View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Erasmus University Digital Repository

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learn and Live℠

J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives

Zoltán Vokó, Michiel L. Bots, Albert Hofman, Peter J. Koudstaal, Jacqueline C. M. Witteman and Monique M. B. Breteler

Hypertension 1999;34;1181-1185

Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 1999 American Heart Association. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/cgi/content/full/34/6/1181

Subscriptions: Information about subscribing to Hypertension is online at
http://hyper.ahajournals.org/subsriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21202-2436. Phone 410-5280-4050. Fax: 410-528-8550. Email: journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/static/html/reprints.html

Downloaded from hyper.ahajournals.org at SWETS SUBS SERVICE on December 4, 2006

J-Shaped Relation Between Blood Pressure and Stroke in Treated Hypertensives

Zoltán Vokó, Michiel L. Bots, Albert Hofman, Peter J. Koudstaal,
Jacqueline C.M. Witteman, Monique M.B. Breteler

Abstract—The objective of this study was to investigate the relationship between hypertension and risk of stroke in the elderly. The study was performed within the framework of the Rotterdam Study, a prospective population-based cohort study. The risk of first-ever stroke was associated with hypertension (relative risk, 1.6; 95% CI, 1.2 to 2.0) and with isolated systolic hypertension (relative risk, 1.7; 95% CI, 1.1 to 2.6). We found a continuous increase in stroke incidence with increasing blood pressure in nontreated subjects. In treated subjects, we found a J-shaped relation between blood pressure and the risk of stroke. In the lowest category of diastolic blood pressure, the increase of stroke risk was statistically significant compared with the reference category. Hypertension and isolated systolic hypertension are strong risk factors for stroke in the elderly. The increased stroke risk in the lowest stratum of blood pressure in treated hypertensive patients may indicate that the therapeutic goal of "the lower the better" is not the optimal strategy in the elderly. **(*Hypertension*. 1999;34:1181-1185.)**

Key Words: cerebrovascular disorders ■ stroke ■ blood pressure ■ cohort studies ■ drug therapy

Hypertension is a well-established risk factor for stroke in elderly people.[1–6] There is increasing evidence showing the importance of isolated systolic hypertension in the etiology of stroke,[1,7–13] and now it is recognized as an independent risk factor for cardiovascular morbidity and mortality.[14–16] The results of clinical trials indicated that treatment of hypertension could reduce the risk of stroke considerably, in the elderly as well.[17–21] Although 2 clinical trials have investigated the optimal target blood pressure level in treated hypertensive patients, it is still a question whether the risk of stroke continues to decrease the further blood pressure is reduced in hypertensive patients.[22–24]

We performed a prospective cohort study in an elderly Dutch population to investigate the relationship between hypertension and stroke in the elderly. Furthermore, we studied the relationship between blood pressure level and the risk of stroke separately in subjects using and not using antihypertensive medication.

Methods

Study Population

This study was conducted within the framework of the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in the suburb of Rotterdam, the Netherlands, were invited. The rationale and design of the Rotterdam Study have been described elsewhere.[25]

Baseline data collection was performed between 1990 and 1993. Written informed consent and permission to retrieve information from medical records were obtained from every participant. The study has been approved by the Medical Ethics Committee of the University Hospital of Rotterdam. In total, 7983 subjects participated (response rate, 78%). Among them, 7725 subjects reported no previous stroke at baseline, and of them, 6927 visited the research center, where their blood pressure was measured. Among them, the distribution of age and gender and the frequency of diabetes, angina, and previous myocardial infarction were similar to the rest of the cohort.

Outcome

Once subjects enter the study, they are continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. Furthermore, bimonthly updates from the municipality records are obtained. When an event or death is reported, additional information is obtained by interviewing the general practitioner and scrutinizing the medical files or hospital discharge records in case of admittance or referral. This analysis concerns events that occurred until December 31, 1996. Complete follow-up was available for 6287 subjects (91%).

All suspected stroke cases reported were reviewed by a neurologist (P.J.K.), who classified them as definite, probable, or possible strokes or as nonstroke events[26] and determined stroke subtypes.

Determinants

Sitting blood pressure was measured at baseline in the right upper arm with a random-zero sphygmomanometer. The average of 2 measurements obtained on 1 occasion, separated by a count of the pulse rate, was used in this analysis.[27] Use of medication was ascertained as part of the baseline interview in the subject's home. Hypertension was defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or use of antihypertensive

Received May 5, 1999; first decision May 26, 1999; revision accepted August 4, 1999.

From the Department of Epidemiology and Biostatistics, Erasmus University Medical School (Z.V., M.L.B., A.H., J.C.M.W., M.M.B.B.), Rotterdam; University Medical Center Utrecht (M.L.B.); and Department of Neurology, University Hospital Rotterdam (P.J.K.), Netherlands.

Correspondence to Monique M.B. Breteler, MD, PhD, Department of Epidemiology and Biostatistics, Erasmus University Medical School, 3000DR Rotterdam, PO Box 1738, Netherlands. E-mail breteler@epib.fgg.eur.nl

© 1999 American Heart Association, Inc.

Hypertension **is available at http://www.hypertensionaha.org**

medication.[27] Isolated systolic hypertension was defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure <90 mm Hg, and no treatment for hypertension.

Potential Confounders

With respect to smoking behavior, subjects were categorized as current or former smokers and those who never smoked. Diabetes mellitus was defined as random or postload serum glucose >11.1 mmol/L or use of antidiabetic medication.[28] Prevalence of angina pectoris and claudication was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[29] Ankle-to-arm systolic blood pressure index was defined as the ratio of the systolic blood pressure measured at the arm and at the ankle at the same side.[30] A history of transient ischemic attack (TIA) was assessed on the basis of answers to the questions about experiencing a short period with disturbances of sensibility, strength, speech, or vision. If a positive answer was given, more detailed information was obtained, and the event was categorized as typical TIA, atypical, or no TIA by a neurologist (P.J.K.).[31] History of stroke or myocardial infarction was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner, cardiologist, or neurologist.[32,33]

Statistical Analysis

All first-ever strokes were included in the analysis. Relative risks and 95% CIs were estimated through Cox regression.

We compared the risk of stroke between hypertensive and normotensive subjects and between subjects with isolated systolic hypertension and nontreated subjects having systolic blood pressure <160 mm Hg and diastolic blood pressure <90 mm Hg. The risk estimates were adjusted for age, gender, smoking habits, and diabetes mellitus. We refrained from adjustment for cardiovascular diseases because they were considered intermediate steps in the disease process or indicators of severe hypertension.

We also investigated the effect of blood pressure level on stroke risk among treated and nontreated subjects. To reduce confounding caused by severe atherosclerosis associated with high systolic and low diastolic blood pressure, these analyses were adjusted for age, gender, smoking habits, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical TIA.

Missing data of potential confounders were handled by the indicator method.[34] On all confounders, >90% of data were available.

Results

Table 1 shows the baseline characteristics of the study population. The study cohort was followed for an average of 4.7 years. Among them, 277 first-ever strokes occurred. Of these strokes, 7.2% were hemorrhagic, 73.7% were ischemic, and 19.1% could not be specified.

TABLE 1. Baseline Characteristics of the Study Population

Characteristic	Hypertensive Subjects (n=2351)	Normotensive Subjects (n=3936)
Age, y	71.5 (8.9)	68.4 (8.9)
Systolic blood pressure, mm Hg	156.7 (22.4)	130.5 (16.1)
Diastolic blood pressure, mm Hg	79.9 (12.4)	70.4 (9.8)
Serum cholesterol, mmol/L	6.7 (1.2)	6.6 (1.2)
Men	34.3	42.4
Current smoker	18.4	25.2
Former smoker	40.4	41.9
Diabetes mellitus	16.4	7.7
Atrial fibrillation	3.2	2.4
Intermittent claudication	2.3	1.2
Angina pectoris	9.7	5.3
Coronary revascularization	3.8	2.6
History of myocardial infarction	16.1	10.8
History of typical TIA	1.9	1.3
History of atypical TIA	2.5	1.4

Values are mean (SD) or percentage.

A statistically significant association between hypertension, isolated systolic hypertension, and the risk of first-ever stroke was observed (Table 2).

In subjects who did not use antihypertensive medication, a continuous increase in risk was observed with increasing level of both systolic (Figure 1) and diastolic (Figure 2) blood pressure. In patients who used antihypertensive drugs, a J-shaped relation was found between both systolic and diastolic blood pressure and the incidence of stroke. For diastolic blood pressure, the increase of the risk in the lowest category compared with the reference was statistically significant.

To examine the possibility that the J-curve that we found was due to the excess number of subjects with isolated systolic hypertension among those with the lowest diastolic blood pressure, we excluded subjects with isolated systolic hypertension. This did not materially change our results. We performed analyses with adjustment for systolic blood pressure and also with exclusion of subjects with history of myocardial infarction or coronary revascularization procedure. This did not change the shape of the relationship between diastolic blood pressure and stroke.

TABLE 2. Association Between Hypertension, Isolated Systolic Hypertension, and Risk of First-Ever Stroke

Determinant	Persons at Risk	Number of Strokes	Strokes/1000 Person-Years	Relative Risk (95% CI)	
				Adjusted for Age and Gender	Additional Adjustment*
Hypertension					
No	3936	130	7.0	1.00 (reference)	1.00 (reference)
Yes	2351	147	13.8	1.59 (1.25–2.02)	1.58 (1.24–2.01)
Isolated systolic hypertension					
No	3241	92	5.9	1.00 (reference)	1.00 (reference)
Yes	345	25	15.8	1.80 (1.15–2.81)	1.69 (1.08–2.64)

*Adjusted for smoking habit and diabetes mellitus.

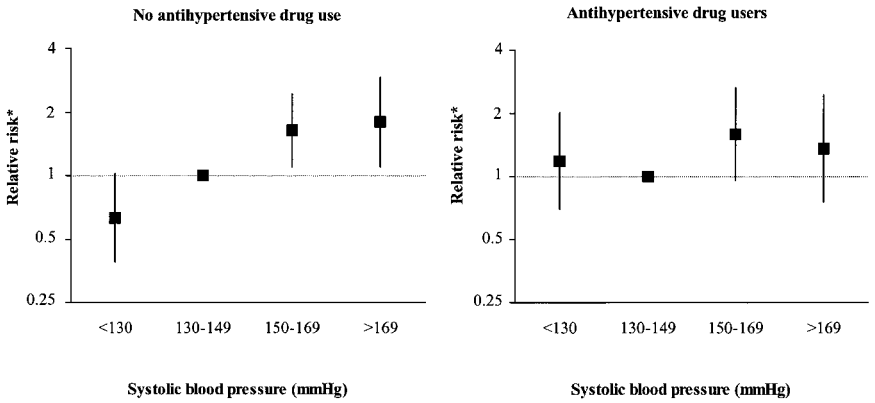

Figure 1. Association between systolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of systolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical TIA.

Discussion

We found associations of hypertension and isolated systolic hypertension with the occurrence of stroke. This is the first study clearly showing a J-shaped relation between diastolic blood pressure and the incidence of stroke in treated hypertensive subjects.

Regarding the relation between hypertension, isolated systolic hypertension, and risk of stroke in the elderly, our results are in accordance with the results of other epidemiological studies.[1–13]

However, we may have slightly underestimated the risk of stroke in hypertensive subjects, since some subjects could have started taking antihypertensive medication after baseline and this could have decreased their risk. Nevertheless, we think that this has not greatly influenced our major findings.

Most of the studies published on the association of blood pressure and the risk of stroke indicate a continuous increase in risk over the whole range of blood pressure,[35] although few could evaluate the relationship between blood pressure and stroke risk in elderly subjects with very low blood pressure.[36] Nonetheless, in a case-control study an increased risk of stroke was reported in treated hypertensive patients with low diastolic or systolic blood pressure.[37] In the Cardiovascular Health Study, a cohort study similar to the Rotterdam Study, the risk of stroke tended to increase in treated hypertensive patients whose systolic blood pressure was <128 mm Hg.[6] In a cohort of Norwegian elderly subjects, an increase of stroke mortality was seen at low diastolic blood pressure.[38] Although none of these results were statistically significant, they are in accord with our findings, and they suggest that the optimal target level of blood pressure in elderly hypertensive patients might be higher than the conventional "normal" level. Similar results have been repeatedly reported on the relation between blood pressure and myocardial infarction.[39,40] In this case, however, the relationship does not seem to be restricted to treated subjects.[41–44]

Two intervention trials have addressed the question of optimal blood pressure reduction. In the Behandla Blodtryck Battre trial, there was no difference in cardiovascular mortality and morbidity between subjects with essential hypertension who had their diastolic blood pressure lowered to <80 mm Hg or to between 90 and 100 mm Hg. However, only few cases of strokes and myocardial infarctions occurred during the follow-up, and thus the power of this study is limited.[22] The Hypertension Optimal Treatment trial investigated the relation between 3 levels of target diastolic blood pressure (≤90, ≤85, or 80 mm Hg) and the incidence of cardiovascular morbidity and mortality in hypertensive patients. For stroke, the lowest risk was in the group with diastolic blood pressure <80 mm Hg and an average systolic blood pressure of 142.2 mm Hg. However, the study did not have enough power to study the relationship at <130 mm Hg systolic blood pressure and <75 mm Hg diastolic blood pressure, and therefore it neither confirmed nor excluded the possibility of a J-shaped relation.[24]

One explanation for the J curve could be that the progression of atherosclerosis causes a wide pulse pressure through vessel wall stiffening accompanied by low diastolic pressure,

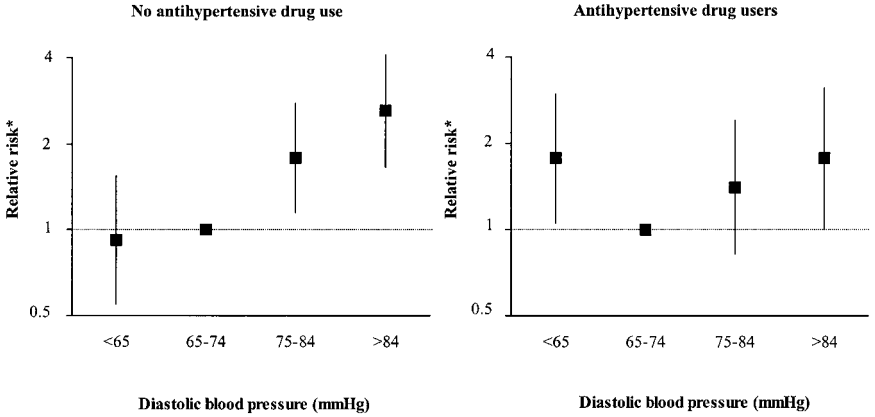

Figure 2. Association between diastolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of diastolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularization procedure), myocardial infarction, atrial fibrillation, and typical and atypical TIA.

and that is why low diastolic blood pressure is associated with excess cardiovascular morbidity.[45–47] Our data suggest that advanced atherosclerosis cannot explain or can only partly explain the phenomenon, since we found the J-shaped relationship after adjustment for major cardiovascular risk factors and cardiovascular diseases and after exclusion of subjects with myocardial infarction and coronary revascularization procedure.

An excess number of subjects having isolated systolic hypertension among those with the lowest diastolic blood pressure could be another plausible explanation for the J curve we found. However, this was not the case in our study. The relationship between diastolic blood pressure and stroke remained essentially the same after adjustment for systolic blood pressure or exclusion of subjects with isolated systolic hypertension.

It is likely that another mechanism can play a role in the increased stroke risk among treated hypertensive subjects with very low blood pressure also. Chronic hypertension shifts the lower and upper blood pressure limits of cerebral blood flow autoregulation toward higher pressure.[48] This adaptive change protects the brain against high intravascular pressure, but at the same time it makes the brain more susceptible to ischemia at low blood pressure. In elderly subjects this change may be irreversible.[49]

Within the group of treated subjects, we could not investigate to what extent low blood pressure was due to the antihypertensive treatment itself. Nevertheless, low blood pressure did not increase the risk of stroke in nontreated subjects.

The risk of stroke in elderly hypertensives seems lowest at blood pressure levels of ≈140/80 mm Hg. In view of current evidence, cautious reduction of blood pressure in elderly individuals is recommended.

Acknowledgments

The Rotterdam Study was supported by the NESTOR stimulation program for geriatric research in the Netherlands (Ministry of Health and Ministry of Education), the Netherlands Organization for Scientific Research (NWO), the Netherlands Prevention Fund, and the municipality of Rotterdam. Dr Vokó was supported by the Ministry of Health of Hungary and by NIHES, Erasmus University, Rotterdam, Netherlands. Dr Bots was supported by the Netherlands Heart Foundation (grant 96.141). Dr Breteler is a fellow of the Royal Netherlands Academy of Arts and Sciences. We are grateful to the participants, general practitioners, and field workers in the Rotterdam Study.

References

1. Shekelle RB, Ostfeld AM, Klawans HL. Hypertension and risk of stroke in an elderly population. *Stroke*. 1974;5:71–75.
2. Davis PH, Dambrosia JM, Schoenberg BS, Schoenberg DG, Pritchard DA, Lilienfeld AM, Whisnant JP. Risk factors for ischemic stroke: a prospective study in Rochester, Minnesota. *Ann Neurol*. 1987;22: 319–327.
3. Evans JG. Blood pressure and stroke in an elderly English population. *J Epidemiol Community Health*. 1987;41:275–282.
4. Vokonas PS, Kannel WB, Cupples LA. Epidemiology and risk of hypertension in the elderly: the Framingham Study. *J Hypertens*. 1988;6(suppl 1):S3–S9.
5. Guzik HJ, Ooi WL, Frishman WH, Greenberg S, Aronson MK. Hypertension: cardiovascular implications in a cohort of old old. *J Am Geriatr Soc*. 1992;40:348–353.
6. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR, for the CHS Collaborative Research Group. Short-term predictors of incident stroke in adults. *Stroke*. 1996;27:1479–1486.
7. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNAmara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke: the Framingham Study. *JAMA*. 1981;245:1225–1229.
8. Forette F, de la Fuentex, Goldmard JL, Henry JF, Hervy MP. The prognostic significance of isolated systolic hypertension in the elderly: results of a ten year longitudinal survey. *Clin Exp Hypertens*. 1982;4: 1177–1191.
9. Garland C, Barreth-Connor E, Suarez L, Criqui MH. Isolated systolic hypertension and mortality after age 60 years: a prospective population-based study. *Am J Epidemiol*. 1983;118:365–376.
10. Rutan GH, Kuller LH, Neaton JD, Wentworth DH, McDonald RH, McFate Smith W. Mortality associated with diastolic hypertension and isolated hypertension among men screened for the Multiple Risk Factor Intervention Trial. *Circulation*. 1988;77:504–514.
11. Petropvich H, Curb D, Bloom-Marcus E. Isolated systolic hypertension and risk of stroke in Japanese-American men. *Stroke*. 1995;26:25–29.
12. Nielsen WB, Vestbo J, Jensen GB. Isolated systolic hypertension as a major risk factor for stroke and myocardial infarction and an unexploited source of cardiovascular prevention: a prospective population-based study. *J Hum Hypertens*. 1995;9:175–180.
13. O'Donell CJ, Ridker PM, Glynn RJ, Berger K, Ajani U, Manson JE, Hennekens CH. Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians. *Circulation*. 1997;95:1132–1137.
14. The Working Group on Hypertension in the Elderly. Statement on hypertension in the elderly. *JAMA*. 1986;256:70–74.
15. Borhani NO. Isolated systolic hypertension in the elderly. *J Hypertens*. 1988;6(suppl 1):S15–S19.
16. Silagy CA, McNeil JJ. Epidemiologic aspects of isolated systolic hypertension and implications for future research. *Am J Cardiol*. 1992;69: 213–218.
17. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ*. 1986;293:1145–1151.
18. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester P-O. Morbidity and mortality in the Swedish Trial in Old Patients With Hypertension (STOP-Hypertension). *Lancet*. 1991;338:1281–1285.
19. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in old persons with isolated systolic hypertension. *JAMA*. 1991;265:3255–3264.
20. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992;304:405–412.
21. Staessen JA, Fagard R, Thijs L, Celis H, Arbidze GG, Birkenhager WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet*. 1997;350:757–764.
22. Hansson L. The BBB Study: the effect of intensified antihypertensive treatment on the level of blood pressure, side effects, morbidity and mortality in "well-treated" hypertensive patients: Behandla Blodtryck Battre. *Blood Press*. 1994;3:248–254.
23. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S, for the 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) randomised trial. *Lancet*. 1998;351:1755–1762.
24. Kaplan N. J-curve not burned off by HOT study. *Lancet*. 1998;351: 1748–1749.
25. Hofman A, Grobbee DE, DeJong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422.
26. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation*. 1997;96:1432–1437.
27. 1988 Joint National Committee. The report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1988;148:1023–1038.
28. Stolk RP, Pols HAP, Lamberts SWJ, de Jong PTVM, Hofman A, Grobbee DE. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinaemia in an elderly population: the Rotterdam Study. *Am J Epidemiol*. 1997; 145:24–32.

29. Rose GA, Blackburn H, Gillum RF, Prineas RL. *Cardiovascular Survey Methods*. Geneva, Switzerland: World Health Organization; 1982.
30. Bots ML, Hofman A, Grobbee DE. Common carotid intima-media thickness and lower extremity arterial atherosclerosis: the Rotterdam Study. *Arterioscler Thromb.* 1994;14:1885–1891.
31. Bots ML, van der Wilk EC, Koudstaal PJ, Hofman A, Grobbee DE. Transient neurological attacks in the general population: prevalence, risk factors, and clinical relevance. *Stroke*. 1997;28:768–773.
32. de Bruyne MC, Mosterd A, Hoes AW, Kors JA, Kruijssen DACM, van Bemmel JH, Hofman A, Grobbee DE. Prevalence, determinants and misclassification of myocardial infarction in the elderly: the Rotterdam Study. *Epidemiology*. 1997;8:495–500.
33. Bots ML, Looman SJ, Koudstaal PJK, Hofman A, Hoes AW, Grobbee DE. Prevalence of stroke in the general population: the Rotterdam Study. *Stroke*. 1996;27:1499–1501.
34. Miettinen OS. *Theoretical Epidemiology*. New York, NY: John Wiley & Sons, Inc; 1985:231–233.
35. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease, part 1: prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. *Lancet*. 1990; 335:765–774.
36. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and coronary heart disease. *Br Med Bull*. 1994; 50:272–278.
37. Al-Roomi KA, Heller RF, Wlodarczyk J. Hypertension control and the risk of myocardial infarction and stroke: a population-based study. *Med J Aust*. 1990;153:595–603.
38. Selmer R. Blood pressure and twenty-year mortality in the city of Bergen, Norway. *Am J Epidemiol*. 1992;136:428–440.
39. Cruickshank JM. Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *BMJ*. 1988;297: 1227–1230.
40. Merlo J, Ranstam J, Liedholm H, Hedblad B, Liendberg G, Lindblad U, Isacsson SO, Melander A, Rastam L. Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs: population based cohort study. *BMJ*. 1996;313:457–461.
41. 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. *BMJ*. 1991;303: 385–389.
42. Staessen J, Bulpitt C, Clement D, De Leeuw P, Fagard R, Fletcher A, Forette F, Leonetti G, Nissinen A, O'Malley K, Tuomilehto J, Webster J, Williams BO. 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.
43. Coope J. Hypertension: the cause of the J-curve. *J Hum Hypertens*. 1990;4:1–4.
44. Flechter AK, Bulpitt CJ. How far should blood pressure be lowered? *N Engl J Med*. 1992;326:251–254.
45. Sleight P. Blood pressure, hearts, and U-shaped curves. *Lancet*. 1988; 1:235. Letter.
46. Witteman JCM, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, Hofman A. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994; 343:504–507.
47. Bots ML, Witteman JCM, Hofman A, de Jong PTVM, Grobbee DE. Low diastolic blood pressure and atherosclerosis in the elderly: the Rotterdam Study. *Arch Intern Med*. 1996;156:843–848.
48. Strandgaard S, Paulson OB. Cerebral blood flow and its pathophysiology in hypertension. *Am J Hypertens*. 1989;2:486–492.
49. Strandgaard S. Cerebral blood flow in the elderly: impact of hypertension and antihypertensive treatment. *Cardiovasc Drugs Ther*. 1991;(suppl 6):1217–1221.