Blood Pressure in Relation to the Incidence of Cerebral Infarction and Intracerebral Hemorrhage

Hypertensive Hemorrhage: Debated Nomenclature Is Still Relevant

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Background and Purpose—Data regarding the association between blood pressure level and incidence of stroke subtype, especially primary intracerebral hemorrhage (PICH) subtypes, is sparse. This population-based study explored the relationship between blood pressure and the incidence of cerebral infarction, and PICH, with lobar and nonlobar location.

Methods—Risk factors were assessed in 27 702 men and women without prior stroke from the city of Malmö, Sweden.

Results—Mean age was 58.1 years. In all, 701 subjects had stroke (613 cerebral infarction and 88 PICH) during the follow-up period (mean, 7.5 years). The age- and sex-standardized incidences of cerebral infarction in subjects with hypertension grade 3 (≥180/110 mm Hg) and normal blood pressure (<140/90 mm Hg) were 6.8 and 1.7 per 1000 person-years, respectively. Compared with the normotensive group, the adjusted relative risk of cerebral infarction was 3.4 (95% CI: 2.6 to 4.5) in subjects with hypertension grade 3. The corresponding incidences of lobar PICH were 0.5 versus 0.08 per 1000 person-years, respectively (adjusted relative risk: 9.2, 95% CI: 2.6 to 32.6) and for nonlobar PICH 1.6 versus 0.09 per 1000 person-years, respectively (adjusted relative risk: 25.9, 95% CI: 8.2 to 82.3).

Conclusions—The incidence of hemorrhagic and ischemic stroke increased progressively with increasing blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in the public health perspective, the relationship with nonlobar PICH was strongest in terms of relative risks. **(*Stroke*. 2007;38:2681-2685.)**

Key Words: blood pressure ■ cerebral hemorrhage ■ cerebral infarction ■ diabetes ■ hypertension ■ intracerebral hemorrhage ■ risk factors ■ smoking ■ stroke

Elevated blood pressure is a major risk factor for stroke in the general population.[1–3] However, few have compared the effect of hypertension, in terms of absolute and relative risks, for the incidence of stroke subtypes. In a Korean cohort study,[4] the relationship between hypertension and hemorrhagic stroke was stronger than that for ischemic stroke, as measured by the adjusted relative risks. Whether this is true also for a Western population, with a lower proportion of primary intracerebral hemorrhage (PICH), is unclear.

The term "hypertensive hemorrhages" has been used to describe PICH with nonlobar location.[5] Some studies have confirmed the association between hypertension and the nonlobar subtype of PICH,[6,7] whereas others have reported a similar association with the risk of lobar PICH.[8] However, most previous studies in this field are case–control studies[7,8] or studies that only include fatal cases.[9,10] Here, we have prospectively studied the effects of hypertension on the absolute and relative risks of ischemic stroke, PICH, and PICH with lobar and nonlobar location.

Methods and Materials

Risk Factor Assessment

Between 1991 and 1996, all men aged 46 to 73 years and all women aged 45 to 73 years, with residency in Malmö (approximately 250 000 habitants), Sweden, were invited by mail or by newspaper advertisement to participate in the Malmö Diet and Cancer Study, a population-based prospective study.[11,12] In all, 28 449 participated out of an eligible population of 74 000. The participants were asked to complete a self-administered questionnaire at home, which included items on lifestyle factors, medication, previous and current diseases. The participants also underwent a health examination at the university hospital, performed by project nurses, including blood pressure, height, and weight.[11] During the visit, the questionnaire was checked for completeness.

Blood pressure was measured twice in the supine position after a rest of 10 minutes using a mercury sphygmomanometer. Blood pressure was grouped according to the European guidelines, ie, <140/<90 mm Hg (normal blood pressure) and systolic blood pressure 140 to 159 and/or diastolic blood pressure 90 to 99 mm Hg, systolic blood pressure 160 to 179 and/or diastolic blood pressure 100 to 109 mm Hg, and systolic blood pressure ≥180 and/or diastolic blood pressure ≥110 mm Hg as hypertension grade 1 to 3,

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respectively.[13] Use of lipid-lowering and/or antidiabetic drugs or history of diabetes was assessed in a questionnaire. High alcohol consumption was defined as >40 g/d for men and >30 g/d for women.[14] Subjects who reported that they smoked daily or regularly were considered current smokers.

Of the participants in the Malmö Diet and Cancer study, 423 subjects with missing information about blood pressure (n=44), body mass index (BMI) (n=46), smoking (n=324), and/or alcohol consumption (n=323) were excluded. After exclusion of participants with a history of stroke, according to self-report or hospital registers, (n=324), 27 702 subjects remained.

Stroke Cases: Ascertainment and Classification

Incidence of first-ever stroke and death was monitored until December 31, 2001, by linkage to the Stroke register of Malmö (STROMA), an incidence register.[15,16] Since 1989 and after, a specialized research nurse continuously searches for cases with stroke at the Malmö University Hospital, which is the only hospital serving the population of Malmö. The case-finding of the STROMA register includes a broad search among patients with neurological symptoms that could indicate stroke. Stroke is defined as rapidly developed clinical signs of local or global loss of cerebral function that lasted for >24 hours or led to death within 24 hours following the World Health Organization's definition.[17] By definition, patients with transient ischemic attacks are excluded. The stroke subtypes are coded according to International Classification of Diseases revision 9. Cerebral infarction (International Classification of Diseases code 434) is diagnosed when CT, MRI, or autopsy verifies the infarction in location corresponding to the focal neurology or excludes hemorrhage and nonvascular disease. Intracerebral hemorrhage (International Classification of Diseases code 431) is considered when CT, MRI, or autopsy shows intraparenchymal blood in the brain. If neither imaging nor autopsy was performed, the stroke is classified as unspecified (International Classification of Diseases code 436). Angiography is carried out in selected cases with hemorrhagic stroke, ie, in whom hematoma location, age, or clinical situation was suggestive of a vascular malformation. The specialized research nurse, supported by a senior neurologist (H.P.R.), validates all stroke cases by review of the patient's records.

To find cases who moved out from the city of Malmö after the screening examination, we also used the national hospital discharge register and the Swedish Causes of Death register using the same diagnosis validation procedures as for STROMA. In cases registered as hemorrhagic stroke, all medical records, images, and/or autopsy records were reviewed by a neurologist (E.Z.) with assistance from a neuroradiologist to make PICH classification by location, ie, lobar (predominantly cortical or subcortical white matter) and nonlobar (predominantly basal ganglia, internal capsule, periventricular white matter, cerebellum, and brain stem), and to identify intracerebral hemorrhage secondary to arteriovenous malformation/aneurysm, thrombolysis of acute myocardial infarction, or hemorrhagic infarction (n=5, all excluded).

In 5 cases with PICH, all hospitalized in other Swedish hospitals, imaging results were verified in hospital records, but hemorrhage location could not be classified. Those were counted as PICH. Seven cases with unspecified stroke, International Classification of Diseases code 436, were counted as cerebral infarctions. Classification of stroke (according to the procedure explained previously), including subclassification of PICH, was made without knowledge of the individual risk factors in the Malmö Diet and Cancer Study.

Statistics

The incidence (per 1000 person-years) was standardized for sex and age (5-year groups) using direct standardization and was weighted for the age-distribution of the present cohort. Confidence intervals were calculated assuming Poisson distribution. Cox regression model was used to calculate the relative risks (RR) with adjustment for age, sex, and other risk factors for stroke (BMI, diabetes, lipid-lowering drug, smoking, high alcohol consumption). One-way analysis of variance with Bonferroni post hoc test was used to compare continuous variables between the diagnostic groups. Logistic regression was used for categorical variables.

Results

Risk Factors at Baseline

During the mean observation time of 7.5 years, 613 cases of cerebral infarction and 88 cases of PICH (38 lobar, 45 nonlobar, 5 not classified) were identified. Baseline characteristics of the participants are presented in Table 1. As compared with those who remained free from stroke, cases with PICH had significantly higher blood pressure, BMI, and age and a higher prevalence of diabetes. Subjects who had cerebral infarction during the follow-up had significantly higher blood pressure, BMI, and age and a higher prevalence of smoking, diabetes, treatment for hyperlipidemia, and high alcohol consumption than subjects without stroke during the follow-up. Male sex was a statistically significant risk factor for cerebral infarction, PICH, and PICH with nonlobar location. Subjects with lobar PICH were significantly older at screening than subjects without stroke during the follow-up period.

Incidence of Stroke in Relation to Blood Pressure

Crude and standardized incidence rates and adjusted relative risk of stroke subtype are presented in the Figure and Table 2. The incidence of stroke increased progressively with degree of hypertension. The age- and sex-standardized incidences of cerebral infarction in subjects with hypertension grade 3 (≥180/110 mm Hg) and normal blood pressure (<140/90 mm Hg) were 6.8 and 1.7 per 1000 person-years, respectively. After adjustment for risk factors, the relative risk was 3.4 (95% CI: 2.6 to 4.5). The corresponding incidences of lobar PICH were 0.46 versus 0.08 per 1000 person-years, respectively (adjusted RR: 9.2, 95% CI: 2.6 to 32.6) and for nonlobar PICH 1.63 versus 0.09 per 1000 person-years, respectively (adjusted RR: 25.9, 95% CI: 8.2 to 82.3).

The proportion of PICH out of all cases with stroke increased from 7% in the normotensive group to 19.5% in the group with hypertension grade 3.

Both systolic blood pressure and diastolic blood pressure were risk factors for cerebral infarction and PICH. Expressed as RRs (adjusted for risk factors) per 10 mm Hg higher systolic blood pressure, the RR was 1.1 (95% CI: 1.1 to 1.2) and 1.5 (95% CI: 1.3 to 1.6), respectively, for cerebral infarction and PICH, and 1.4 (95% CI: 1.2 to 1.7) and 1.5 (95% CI: 1.3 to 1.7), respectively, for lobar and nonlobar PICH. For 10 mm Hg higher diastolic blood pressure, adjusted RRs were 1.5 (95% CI: 1.3 to 1.6) and 2.2 (95% CI: 1.8 to 2.7), respectively, for cerebral infarction and PICH, and 1.8 (95% CI: 1.2 to 2.5) and 2.7 (95% CI: 1.2 to 3.5) for lobar and nonlobar PICH.

Other Risk Factors for Stroke

Of the other risk factors in the multivariate Cox model (see footnote, Table 2), age (RR per year: 1.04, 95% CI: 1.003 to 1.07) and male sex (RR: 1.59, 95% CI: 1.04 to 2.4) showed significant associations with incidence of PICH.

Age was statistically significant associated with lobar PICH (RR per year: 1.08, 95% CI: 1.03 to 1.14). The relative

Table 1. Risk Factors at Screening for Stroke Subtypes

	No Stroke	PICH	PICH, Lobar	PICH, Nonlobar	Cerebral Infarction
N	27 001	88	38	45	613
Risk factors					
Age, years	58.1±7.6	61.8±6.6*	62.9±6.7*	60.6±6.2	62.8±6.4*
Men, n (%)	10 436 (38.7)	49 (55.7)*	19 (50.0)	27 (60.0)*	361 (58.9)*
Smoking, n (%)	7560 (28.0)	2605 (29.6)	13 (34.2)	10 (22.2)	233 (38.0)*
Alcohol, n (%)†	1161 (4.3)	3 (3.4)	1 (2.6)	2 (4.4)	44 (7.2)*
Diabetes, n (%)	810 (3.0)	7 (8.0)*	0 (0)	6 (13.3)*	70 (11.4)*
Lipid-lowering drug, n (%)	810 (3.0)	3 (3.4)	1 (2.6)	1 (2.2)	27 (4.4)*
BMI, kg/m^2	25.7±4.0	27.0±4.1*	27.2±4.6	26.8±3.4	26.8±3.9*
Blood pressure treatment, n (%)	4628 (17.1)	24 (27.3)*	7 (18.4)	16 (35.6)*	222 (36.2)*
Blood pressure (mm Hg) in subjects without blood pressure treatment					
Systolic blood pressure	138.6±19.1	157.7±20.1*	159.60.0±21.0*	157.6±19.9*	151.0±21.3*
Diastolic blood pressure	84.5±9.6	93.8±10.8*	92.3±10.6*	95.4±10.4*	90.0±10.1*
Blood pressure (mm Hg) in subjects with blood pressure treatment					
Systolic blood pressure	152.2±19.8	167.8±20.6*	169.0±25.3*	167.1±19.8*	157.4±19.7*
Diastolic blood pressure	90.3±9.6	98.6±14.2*	97.0±12.9*	100.0±15.2*	92.0±10.1*

Values are mean±SD or percentages.
*Statistical significant difference as compared with no stroke ($P<0.05$).
†High alcohol consumption defined as >40 g/day for men and >30 g/day for women.[14]

risk between smoking and lobar PICH was 1.97 (95% CI: 0.99 to 3.9). Diabetes (RR: 3.8, 95% CI: 1.6 to 9.2) and male sex (RR: 1.9, 95% CI: 1.02 to 3.4) were statistically significant risk factors for nonlobar PICH.

The statistically significant risk factors for cerebral infarction included age (RR per year: 1.09, 95% CI: 1.08 to 1.11), male sex (RR: 1.8, 95% CI: 1.5 to 2.1), BMI (RR per unit: 1.03, 95% CI: 1.01 to 1.06), alcohol consumption (RR: 1.7, 95% CI: 1.2 to 2.3), diabetes (RR: 3.1, 95% CI: 2.4 to 4.0), and smoking (RR: 2.1, 95% CI: 1.8 to 2.5).

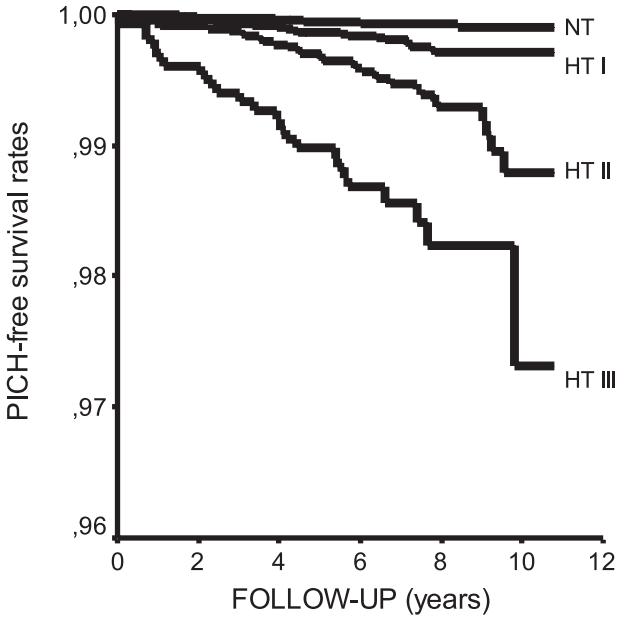

Figure. Crude incidence of PICH in relation to blood pressure category (NT [normotensive] <140/90 mm Hg; hypertension [HT] I, 140 to 159/90 to 99 mm Hg; HT II, 160 to 179/100 to 109 mm Hg; and HT III, ≥180/≥110 mm Hg).

Discussion

Risks in prospective studies are for convenient reasons often expressed in terms of relative risks. However, to assess the clinical and public health implications, relative risks need to be translated in terms of the incidence during a specified time period. Few studies have compared the incidence of stroke subtypes, in terms of absolute and relative risks, in relation to hypertension. Studies of incidence of lobar and nonlobar PICH are particularly uncommon. This study shows that in terms of relative risk, elevated blood pressure is associated with a higher risk of hemorrhagic, especially nonlobar, PICH than of ischemic stroke. However, in terms of number of cases, ie, the standardized incidence during a defined period of time, elevated blood pressure is associated with a greater number of cases of ischemic stroke.

The results are in accordance with those from a Korean study.[4] A Finnish prospective study showed lower relative risks and a less steep blood pressure gradient for both stroke subtypes compared with our results,[18] maybe because only male smokers were included in their study.

Approximately 28 000 individuals in Sweden are hospitalized attributable to stroke every year. Of them, approximately 22 000 have cerebral infarction, 3000 intracerebral hemorrhage, and another 3000 are unspecified stroke.[19] The age- and sex- standardized incidence of cerebral infarction increased with higher blood pressure (hypertension grade 3), from 1.7 to 6.8 per 1000, whereas the corresponding incidences of PICH increased from 0.2 to 2.1 per 1000. These figures reflect the numbers of patients with stroke and thereby

Table 2. Incidence (per 1000 person-years) and Adjusted RR of Stroke Subtypes in Relation to Blood Pressure

	<140/<90 mm Hg	140–159/90–99 mm Hg	160–179/100–109 mm Hg	≥180/≥110 mm Hg
n	11 631	9551	4980	1540
Age, y, mean±SD	55.4±6.9	58.9±7.3	61.5±7.4	63.4±7.4
Men, %	32.2	42.8	45.4	48.5
Blood pressure treatment, %	7.6	19.6	31.0	37.4
Primary intracerebral hemorrhage				
n	9	24	32	23
Crude incidence	0.10	0.33	0.88	2.2
Standardized incidence* (CI)	0.20 (0.05–0.04)	0.33 (0.19–0.46)	0.90 (0.55–1.2)	2.09 (1.1–3.1)
RR†	Ref	2.6 (1.2–5.7)	6.3 (2.9–14)	14.4 (6.4–32)
Lobar				
n	4	13	13	8
Crude incidence	0.05	0.18	0.36	0.75
Standardized incidence* (CI)	0.08 (0.008–0.16)	0.18 (0.08–0.28)	0.33 (0.14–0.52)	0.46 (0.13–0.79)
RR†	Ref	3.0 (0.97–9.3)	5.1 (1.6–16)	9.2 (2.6–33)
Nonlobar				
n	4	11	15	15
Crude incidence	0.05	0.15	0.41	1.4
Standardized incidence* (CI)	0.09 (0–0.18)	0.15 (0.06–0.24)	0.43 (0.19–0.68)	1.6 (0.7–2.6)
RR†	Ref	3.0 (0.93–9.4)	7.7 (2.5–24)	25.9 (8.2–82)
Cerebral infarction				
n	116	223	179	95
Crude incidence	1.32	3.07	4.92	8.95
Standardized incidence* (CI)	1.7 (1.4–2.1)	3.0 (2.6–3.4)	4.0 (3.4–4.6)	6.8 (5.2–8.4)
RR†	Ref	1.6 (1.3–2.1)	2.1 (1.7–2.7)	3.4 (2.6–4.5)

*Age, gender.

†Adjusted for BMI, diabetes, lipid-lowering drug, smoking, high alcohol consumption (>40 g/day for men and >30 g/day for women[14]), age, and gender.

the importance of hypertension on stroke incidence from a public health perspective.

Relative risks depend entirely on the risk of the reference group. PICH, as compared with cerebral infarction, is unusual in normotensive individuals (Table 2), which could explain why the gradient of the RR associated with blood pressure is steeper for PICH than for cerebral infarction. However, it also underlines the strong relationship between elevated blood pressure and PICH, whereas other risk factors than hypertension (eg, smoking, diabetes, alcohol, and BMI) also are important for the incidence of cerebral infarction.

Nonlobar PICH has historically been going by the name "hypertensive hemorrhages,"[5] although some authors have highlighted the importance of hypertension for lobar PICH as well.[8,20] A recent autopsy study showed that severe hypertension was related to nonlobar, but not to lobar PICH.[9] Our results suggest that elevated blood pressure is related to both PICH subtypes, in particular nonlobar PICH, both in terms of absolute and relative risks. This is in line with the results of a recent meta-analysis[21] in which, however, only qualitative data on prestroke hypertension, in most cases established after a stroke event, was available. To our knowledge, only one previous prospective study has explored the risk factors for incidence of subtypes of PICH.[22] In that study, smoking was significantly associated with incidence of lobar PICH, but not with nonlobar PICH, and diabetes was a risk factor for nonlobar PICH. This is consistent with the present results. However, the number of PICH cases is small in prospective cohort studies, even if the cohort is very large. Absence of significant associations could be explained by low statistical power.

We do not know whether blood pressure changed during the follow-up period. However, change of blood pressure would largely have the same effects on all stroke subtypes. Change of blood pressure and "regression dilution bias"[3] would, if anything, dilute the relationships with incidence of stroke. The Figure shows, however, that the differences between the blood pressure groups increase continuously over the entire follow-up period. Exclusion of subjects taking antihypertensive medication did not change the results (data not shown).

Diabetes and hyperlipidemia were based on self-reported data, and we lacked information of plasma glucose and lipids. Despite this limitation, self-reported diabetes showed significant relationships both with CI and nonlobar PICH. Hypercholesterolemia is associated with ischemic stroke,[23] whereas the relationships with PICH are less clear. It is possible that adjustments for lipids slightly would reduce the relative risk of cerebral infarction in hypertensive subjects.

As have been reported in previous publication from our group, uncontrolled hypertension, despite pharmacological treatment, is highly prevalent.[12] We lack information about treatment compliance, but an Australian case–control study showed a nearly 5-fold elevated risk for PICH if medication for hypertension was stopped.[8] They did not report blood pressure levels, but in our cohort, the mean blood pressure levels (Table 1) are higher than recommended[13] in all treated groups.

The stroke register has continuously searched for patients with symptoms of stroke during the entire follow-up period and included both hospitalized and nonhospitalized patients. National registers were used to find those who moved away from the city.

In this study, much effort was made to classify the intracerebral hemorrhages. A clinical approach was used to identify vascular malformations.[24] For ethical and practical reasons, it is not feasible to perform angiography in all cases with intracerebral hemorrhage, and some vascular malformations could have been missed.

The incidence of hemorrhagic and ischemic stroke increased progressively with increasing blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in a public health perspective, the relationship with PICH, especially with nonlobar location, was strongest in terms of relative risks.

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Disclosures

None.

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