44. Laird N, Ware J. Random-effects models for longitudinal data. Biometrics 1982;38:1963–1974.
45. Gussekloo J, Westendorp RGJ, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997; 315:1053–1054.
46. Frisoni GB, Fratiglioni L, Fastbom J, Viitanene M, Winblad B. Mortality in nondemented subjects with cognitive impairment: the influence of health-related factors. Am J Epidemiol 1999;150:1031–1044.
47. Tierney MC, Szalai JP, Snow WG, et al. Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. Neurology 1996;46:661–665.
48. Flicker C, Ferris SH, Reisberg B. Mild cognitive impairment in the elderly: predictors of dementia. Neurology 1991;41: 1006–1009.
49. Devanand DP, Folz M, Gorlyn M, Moeller JR, Stern Y. Questionable dementia: clinical course and predictors of outcome. J Am Geriatr Soc 1997;45:321–328.
50. Daly E, Zaitchik D, Copeland M, Schmahmann J, Gunther J, Albert M. Predicting conversion to Alzheimer disease using standardized clinical information. Arch Neurol 2000;57:675–680.
51. Bowen J, Teri L, Kukull W, McCormick W, McCurry SM, Larson EB. Progression to dementia in patients with isolated memory loss. Lancet 1997;349:763–765.
52. Goldman WP, Price JL, Storandt M, et al. Absence of cognitive impairment or decline in preclinical Alzheimer's disease. Neurology 2001;56:361–367.
53. Bäckman L, Small BJ, Fratiglinoi L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain 2001;124:96–102.

Long-term prognosis after recovery from primary intracerebral hemorrhage

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Abstract—*Background:* Little is known about the long-term outcome for patients who recover from a primary intracerebral hemorrhage. The authors examined the rate of recurrence, vascular events, and death in survivors of a primary intracerebral hemorrhage and the factors related to the long-term prognosis. *Methods:* All 243 patients admitted to one of three hospitals with a primary intracerebral hemorrhage who regained independence were interviewed about vascular events after the index hemorrhage. The authors used the Kaplan–Meier method to estimate the event-free survival and Cox proportional hazards regression analysis to identify predictors of recurrence, any vascular event, or death. *Results:* During a mean follow-up of 5.5 years, the annual rates of recurrent primary intracerebral hemorrhage, vascular events, and vascular death were 2.1% (95% CI, 1.4 to 3.3%), 5.9% (95% CI, 4.5 to 7.7%), and 3.2% (95% CI, 2.2 to 4.5%). Age of 65 years or older was the only predictor of a recurrence (hazard ratio [HR], 2.8; 95% CI, 1.3 to 6.1) and vascular death (HR, 3.7; 95% CI, 2.0 to 7.0). In addition to age, male sex predicted the occurrence of vascular events (HR, 1.8; 95% CI, 1.1 to 3.0). Use of anticoagulation after the index bleeding tripled the risk of hemorrhagic events (HR, 3.0; 95% CI, 1.3 to 7.2). *Conclusion:* Patients who recovered from a primary intracerebral hemorrhage had a 2.1% to 5.9% annual rate of recurrence, vascular death, or vascular events. Age of 65 years or older more than doubled the risk of recurrence, vascular event, or death. The risk of vascular events in men was increased twofold.

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About one-half of all patients with a primary intracerebral hemorrhage die within the first month after the hemorrhage. Knowing the risk of recurrent hemorrhages or other vascular events is important to patients who survive the initial phase, particularly to those who regain independence. The long-term outcome of intracerebral hemorrhage is not very clear. Some previous studies had too few patients to yield stable recurrence rates[1-4]; others lacked data on prognostic factors.[5-7] No studies addressed other vascular outcomes such as myocardial infarction or vascular death. Therefore, we examined the rate of recurrence and other vascular events among patients who had recovered from a PICH and the factors related to the long-term prognosis.

Methods. *Participants.* This study was performed at the University Medical Center Utrecht, the Erasmus Medical Center, Rotterdam, and the Atrium Medical Center Heerlen, the Netherlands. The medical ethics committees approved the study. We retrieved the records of all 1,731 patients admitted to all hospital departments (including emergency) with an intracerebral hemorrhage from 1986 through 1995. Each patient included in this study, or a close relative in cases where the patient had died before the interview, consented to participate.

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We included all patients admitted with a first primary intracerebral hemorrhage who returned home. Primary intracerebral hemorrhage was defined as a spontaneous intracerebral hemorrhage without a secondary cause. Intracerebral hemorrhage with a secondary cause was defined as an intracerebral hemorrhage with one of the following causative factors: vascular malformation, aneurysm, neoplasm, coagulation disorders other than those from anticoagulant drugs, trauma, previous operation, hemorrhagic transformation of an ischemic stroke, and sinus thrombosis. We excluded 358 patients with a secondary cause of the intracerebral hemorrhage. Another 57 patients were excluded, because their first intracerebral hemorrhage occurred before 1986. We excluded patients who did not undergo MRI or CT within the first week or not at all (n = 63). Seven patients with an intraventricular or subependymal hemorrhage were excluded. Furthermore, we excluded children younger than 14 years of age (n = 31), because of the great likelihood of secondary causes in children. Twenty-five patients (all nonwhite) were excluded, because they could not be interviewed in Dutch. After these exclusions, 1,190 patients were left.

Further information on death during hospital stay and discharge destination was retrieved from the medical records to select patients who regained independence and returned home. Most patients died after their hemorrhage: 505 (42%) in the first week, another 110 (9%) in the first month, and an additional 67 (6%) within the first year in the hospital or a nursing home. Fifty-two percent (n = 265) of the survivors had moved permanently to a nursing home. Only 243 (20%) of 1,190 patients returned home, either directly after discharge or via a rehabilitation facility. These 243 patients were included in the study. For the follow-up, we first checked with the general practitioner whether the patient was still alive. All patients who were still alive received a letter explaining the study and announcing a telephone call. If they were not alive, this letter was sent to a close relative instead.

Measurement of risk factors. We reviewed medical records to identify risk factors at the time of the index hemorrhage. We retrieved the site (basal ganglia, lobar, cerebellar, or brain stem localization and right or left hemisphere) of the primary intracerebral hemorrhage from MRI or CT reports. We collected information on age, sex, (cardio)vascular history, smoking habits, alcohol consumption, and use of medication before the index hemorrhage. Patients had a history of (cardio)vascular disease if the record reported a myocardial infarction, angina pectoris, coronary or peripheral artery bypass surgery, atrial fibrillation, ischemic stroke, TIA, or intermittent claudication. We categorized smoking status into ever and never and alcohol consumption into 0 to 2 units/day or >2 units/day. We recorded the use of antihypertensive medication, antidiabetic drugs, and anticoagulant medication before the index hemorrhage.

We asked all patients by telephone about the use of anticoagulant drugs in the period after the index hemorrhage. If they reported the use of anticoagulant therapy, we verified the indication and duration of use with the general practitioner.

Recurrence and other vascular events. From February 1998 through January 2000, a research physician (S.E.V.) interviewed all patients or close relatives using a structured questionnaire addressing vascular events in the period after the index hemorrhage. The date of interview was recorded to calculate the duration of follow-up. If patients or relatives reported a vascular event (stroke, myocardial infarction, or major extracranial hemorrhage), we retrieved medical records and radiology reports from the hospital were the patients had been treated. If they had not been hospitalized, we collected all available information from the general practitioner's office. By reviewing these documents, we assessed the day of onset of the event and classified it as follows: 1) stroke, defined as episodes of relevant focal deficits with acute onset, documented by neurologic examination, and lasting for >24 hours (based on MRI or CT findings, we subdivided episodes into hemorrhagic and ischemic strokes, and compared the site of the index hemorrhage with that of recurrent hemorrhages); 2) myocardial infarction, documented as having at least two of the following characteristics—a history of chest discomfort, cardiac enzyme levels more than twice the upper limit of normal, and/or development of Q waves on the standard 12-lead electrocardiogram; 3) major extracranial hemorrhage, defined as severe spontaneous hemorrhages outside the brain leading to death or hospitalization; and 4) sudden death, defined as an unexpected death of presumed or proven cardiac origin occurring within 1 hour after the onset of symptoms or within 12 hours given convincing circumstantial evidence. Follow-up of three patients was incomplete, because they had moved to an unknown destination.

Data analysis. We used the Kaplan–Meier method to estimate the event rates. The follow-up time was calculated from the date of onset of the index hemorrhage until the date of recurrence, vascular event, death or the date of interview. In the analysis of recurrent intracerebral hemorrhages, hemorrhagic events, and ischemic events, we censored patients the moment that they had an unspecified stroke.

We did Cox proportional hazards regression analysis to determine whether risk factors at the time of the index hemorrhage were predictive of recurrent intracerebral hemorrhage or other vascular events. The following pos-

Table 1 *Characteristics of 243 patients at the time of onset of a primary intracerebral hemorrhage*

Characteristic	Patients, %
Female sex	37
Location	
Lobar	55
Basal ganglia	33
Cerebellar/brain stem	12
History of (cardio)vascular disease	38
Smoking, ever	68
Alcohol consumption of >2 units/d	12
Medication use	
Antihypertensive	23
Antidiabetic	4
Oral anticoagulation	24

The mean age ± SD of the patients was 64 ± 13 years.

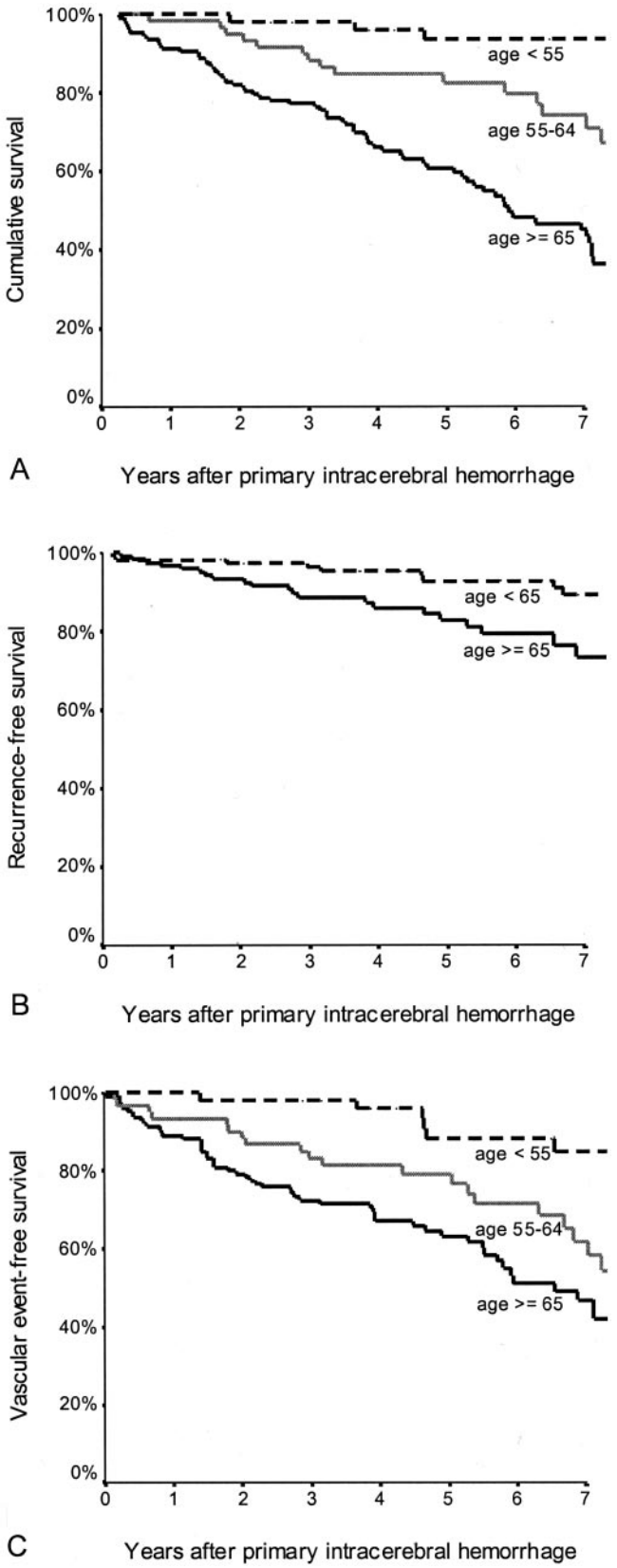

Figure. Kaplan–Meier curves of cumulative survival (A), recurrence-free survival (B), and vascular event–free survival (C) in patients who regained independence after a primary intracerebral hemorrhage; survival was stratified according to the patient's age at the time of onset.

***Table 2** Predictors of a recurrence in survivors of a primary intracerebral hemorrhage*

Finding	No. of patients with recurrence/ total no. of patients	Hazard ratio (95% CI)
Age, y		
<65	9/115	1
≥65	21/128	2.8 (1.3–6.1)
Sex		
Female	8/89	1
Male	22/154	1.7 (0.7–3.8)
Location		
Lobar	18/134	1
Basal ganglia	8/81	0.7 (0.3–1.5)
Cerebellar/brain stem	4/28	1.1 (0.4–3.3)
(Cardio)vascular disease?		
No	21/151	1
Yes	9/92	0.8 (0.4–1.7)
Smoking		
Never	7/72	1
Ever	21/156	1.4 (0.6–3.2)
Alcohol consumption, units/d		
0–2	24/200	1
>2	4/26	1.1 (0.4–3.1)
Antihypertensive drugs?		
No	22/187	1
Yes	8/56	1.5 (0.6–3.3)
Antidiabetic medication?		
No	28/234	1
Yes	2/9	1.8 (0.4–7.7)
Oral anticoagulation?		
No	23/186	1
Yes	7/57	1.1 (0.5–2.6)

sible predictors were examined: age (dichotomized at median), sex, site of the index hemorrhage, history of (cardio)vascular disease, smoking, alcohol consumption, and use of antihypertensive drugs, antidiabetic drugs, and oral anticoagulation. We calculated univariate hazard ratios of these predictors with 95% CI. In addition, we included factors that were significant at the 0.20 level in the final regression model and retained only those with a p value of <0.05 in backward elimination. We used a Cox proportional hazards model with anticoagulant medication as time-varying exposure to analyze the risk of anticoagulant treatment.

Results. Table 1 shows the baseline characteristics of the patients. The site of the hemorrhage recorded in radiology reports was verified on MRI or CT scans for a random sample of 40 patients, which proved to be correct in all patients. The mean follow-up was 5.5 years. The overall case-fatality after 5 years was 24% (95% CI, 18 to 30%), and this depended on age (figure, A).

Table 3 *Predictors of a vascular event in survivors of a primary intracerebral hemorrhage*

Finding	No. of patients with vascular event/total no. of patients	Hazard ratio (95% CI)
Age, y		
<65	30/115	1
≥65	55/128	2.5 (1.6–3.9)
Sex		
Female	24/89	1
Male	61/154	1.6 (1.0–2.6)
Location		
Lobar	47/134	1
Basal ganglia	24/81	0.8 (0.5–1.3)
Cerebellar/brain stem	14/28	1.7 (0.9–3.1)
(Cardio)vascular disease?		
No	47/151	1
Yes	38/92	1.7 (1.1–2.6)
Smoking		
Never	19/72	1
Ever	59/156	1.5 (0.9–2.5)
Alcohol consumption, units/d		
0–2	67/200	1
>2	9/26	0.8 (0.4–1.7)
Antihypertensive drugs?		
No	62/187	1
Yes	23/56	1.5 (0.9–2.5)
Antidiabetic medication?		
No	82/234	1
Yes	3/9	0.9 (0.3–2.7)
Oral anticoagulation?		
No	60/186	1
Yes	25/57	1.8 (1.1–2.9)

Thirty patients (12%) had a recurrent intracerebral hemorrhage during follow-up; in seven, the location was the same as the index hemorrhage. The recurrence rate was 2.1% per year (95% CI, 1.4 to 3.3%), and this rate was higher among old patients (see figure, B). Age of 65 years or older was the only significant predictor of recurrent hemorrhage in the univariate analysis (table 2). Results were similar for patients with and without anticoagulant treatment before the index hemorrhage.

Eighty-five patients (35%) had one or more vascular events; first events were a recurrent intracerebral hemorrhage (n = 28), ischemic stroke (n = 16), subarachnoid hemorrhage (n = 3), unspecified stroke (n = 11), major extracranial hemorrhage (n = 6), myocardial infarction (n = 19), and sudden death (n = 2). The annual rate of ischemic stroke was 1.4% (95% CI, 0.8 to 2.3%), and that of any vascular event was 5.9% (95% CI, 4.5 to 7.7%); these rates were higher among older patients (see figure, C). Table 3 shows the risks of the possible predictors of a vascular event that were revealed by univariate analysis.

Table 4 *Use of oral anticoagulant medication after a primary intracerebral hemorrhage as a predictor of recurrence, hemorrhagic and ischemic events, and vascular death*

Finding	Use of oral anticoagulation: hazard ratio (95% CI)
Recurrent intracerebral hemorrhage*	2.7 (0.9–7.8)
Hemorrhagic vascular event*†	3.0 (1.3–7.2)
Ischemic vascular event*‡	1.0 (0.2–4.1)
Vascular death	1.5 (0.5–4.2)

* Unspecified strokes were censored.
† Hemorrhagic stroke (including recurrent intracerebral hemorrhage) and major extracerebral hemorrhages.
‡ Ischemic stroke, myocardial infarction, and sudden death.

Old age (hazard ratio [HR], 2.3; 95% CI, 1.4 to 3.7) and male sex (HR, 1.8; 95% CI, 1.1 to 3.0) were the only predictors that were retained in the multivariate model.

Fifty-one patients (21%) died of a vascular cause. The rate of vascular death was 3.2% per year (95% CI, 2.2 to 4.5%). Only old age predicted vascular death independently in the multivariate analysis (HR, 3.7; 95% CI, 2.0 to 7.0).

Twenty-two patients received anticoagulant medication after the index hemorrhage for the following indications: prosthetic heart valves (n = 5), atrial fibrillation (n = 4), arterial occlusive disease (n = 10), and pulmonary embolism (n = 3). Anticoagulant medication during follow-up nearly tripled the risk of hemorrhagic events, whereas the risk of ischemic events was not increased (table 4). None of the HR changed significantly in multivariate analysis.

Discussion. Patients who regain independence after a primary intracerebral hemorrhage have a 2.1% annual rate of a recurrence. The rate of occurrence of any vascular event was 5.9% per year, and that of occurrence of vascular death was 3.2%. Old age strongly predicted a recurrence, any vascular event, or vascular death. Men had a twofold higher risk than women of vascular events. Anticoagulant medication after the index hemorrhage tripled the risk of subsequent hemorrhagic events.

Our study had a large number of patients and a long follow-up. It produced reliable rates of recurrent intracerebral hemorrhage, vascular events, and death over a period of at least 5 years. Yet some methodological limitations remain. Our study was hospital-based and did not include patients who (presumably with minor symptoms) were not admitted to the hospital. Therefore, our results cannot be used for estimation of recurrence rates in general. A population-based study is hardly feasible, because about 6 million observation-years are needed to obtain the same number of index patients. One population-based study of 36 patients estimated the long-term risk of recurrent intracerebral hemorrhage, but it included all patients who survived >2 days after the index hemorrhage.[8] Another limitation of our study was the retrospective retrieval of information on prognostic factors and occurrence of events. A prospective design, although better, would have taken many years to collect an adequate num-

ber of events. Because we examined only those prognostic factors that were reliably registered in medical records,[9] or could be verified from prescribed medication, it is unlikely that this retrospective design introduced a major bias. The use of antihypertensive drugs as a proxy of hypertension may have led to both underdiagnosis and overdiagnosis of hypertensive patients, which may have distorted the true association. Furthermore, we included only outcome events that were confirmed by ancillary investigation and reliably verified. Because minor events were not included and patients might underreport events, our event rates probably are underestimations of true rates. Finally, we could not validate the strength of the prognosticators within our sample, because numbers were too small. Proper validation will require an external data set.

Previous studies reported various proportions of patients with a recurrent intracerebral hemorrhage ranging from 5% to 24%,[1,2,5-7,10] but the inclusion criteria differed strongly. Moreover, the number of recurrences depends on the duration of follow-up, which strongly varied between studies. Our annual recurrence rate of 2.1% agrees with findings of two other studies and with those of a systematic review and is four times higher than the incidence of a first intracerebral hemorrhage observed among a similarly aged population.[3,4,11,12] A study of lobar hemorrhages only reported an annual recurrence rate of 14.3%, but it included patients with a previous hemorrhage before the index hemorrhage.[13]

The rates of vascular events and death were similar to those observed for patients who had TIA or minor ischemic stroke.[14] Our annual rate of ischemic stroke is in line with that of an Italian study.[1] Another study found twice our rate, but it included TIA.[4]

Old age was the only baseline risk factor in our study that strongly predicted recurrent intracerebral hemorrhage. One study found the opposite, but this effect disappeared in the multivariate analysis.[2] Other studies did not find a relationship with age.[1,3,4] The lack of association with some risk factors (e.g., antidiabetic medication) might be due to the small number of patients and the fact that we counted recurrences after discharge only. Other studies included hemorrhages that occurred when patients were still in the hospital, when hematoma-related factors may play a major role in prediction.[15] The site of the index hemorrhage was not predictive in our study, contrary to findings of six previous studies: four reported an increased risk of a recurrence when the index hemorrhage was lobar,[1,2,4,16] and two reported an increased risk after a hemorrhage in the basal ganglia.[7,10] Such conflicting results might be explained by differences in the various etiologies of primary intracerebral hemorrhage. Unfortunately, numbers were too small to allow analyses according to etiology.

Anticoagulant medication after the index hemorrhage tripled the risk of hemorrhagic events. However, it did not change the risk of ischemic events. These observations accord with the anticipated actions of anticoagulant drugs.

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References

1. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke 1995;26:1189–1192.
2. Neau JP, Ingrand P, Couderq C, et al. Recurrent intracerebral hemorrhage. Neurology 1997;49:106–113.
3. Arakawa S, Saku Y, Ibayashi S, Nagao T, Fujishima M. Blood pressure control and recurrence of hypertensive brain hemorrhage. Stroke 1998;29:1806–1809.
4. Hill MD, Silver FL, Austin PC, Tu JV. Rate of stroke recurrence in patients with primary intracerebral hemorrhage. Stroke 2000;31:123–127.
5. Chen ST, Chiang CY, Hsu CY, Lee TH, Tang LM. Recurrent hypertensive intracerebral hemorrhage. Acta Neurol Scand 1995;91:128–132.
6. Maruishi M, Shima T, Okada Y, Nishida M, Yamane K, Okita S. Clinical findings in patients with recurrent intracerebral hemorrhage. Surg Neurol 1995;44:444–449.
7. González-Duarte A, Cantú C, Rúiz-Sandoval JL, Barinagarrementeria F. Recurrent primary cerebral hemorrhage: frequency, mechanisms, and prognosis. Stroke 1998;29:1802–1805.
8. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke 1998;29:2491–2500.
9. Brueren BRG, Rinkel GJE, Algra A, Vermeulen M, van Gijn J. Registration of risk factors for stroke in hospital records. Cerebrovasc Dis 1995;5:366–368.
10. Bae HG, Jeong DS, Doh JW, Lee KS, Yun IG, Byun BJ. Recurrence of bleeding in patients with hypertensive intracerebral hemorrhage. Cerebrovasc Dis 1999;9:102–108.
11. Bailey RD, Hart RG, Benavente O, Pearce LA. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. Neurology 2001;56:773–777.
12. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project—1981–86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 1990; 53:16–22.
13. O'Donnell HC, Rosand J, Knudsen KA, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000;342:240–245.
14. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. N Engl J Med 1991;325:1261–1266.
15. Franke CL, van Swieten JC, Algra A, van Gijn J. Prognostic factors in patients with intracerebral haematoma. J Neurol Neurosurg Psychiatry 1992;55:653–657.
16. Beldman TFJ, Rinkel GJE, Algra A. Prediction of long-term outcome after primary intracerebral haemorrhage: the importance of the site of the lesion. Cerebrovasc Dis 1997;7:85–88.