Background and Purpose—Little is known in regard to cerebral arterial reocclusion after successful thrombolysis. In the absence of arteriographic information, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial investigators prospectively identified clinical deterioration following improvement (DFI) as a possible surrogate marker of cerebral arterial reocclusion after rt-PA–induced recanalization. Also, we identified any significant clinical deterioration (CD) even if not preceded by improvement. This observational analysis was designed to determine the incidence of DFI and CD in each treatment group, to identify baseline or posttreatment variables predictive of DFI or CD, and to determine any relationship between DFI, CD, and clinical outcome.

Methods—DFI was defined as any 2-point deterioration on the NIH Stroke Scale after an initial 2-point improvement after treatment. CD was defined as any 4-point worsening after treatment compared with baseline. All data were collected prospectively by investigators blinded to treatment allocation. A noncontrast brain CT was mandated when a 2-point deterioration occurred. All cases were validated by a central review committee.

Results—DFI was identified in 81 of the 624 patients (13%); 44 were treated with rt-PA and 37 were treated with placebo ($P = 0.48$). DFI occurred more often in patients with a higher baseline NIH Stroke Scale score. CD within the first 24 hours occurred in 98 patients (16% of all patients); 43 were given rt-PA and 55 were given placebo ($P = 0.19$). Baseline variables associated with CD included a less frequent use of prestroke aspirin and a higher incidence of early CT changes of edema or mass effect or dense middle cerebral artery sign. Patients with CD had higher rates of increased serum glucose and fibrin degradation products, and they also had higher rates of symptomatic intracranial hemorrhage and death. Patients who experienced either DFI or CD were less likely to have a 3-month favorable outcome.

Conclusions—We found no association between DFI, CD, and rt-PA treatment, and no clinical evidence to suggest reocclusion. Deterioration was strongly associated with stroke severity and poor outcome and was less frequent in patients whose stroke occurred while they were on aspirin. (Stroke. 2001;32:661-668.)

Key Words: deterioration n reocclusion n stroke n thrombolysis
In comparing the incidence of DFI in the 2 treatment groups, the denominator used was those patients in each group who improved 2 points on the NIHSS during the time interval being evaluated.

We studied DFI or CD in relationship to stroke outcome including symptomatic or asymptomatic intracranial hemorrhages (ICH) within 36 hours, death within 90 days, or complete or nearly complete recovery measured from 4 neurological scales defined in the previous publication.8 We began with testing treatment by DFI or CD interactions using the a level 0.10, followed with testing the individual effect of DFI or CD at a level of 0.05 if the interaction was not detected. All analyses were conducted using logistic regression with calculation of the odds ratio (OR) and 95% confidence limits. For worse outcomes, an OR and confidence limit >1 indicated that patients with DFI or CD were more likely to have a worse outcome compared with patients who did not. For a favorable outcome, an OR and confidence limit <1 indicated that patients who suffered DFI or CD were less likely to have a favorable outcome compared with patients who did not. The analyses were rerun by including those baseline variables associated with ICH or a 3-month favorable outcome identified in previous studies of the NINDS Trial database.4,9

To detect baseline variables that might be associated with either DFI or CD, we included all variables tested in a previous analysis of baseline predictors of outcome and treatment response in the NINDS rt-PA Stroke Trial9 as well as the following: serum glucose, white blood cell count (WBC), hematocrit (HCT), fibrinogen and fibrin degradation products (FDP), use of calcium channel blockers, aspirin, heparin, and antihypertensive therapy. The following posttreatment variables obtained over the first 24 hours after treatment were also tested: NIHSS, serum glucose, WBC, HCT, fibrinogen and FDP, maximum mean arterial blood pressure (MAP), a decrease of MAP by 20 mm Hg (mean of 3 consecutive reads compared with mean of first 4 reads), maximum decline of MAP between 2 consecutive reads, cardiac arrhythmia, syncope, angina, cardiac arrest, congestive heart failure, antihypertensive therapy, and calcium channel blocker therapy.

The statistical analysis of pretreatment and posttreatment variables and DFI or CD began with univariate tests at a critical value of 0.2 to include candidates for the multivariable model, followed by multivariable analyses using a logistic model, adjusting by treatment for the posttreatment model and by centers if the incidence of DFI was unbalanced among the centers. Any individual variable with P<0.05 or variable interactions with P<0.10 were retained in the final model. This modeling process has been described in detail previously.4 The quantified association, OR, and its confidence of each pretreatment or posttreatment variable (eg, treatment with rt-PA) with DFI or CD were reported. An OR >1.0 of rt-PA versus placebo and confidence limits excluding 1, for example, indicated that patients treated with rt-PA were less likely to have DFI or CD compared with patients treated with placebo. As another example, an OR of MAP drop over 20 mm Hg <1.0 and confidence limits excluding 1 indicated that patients with such an MAP drop were less likely to experience DFI or CD compared with patients without this change in MAP.

Separate models were developed on the basis of the data collected at baseline and over the first 24-hour posttreatment interval. The treatment variable was included in the posttreatment models to adjust for the effect of rt-PA on stroke outcome. DFI models were also adjusted for the clinical centers because of unbalanced incidence of DFI among centers.

Results
A total of 81 patients with DFI were identified: 13% of all 624 patients randomized. DFI occurred in 44/312 (14%) of rt-PA–treated patients, and 37/312 (12%) given placebo. DFI occurred within 24 hours in 31/312 (10%) of rt-PA–treated patients and 29/312 (9%) of placebo patients. None of these treatment group differences were significant (P=0.48 and P=0.82, respectively). Because a difference between clinical
Figure 1. NIHSS scores over the first 24 hours in patients with DFI. A, rt-PA patients. B, placebo patients.
centers was found in the frequency of DFI (range 6% to 25%, \( P<0.05 \)), the testing for differences in DFI between treatment groups, and subsequent analyses of DFI with baseline and posttreatment covariates, were adjusted by clinical centers. A graphic representation of NIHSS scores over the first 24 hours for rt-PA and placebo DFI patients is depicted in Figure 1.

Fifty-nine of all DFI were attributed to reocclusion (32 rt-PA versus 27 placebo, \( P=0.49 \)), 3 were attributed to cerebral hemorrhage (2 treated with rt-PA and 1 with placebo), and 8 to cerebral edema (5 treated with rt-PA and 3 with placebo). Eleven were caused by “other” conditions (5 treated with rt-PA and 6 with placebo).

A total of 98 patients with CD within 24 hours after treatment were identified, which was 16% of all patients randomized, excluding 1 patient who died before 24 hours. Forty-three patients with CD had been treated with rt-PA compared with 55 who received placebo (\( P=0.19 \)). Figure 2 illustrates the proportion of patients deteriorating 2 or more points, 3 or more points, and up to 14 or more points on the NIHSS in the first 24 hours compared with baseline by treatment group with 95% confidence limits. No treatment difference was detected at any cutoff point (all \( P>0.19 \), respectively). Another 13 patients suffered CD by 7 to 10 days, but the difference between treatment groups was still not significant. A graphic representation of NIHSS scores over the first 24 hours for rt-PA and placebo CD patients is depicted in Figure 3. Of the 98 patients with CD within 24 hours, 12 (12.4%) were due to symptomatic hemorrhage.

Because no treatment group differences were detected in the incidence of DFI or CD, the treatment variable was excluded from pretreatment models. Because rt-PA treatment might influence some posttreatment variables (eg, FDP), the treatment variable was retained in posttreatment models.

**DFI or CD in Relationship to Hemorrhage Within 36 Hours, Death, or 3-Month Favorable Outcomes**

DFI was not associated with ICH or death at 90 days. CD at 24 hours and death at 7 to 10 days was highly associated with symptomatic ICH within 36 hours (\( P<0.001; \) OR 9.7; 95% CI 3.9 to 24.5) and death at 90 days (\( P<0.001; \) OR 4.4; 95% CI 2.7 to 7.1). Patients who experienced either DFI or CD were less likely to have a 3-month favorable outcome compared with patients who did not (OR 0.01 to 0.92, \( P<0.03 \)). Among patients with CD within 24 hours after treatment, the rt-PA–treated group had a less chance of a favorable outcome compared with the placebo-treated group.

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**Figure 2.** Percentage of rt-PA and placebo patients with CD of 2 to 14 points on the NIHSS at 24 hours, with 95% confidence limits.
Figure 3. NIHSS scores over the first 24 hours in patients with CD. A, rt-PA patients. B, placebo patients.
(OR 0.15; 95% CI, 0.03 to 0.94). On the other hand, for patients without deterioration at 24 hours, the rt-PA–treated group had a much greater chance of a 3-month favorable outcome compared with the placebo-treated group (OR 2.03; 95% CI, 1.48 to 2.79).

**DFI or CD Associated With Pretreatment or Posttreatment Variables**

Baseline variables significantly associated with any DFI, DFI occurring within 24 hours, CD within 24 hours, and CD within 7 to 10 days are presented in Table 1. A higher baseline NIHSS score was associated with DFI (OR 1.05; 95% CI, 1.01 to 1.08 for all DFI; OR 1.04, 95% CI, 1.00 to 1.08 for DFI within 24 hours). The mean (25 to 75th quartile) baseline NIHSS score of DFI patients was 16.6 11–22 versus 14.5 9 –19 in non-DFI patients.

No aspirin use before randomization (OR 0.53; 95% CI, 0.32 to 0.88) and early CT findings of edema or mass effect or dense middle cerebral artery sign (OR 1.91, 95% CI 1.13 to 3.23) were strongly associated with CD within 24 hours. Baseline NIHSS, glucose, and FDP $\geq$10 mcg/mL were predictive of CD within 7 to 10 days. Mean (25 to 75th quartile) baseline NIHSS of CD patients was 17.3 12–23 versus 14.3 8 –19 in non-CD patients.

Posttreatment variables significantly associated with any DFI, DFI occurring within 24 hours, and CD within 24 hours and 7 to 10 days are presented in Table 2. Both DFI occurring within 24 hours of treatment and CD were associated with a worse NIHSS at 24 hours.

Patients with a 20 mm Hg MAP drop from baseline during the first 24 hours after treatment were less likely to have DFI compared with patients who did not have such a MAP decline (OR 0.34; 95% CI, 0.13 to 0.88).

The association of HCT with DFI was treatment dependent ($P=0.04$). When there was an abnormal HCT at 24 hours (35<HCT>55 for males and 40>HCT>60 for females), patients treated with rt-PA were more likely to have DFI compared with rt-PA patients with normal HCT (OR 1.98; 95% CI, 0.97 to 4.00).

The association of WBC with DFI was also dependent on treatment ($P=0.01$ for interaction. Patients who were treated with rt-PA and with a WBC increment of 1000 cells were more likely to have DFI compared with the patients who were treated with rt-PA without such a WBC increment (OR 1.14; 95% CI, 1.04 to 1.24). A similar relationship with WBC was observed for early DFI occurring within 24 hours. CD by 7 to 10 days was associated with increased glucose at 24 hours (OR 1.07; 95% CI, 1.06 to 1.07).

**Discussion**

The main finding of this study, resulting from careful clinical observation of patients receiving rt-PA compared with placebo, is that there was no difference detected between these treatment groups in the incidence of CD following initial improvement. This provides indirect but strong evidence that recanalization and increased reperfusion that has been associated with intravenous rt-PA therapy is not frequently followed by reocclusion as clinically defined in this study. This is true despite the fact that we had hypothesized DFI would occur more frequently in rt-PA–treated patients. Becker has documented reocclusion after intra-arterial lysis of basilar artery lesions, but there are few other published

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>All DFI</th>
<th>DFI Within 24 Hours</th>
<th>CD Within 7–10 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS, 5-point increments</td>
<td>1.05 (1.01, 1.08)</td>
<td>1.05 (1.00, 1.08)</td>
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</tr>
<tr>
<td>CT findings of early ischemia</td>
<td>...</td>
<td>...</td>
<td>1.91 (1.13, 3.23)</td>
</tr>
<tr>
<td>Aspirin use at baseline</td>
<td>...</td>
<td>...</td>
<td>0.53 (0.32, 0.88)</td>
</tr>
<tr>
<td>Serum glucose, 10 mg/dL increments</td>
<td>...</td>
<td>...</td>
<td>1.01 (1.00, 1.01)</td>
</tr>
<tr>
<td>FDP $\geq$10 mcg/mL</td>
<td>...</td>
<td>...</td>
<td>2.77 (1.30, 5.90)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Posttreatment Variables</th>
<th>All DFI</th>
<th>DFI Within 24 Hours</th>
<th>CD Within 7–10 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS, 5-point increments</td>
<td>...</td>
<td>1.32 (1.27, 1.37)</td>
<td>2.18 (2.11, 2.25)</td>
</tr>
<tr>
<td>MAP drop of 20 mm Hg systolic</td>
<td>0.34 (0.13, 0.88)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Serum glucose, 10 mg/dL increments</td>
<td>...</td>
<td>...</td>
<td>1.07 (1.06, 1.07)</td>
</tr>
<tr>
<td>HCT X treatment</td>
<td>$P=0.04$</td>
<td>...</td>
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<tr>
<td>WBC X treatment</td>
<td>$P=0.01$</td>
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</tr>
<tr>
<td>FDP $\geq$10 mcg/mL X treatment</td>
<td>...</td>
<td>...</td>
<td>$P=0.03$</td>
</tr>
</tbody>
</table>

* $P$ value for interaction.
reports of documented reocclusion of cerebral vessels after thrombolysis.

The main limitation of our study is that we relied on indirect clinical correlation rather than direct arteriographic observation and used arbitrary (but logical) NIHSS cutoffs to define improvement or deterioration. Perhaps limiting our analysis to patients with more dramatic improvement or deterioration or basing our results on arteriographic imaging would have revealed some treatment difference. Nonetheless, clinical fluctuation in acute stroke patients has been increasingly recognized and related to the state of perfusion in the acute stroke setting. Therefore, we infer from our clinical data that it is unlikely that a substantial number of rt-PA cases have symptomatic reocclusion following physiologically meaningful reperfusion.

Because DFI was not increased in rt-PA–treated patients, the present study does not support the routine use of anticoagulation to prevent reocclusion after intravenous rt-PA for acute ischemic stroke. However, our results should be considered “hypothesis generating.” Additional study of this question is certainly worthwhile, especially if done with arteriographic correlation to determine the exact incidence and timing of recanalization and reocclusion. Experience with thrombolysis for acute coronary occlusion has demonstrated that arterial recanalization can be augmented and reocclusion can be prevented by use of antiplatelet therapy, especially the GPIIb/IIIa antagonists.

Clinical fluctuation manifest as either DFI or CD was relatively common in this series, occurring in roughly 15% of patients within the first 24 hours, which was consistent with previous clinical observations. Early deterioration within 6 hours of stroke onset was found in 37.5% of patients enrolled in the European Cooperative Acute Stroke Study (ECASS). In our study, as in ECASS, both DFI and CD were closely related to the severity of the initial stroke because both were predicted by a worse baseline NIHSS score and CD was predicted by more prominent early CT changes.

Surprisingly, DFI occurred less frequently in patients with a drop in blood pressure during the first 24 hours after treatment. It is well known that a reduction of blood pressure in the acute stroke setting may result in neurological worsening. However, in a previous analysis, we showed that treatment of blood pressure in the NINDS rt-PA Stroke Trial was not associated with adverse outcome in the placebo-treated patients. Furthermore, in the present study, we did not find that DFI was associated with a higher incidence of antihypertensive treatment. Therefore, our data suggest that some mechanism other than reduced perfusion pressure was responsible for most of the DFI occurring in our patients.

Other potentially treatable mechanisms may explain some cases of DFI. Animal models and human MRI studies have demonstrated progressive enlargement of the irreversibly damaged ischemic core to incorporate surrounding penumbra regions over the first 24 hours after stroke. Other studies have shown that reperfusion may aggravate damage in regions of moderate ischemia. Both these pathophysiological processes could cause CD and may be targeted by neuroprotective therapy. In our study, the use of calcium channel blockers before treatment, which have sometimes been neuroprotective in animal models, did not effect the incidence of DFI.

CD was more likely in patients not on aspirin at the time of their stroke. Aspirin improves outcome after stroke, and some studies have suggested that strokes are less severe in patients taking aspirin. Because our patients with CD had both more severe strokes and poorer outcomes, our data would support both these effects of aspirin. Because of its antithrombotic and anti-inflammatory properties, aspirin might reduce stroke severity and improve outcome by more than 1 mechanism.

CD was also associated with elevated blood glucose and increased FDP. Previous studies have correlated elevated blood glucose levels with poor outcome. Studies have also shown a relationship of stroke severity with hemostatic factors including FDP. It is unlikely that the relationship of CD to increased FDP in our study was due to fibrinolysis resulting from rt-PA administration because CD was, if anything, less frequent in rt-P–treated patients. It is not clear if elevated glucose and FDP are causally related to poor outcome and not just the result of a more severe stroke. However, the association of these variables to CD occurring over the next 7 to 10 days after the stroke might support therapeutic attempts to normalize these variables in acute stroke patients.

Finally, experimental neuronal cytotoxicity has been linked to rt-PA. However, this explanation for the CD seen in our patients was not supported by our observation that rates of DFI and CD were not different between placebo and rt-PA–treated patients.

In conclusion, DFI and CD occur in at least 15% of stroke patients during the first 24 hours, but neither DFI or CD are more frequent in patients treated with rt-PA. Our data suggest that mechanisms other than cerebral arterial reocclusion may explain the majority of these clinical fluctuations. These mechanisms deserve further study to avoid the poor clinical outcome associated with both DFI and CD.

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