (11)	72 (11)
Hypertension, %	14	12
Mean (SD) cholesterol level, mmol/L†		
Total	6.9 (1.2)	6.3 (1.2)
High-density lipoprotein	1.4 (0.3)	1.2 (0.3)
Prevalent cardiovascular disease, %		
Angina pectoris	4.5	2.2
Myocardial infarction	1.9	5.9
Stroke	1.4	4.3
Mean (SD) intima-media thickness, mm	0.75 (0.16)	0.80 (0.18)

*Subjects were currently not using blood pressure-lowering drugs.

†Conventional units (in milligrams per deciliter) for the mean (SD) cholesterol values were as follows: total, 267 (46) for women and 244 (46) for men; high-density lipoprotein, 54 (12) for women and 46 (12) for men.

yond a diastolic pressure of 70 mm Hg, no difference in the mean intima-media thickness of the common carotid artery was observed.

COMMENT

The present study has shown a J-shaped relationship between diastolic blood pressure and the intima-media thickness of the common carotid artery. The J-shaped curve was most prominent in subjects with relatively high pulse pressures.

Before the findings can be accepted, some aspects of the study need to be considered. Some investigators have suggested that an increased intima-media thick-

Figure 2. Association between diastolic blood pressure and the intima-media thickness of the common carotid artery for all subjects and for those free from cardiovascular disease (CVD). Subjects who were currently using blood pressure-lowering drugs were excluded. Results are adjusted for differences in age and gender. Values are means with SEs. The number at the bottom of each bar indicates the number of subjects in that category; asterisk, $P < .05$ compared with subjects with a diastolic blood pressure between 60 and 69 mm Hg.

Figure 3. Association between diastolic blood pressure and the intima-media thickness of the common carotid artery and pulse pressure (tertiles). Asterisk indicates $P < .05$ compared with subjects with a diastolic blood pressure between 60 and 69 mm Hg. Data were adjusted for age, gender, and history of cardiovascular disease.

ness of the common carotid artery may not reflect atherosclerosis and may, at least in part, be a reflection of an adaptive response of the vessel wall to changes in shear and tensile stresses.³⁰ Yet, an increased intima-media thickness of the common carotid artery has consistently been associated with elevated levels of cardiovascular risk factors,³¹⁻³⁶ with prevalent cardiovascular disease³⁶ and with atherosclerosis elsewhere in the arterial system.³⁷⁻³⁹ In addition, progression of the intima-media thickness of the common carotid artery over time has been associated with risk factors for atherosclerosis,⁴⁰ and an increased intima-media thickness has been shown to be a strong predictor of myocardial infarction.⁴¹ Furthermore, trials have shown a reduced progression of intima-media thickness in patients who were treated with lipid-lowering drugs compared with that in a placebo-treated group.^{42,43} These results support the view that a noninvasively assessed intima-media thickness of the common carotid artery may be used as an indicator of generalized atherosclerosis.⁴⁴

At present, results from studies on the association between ultrasonographically assessed intima-media

thickness of the common carotid artery and diastolic blood pressure are not consistent. Some investigators have found no association,³³ whereas others have reported a direct association.³¹ The Atherosclerosis Risk in Communities Study, performed among younger subjects, reported results from a case-control study in which the presence of a J-shaped association could not be evaluated.³¹ Salonen and Salonen³³ observed no association between diastolic blood pressure and intima-media thickness in their younger cohort. The Cardiovascular Health Study of 2189 subjects (age, ≥ 65 years) who were not receiving antihypertensive treatment and who were free from cardiovascular disease showed a continuous inverse association between diastolic blood pressure and the intima-media thickness of the common carotid artery across all levels of systolic blood pressure, with no evidence of a J-shaped relationship.³⁵ In a study of older subjects with and without isolated systolic hypertension, Sutton-Tyrell et al⁴⁵ found that a diastolic blood pressure less than 75 mm Hg was a strong marker for carotid atherosclerotic plaques. This association was confined to subjects with isolated systolic hypertension only. Part of the conflicting findings may be related to the presence and extent of a J-shaped relationship and the importance of age. In younger age groups, a linear direct association between diastolic blood pressure and atherosclerosis is present. With increasing age, the proportion of subjects with a reduced compliance of the large arteries due to atherosclerosis increases. Thus, at an older age, the distribution of diastolic blood pressure shifts to the left, and analyses among elderly people probably address predominantly the left part of the J-shaped curve.

The hypothesis of Sleight²⁰ is based on the observation that in elderly subjects, in addition to a rise in systolic blood pressure, diastolic blood pressure may actually fall as a result of reduced arterial compliance of the aorta and large arteries.^{46,47} A reduced compliance has been associated with atherosclerotic abnormalities.^{21,22} As a consequence, a considerable proportion of older subjects with a relatively low diastolic blood pressure may have existing vascular damage (ie, increased arterial stiffness and atherosclerosis)—in particular, those with a relatively high pulse pressure. The results of the present study, which have indicated a J-shaped association of intima-media thickness of the common carotid artery to diastolic blood pressure, are in agreement with the hypothesis that in elderly people, a low diastolic blood pressure may reflect prevalent atherosclerosis. The finding that this phenomenon is more pronounced in subjects with higher pulse pressures, as has recently been confirmed by findings from a study among hypertensive subjects,⁴⁸ lends further support to this hypothesis. Furthermore, a recent report of longitudinal studies have shown that a fall in diastolic blood pressure is associated with progression of aortic atherosclerosis²³ and with an increased risk of mortality.¹⁹

Following the hypothesis that a low diastolic blood pressure may compromise coronary circulation,¹⁶ results from several studies among hypertensive middle-aged subjects have indicated that the use of antihypertensive medication and the degree of blood

pressure reduction following antihypertensive drug treatment may be important factors that contribute to the J-shaped association.^{49,50} These findings have given rise to a continuing debate on the level of diastolic blood pressure that should be achieved with antihypertensive treatment in hypertensive subjects.⁵⁰⁻⁵² Strong evidence against an important contribution of antihypertensive treatment to the J-shaped association comes from the observation that a J-shaped association was also found in control groups of two antihypertensive trials.^{5,6} Furthermore, in observational studies, the J-shaped association between diastolic blood pressure and cardiovascular risk was also found in subjects who were not taking blood pressure-lowering drugs.^{4,13} In addition, our finding among subjects who were receiving blood pressure-lowering drugs of a similar tendency toward an increased intima-media thickness of the common carotid artery in subjects with a diastolic blood pressure less than 60 mm Hg may point toward the presence of atherosclerosis as an explanation for at least part of the J-shaped curve with myocardial infarction and mortality in this group. It should be noted, however, that the cross-sectional nature of our data precludes a definitive causal explanation.

In conclusion, the present findings support the hypothesis that atherosclerosis in elderly persons with a low diastolic blood pressure may, in part, explain the J-shaped association between diastolic blood pressure and cardiovascular risk and mortality in older subjects.

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REFERENCES

1. Rajala S, Haavisto M, Heikinheimo R, Matilla K. Blood pressure and mortality in the very old. *Lancet*. 1983;2:520-521.
2. Langer RD, Ganiats TG, Barrett-Connor E. Paradoxical survival of elderly men with high blood pressure. *BMJ*. 1989;298:1356-1357.
3. Mattila K, Haavisto M, Rajala S, Heikinheimo R. Blood pressure and five-year survival in the very old. *BMJ*. 1988;296:887-889.
4. Taylor JO, Cornoni-Huntley J, Curb JD, et al. Blood pressure and mortality risk in the elderly. *Am J Epidemiol*. 1991;134:489-504.
5. Coope J, Warrender TS, McPherson K. The prognostic significance of blood pressure in the elderly. *J Hum Hypertens*. 1988;2:79-88.
6. 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. *BMJ*. 1989;298:1552-1556.

7. Stewart IMcDG. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet*. 1979;1:861-865.
8. McCruishank JM, Thorp JM, Zacharias FJ. Benefits and potential harms of lowering high blood pressure. *Lancet*. 1987;1:581-584.
9. Lindblad U, Rastam L, Ryden L, Ranstam J, Isacson SO, Berglund G. Control of blood pressure and risk of first acute myocardial infarction: Skaraborg Hypertension Project. *BMJ*. 1994;308:681-686.
10. Fletcher AE, Beevers DG, Bulpitt CJ, et al. The relationship between a low treated blood pressure and IHD mortality: a report of the DHSS Hypertension Care Computing Project. *J Hum Hypertens*. 1988;2:11-15.
11. Samuelsson OG, Wilhelmsson 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. D'Agostino RB, Belanger AL, Kannel WB, Cruishank JM. Relation of low diastolic blood pressure to coronary heart disease death in presence of myocardial infarction: the Framingham Study. *BMJ*. 1991;303:385-388.
13. Lindholm L, Lanke J, Bengtsson B. U-shaped association between mortality and blood pressure in a thirteen-year prospective study. *Fam Pract*. 1986;3:3-8.
14. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. *Lancet*. 1990;335:765-774.
15. Cruickshank JM. Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *BMJ*. 1988;297:1227-1230.
16. Strangard S, Haunso S. Why does antihypertensive treatment prevent stroke but not myocardial infarction? *Lancet*. 1987;2:658-660.
17. Uren NG, Melin JA, de Bruyne B, Wijns W, Baudhuin TM, Camici PG. Relation between myocardial blood flow and the severity of coronary artery stenosis. *N Engl J Med*. 1994;330:1782-1788.
18. Report by the Management Committee of the Australian Therapeutic Trial in Mild Hypertension: untreated mild hypertension. *Lancet*. 1982;1:185-191.
19. Langer RD, Criqui MH, Barrett-Connor EL, Klauber MR, Ganiats TG. Blood pressure change and survival after age 75. *Hypertension*. 1993;22:551-559.
20. Sleight P. Blood pressures, hearts, and U-shaped curves. *Lancet*. 1988;1:235.
21. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction: a noninvasive method to predict severity of coronary atherosclerosis. *Circulation*. 1989;80:78-86.
22. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor. *Am J Epidemiol*. 1994;140:669-682.
23. Witteman JCM, Grobbee DE, Valkenburg HA, et al. A J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994;343:504-507.
24. Hofman A, Grobbee DE, de Jong PTVM, VandenOuweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403-422.
25. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles, and description of a computerized analyzing system. *Clin Physiol*. 1991;11:565-577.
26. Bots ML, Swieten J van, Breteler MMB, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet*. 1993;341:1232-1237.
27. Bots ML, Mulder PGH, Hofman A, Es GA van, Grobbee DE. Reproducibility of carotid intima-media thickness measurements: the Rotterdam Study. *J Clin Epidemiol*. 1994;47:921-930.
28. Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*. Geneva, Switzerland: World Health Organization; 1982.
29. WHO Collaborating Centre for Drug Statistics Methodology. *Anatomical Therapeutic Chemical (ATC) Classification*. Oslo, Norway: World Health Organization; 1992.
30. Stry HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. *Arterioscler Thromb Vasc Biol*. 1992;12:120-134.
31. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC Study. *Am J Epidemiol*. 1991;134:250-256.
32. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolaemia: ultrasound measurement of intima-media thickness in the common carotid artery. *Arterioscler Thromb Vasc Biol*. 1992;12:70-77.
33. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in eastern Finnish men. *J Intern Med*. 1991;229:225-231.
34. Bots ML, Hofman A, de Bruyn AM, de Jong PTVM, Grobbee DE. Isolated systolic hypertension and vessel wall thickness of the carotid artery: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 1993;13:64-69.
35. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly: initial findings from the Cardiovascular Health Study. *JAMA*. 1992;268:1287-1291.
36. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke*. 1992;23:1752-1760.
37. Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media wall thickness in women with and without atherosclerosis of the abdominal aorta. *Atherosclerosis*. 1993;102:99-105.
38. Polak JF, O'Leary DH, Kronmal RA, et al. Sonographic evaluation of the carotid artery atherosclerosis in the elderly: relationship of disease severity to stroke and transient ischemic attack. *Radiology*. 1993;188:363-370.
39. Bots ML, Hofman A, Grobbee DE. Common carotid intima-media thickness and lower extremity arterial atherosclerosis: the Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 1994;14:1885-1891.
40. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study. *Atherosclerosis*. 1990;81:33-40.
41. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb Vasc Biol*. 1991;11:1245-1249.
42. Blankenhorn D, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery: two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation*. 1993;88:20-28.
43. Furberg CD, Adams HP, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90:1679-1687.
44. Grobbee DE, Bots ML. Carotid intima-media thickness as an indicator of generalized atherosclerosis. *J Intern Med*. 1994;236:567-573.
45. Sutton-Tyrell K, Alcorn HG, Wolfson SK, Kelsey SF, Kuller LH. Predictors of carotid stenosis in older adults with and without isolated systolic hypertension. *Stroke*. 1993;24:355-361.
46. Fineberg MH. Systolic hypertension: its relationship to atherosclerosis of the aorta and larger arteries. *Am J Med*. 1927;127:835-842.
47. Wiggers CJ. Physical and physiological aspects of arteriosclerosis and hypertension. *Ann Intern Med*. 1932;6:12-30.
48. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23:395-401.
49. Alderman MH, Ooi LVL, Madhavan S, Cohen H. Treatment-induced blood pressure reduction and the risk of myocardial infarction. *JAMA*. 1989;262:920-924.
50. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-shaped phenomenon and the treatment of hypertension: is there a point beyond which pressure reduction is dangerous? *JAMA*. 1991;265:489-495.
51. Zanchetti A, Amery A, Berglund G, et al. How much should blood pressure be lowered? the problem of the J-shaped curve. *J Hypertens*. 1989;7(suppl 6):S338-S348.
52. Flechter AE, Bulpitt CJ. How far should blood pressure be lowered? *N Engl J Med*. 1992;326:251-254.