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# U-shaped relationship between mortality and admission blood pressure in patients with acute stroke

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**Abstract.** Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M (University of Athens, 'Alexandra' Hospital; and University of Athens, 'Eginition' Hospital; Athens, Greece). U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004; **255:** 257–265.

**Objective.** To evaluate the relationship between systolic blood pressure (SBP) or diastolic blood pressure (DBP) on admission and early or late mortality in patients with acute stroke.

**Design.** Prospective study of hospitalized first-ever stroke patients over 8 years.

**Setting.** Stroke unit and medical wards in a University hospital.

**Subjects.** A total of 1121 patients admitted within 24 h from stroke onset and followed up for 12 months.

**Main outcome measures.** Mortality at 1 and 12 months after stroke in relation to admission SBP and DBP.

**Results.** Early and late mortality in patients with acute ischaemic or haemorrhagic stroke in relation to admission SBP and DBP followed a 'U-curve pattern'. After adjusting for known outcome predictors, the relative risk of 1-month and 1-year mortality associated with a 10-mmHg SBP increase above 130 mmHg (U-point of the curve) increased by 10.2% (95% CI: 4.2–16.6%) and 7.2% (95% CI: 2.2–12.3%), respectively. For every 10 mmHg SBP decrease, below the U-point, the relative risk of 1-month and 1-year mortality rose by 28.2% (95% CI: 8.6–51.3%) and 17.5% (95% CI: 3.1–34.0%), respectively. Low admission SBP-values were associated with heart failure ($P < 0.001$) and coronary artery disease ($P = 0.006$), whilst high values were associated with history of hypertension ($P < 0.001$) and lacunar stroke ($P < 0.001$). Death due to cerebral oedema was significantly ($P = 0.005$) more frequent in patients with high admission SBP-values, whereas death due to cardiovascular disease was more frequent ($P = 0.004$) in patients with low admission SBP-values.

**Conclusion.** Acute ischaemic or haemorrhagic stroke patients with high and low admission BP-values have a higher early and late mortality. Coincidence of heart disease is associated with low initial BP-values. Death due to neurological damage from brain oedema is associated with high initial BP-values.

**Keywords:** acute stroke, blood pressure, intra cerebral haemorrhage, ischaemic stroke, mortality.

## Introduction

Blood pressure (BP) is initially elevated in patients with acute stroke and usually declines spontaneously within the first few days after admission [1, 2]. It is still unknown whether reactive post-stroke hypertension represents a pathophysiological response to ischaemia in order to maintain collateral blood flow to the ischaemic penumbra or whether it is a sign of the severity of stroke [3–6]. Data on the prognostic significance of BP levels following acute stroke are conflicting. Observational studies have suggested that high initial BP is associated with increased stroke mortality [7–10], impairment of

functional outcome [10, 11] and stroke recurrence [10, 12], whilst others failed to support these findings [13–15]. Some studies also indicated that low admission BP correlates with poor prognosis [10, 12]. Methodological differences in the design of studies assessing the prognostic significance of BP after acute stroke may explain some of the conflicting evidence. Some reports studied patients with intracerebral haemorrhage (ICH) [8, 13], whilst others analysed data of highly selected patients (e.g. only those admitted to a stroke unit or participating in a clinical trial) [6, 10, 11]. Certain studies either continued or started antihypertensive medication after admission [8], whilst others examined patients admitted to the hospital beyond 48 h after symptom onset, when the acute phase BP changes had already started to resolve [6, 7].

The aim of the present study is the evaluation of the relationship between systolic blood pressure (SBP) or diastolic blood pressure (DBP) on admission and early (at 1 month) or late (at 12 months) mortality in acute stroke patients. We examined the effects of the different stroke subtypes on the BP-stroke mortality curves, as well as the relationship between BP-values and cause of death. We finally investigated stroke risk factors that possibly influence admission BP-values.

## Subjects and methods

A consecutive series of 1428 first-ever stroke patients were admitted to our hospital between July 1992 and November 2000 and were all included in 'The Athens Stroke Registry', a prospective observational stroke data bank [16]. Our hospital is a university institution providing tertiary care services to the urban population of the city of Athens. A total of 1154 (80.8%) patients presented in the emergency room of our hospital in <24 h after symptom onset and were hospitalized either in the acute stroke unit (62%) or in the medical wards (38%) of our department. After admission an internist specialized in stroke and a neurologist examined all patients. The Glasgow Coma Scale and the Scandinavian Stroke Scale [17] were used for the estimation of the neurological status on admission. Patients with transient ischaemic attack, age below 18, recurrent stroke and subarachnoid haemorrhage were excluded from our study. On admission all patients underwent an initial computed tomography (CT) scan of the brain and 65% had a second CT or MRI scan during hospitalization. Stroke cases were classified based on pathogenic mechanisms as large vessel atherosclerotic (LVA) stroke, cardioembolic (CE) stroke, lacunar (LAC) stroke, infarct of undetermined cause (IUC) and intracerebral haemorrhage (ICH) [16]. Risk factors such as history of hypertension, atrial fibrillation, coronary artery disease, heart failure, cigarette smoking, diabetes mellitus and hypercholesterolaemia were documented. Hypercholesterolaemia was defined if a cholesterol concentration >6.5 mmol $L^{-1}$ was detected during hospitalization, or if the patient was already on lipid lowering medication before the cerebrovascular event.

Casual supine BP was measured by an internist at hospital admission, in both arms at three occasions every 15 min using a standard mercury sphygmomanometer. Because of the fact that BP may be higher or lower in the paretic arm of stroke patients [18] and in order to increase the accuracy of our BP readings we excluded patients with a BP difference >10 mmHg between the two arms. This was the case in six patients, who were therefore excluded from further evaluation. In addition 27 cases were excluded because of missing admission BP-values. Patients were diagnosed as having a history of hypertension, if they had evidence of SBP above 160 mmHg or DBP above 95 mmHg at any time before or 4 weeks after stroke onset or if they had received any antihypertensive medication, according to the WHO hypertension criteria, which were actual at the time when the study was conducted [12, 16, 19]. Patients were followed up at 1 month and at 12 months after stroke onset. Causes of death were divided into the following subgroups: (i) death due to neurological damage (e.g. brain oedema, mass effect, transtentorial herniation); (ii) death due to infections (pulmonary infections, urinary infections and septic shock); (iii) death due to cardiovascular disease (myocardial infarction, sudden death due to cardiac arrhythmia, acute pulmonary oedema or heart failure, ruptured aortic aneurysm, recurrent stroke); and (iv) death due to other or unknown cause (e.g. renal failure, cancer).

The stroke mortality rate was calculated and then was statistically analysed in relation to admission SBP and DBP and stroke subtypes. Kaplan–Meier curves of groups stratified by admission SBP and

DBP are presented and survival was compared between the subgroups of SBP and DBP using the log-rank method. Statistical comparisons for continuous data were made by use of the independent-sample *t*-test. For binary outcomes, the chi-square test or in cases of expected low frequencies Fischer's exact test was used. Multiple variable linear regression analysis models were constructed to explore the relationship between admission SBP and different stroke risk factors. Cox proportional-hazard models were used to evaluate the relationship between SBP and 1-month or 1-year mortality, after adjusting for known prognostic factors. A two-tailed probability value of $<0.05$ was considered significant. The Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA; version 10.0 for Windows) was used for statistical analyses.

## Results

### *Baseline characteristics*

The patient population selected for the purpose of the present study ($n = 1121$) consisted of 639 male and 482 female subjects (mean age 69.4 ± 9.0 and 72.3 ± 10.1, respectively). The detailed demographic and clinical characteristics of the entire collective are presented in Table 1. The median delay from symptom onset to hospital admission was almost 2 h. Ischaemic stroke was diagnosed in 930 patients (83.0%), whilst 191 patients (17.0%) presented with stroke symptoms due to ICH. The distribution of ischaemic stroke subtypes was as follows: LVA 14.2%, CE 34.3%, LAC 16.0% and IUC 18.5%. Histories of hypertension (65.6%) and atrial fibrillation (33.7%) were the most common stroke risk factors. Hypertension had a significantly ($P = 0.004$) higher prevalence amongst patients suffering from ICH (75.9%) than in patients suffering from ischaemic stroke (63.5%). A decreased level of consciousness on admission (Glasgow Coma Scale <14; Table 1) was observed in 457 patients (40.8%). A severe neurological deficit on admission (Scandinavian Stroke Scale <15; Table 1) was present in 392 patients (35%). A recurrent cerebrovascular event at 1- and 12-month follow-up was noted in 37 (3.2%) and 91 patients (7.8%), respectively. The estimated case fatality rate at 1 month and 1 year was 20.7% (233 deaths) and 32.9% (369 deaths), respectively.

**Table 1** Demographics, risk factors, clinical and radiographic characteristics of 1121 first-ever acute stroke patients

| Characteristics | *n* (%) |
|---|---|
| Demographics/risk factors | |
| Mean age (SD) (years) | 70.6 (11.6) |
| Sex (male) | 639 (57.1) |
| Median elapsed time from stroke onset (Q1, Q3) (h) | 2.0 (1.0, 5.3) |
| History of hypertension | 736 (65.6) |
| Diabetes mellitus | 276 (24.6) |
| Hypercholesterolaemia | 259 (23.1) |
| Cigarette smoking | 300 (29.4) |
| Coronary artery disease | 226 (20.2) |
| Atrial fibrillation | 378 (33.7) |
| Heart failure | 88 (7.9) |
| Stroke subtype | |
| Cerebral infarction | 930 (83.0) |
| Large vessel atherosclerosis | 159 (14.2) |
| Cardioembolism | 385 (34.3) |
| Lacunes | 179 (16.0) |
| Infarcts of undetermined aetiology | 208 (18.5) |
| Intracerebral haemorrhage | 191 (17.0) |
| Level of consciousness (Glasgow Coma Scale score) | |
| 3 | 59 (5.3) |
| 4–7 | 117 (10.4) |
| 8–13 | 281 (25.1) |
| 14–15 | 664 (59.2) |
| Neurological deficit (Scandinavian Stroke Scale score) | |
| 2–14 | 392 (35.0) |
| 15–29 | 194 (17.3) |
| 30–44 | 169 (15.1) |
| 45–58 | 366 (32.6) |
| Imaging findings | |
| Haemorrhagic infarct transformation | 122 (13.1) |
| Brain oedema | 298 (26.6) |
| Transtentorial herniation | 99 (8.8) |

Glasgow Coma Scale score: 3 = comatose patient, 14–15 = fully alert patient. Scandinavian Stroke Scale score: 2–14 = severe neurological deficit, 45–58 = mild neurological deficit.

### *Blood pressure and stroke mortality rate associations*

The distribution of stroke mortality rate at 1 month after stroke relative to the documented SBP-values on admission shows a typical U-shaped curve with the nadir or U-point in the range of 121–140 mmHg (Fig. 1a; Table 2). Patients with admission SBP of 121–140 mmHg had the lowest stroke mortality rate (14.7%) when compared with those with admission SBP of <101 mmHg (mortality rate 40%; $P < 0.001$ by log-rank test) or those with admission SBP-values >220 mmHg (mortality rate 46.7%; $P < 0.001$). Distribution of stroke mortality rate at 12 months after the initial event according to

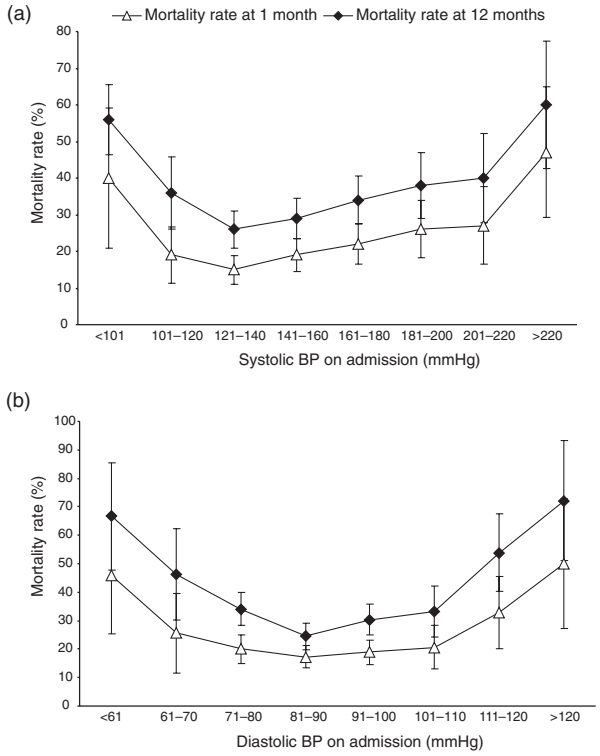


**Fig. 1** Line graphs showing the relationship between blood pressure and overall stroke mortality rate at 1 and 12 months: (a) systolic blood pressure and (b) diastolic blood pressure, on admission. Triangles and squares indicate early and late stroke mortality rate, respectively, within groups A and B; 95% confidence intervals are indicated by T-bars.

the admission SBP-values demonstrated again the U-curve phenomenon (Fig. 1a; Table 2). Kaplan–Meier curves of groups stratified by admission SBP showed that patients with admission SBP of 121–140 mmHg had the best prognosis compared with those with admission SBP < 101 mmHg and with admission SBP>220 mmHg (Fig. 2a; log-rank test, $P < 0.001$).

Early stroke mortality rate also exhibited a U-shaped relationship to admission DBP (Fig. 1b; Table 2). The nadir or U-point of the curve was found in the group of patients with admission DBP between 81 and 90 mmHg (17.2% mortality rate). The patient group with admission DBP <61 mmHg (45.8% mortality rate) and the patient group with admission DBP >120 mmHg (50% mortality rate) had a significantly higher mortality rate ($P < 0.001$) than patients with BP ranging around the U-point of the curve. The distribution of late stroke mortality relative to the observed DBP-values

**Table 2** Relationship between admission systolic blood pressure (SBP) or diastolic blood pressure (DBP) and mortality in overall stroke patients

| | Patients ($n = 1121$) | % Mortality rate at 1 month (95% CI) | % Mortality rate at 12 months (95% CI) |
|---|---|---|---|
| SBP (mmHg) | | | |
| <101 | 25 | 40.0 (20.8–59.2)[a] | 56.0 (36.4–75.6)[a] |
| 101–120 | 92 | 18.5 (10.7–26.3) | 35.9 (26.1–45.7) |
| 121–140 | 292 | 14.7 (10.8–18.6) | 26.4 (21.3–31.5) |
| 141–160 | 282 | 19.2 (14.7–23.7) | 28.7 (23.2–34.2) |
| 161–180 | 212 | 22.2 (16.7–27.7) | 34.4 (27.9–40.9) |
| 181–200 | 121 | 25.6 (17.8–33.4) | 38.0 (37.0–55.0) |
| 201–220 | 67 | 26.9 (16.3–37.5) | 40.3 (28.1–52.5) |
| >220 | 30 | 46.7 (28.9–64.5)[a] | 60.0 (42.6–77.4)[a] |
| DBP (mmHg) | | | |
| <61 | 24 | 45.8 (25.4–66.2)[b] | 66.7 (47.9–85.5)[b] |
| 61–70 | 39 | 25.6 (11.7–39.5) | 46.2 (30.1–62.3) |
| 71–80 | 255 | 20.0 (15.1–24.9) | 34.1 (28.3–39.9) |
| 81–90 | 326 | 17.2 (13.2–21.1) | 24.5 (20.2–29.2) |
| 91–100 | 296 | 18.9 (14.6–23.2) | 30.4 (24.9–35.9) |
| 101–110 | 111 | 20.7 (13.1–28.3) | 33.3 (24.3–42.3) |
| 111–120 | 52 | 32.7 (20.0–45.4) | 53.9 (40.2–67.6) |
| >120 | 18 | 50.0 (27.1–72.9)[b] | 72.2 (51.2–93.2)[b] |

CI, confidence interval. [a]$P < 0.001$ versus SBP 121–140 on admission by log-rank test. [b]$P < 0.001$ versus DBP 81–90 mmHg on admission by log-rank test.

also manifested the U-curve phenomenon (the patient group with admission DBP ranging between 81 and 90 mmHg and a mortality rate of 24.5% was again the U-point of the curve; Fig. 1b; Table 2). As shown by the Kaplan–Meier estimates (Fig. 2b) this group of patients fared better than the subject groups with admission DBP <61 mmHg and DBP >120 mmHg (log-rank test, $P < 0.001$).

The U-curve phenomenon was present amongst patients with both major stroke subtypes (ischaemic and haemorrhagic stroke). Early (16.6%) and late (29.0%) mortality rate in patients with acute ischaemic stroke showed the characteristic U-shaped distribution relative to the registered admission BP-values (Table 3). However, when examining the different ischaemic stroke subtypes separately, a U-shaped pattern was demonstrated only in patients with CE stroke. There was no U-shaped relationship between mortality and admission BP in patients with LVA, LAC and IUC. Distribution of early (40.8%) and late (51.8%) mortality rate in patients with ICH according to the measured SBP- and DBP-values on admission also demonstrated the U-curve phenomenon (Table 4). The U-point of the curve relating admission SBP and DBP to early and late

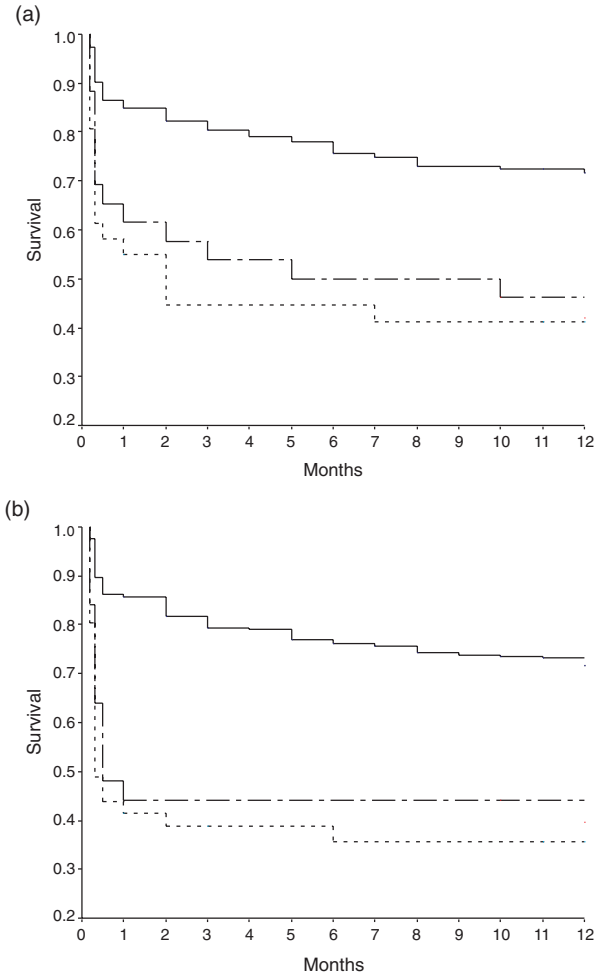


**Fig. 2** Kaplan–Meier curves of groups stratified by admission (a) systolic blood pressure (SBP)-values in overall stroke patients: – – – –, SBP >220 mmHg; –·–·–·–, SBP <101 mmHg; ——, SBP 121–140 mmHg; and (b) diastolic blood pressure (DBP)-values in overall stroke patients: – – – –, DBP >120 mmHg; –·–·–·–, DBP < 61 mmHg; ——, DBP 81–90 mmHg.

mortality in patients with ICH was in the patient group with admission SBP ranging between 141 and 160 mmHg. When considering the admission DBP-values the nadir of the curve was found in the group between 101 and 110 mmHg. Both U-points were at higher BP-values than those already described for ischaemic stroke. The U-curve phenomenon was also present both amongst hypertensive and nonhypertensive patients. However, the optimal range of admission SBP-values for early and late survival was higher in subjects with history of hypertension (141–160 mmHg) than in nonhypertensives (121–140 mmHg).

**Table 3** Relationship between admission systolic blood pressure (SBP) or diastolic blood pressure (DBP) and mortality in patients with ischaemic stroke

| | Patients ($n = 930$) | % Mortality rate at 1 month (95% CI) | % Mortality rate at 12 months (95% CI) |
|---|---|---|---|
| SBP (mmHg) | | | |
| <100 | 23 | 35.0 (15.6–54.4)[a] | 52.2 (31.4–73.0)[b] |
| 101–120 | 87 | 13.8 (06.5–21.1) | 32.2 (22.2–42.2) |
| 121–140 | 268 | 12.7 (08.8–16.6) | 24.6 (14.2–35.0) |
| 141–160 | 248 | 17.3 (12.6–22,0) | 27.0 (21.3–32.7) |
| 161–180 | 162 | 17.9 (12.1–23.7) | 30.3 (23.0–37.6) |
| 181–200 | 82 | 19.5 (08.9–27.9) | 31.7 (21.3–42.1) |
| 201–220 | 43 | 18.6 (08.0–29.2) | 32.6 (17.7–47.5) |
| >220 | 17 | 29.4 (07.8–51.0)[b] | 47.0 (23.3–70.7)[b] |
| DBP (mmHg) | | | |
| <60 | 18 | 39.0 (16.6–61.3)[c] | 61.1 (38.8–83.4)[c] |
| 61–70 | 32 | 21.9 (07.6–36.2) | 40.6 (23.4–57.8) |
| 71–80 | 213 | 16.0 (11.1–20.9) | 30.0 (23.9–36.1) |
| 81–90 | 278 | 13.3 (09.4–17.2) | 20.9 (16.0–25.8) |
| 91–100 | 249 | 15.7 (13.1–18.3) | 27.7 (22.4–33.0) |
| 101–110 | 94 | 19.2 (11.4–27.0) | 31.9 (22.3–41.5) |
| 111–120 | 35 | 25.7 (11.4–40.0) | 51.4 (34.3–68.5) |
| >120 | 11 | 36.0 (07.6–64.4)[d] | 63.6 (34.4–92.8)[d] |

CI, confidence interval. [a]$P < 0.01$ versus SBP 121–140 mmHg on admission by log-rank test. [b]$P < 0.05$ versus SBP 121–140 - mmHg on admission by log-rank test. [c]$P < 0.001$ versus DBP 81–90 mmHg on admission by log-rank test. [d]$P < 0.05$ versus DBP 81–90 mmHg on admission by log-rank test.

*Data from secondary analyses*

Cox proportional-hazard models were used to estimate hazard ratios for 1-month and 1-year mortality associated with admission SBP-values, with adjustment for known prognostic factors (age, sex, hypertension, diabetes mellitus, hypercholesterolaemia, atrial fibrillation, heart failure, coronary artery disease and neurological impairment on admission documented by the Scandinavian Stroke Scale score). The lowest mortality rate occurred in patients with admission SBP between 121 and 140 mmHg, with the nadir or U-point around 130 mmHg. Therefore, we subsequently used this value as a reference point. The hazard ratios for 1-month and 1-year mortality associated with a 10 mmHg increment in SBP above 130 mmHg were 1.102 (95% CI: 1.042–1.166) and 1.072 (95% CI: 1.022–1.123), respectively (Table 5). For every 10 mmHg SBP decrease below the U-point the relative risk of 1-month and 1-year mortality rose by 28.2% (95% CI: 8.6–51.3%) and 17.5% (95% CI: 3.1–34.0%), respectively (Table 5).

**Table 4** Relationship between admission systolic blood pressure (SBP) or diastolic blood pressure (DBP) and mortality in patients with intracerebral haemorrhage

| | Patients ($n = 191$) | % Mortality rate at 1 month (95% CI) | % Mortality rate at 12 months (95% CI) |
|---|---|---|---|
| SBP (mmHg) | | | |
| <120 | 7 | 85.7 (NC)[a] | 100 (NC)[a] |
| 121–140 | 24 | 37.5 (17.9–57.1) | 45.8 (25.4–66.2) |
| 141–160 | 34 | 32.3 (16.6–48.0) | 41.2 (24.3–58.1) |
| 161–180 | 50 | 36.0 (22.3–49.7) | 48.0 (33.7–62.3) |
| 181–200 | 39 | 38.5 (22.8–54.2) | 51.3 (35.0–67.6) |
| 201–220 | 24 | 41.7 (22.1–61.3) | 54.2 (34.0–74.4) |
| >220 | 13 | 69.2 (44.2–94.2)[b] | 76.9 (54.2–99.6)[b] |
| DBP (mmHg) | | | |
| <61 | 6 | 66.7 (NC)[c] | 83.3 (NC)[c] |
| 61–70 | 7 | 42.9 (NC) | 71.4 (NC) |
| 71–80 | 42 | 40.5 (25.6–55.4) | 54.8 (39.5–70.1) |
| 81–90 | 48 | 39.6 (25.7–53.5) | 45.8 (31.5–60.1) |
| 91–100 | 47 | 36.2 (22.1–50.3) | 44.7 (29.6–59.8) |
| 101–110 | 17 | 29.4 (07.3–51.5) | 41.2 (17.1–65.3) |
| 111–120 | 17 | 47.1 (33.0–61.2) | 58.8 (35.5–82.1) |
| >120 | 7 | 71.4 (NC)[c] | 85.7 (NC)[c] |

CI, confidence interval; NC, not calculated because of <8 cases. [a]$P < 0.001$ versus SBP 141–160 mmHg on admission by log-rank test. [b]$P < 0.05$ versus SBP 141–160 mmHg on admission by log-rank test. [c]$P < 0.05$ versus DBP 101–110 mmHg on admission by log-rank test.

**Table 5** Relationship between early or late stroke mortality and admission systolic blood pressure (SBP) values

| Outcome | SBP (mmHg) | Hazard ratios (95% CI) | *P*-value |
|---|---|---|---|
| 1-month mortality | ≤130 | 1.282 (1.086–1.513) | 0.003 |
| | >130 | 1.102 (1.042–1.166) | 0.001 |
| 1-year mortality | ≤130 | 1.175 (1.031–1.340) | 0.016 |
| | >130 | 1.072 (1.022–1.123) | 0.004 |

CI, confidence interval. Hazards ratios are presented in terms of a 10-mmHg difference relative to a reference value of 130 mmHg. The relationship between blood pressure and mortality was adjusted for the following known prognostic factors: age, sex, hypertension, diabetes mellitus, hypercholesterolaemia, atrial fibrillation, heart failure, coronary artery disease and neurological impairment on admission documented by the Scandinavian Stroke Scale score.

We examined mortality and cause of death further in patients with admission SBP beneath and above the reference value of 130 mmHg. From 238 patients with admission SBP-values lower or equal to the U-point of the curve (130 mmHg), 47 and 86 died within 1 and 12 months, respectively. The most frequent cause of death in this patient subgroup was cardiovascular disease (Table 6). In patients with admission SBP-values higher than the U-point of the curve (883 cases) the main cause of death within 1 month (50.5%) and 12 months (37.8%) was severe brain damage (Table 6). By using chi-square techniques we then compared the different causes of death between patients with admission SBP-values lower and higher than the SBP U-point. Death due to neurological disease was significantly more frequent ($P = 0.005$) amongst patients with admission SBP >130 mmHg. In contrast, cardiovascular disease was significantly more common ($P = 0.004$) amongst patients with admission SBP <130 mmHg (Table 6).

**Table 6** Relationship between admission systolic blood pressure (SBP) values and causes of death at 1 and 12 months after acute stroke

| Causes of death | SBP ≤130 mmHg ($n = 247$) | SBP >130 mmHg ($n = 883$) | *P*-value |
|---|---|---|---|
| 1 month | | | |
| Neurological damage | 13 (27.7) | 94 (50.5) | 0.005 |
| Cardiovascular disease | 14 (29.7) | 23 (12.4) | 0.004 |
| Infections | 13 (27.7) | 52 (28.0) | 0.968 |
| Other or unknown | 7 (14.9) | 17 (09.1) | 0.246 |
| 12 months | | | |
| Neurological damage | 14 (16.3) | 107 (37.8) | 0.001 |
| Cardiovascular disease | 27 (31.4) | 59 (20.8) | 0.043 |
| Infections | 22 (25.6) | 75 (26.5) | 0.865 |
| Other or unknown | 23 (26.7) | 42 (14.9) | 0.011 |

Values are given as *n* (%).

Multiple variable linear regression models adjusted for age, sex and stroke subtype were used in order to examine the influence of vascular risk factors on the initial SBP-values in acute ischaemic stroke patients. It was thus demonstrated that in patients with ischaemic stroke low admission SBP-values were associated with heart failure ($P < 0.001$) and coronary artery disease ($P = 0.006$; Table 7). Conversely high admission SBP-values were associated with lacunar stroke ($P < 0.001$) and a history of hypertension ($P < 0.001$; Table 7).

## Discussion

The present study demonstrates that the relationship of stroke mortality rate at 1 month after stroke onset to the SBP- and DBP-values on admission follows a U-shaped curve. Late stroke mortality rate (at 12 months) also exhibits a U-shaped

**Table 7** Factors associated with admission systolic blood pressure (SBP) values in patients with acute ischaemic stroke

| Risk factors | Linear regression coefficients | 95% CI | *P*-value |
|---|---|---|---|
| Heart failure | −13.47 | −19.65 to −7.29 | <0.001 |
| Coronary artery disease | −0.06 | −0.11 to −0.02 | 0.006 |
| History of hypertension | 18.93 | 15.19 to 22.67 | <0.001 |
| Lacunar stroke | 10.09 | 5.65 to 14.53 | <0.001 |

CI, confidence interval. Risk factors were adjusted for age, sex and stroke subtype using multiple variable linear regression models.

relationship with SBP and DBP upon admission. The nadir or U-point of the curve occurred in the range of 121–140 and 81–90 mmHg for SBP- and DBP-values, respectively. Although our aim was to determine the optimal range of BP control, we did not select the DBP or SBP range by quartile or quintile methods. We preferred to use an arbitrary ranging of SBP and DBP, which may be more appropriate from a clinical point of view [12]. Regarding stroke subtypes the U-curve phenomenon was clearly observed in both major stroke groups (ischaemic stroke and ICH). However, the U-point was at higher BP-values in patients with ICH than in ischaemic stroke patients. We came to the same conclusions even after redefining BP groups with 10- or 40-mmHg intervals.

Our study demonstrates that in acute stroke patients arriving at the hospital within the first 24 h after stroke onset, both admission SBP- and DBP-values have a nonlinear relation to mortality rate at 1 and 12 months after the event. These results are in agreement with findings of the 'International Stroke Trial' (IST), which showed that low and high admission SBP-values were related to higher stroke mortality in ischaemic stroke patients [10].

Methodological issues in the analyses of data may influence the relationship between BP on admission and acute stroke outcome. The choice of the outcome event may be such an issue. Conflicting results may arise from researchers using death and dependency as one variable [8, 10, 11, 15, 20]. Considering dependency with a Rankin score of 3 and death as two completely different outcomes we strictly selected only death as the outcome variable for our study. The dichotomization of the measured BP is another important methodological issue. Admission SBP in acute stroke as an independent factor is a continuous variable. SBP-values between 120 and 180 mmHg are more common than values >200 or <100 mmHg. A similar pattern also exists for DBP. Dichotomization of these variables may result in considerable bias [8, 9]. Furthermore, several outcome studies in acute stroke patients using admission BP as a continuous variable in single variable and multiple variable analyses failed to identify a linear relationship between BP and mortality [11, 14, 15]. An almost U-shaped relation of 24-h SBP to late mortality was found in a recent study, where 24-h BP recordings were used [9]. Therefore, we preferred to avoid stratification of BP-values in our analyses. In addition, the inclusion criteria can also cause bias and lead to conflicting findings. Some studies have an inadequate number of cases, whilst others exclude patients with severe stroke or a long time interval between symptom onset and BP measurement. Others studied highly selected cases, which were included in randomized trials [8, 10, 11]. Finally, most studies have not reported basic clinical data, major risk factors and other concomitant vascular disease (e.g. heart failure and coronary artery disease), which are important variables that may influence stroke outcome. We therefore studied an unselected sample of acute stroke patients and tried to describe accurately their vascular risk profile and the major clinical features.

Our results clearly indicate that both high and low admission BP-values are associated with a poor outcome in stroke patients. Previous studies have addressed the association of high admission BP with stroke mortality in patients with very high admission BP-values or in those with impaired consciousness [7, 14], whilst some others have found an association of high admission BP-values with poor functional outcome [10, 11, 20]. We showed that for every 10-mmHg rise in admission SBP above the 130-mmHg-reference point both early and late mortality increase by 10.2 and 7.2%, respectively. The mechanisms underlying this relationship are poorly defined but it can presumably be explained by the hypothesis that hypertension promotes early stroke recurrence, symptomatic haemorrhagic transformation and formation of cerebral oedema [10, 12, 21, 22]. According to the IST study, which included nearly 18 000 ischaemic stroke patients, high BP-values were associated with early recurrent stroke and fatal brain oedema [10]. The most

common causes of death in our patients with admission BP-values >130 mmHg was neurological damage due to extensive brain oedema as shown on repeated brain CT scans. It remains unclear whether oedema formation after ischaemic or haemorrhagic stroke leads to higher BP-values or BP rises in order to maintain sufficient cerebral perfusion pressure [23, 24].

Low admission BP-values were also associated with high mortality rates. Early and late mortality increased by 28.2 and 17.5%, respectively, for every 10-mmHg decrease of admission SBP below the U-point of 130 mmHg. Patients with heart failure and ischaemic myocardial disease are usually on antihypertensive medication and have, in comparison with other patients, a significantly lower cardiac output. It has been supported that low BP and low cardiac output result in cerebral hypoperfusion, which may cause larger ischaemic infarcts [25]. In the IST low admission SBP-values were associated with a severe clinical stroke (total anterior circulation syndrome) [10]. Moreover, the most common cause of early and late death amongst our study population with low SBP-values on admission was cardiovascular disease, presumably reflecting the high prevalence of this ominous comorbidity. This association between low admission SBP and cardiac disease (heart failure and coronary artery disease) has been also described in other studies [10, 26]. In addition, stroke recurrence rate in patients with acute ischaemic stroke appears to have a J-curve association with SBP [10] or DBP [12]. The association between low admission BP-values and high early and late mortality may be attributed not only to the hypoperfusion of brain tissue during the acute phase of stroke but also to the concomitant severe cardiac disease.

We also investigated the relation of admission BP to each stroke subtype, separately. The U-shaped phenomenon was present amongst patients with ICH and CE infarction. These two stroke subtypes, compared with the others, had the highest mortality rates. In patients with LAC (one death at 1 month and 12 deaths at 12 months) and LVA (13 deaths at 1 month and 29 deaths at 12 months) the U-curve relationship was not present probably because of the low number of deaths within these stroke subgroups. Our data allow no further conclusions on this issue. The U-shaped pattern observed amongst CE-stroke patients demonstrates the relevance of the concomitant severe cardiac diseases, which in combination with low admission BP-values may lead to fatal complications or cerebral hypoperfusion, as already discussed. To our knowledge such a U-shaped distribution of mortality relative to SBP- and DBP-values in patients with ICH has not been previously described. Significantly higher mortality rates were observed in patients with SBP-values >220 mmHg or <120 mmHg when compared with the optimal SBP-range of 141–160 mmHg. A higher mortality and morbidity in patients with marked elevation of the mean BP (>145 mmHg) compared with those with lesser degrees of BP elevation was reported in a study which used a BP cut-off point [8]. Very high initial BP-values in patients with ICH increase cerebral blood flow and intracranial pressure, augmenting vasogenic oedema and presumably leading to further bleeding during the first few hours after ictus [27]. An independent association between a rapid BP decline within 24 h after symptom presentation and an increased mortality in ICH patients has been also reported in a retrospective random study [28]. It is not known if this BP decline could have occurred in the time interval between stroke onset and presentation at the hospital. This speculation may support the hypothesis of hypoperfusion, causing further cerebral damage and neurological deterioration.

The BP level for optimal survival (U-point of the curve) in patients with ICH was higher than in those with ischaemic stroke. Due to the mass effect of the developing haematoma an acute increase of the intracranial pressure can cause a higher venous pressure in patients with ICH. This may then lead to further BP elevation in order to overcome the increased venous pressure and perfuse sufficiently the cerebral tissue [29].

## Conclusions

We investigated the prognostic value of admission SBP and DBP in an unselected sample of acute stroke patients. In accordance to several previous reports the relationship between admission BP and early and late stroke mortality is nonlinear [10, 11, 15, 21]. The described U-shaped curve appears to relate BP to clinical outcome, with the best outcome observed in normal or mildly elevated admission BP-values, suggesting that both extremely high and extremely low admission BP-values are likely to

affect outcome adversely. Concerning pathogenic mechanisms, stroke is a heterogeneous group of cerebrovascular diseases, in which some subgroups having a direct cause–effect relation to BP (ICH, LAC) also present the highest admission BP-values. Mortality varies widely amongst subgroups of stroke patients and may depend on different factors in each stroke subgroup. Prospective clinical studies with sufficient numbers of cases for each stroke subgroup are needed in order to analyse separately the relationship of admission BP on stroke outcome and identify in which acute stroke subgroups reducing or increasing BP could be of benefit.

## Conflict of interest statement

No conflict of interest was declared.

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