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

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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, bi-monthly 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 events²⁶ 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

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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.

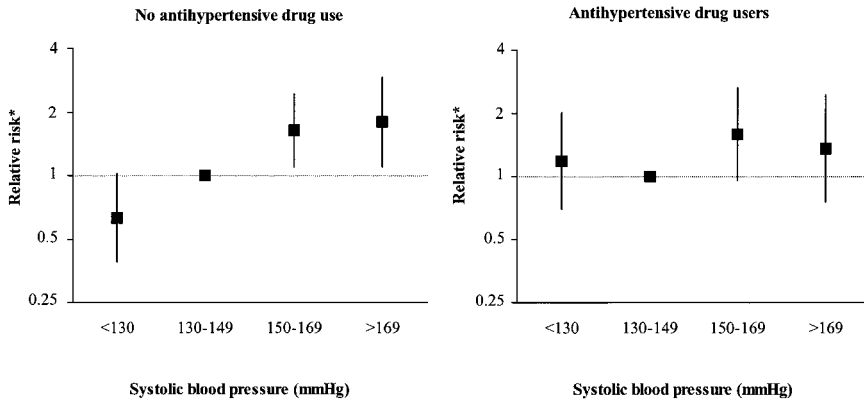


Figure 1. Association between systolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of systolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, 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,

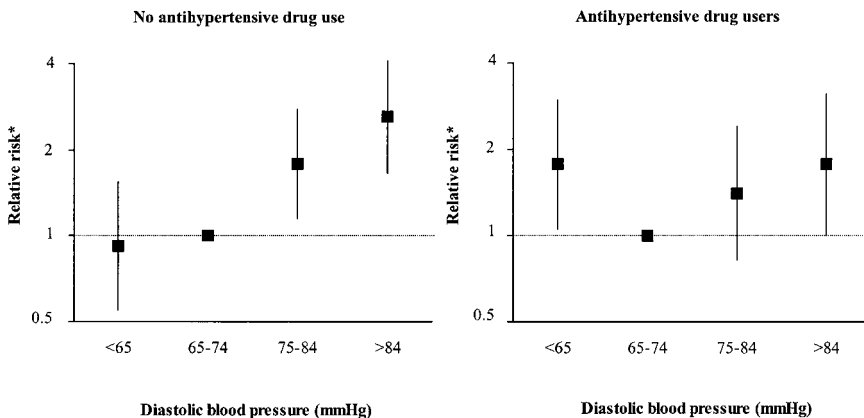


Figure 2. Association between diastolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of diastolic blood pressure. Values are plotted on logarithmic scale. *Adjusted for age, gender, smoking habit, diabetes mellitus, 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 $\approx 140/80$ mm Hg. In view of current evidence, cautious reduction of blood pressure in elderly individuals is recommended.

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