Background and Purpose—Early identification of acute stroke patients at risk of fatal brain swelling is necessary to facilitate implementation of aggressive therapies. Initial clinical, laboratory, and CT characteristics that may be used as selection criteria were analyzed to determine predictors of herniation and neurological death.

Methods—Data from the placebo arm of the Lubeluzole-International-9 trial were reviewed to identify patients with fatal brain edema. Early clinical, laboratory, and radiographic parameters were evaluated in a case-control design. Initial CT scans were analyzed for early ischemic abnormalities by 2 blinded investigators.

Results—Twenty-three patients died from brain swelling, with minimum baseline National Institutes of Health Stroke Scale (NIHSS) scores of 20 (n = 12; mean, 23.2 ± 1.8) with left and 15 (n = 11; mean, 17.6 ± 2.2) with right hemispheric infarctions (P = 0.0001). A sample of 112 subjects with comparably severe strokes, but who did not die from brain swelling, was selected from the remaining population according to the same NIHSS scores. Among clinical and laboratory characteristics, nausea/vomiting within 24 hours after onset (odds ratio [OR], 5.1; 95% CI, 1.7 to 15.3; P = 0.003) and 12-hour systolic blood pressure ≥ 180 mm Hg (OR, 4.2; 95% CI, 1.4 to 12.9; P = 0.01) were independently associated with fatal brain swelling. Among radiographic factors, only hypodensity of > 50% of the middle cerebral artery territory on initial CT scan was an independent predictor (OR, 6.1; 95% CI, 2.3 to 16.6; P = 0.0004).

Conclusions—Patients with baseline NIHSS score ≥ 20 with left or ≥ 15 with right hemispheric infarctions within 6 hours of symptom onset who also have nausea/vomiting or > 50% middle cerebral artery territory hypodensity are at high risk for developing fatal brain swelling. (Stroke. 1999;30:287-292.)

Key Words: brain edema ■ risk assessment ■ stroke, acute ■ stroke mortality

The consequences of cerebral ischemia are determined by the nature and site of arterial occlusion, collateral blood flow, and the duration of perfusion deficit. Treatment of severe hemispheric strokes requires rapid reperfusion and prevention of ischemic cerebral edema. Progressive deterioration of clinical status due to massive hemispheric edema occurs in Approximately 10% of patients and is described as the “malignant middle cerebral artery syndrome.” Ischemic edema occurs within hours after stroke onset and is associated with an 80% mortality.1

Cerebral edema due to ischemia is initially cytotoxic, characterized by intracellular water accumulation, and later vasogenic, in which water moves across the blood-brain barrier (BBB) into the extracellular interstitial space. The disruption of the BBB can be demonstrated as early as 20 minutes after transient global forebrain ischemia in rats and is critically determined by small variations in intraischemic brain temperature.2,3 Reduced intraischemic brain temperature protects the brain from BBB disruption and alleviates neuronal damage. Studies of the usefulness and feasibility of induced hypothermia for severe ischemic strokes are currently under way.4

Decompressive surgery is another approach to decrease the devastating consequences of mass effect associated with large hemispheric strokes. Specifically, hemicraniectomy and duratomy is a neurosurgical procedure for hemispheric swelling that involves removal of the bone on one side of the skull with simultaneous generous dural opening.5 This procedure achieves a new pathway of least resistance for the swelling brain, decreasing pressure on the brain stem and other brain structures not directly affected by the primary infarction. Recent animal evidence even suggests reduction of infarct size if decompressive surgery can be implemented early in the disease stage.6 In a recent nonrandomized, controlled trial of hemicraniectomy for large hemispheric infarction, in-hospital mortality was reduced from 76.2% to 34.4% in the
surgically treated group. It is suggested that expedited hemicraniectomy in suitable candidates further reduces mortality and improves outcome.

The therapeutic hypothermia and decompressive surgery in severe stroke patients require further study with properly designed, randomized clinical trials. The first step in study design is the selection of appropriate candidates for intervention. To facilitate recruitment and patient selection, predictors for massive ischemic edema formation need to be determined that are readily identified early in the clinical course of ischemic stroke, particularly in the emergency department and intensive care unit settings. We investigated early prognostic factors for massive ischemic edema formation in patients with severe hemispheric stroke, using prospective data from a recent randomized controlled trial.

**Subjects and Methods**

The Lubeluzole-International-9 (LUB-INT-9) trial was a randomized clinical trial of a potential neuroprotective agent for acute stroke, administered within 6 hours of stroke onset. The methods of this study are reported elsewhere. The present study evaluated only those patients in the placebo arm of the study.

All recorded patient information, including detailed clinical summaries, was reviewed to verify causes of deaths and to determine which patients died as a consequence of massive brain swelling. The case population consisted of those patients with anterior circulation strokes with progressive neurological deterioration (based on the National Institutes of Health Stroke Scale [NIHSS] score) leading to coma (NIHSS, item 1a: level of consciousness=3) and death. All patients dying as a result of other causes, such as intracranial hemorrhage, recurrent stroke, cardiopulmonary events, or infection, were excluded from the case population. Patients with “do-not-resuscitate” orders implemented before neurological decline (NIHSS, item 1a: level of consciousness ≥2) were also excluded from the case population. A threshold NIHSS score was determined for each hemisphere by the lowest baseline NIHSS score for a patient who ultimately suffered a neurological death. The control population consisted of subjects with anterior circulation strokes of clinical severity comparable to those of the cases, defined as all those with NIHSS scores greater than or equal to the hemispheric threshold scores.

Demographic baseline stroke characteristics, preexisting conditions, arterial blood pressures (BPs), and laboratory data were extracted from the original database (Janssen Research Foundation, Titusville, NJ). Stroke severity was monitored with the NIHSS scores at baseline and 24 and 48 hours after onset. In addition, arterial BPs recorded at baseline, 1 hour, and 12 hours were recorded. Laboratory data at baseline included ECG parameters (heart rate and QTc interval); serum glucose, sodium, potassium, and magnesium; and white blood cell count.

Original CT films were reviewed by 2 independent stroke neurologists (D.W.K. and S.E.K.) blinded to follow-up imaging and clinical details except for side of hemiparesis. Every CT scan was evaluated allowing for technical factors, including window settings, movement artifacts, or head positioning in the gantry, all of which may influence interpretation. Particular attention was directed toward early signs of infarction, vascular distribution, occlusion site, intracerebral hemorrhage, and result of mass effect. Early signs of infarction were interpreted according to von Kummer et al.

Early CT signs evaluated included the following: Hyperdense middle cerebral artery (MCA) sign was defined as spontaneous high contrast in the MCA that is brighter than adjacent brain tissue and other intracranial arteries (particularly contralateral MCA) not attributable to calcification. Hyperdense internal cerebral artery (ICA) sign was defined on the same terms as spontaneous high contrast in the terminal ICA distinguishable from opposite ICA and surrounding bony structures. Lentiform obstruction was defined as a loss of the precise delineation of the lentiform nucleus due to a decrease in density compared with the contralateral nucleus. Sylvian fissure obscuration was defined as effacement of the sylvian fissure compared with the contralateral side. Other vascular territory involvement was defined as hypodensity in the anterior cerebral, anterior choroidal, or posterior cerebral arteries. Determination of vascular distribution was based on the anterior circulation vascular territory templates provided by Tatu et al. Mass effect and infarct size were determined by grading hemispheric swelling. Interrater reliability for all radiographic determinations was established with ratings of 2 readers, as measured by the k statistic. All disagreements were then resolved by consensus, and the consensus determinations were used in all subsequent logistic regression analyses.

Statistical analysis was performed to compare cases and controls in terms of demographic features, preexisting conditions, clinical characteristics, laboratory results, and CT findings. In the initial univariate analysis, dichotomous or categorical variables were compared with the x2 test, and continuous variables were compared with the unpaired t test or Mann-Whitney U test, as indicated. A difference was considered significant if P<0.05. However, when multiple comparisons were made, a threshold of P<0.25 was used to identify candidate variables (because of the risk of a type II error due to low statistical power in such an analysis).

Multivariate analysis was performed with the use of logistic regression (PROC LOGISTIC, SAS Version 6.12, SAS Institute) to identify predictor variables for severe brain swelling. A stepwise model-building procedure was then performed for parameters, with P<0.25 required for inclusion as a candidate variable in the final model. In the final multivariate analysis, statistical significance was achieved if P≤0.05. Significance was calculated by the likelihood ratio test.

Principal components analysis with subsequent orthogonal rotation for all items of NIHSS was used to identify underlying patterns of neurological impairment that may have had an association with fatal brain swelling. Standard VARIMAX rotation was used, under the assumption that no external criterion exists to test the validity of the patterns observed within the data. Factors with high intercorrelation were distinguished as separate components of the baseline NIHSS and submitted to unpaired Student’s t test to detect differences between cases and controls.

**Results**

**Patients**

There were a total of 89 deaths (25.2%) in the placebo arm of the trial (n=353). Twenty-three cases (6.5%) of fatal ischemic brain swelling were identified. Death among the cases occurred 1 to 11 days (median, 3 days) after stroke onset. Other causes of death included infection (n=26, 7.4%), cardiopulmonary arrest (n=10, 2.8%), recurrent stroke (n=10, 2.8%), intracerebral hemorrhage (n=7, 2.0%), withdrawal of care (n=6, 1.7%), and other causes (n=7, 2.0%). Death in the controls occurred 1 to 321 days (median, 85 days) after stroke onset. Case patients were significantly younger than controls (Table 1).

Etiology of stroke was classified according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) as cardioembolic, large-vessel atherosclerosis, small-vessel occlusive disease, other causes, and undetermined. Stroke etiology was not significantly different among groups. There were 9 (39.1%) cardioembolic, 7 (30.4%) large-vessel atherosclerosis, 2 (8.6%) other (both were carotid dissections), and 5 (21.7%) undetermined among the cases. The distribution in the control population was 50 (44.6%) cardioembolic, 41 (36.6%) large-vessel atheroscle-
TABLE 1. Demographics and Preexisting Conditions in Cases and Controls

<table>
<thead>
<tr>
<th>Demographics and Preexisting Conditions</th>
<th>Cases (n=23)</th>
<th>Controls (n=112)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12 (52%)</td>
<td>39 (35%)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Age (mean), y</td>
<td>61.6±16.0</td>
<td>70.6±12.4</td>
<td>0.003†</td>
</tr>
<tr>
<td>Left hemispheric</td>
<td>12 (52%)</td>
<td>50 (45%)</td>
<td>0.57*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (78%)</td>
<td>68 (61%)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (22%)</td>
<td>46 (41%)</td>
<td>0.13*</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (30%)</td>
<td>36 (32%)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (17%)</td>
<td>29 (26%)</td>
<td>0.55*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (22%)</td>
<td>28 (25%)</td>
<td>0.74*</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (13%)</td>
<td>23 (21%)</td>
<td>0.41*</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0%)</td>
<td>10 (9%)</td>
<td>0.14*</td>
</tr>
</tbody>
</table>

Values are number of patients, unless otherwise indicated.
*χ² test.
†Unpaired Student’s t test.

Clinical Factors
Nausea/vomiting within 24 hours of stroke onset was a highly statistically significant predictor of subsequent fatal brain edema (Table 2). Baseline stroke severity, as measured by NIHSS scores, did not vary among groups (Table 3). Additionally, analysis of the principal components of the NIHSS did not reveal any individual element of the NIHSS to distinguish between groups on the 0.05 level. NIHSS scores 24 hours after stroke onset were significantly higher in cases than controls. This was particularly apparent in cases with right hemispheric involvement. Systolic BPs tended to increase in cases at 12 hours, but this did not reach statistical significance (Table 4).

Laboratory Factors
Laboratory parameters assessed at baseline were not significantly different between groups (Table 2). Mean serum glucose at admission was 8.0±2.9 mmol/L for cases and 8.5±3.7 mmol/L for controls. Mean serum sodium was 140.3±2.2 mmol/L for cases and 139.0±3.7 mmol/L for controls. Mean baseline potassium was 4.3±0.4 mmol/L for cases and 4.2±0.4 mmol/L for controls. Mean magnesium concentration was 0.85±0.15 mmol/L in both groups. White blood count was 10.5±4.0 m/m³ in cases and 9.9±4.3 m/m³ in controls. Mean heart rate on baseline ECG recordings was 83.5±7.4 bpm in cases and 82.4±9.1 bpm in controls. In the case group, 7 of 23 patients (30.4%) had atrial fibrillation on baseline ECG recording. Similarly, in the control group, 34 of 112 patients (30.4%) presented with atrial fibrillation. The incidence of atrial fibrillation on baseline ECG concurred with the past medical history of this arrhythmia. Computation of mean QTc intervals revealed no significant differences (427.2±36.3 ms for cases and 430.0±42.8 ms for controls).

Logistic Regression of Laboratory Values and Clinical Factors
In the initial univariate analysis, baseline serum sodium, potassium, magnesium, and white blood cell counts, as well as ECG variables, were not associated with an increased risk of fatal brain swelling. Multivariate logistic regression of laboratory factors did not reveal any individual element of the NIHSS to distinguish between groups. The NIHSS scores did not vary among groups (Table 3). Additional analysis of the principal components of the NIHSS did not reveal any individual element of the NIHSS to distinguish between groups on the 0.05 level. NIHSS scores 24 hours after stroke onset were significantly higher in cases than controls. This was particularly apparent in cases with right hemispheric involvement. Systolic BPs tended to increase in cases at 12 hours, but this did not reach statistical significance (Table 4).

TABLE 2. Clinical Characteristics Within 24 Hours After Stroke Onset in Cases and Controls

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Cases (n=23)</th>
<th>Controls (n=112)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &lt;24 h</td>
<td>5 (22%)</td>
<td>16 (14%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Headache &lt;24 h</td>
<td>6 (26%)</td>
<td>11 (10%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Nausea/vomiting &lt;24 h</td>
<td>9 (39%)</td>
<td>11 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>8.0±2.9</td>
<td>8.5±3.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.3±2.2</td>
<td>139.0±3.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.3±0.4</td>
<td>4.2±0.4</td>
<td>0.28</td>
</tr>
<tr>
<td>Magnesium, mmol/L</td>
<td>0.85±0.15</td>
<td>0.85±0.15</td>
<td>0.65</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>83.5±7.4</td>
<td>82.4±9.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (30%)</td>
<td>34 (30%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Corrected QT interval, ms</td>
<td>427.2±36.3</td>
<td>430±42.8</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Values are number of patients or mean±SD.
*χ² test.

TABLE 3. Clinical Stroke Severity at Baseline and 24 and 48 Hours After Stroke Onset in Cases and Controls

<table>
<thead>
<tr>
<th>NIHSS</th>
<th>No. of Patients</th>
<th>NIHSS</th>
<th>No. of Patients</th>
<th>NIHSS</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 23</td>
<td>20.5±3.4</td>
<td>112</td>
<td>20.5±3.7</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>24 h 21</td>
<td>23.2±5.4</td>
<td>110</td>
<td>18.8±6.1</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>48 h 19</td>
<td>31.8±7.4</td>
<td>109</td>
<td>18.3±6.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>3 mo 0</td>
<td>NA</td>
<td>74</td>
<td>10.1±7.1</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS values are mean±SD. NA indicates not applicable.
*Mann-Whitney U test.
laboratory and clinical factors revealed nausea/vomiting within 24 hours after stroke onset (OR, 5.1; 95% CI, 1.7 to 15.3; \( P < 0.003 \)) and systolic BP $\geq 180$ mm Hg after 12 hours (OR, 4.2; 95% CI, 1.4 to 12.9; \( P < 0.01 \)) as independent predictors of fatal brain swelling. No baseline laboratory parameter was significantly associated with fatal brain swelling.

**Radiographic Factors**

Baseline CT was obtained a median of 187 minutes (mean, 373±494 minutes) after stroke onset in cases and a median of 153 minutes (mean, 221±249 minutes) in controls. Interrater reliability was excellent for all variables (Table 5) except for obscuration of the sylvian fissure (\( \kappa = 0.63 \)) and temporal lobe involvement (\( \kappa = 0.44 \)). Early involvement of the temporal lobe and additional hypodensities in vascular territories other than MCA on baseline CT significantly predicted subsequent fatal ischemic brain swelling. Among the cases, the caudate nucleus was involved in 4, distal anterior cerebral artery in 1, anterior choroidal artery in 1, and anterior choroidal and posterior cerebral artery in 1 patient. In the controls there were 6 with involvement of the caudate nucleus, twice in combination with anterior choroidal artery involvement, 2 with involvement of the anterior choroidal artery, and 1 with involvement of the posterior cerebral artery. Graded size and location of initial hypodensity significantly distinguished between groups; however, simplified determination of $>50\%$ involvement of MCA territory on baseline CT was the most robust predictor.

**Logistic Regression of Radiographic Findings**

In the initial univariate analysis, involvement of $>50\%$ of the MCA territory, sylvian fissure obscuration, temporal lobe hypodensity, other territory involvement, and hemispheric edema were associated with increased risk of fatal brain swelling, while brain volume loss was associated with a decreased risk. Multivariate logistic regression including all of these CT variables revealed only $>50\%$ MCA territory involvement as an independent predictor of fatal brain swelling (OR, 6.1; 95% CI, 2.3 to 16.6; \( P = 0.0004 \)).

**Discussion**

Currently, there are only few therapeutic options for severe anterior circulation stroke patients. Induced moderate hypothermia and hemicraniectomy are currently being evaluated as potential therapies for these patients. Animal evidence suggests that both modalities may have neuroprotective effects and may prevent herniation. Thus far, there is little information to guide clinicians in selecting which patients are most suitable for these aggressive and invasive interventions. The main goal of this study was to define clinical and radiographic predictors of fatal ischemic brain swelling in a prospectively evaluated population with anterior circulation infarcts. The rationale for this effort was to provide clinicians caring for acute stroke patients with early prognostic factors that may influence treatment decisions in these patients.

We analyzed the LUB-INT-9 database because this randomized controlled trial provided prospectively collected data on patients with acute anterior circulation infarctions.
within 6 hours after onset, including CT and laboratory data, continuous ECG monitoring, frequent BP measurements, daily standardized neurological assessments, and outcomes at 3 months.

Comparison of baseline characteristics revealed that patients developing fatal brain swelling were significantly younger than control patients with comparable severe strokes that did not further deteriorate. This finding is in agreement with previous findings in consecutive case series. We believe that it may reflect some degree of age-related “protective” brain volume loss that makes fatal brain swelling less likely, as indicated in Table 5.

The NIHSS is a widely used clinical measure of stroke severity. Previous studies have used NIHSS scores ≥22 as the threshold in describing severe strokes. However, there may be inequity in the NIHSS for severe strokes in one hemisphere versus the other. We have observed an emphasis of aphasia in this score, which may lead to an overestimate of the score in dominant hemispheric patients. The results of this study support such a dichotomy. Analysis of baseline (total) NIHSS scores of patients who died from fatal brain swelling revealed a minimum cutoff NIHSS score 5 points lower on the right than the left hemisphere. Additionally, the mean NIHSS score was also 5.5 points lower. This dichotomy appears to occur as a result of 3 domains of the scale (level of consciousness questions, level of consciousness commands, and language) measuring entirely left hemispheric functions and only 1 (neglect) measuring predominantly right hemispheric dysfunction. Additionally, aphasic patients may not follow instructions to lift their nonparetic limbs. Adding maximal scores for level of consciousness questions, level of consciousness commands, and language and subtracting the score for neglect reveals a 5-point difference, exactly matching the findings in this study. However, no single item or cluster of items in the NIHSS was a better predictor of fatal brain swelling. The early involvement of hemispheric functions and only 1 (neglect) measuring the frequency of this finding between groups. Although the hyperdense MCA sign may signal MCA occlusion, collateral blood supply may prevent subsequent large infarction and eventual herniation. The hyperdense ICA sign has not been described previously. Despite the evidence that a distal carotid occlusion may be associated with fatal outcome, we observed no such correlation. This sign may lack specificity given the location, surrounding bone artifacts, and frequent calcification of the artery in this location.

Individually, the early CT hypodensity findings were not statistically significantly associated with herniation, but when combined as a >50% hypodensity, this was shown to be a strong predictor. Early tissue hypodensity or loss of gray-white matter interface may be appreciated in the deep structures (usually putamen and caudate). In most instances, additional mass effect, such as sulcal effacement or ventricular compression or shift, can be detected. Several prior case series and prospective cohorts were evaluated to identify predictors of outcome among various CT abnormalities. The early presence of large areas of hypodensity was identified as a robust predictor of poor outcome in most studies. Quality of baseline CT is crucial for interpretation of subtle abnormalities. We reviewed and included all available baseline CTs despite quality concerns to provide a real-life situation in an emergency department. However, in this study, poor-quality scans did not appear to pose a problem, as reflected by the high interrater reliability. Early involvement of other arterial territories and temporal lobe was less reliable, possibly because skewed imaging planes and beam-hardening artifacts by skull bones obscured the lower temporal lobe. Multivariate analysis revealed that only major (>50%) early hypodensity is an independent predictor of fatal ischemic brain swelling. The early involvement of >50% MCA and
Adjacent vascular territories was very uncommon in the control group. We speculate that involvement of these adjacent territories is an additional key factor in whether the resulting infarct will be large enough to produce herniation. Reduction of leptomeningeal collaterals from these adjacent territories may also drastically reduce blood flow and allow for further ischemia and edema. 10,21,28

The main limitation of this study is the selection of the control population. We chose a group of patients with similar clinical severity, but using such a control group may have obscured clinical and radiographic factors by introducing a type II error. On the other hand, previous studies have used a single NIHSS score threshold to define severe strokes. We feel justified using a 5-point dichotomy in the NIHSS as our selection criterion because outcomes are almost identical. This approach corrects for the left hemispheric dominance of the NIHSS to select severe stroke patients most appropriate for novel aggressive interventions. The other major limitation in predicting fatal brain swelling in severe stroke patients is the imaging modality. The great variation in reading ultra-early scans can make widespread implementation of these findings difficult. A recent survey on CT image analysis revealed a relevant discordance of different raters analyzing early infarct signs. 29 This study, combined with recent thrombolytic CT studies, further proves the importance of educating neurologists and emergency physicians about early infarct signs on CT.

In conclusion, this investigation revealed clinical and radiographic parameters that may identify those acute ischemic stroke patients who are at greatest risk for fatal brain swelling. These parameters may be used to define an appropriate study population for aggressive intervention. Patients presenting with severe strokes may be selected for experimental protocols that target this particular population. When acute stroke trials are designed, the clinically severe population should be defined by a hemispheric dichotomy in the NIHSS score rather than by a single threshold score.

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