Neurological Deterioration in Acute Ischemic Stroke
Potential Predictors and Associated Factors in the European Cooperative
Acute Stroke Study (ECASS) I

A. Dávalos, MD; D. Toni, MD; F. Iweins, MSc; E. Lesaffre, PhD; S. Bastianello, MD;
J. Castillo, MD; for the ECASS Group

Background and Purpose—The present study was undertaken to identify potential predictors of and factors associated
with early and late progression in acute stroke. We performed secondary analysis of the clinical, biochemical, and
radiological data recorded in the acute phase of stroke patients enrolled in the European Cooperative Acute Stroke Study
(ECASS) I.

Methods—Early progressing stroke (EPS) was diagnosed when there was a decrease of ≥2 points in consciousness or
motor power or a decrease of ≥3 points in speech scores in the Scandinavian Neurological Stroke Scale from baseline
to the 24-hour evaluation, and late progressing stroke (LPS) was diagnosed when 1 of these decreases occurred between
the 24-hour evaluation and the evaluation at day 7. Using logistic regression analyses, we looked for baseline variables
that predicted EPS and LPS and for factors measured after the early or late acute phase and associated with the 2 clinical
courses.

Results—Of the 615 patients studied, 231 (37.5%) worsened during the first 24 hours after inclusion. The overall incidence
of EPS was 37% in the placebo group and 38% in the recombinant tissue plasminogen activator group (P = 0.68, Fisher’s
Exact Test). Focal hypodensity (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.3 to 2.9) and hyperdensity of the
middle cerebral artery sign (OR, 1.8; 95% CI, 1.1 to 3.1) on baseline computed tomography, longer delay until treatment
(OR, 1.2; 95% CI, 1.1 to 1.4) and history of coronary heart disease (OR, 1.7; 95% CI, 1.1 to 2.8) and diabetes (OR, 1.8;
95% CI, 1.0 to 3.1) were independent prognostic factors for EPS. Extent of hypodensity >33% in the middle cerebral
artery territory (OR, 2.5; 95% CI, 1.6 to 4.0) and brain swelling (OR, 1.8; 95% CI, 1.1 to 3.2) on CT at 24 hours but
not hemorrhagic transformation of cerebral infarct nor decrease in systolic blood pressure within the first 24 hours after
treatment were associated with EPS in multivariate analyses. LPS was observed in 20.3% of patients. Older age, a low
neurological score, and brain swelling at admission independently predicted late worsening.

Conclusions—In the setting of a multicenter trial, EPS and LPS are mainly related to computed tomographic signs of
cerebral edema. Treatment with recombinant tissue plasminogen activator, hemorrhagic transformation, and moderate
changes in systolic blood pressure did not influence the early clinical course. (Stroke. 1999;30:2631-2636.)

Key Words: brain edema ▪ stroke outcome ▪ stroke, acute ▪ thrombolytic therapy ▪ tomography, x-ray computed

Early neurological deterioration is a common event that
occurs as part of 20% to 40% of acute strokes, and it is
burdened with a severe prognosis.1 Consequently, it is ex-
tremely important to advance the search for the underlying
pathogenic mechanisms and for predictors of neurologic
worsening. To this purpose, particularly in the last few years,
some studies have been performed with the aim of ascertain-
ing whether intracerebral conditions or systemic factors are
major determinants of stroke progression. High serum glu-
cose levels2,3 and fibrinogen concentrations,4 history of dia-
betes,5 high body temperature,4 stroke severity at admission,4
and early focal hypodensity with cortical and cortical-
subcortical distribution and brain swelling on initial cranial
computed tomography (CT)3,4 have been associated with
neurological worsening occurring within the first 2 to 4 days
after stroke onset. As to the role of arterial blood pressure,
both high2 and low5 blood pressure have been related to
stroke progression, whereas other studies found comparable
blood pressures in patients with subsequent progressing or
nonprogressing course.3,4

In all the abovementioned studies, cranial CT was not
systematically repeated during progression or shortly after its
occurrence, and, therefore, the contribution to clinical course
of early development of brain edema or of hemorrhagic

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From the Departments of Neurology (A.D.), Hospital Universitari Doctor Josep Trueta, Girona; Hospital Universitario Xeral de Galicia (J.C.), Santiago
de Compostela, Spain; Departments of Neurological Sciences (D.T.) and Neuroradiology (S.B.), University La Sapienza, Rome, Italy; and the
Biostatistical Centre for Clinical Trials (F.I., E.L.), Leuven, Belgium.
Reprint requests to Dr Antoni Dávalos, Section of Neurology, Hospital Universitari, Doctor Josep Trueta, E-17007 Girona. E-mail
adavalose@meditex.es
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transformation was not thoroughly assessed, particularly in those patients who died before the second CT scan could be performed. Moreover, those studies did not evaluate all the same variables, so different results also may be attributed to different study plans.

To clarify these apparent discrepancies, we decided to exploit the clinical, biochemical, and radiological data recorded in the acute phase of stroke patients enrolled in the European Cooperative Acute Stroke Study (ECASS) I. Our objective was to identify factors that potentially predicted or were associated with progression of stroke and to evaluate the influence of stroke progression on clinical outcome.

Subjects and Methods
We performed a secondary analysis on the ECASS I data bank. The design and primary results of ECASS I have been reported elsewhere.\(^6\) In summary, ECASS I was a double-blinded, randomized multicenter trial performed between 1992 and 1994 in 14 European countries. A total of 620 patients with acute ischemic hemispheric stroke received either recombinant tissue plasminogen activator (rtPA; 1.1 mg/kg IV) or placebo within 6 hours after onset of symptoms. Eligibility was based on clinical symptoms and results of CT: patients with moderate-to-severe neurological deficit and with no or only minor early infarct signs on initial CT scan were enrolled. Patients who presented with hemiplegia and impairment of consciousness or forced head and eye deviation; with major infarct signs on initial CT scan, such as diffuse swelling of the affected hemisphere; or with parenchymal hypodensity in >33% of the middle cerebral artery (MCA) territory were excluded from the study. However, 52 randomized patients had extended early infarct signs and 2 had primary hemorrhage. Systolic blood pressure (SBP) >200 mm Hg or diastolic blood pressure (DBP) >110 mm Hg on repeated measurements before study entry were criteria of exclusion. Patients could not be treated with full-dose intravenous heparin or antiplatelet agents during the first 24 hours after randomization, but use of low-dose subcutaneous heparin was permitted to prevent deep-vein thrombosis and pulmonary thromboembolism.

Stroke severity was assessed by the Scandinavian Stroke Scale (SSS)\(^8\) on admission, and evaluated again at 120 minutes, 8 hours, 24 hours, and 7 days after treatment. The SSS consists of 7 items (consciousness; speech; facial, arm, hand, and leg motor power; and gait) with 3 possible grades of deficit sampled in decreasing order; that is, the lower the score, the worse the deficit. We considered early progressing stroke (EPS) to be indicated by a decrease of ≥3 points for speech, or ≥2 points for consciousness or arm, hand, or leg motor power, or ≥1 in the SSS from baseline to the 24-hour evaluation. Late progressing stroke (LPS) was considered to be indicated when SSS dropped by the same score between the 24-hour and the 7-day evaluations. If no selected items of the SSS dropped between baseline and the 24-hour evaluation or between the 24-hour and 7-day evaluations, the patients were classified as non-EPS or non-LPS, respectively. Patients who died within the first 24 hours were classified in the EPS group if they had progressed at the last observation at 2 or 8 hours after inclusion. Of a total 620 patients, 5 were excluded from the EPS analyses and additional 69 were excluded from the LPS analyses; causes for exclusion are shown in the Figure. Therefore, 615 patients were included from the EPS analyses and 546 from the LPS analyses.

To look for potential predictors of both EPS and LPS, we recorded age, sex, past medical history of hypertension, diabetes, previous transient ischemic attack or stroke, coronary heart disease and congestive heart failure, atrial fibrillation on admission, body temperature (the place on the body from which temperature was taken was not registered), SBP and DBP on admission, time from onset of symptoms to initiation of treatment, laboratory parameters on admission (serum glucose levels, fibrinogen, and activated partial thromboplastin time), and CT findings before randomization. In addition to these factors, EPS was considered to be a potential predictor of LPS.

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Statistics
Tests performed were the 2-sided Fisher Exact and Wilcoxon tests (Stataxct or SAS software) for categorical variables and the t test (SAS software) for continuous variables. Percentage of change in SBP between admission and each of the subsequent measurements was calculated as follows: %Change = [(SBP(n)−SBP(0))/SBP(0)]×100, where SBP(0) is the value on admission and SBP(n) is the value at subsequent measurement. Potential predictors and factors associated with EPS or LPS were analyzed by the stepwise logistic regression procedure (SAS software; level 0.05). Treatment, age, and sex were forced into all the models, whereas, whereas EPS was forced into the model concerning predictors of LPS. Results were expressed as adjusted odds ratios (OR) and corresponding 95% confidence intervals (CIs). According to the characteristics of a secondary analysis, all probability values must be regarded as exploratory.

Results
Of the 615 patients studied, 231 (37.5%) worsened during the first 24 hours after inclusion; 112 were in the placebo group (37%) and 119 in the rtPA group (38%) (P=0.68, Fisher’s Exact Test). Given the almost identical frequency of EPS in
treated and placebo patients, all patients were considered together in the analyses. Neurological deterioration occurred within the first 2 hours after treatment in 23% and within the first 8 hours in 32% of the total patients. Four patients who died within the first 24 hours without showing any impairment in neurological deficit at 2 or 8 hours after inclusion were classified as being in the non-EPS group. Deterioration involved the level of consciousness in 110 (48%) patients (of whom 54 had additional impaired limb strength and 41 had an additional speech impairment), limb strength in 102 (44%) (11 of whom had associated speech impairment), and speech alone in 19 (8%).

Table 1 shows the demographic data, past medical history, clinical characteristics, laboratory parameters on admission, and findings of the initial CT scan. EPS patients were significantly older and had a longer delay until randomization, lower SSS score, and higher serum glucose levels at entry than non-EPS patients. Regarding risk factors, EPS patients showed significantly higher frequency of history of diabetes and coronary heart disease. Results of CT scans exhibited HMCA sign, focal hypodensity, and brain swelling more frequently in the EPS than in the non-EPS patients. Of all these variables, focal hypodensity, HMCA sign, longer delay until treatment, and history of coronary heart disease and diabetes remained significant predictors for EPS in the final logistic model (Table 2).

Among the variables recorded at 24 hours, higher body temperature, HMCA sign, size of infarct, brain swelling, and hemorrhagic transformation on cranial CT were significantly associated with EPS in the univariate analyses (Table 3). Maximum decrease in SBP within the first 24 hours after randomization, type of treatment (rtPA or placebo), and subcutaneous heparin administration within the first 24 hours were not related to EPS. Size of infarct involving >33% of the MCA territory (OR, 2.5; 95% CI, 1.6 to 4.0; \( P < 0.001 \)) and brain swelling (OR, 1.8; 95% CI, 1.1 to 3.2; \( P = 0.023 \)) were the only factors independently associated with EPS in the final logistic model. Hemorrhagic transformation was not associated with EPS nor was PH (yes or no) in further logistic analysis.
Among the 546 patients for whom the evolution of the SSS at day 7 was available, 111 patients (20.3%) had LPS. Forty-one LPS patients and 145 non-LPS patients had also had an EPS \((P=0.502)\). LPS involved the level of consciousness in 23 (21%) patients (of whom 6 had additional impaired limb strength and 6 had an additional speech impairment), limb strength in 81 (73%) (8 of whom had associated speech impairment), and speech alone in 7 (6%). LPS patients were older and had higher systolic blood pressure and mainly lower SSS scores at entry compared with their non-LPS counterparts, whereas history of coronary disease, diabetes, and serum glucose levels was comparable in the 2 groups. HMCA sign, focal hypodensity, and brain swelling on initial CT were significantly more frequent in LPS than in non-LPS patients (Table 1). Older age, a low SSS score, and brain swelling independently predicted LPS (see final logistic model) (Table 2). In a further analysis that included the CT variables recorded at 24 hours, we obtained similar results.

CT scan findings between days 4 and 10 and low SSS score at 24 hours were associated with LPS in the univariate analysis (Table 4). HMCA sign (OR, 3.0; 95% CI, 1.3 to 6.6), hemorrhagic transformation (OR, 1.8; 95% CI, 1.1 to 3.0), low SSS score (OR, 0.98; 95% CI, 0.96 to 0.99) and no treatment with intravenous heparin within the first week (OR, 0.55; 95% CI, 0.30 to 0.96) were the factors independently associated with LPS in the final logistic model. When hemorrhagic transformation was dichotomized as PH (yes or no), brain swelling (OR, 2.76; 95% CI, 1.60 to 4.98) but not PH was selected by the model.

Poor outcome was significantly more frequent in EPS than in non-EPS patients. At 90 days, mortality was 31.2% in the former and 11.5% in the latter \((P<0.0001)\). At the end of the study period, only 9.7% of EPS patients had any or mild nondisabling deficit (modified Rankin score, grade 0 or 1) as opposed to 46.4% of non-EPS patients \((P<0.0001)\). EPS also represented a high risk of bad outcome: mortality (21.6% versus 6.4%, \(P<0.0001)\) and the rate of combined mortality and functional disability (modified Rankin score, grade >1; 91.7% versus 56.3%; \(P<0.0001)\) were significantly more frequent in EPS than in non-EPS patients.

Brain edema (44%), parenchymal hemorrhage (25%), and noncerebrovascular complications (24%) were causes of death in EPS patients, whereas noncerebrovascular complications (55%), parenchymal hemorrhage (16%), and brain edema (14%) were those attributed to non-EPS patients. The cause was undetermined in 7% of the first group and 15% of the second group. Causes of mortality in LPS patients were comparable with those of non-LPS patients: noncerebrovascular complications in 75% and 68%, brain edema in 8% and 11%, parenchymal hemorrhage in 8% and 7%, and undetermined in 8% and 14%, respectively.

### Discussion

This study is a secondary analysis of a clinical trial database. Although conclusions may be applicable in similar clinical settings, they should not be generalized to all ischemic stroke patients. However, interestingly, we found a predictive profile of deterioration over the initial 24 hours after stroke onset that shares risk factors with those of other studies of less selected populations.\(^2\)\(^-\)\(^5\) Nevertheless, in contrast to previous reports,\(^2\)\(^-\)\(^3\) initial serum glucose levels were not related to progression of stroke after adjusting for the concomitant history of diabetes, which instead was indicated to be a predictor of progression. Diabetic microangiopathy that leads to chronic impairment of cerebral autoregulation and insufficient cerebral perfusion pressure might, at least in part, explain this finding.\(^4\) Moreover, diabetic microangiopathy may also be responsible for inadequate collateral blood supply after arterial occlusion, which thus favors an uncoupling between enhanced glucose support and reduced oxygen delivery, which may aggravate cellular damage by enhancing brain edema and free radical injury.\(^9\)\(^-\)\(^11\) A contributing role of poor collateral blood supply, irrespective of diabetes, also is suggested by the fact that coronary artery disease, which in this study was related to EPS, is generally associated with a
higher prevalence of severe extracranial or intracranial ath-erosclerotic disease.13

The presence of early hypodensity at initial CT has already been pointed out as a predictor of early deterioration in previous studies.13 Focal hypodensity and HMCA sign herald subsequent large cerebral infarcts14 that may, in turn, favor the development of mass effect. In fact, cerebral infarcts involving >33% of the MCA territory and brain edema on CT at 24 hours were the only factors independently associated with EPS in the present study. However, one third of EPS patients did not have extended infarcts at repeat CT scan, which suggests that other causes may be implicated. In a recently published article,14 patients with nonextended subcortical infarcts and early neurological deterioration were found to have higher serum glutamate levels than those who did not deteriorate, which suggests a crucial role of excitotoxic mechanisms in the pathogenesis of stroke progression, also irrespective of the extent of the infarct.16–18 In this study, neither SBP or DBP at entry nor changes in systolic blood pressure within the first 24 hours were associated with EPS. Although a minority of patients was excluded from randomization as a result of untreatable hypertension, our results suggest that high SBP does not contribute to early neurological deterioration in patients in whom remarkable changes in blood pressure over the acute phase are avoided. On the context of the still-open debate on whether to treat hypertension in the acute phase of ischemic stroke,19 our data may be useful for indicating a policy in the management of moderately elevated blood pressure.

LPS was seen in one fifth of patients and was preceded by a stable neurological condition during the first 24 hours in 63% of them. We have identified some risk factors for LPS that are different from those found in EPS. Worsening was related to older age, poorer neurological condition at admission, and mass effect on the baseline CT and also in the CT performed at 24 hours. This means that brain edema may play a role in both EPS and LPS, which is in keeping with the notion that brain edema reaches its maximum expression within the initial 5 days after stroke onset. CT findings between days 4 and 10 confirm the importance of cerebral edema on LPS. In fact, when we considered together all types of hemorrhagic transformation (PH and HI), this was selected

### TABLE 3. Potential Factors at 24 Hours Associated With EPS

<table>
<thead>
<tr>
<th></th>
<th>EPS (0 to 24 h)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=231)</td>
<td>No (n=384)</td>
</tr>
<tr>
<td>Treatment with rtPA/placebo, n</td>
<td>119/112</td>
<td>191/193</td>
</tr>
<tr>
<td>Subcutaneous heparin administration, n</td>
<td>55 (24)</td>
<td>120 (31)</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37.3±0.7</td>
<td>37.2±0.6</td>
</tr>
<tr>
<td>Maximum negative change in SBP within 24 h</td>
<td>−14.3±13.5</td>
<td>−16.3±13.3</td>
</tr>
<tr>
<td>aPTT, s</td>
<td>30.7±9.6</td>
<td>31.3±11.5</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>303±125</td>
<td>295±124</td>
</tr>
<tr>
<td>CT findings at 24 h*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMCA sign</td>
<td>43 (19)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>Extent of MCA territory hypodensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (12)</td>
<td>104 (27)</td>
</tr>
<tr>
<td>≥33%</td>
<td>60 (27)</td>
<td>158 (42)</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>138 (61)</td>
<td>118 (31)</td>
</tr>
<tr>
<td>Brain swelling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>37 (16)</td>
<td>151 (40)</td>
</tr>
<tr>
<td>Effacement</td>
<td>38 (17)</td>
<td>71 (19)</td>
</tr>
<tr>
<td>Midline shift</td>
<td>48 (21)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Ventricular compression</td>
<td>103 (46)</td>
<td>131 (34)</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>0.010§</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>165 (73)</td>
<td>312 (82)</td>
</tr>
<tr>
<td>HI</td>
<td>21 (9)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>PH</td>
<td>40 (18)</td>
<td>30 (8)</td>
</tr>
</tbody>
</table>

Values between parentheses are percentages. *In 226 patients with EPS and 380 without EPS. †For the comparison no or ≥33% hypodensity vs hypodensity >33%. ‡For comparison no brain swelling vs effacement, midline shift, or ventricular compression. §For the comparison no hemorrhagic transformation vs HI or PH.

### TABLE 4. Potential Factors Between 24 Hours and Day 7 Associated With LPS

<table>
<thead>
<tr>
<th></th>
<th>LPS (24 h to day 7)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=111)</td>
<td>No (n=435)</td>
</tr>
<tr>
<td>Treatment rtPA/placebo, n</td>
<td>47/64</td>
<td>222/213</td>
</tr>
<tr>
<td>SSS score at 24 hours</td>
<td>27.1±12.9</td>
<td>34.7±15.1</td>
</tr>
<tr>
<td>Intravenous heparin administration from 24 h to 7 days, n</td>
<td>21 (19)</td>
<td>118 (27)</td>
</tr>
<tr>
<td>CT findings at days 4 to 10, n*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMCA sign</td>
<td>14 (13)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Parenchymal hypodensity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA territory</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (19)</td>
<td>98 (23)</td>
</tr>
<tr>
<td>≥33%</td>
<td>26 (23)</td>
<td>159 (38)</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>62 (60)</td>
<td>162 (39)</td>
</tr>
<tr>
<td>ACA territory</td>
<td>13 (13)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>PCA territory</td>
<td>2 (2)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Brain swelling</td>
<td>&lt;0.001‡</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18 (17)</td>
<td>156 (37)</td>
</tr>
<tr>
<td>Effacement</td>
<td>12 (12)</td>
<td>74 (18)</td>
</tr>
<tr>
<td>Midline shift</td>
<td>31 (30)</td>
<td>61 (15)</td>
</tr>
<tr>
<td>Ventricular compression</td>
<td>42 (41)</td>
<td>128 (30)</td>
</tr>
<tr>
<td>Hemorrhagic transform</td>
<td>&lt;0.001§</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>46 (43)</td>
<td>268 (64)</td>
</tr>
<tr>
<td>HI</td>
<td>42 (41)</td>
<td>112 (27)</td>
</tr>
<tr>
<td>PH</td>
<td>15 (14)</td>
<td>39 (9)</td>
</tr>
</tbody>
</table>

Values between parentheses are percentages. *Third CT was not available in 8 patients with LPS and 16 without LPS. †For the comparison no or ≥33% MCA hypodensity vs hypodensity >33%. ‡For the comparison no brain swelling vs effacement, midline shift, or ventricular compression; §For the comparison no hemorrhagic transformation vs HI or PH.
as a predictor of LPS, whereas PH taken separately was rejected by the model, and brain swelling was selected as independent predictor of LPS. This is in agreement with previous observations that the mass effect of the underlying infarct rather than HI contributes to deterioration.20,21

The association between HMCA sign at the third CT and LPS found in the present study is in agreement with the observation that MCA occlusion is related to neurological deterioration.4 The presumably higher rate of recanalization achieved in recombinant tissue plasminogen activator (rtPA) patients did not exert a protective role, because the frequency of both EPS and LPS was similar in treated and placebo patients. However, recanalization rate and its effect on EPS and LPS should be elucidated by a specifically targeted study.

Finally, it is of interest that most of LPS patients had an impairment of motor function in contrast with a higher frequency of deterioration of level of consciousness seen in EPS patients. This suggests that although brain edema played a role both in EPS and LPS, as mentioned previously, it exerted a less important mass effect in the latter than in the former. An indirect confirmation of this hypothesis is the fact that mortality was attributed to cerebral causes in 69% of EPS patients versus only in 16% of LPS patients.

In conclusion, progression of stroke is a likely multifactorial event only partially predictable basing on the clinical, laboratory, and imaging data routinely available in the current clinical practice. Hence, we need to advance in the search for biochemical markers and for new neuroimaging tags of stroke progression. However, at present, because CT signs of brain swelling are the main visible indexes of possible early and late progression, antiedema strategies should be considered in future clinical trials.

References
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