Mismatch-Based Delayed Thrombolysis
A Meta-Analysis

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Background and Purpose—Clinical benefit from thrombolysis is reduced as stroke onset to treatment time increases. The use of “mismatch” imaging to identify patients for delayed treatment has face validity and has been used in case series and clinical trials. We undertook a meta-analysis of relevant trials to examine whether present evidence supports delayed thrombolysis among patients selected according to mismatch criteria.

Methods—We collated outcome data for patients who were enrolled after 3 hours of stroke onset in thrombolysis trials and had mismatch on pretreatment imaging. We selected the trials on the basis of a systematic search of the Web of Knowledge. We compared favorable outcome, reperfusion and/or recanalization, mortality, and symptomatic intracerebral hemorrhage between the thrombolysed and nonthrombolysed groups of patients and the probability of a favorable outcome among patients with successful reperfusion and clinical findings for 3 to 6 versus 6 to 9 hours from poststroke onset. Results are expressed as adjusted odds ratios (a-ORs) with 95% CIs. Heterogeneity was explored by test statistics for clinical heterogeneity, $I^2$ (inconsistency), and L’Abbé plot.

Results—We identified articles describing the DIAS, DIAS II, DEDAS, DEFUSE, and EPITHET trials, giving a total of 502 mismatch patients thrombolysed beyond 3 hours. The combined a-ORs for favorable outcomes were greater for patients who had successful reperfusion (a-OR=5.2; 95% CI, 3 to 9; $I^2=0$%). Favorable clinical outcome was not significantly improved by thrombolysis (a-OR=1.3; 95% CI, 0.8 to 2.0; $I^2=20.9$%). Odds for reperfusion/recanalization were increased among patients who received thrombolytic therapy (a-OR=3.0; 95% CI, 1.6 to 5.8; $I^2=25.7$%). The combined data showed a significant increase in mortality after thrombolysis (a-OR=2.4; 95% CI, 1.2 to 4.9; $I^2=0$%), but this was not confirmed when we excluded data from desmoteplase doses that were abandoned in clinical development (a-OR=1.6; 95% CI, 0.7 to 3.7; $I^2=0$%). Symptomatic intracerebral hemorrhage was significantly increased after thrombolysis (a-OR=6.5; 95% CI, 1.2 to 35.4; $I^2=0$%) but not significant after exclusion of abandoned doses of desmoteplase (a-OR=5.4; 95% CI, 0.9 to 31.8; $I^2=0$%).

Conclusions—Delayed thrombolysis amongst patients selected according to mismatch imaging is associated with increased reperfusion/recanalization. Recanalization/reperfusion is associated with improved outcomes. However, delayed thrombolysis in mismatch patients was not confirmed to improve clinical outcome, although a useful clinical benefit remains possible. Thrombolysis carries a significant risk of symptomatic intracerebral hemorrhage and possibly increased mortality. Criteria to diagnose mismatch are still evolving. Validation of the mismatch selection paradigm is required with a phase III trial. Pending these results, delayed treatment, even according to mismatch selection, cannot be recommended as part of routine care. (Stroke. 2010;41:e25-e33.)

Key Words: thrombolysis ■ mismatch ■ perfusion ■ desmoteplase

Thrombolysis is the primary therapy for acute stroke patients in the early hours after symptom onset1−3 but has a short treatment window. In a meta-analysis of data derived from 2775 patients (pooled from the ATLANTIS, ECASS, and NINDS trials), there was a gradually diminishing benefit toward 6 hours from stroke onset [(odds ratio |OR|=2.8; 95% CI, 1.8 to 4.5) for 0 to 90 minutes, 1.6 (95% CI, 1.1 to 2.2) for 91 to 180 minutes, 1.4 (95% CI, 1.1 to 1.9) for 181 to 270 minutes, and 1.2 (95% CI, 0.9 to 1.5) for 271 to 360 minutes].4 Recently, the ECASS III trial (N=821; treatment...
Several trials have tested approaches to select patients who have remaining salvageable tissue for delayed treatment has been proposed, most notably thrombolysis even beyond 4.5 hours. Conversely, others may be at increased risk from late treatment. The use of imaging approaches to select patients who have remaining salvageable tissue for delayed treatment has been proposed, most notably approaches that include magnetic resonance imaging (MRI) perfusion/diffusion “mismatch.” Several trials have tested thrombolysis in patients selected after MRI; some centers have also incorporated mismatch imaging and delayed thrombolysis into their routine clinical practice. We undertook a meta-analysis of data in the public domain to examine whether extension of the treatment window among patients selected according to the presence of mismatch can be recommended for routine clinical practice.

Methods

Selection of Trials

We planned to include only relevant articles that described the findings of studies that either undertook prospective enrollment of consecutive stroke patients with a mismatch profile suitable for delayed thrombolysis (beyond 3 hours of stroke onset) or had studied mismatch-based, delayed thrombolysis in a randomized controlled design. We excluded case reports, case series, and studies restricted to specific anatomic brain locations. We defined the (1) mismatch profile as a perfusion volume at least 1.2 times that of the infarct core with use of the imaging methodology available at the specific trial center, (2) symptomatic intracerebral hemorrhage (SICH) as a radiologically confirmed cerebral hemorrhage in association with clinical worsening after thrombolytic therapy (within 36 hours in the case of therapy with recombinant tissue-type plasminogen activator [rt-PA] and 72 hours in the case of therapy with desmoteplase), (3) reperfusion and/or recanalization according to the respective studies’ definitions, (4) favorable clinical outcome as a National Institutes of Health Stroke Scale (NIHSS) improvement of 8 points from baseline or attainment of an NIHSS score of 0 or 1 and/or a modified Rankin Scale score of 0 or 1, and (5) mortality as death (Rankin Scale score of 6) in the 90 days after thrombolytic therapy. We considered rt-PA and 72 hours in the case of therapy with desmoteplase), (3) reperfusion and/or recanalization according to the respective studies’ definitions, (4) favorable clinical outcome as a National Institutes of Health Stroke Scale (NIHSS) improvement of 8 points from baseline or attainment of an NIHSS score of 0 or 1 and/or a modified Rankin Scale score of 0 or 1, and (5) mortality as death (Rankin Scale score of 6) in the 90 days after thrombolytic therapy. We considered rt-PA and desmoteplase together because both are thrombolytic agents.

They differ in some features: desmoteplase lacks the second kringle site in its molecular structure, does not need to be cleaved by plasmin, is active in its single-chain form, has reduced neurotoxicity, and has limited passage through the blood-brain barrier. Desmoteplase has a theoretical advantage over rt-PA because the former is almost nonfunctional when fibrin is absent. Alteplase is already a proven therapy for treating stroke patients within the early hours after stroke onset (NINDS16 and ECASS III). Doses that have acceptable safety and efficacy have been identified. Both desmoteplase and alteplase remain investigational for delayed thrombolysis. However, we undertook a sensitivity analyses for any differential effect between desmoteplase and alteplase.

Until the DIAS II study, identification of the ischemic penumbra was based on the mismatch between MRI perfusion-weighted imaging and diffusion-weighted imaging. For the first time, the DIAS II investigators were permitted to select patients on the basis of visual inspection of the mismatch on perfusion computed tomography (CT) images as an alternative to MRI perfusion studies, depending on the local expertise of the imaging center. We included data from either method as reported in the DIAS II publication.

We included all trials that defined the mismatch profile as the perfusion volume being 1.2 times the infarct core. We placed no restriction on the manner in which perfusion was measured in these trials. For example, in DIAS II, the mismatch population was identified on the basis of either CT perfusion or MRI perfusion, according to center preference. The determination of mismatch in DEFUSE and EPITHET trials was based on postprocessed perfusion-weighted imaging data that included correction for arterial input and thresholding. In contrast, in the desmoteplase studies, mismatch was determined in “real time,” without postprocessing, by the investigator using the “eyeball” technique.

End Points

End points of interest for our meta-analysis were comparisons between thrombolysed and nonthrombolysed patients in (1) favorable outcome, (2) reperfusion and/or recanalization, (3) mortality, and (4) SICH. We also examined the rates of favorable versus unfavorable clinical outcome amongst successfully reperfused patients.

Search

We first searched the Web of Knowledge for 10 broad terms: “clinical trial,” “prospective study,” “stroke trial,” “thrombolytic agent,” “desmoteplase,” “tissue plasminogen activator,” “recanalization in stroke,” “reperfusion therapy in stroke,” “penumbra in stroke,” and “mismatch hypotheses.” Then we refined our search by combining these with terms that underlie the mismatch hypotheses and thrombolysis. Our last search was undertaken on March 1, 2009. From a review of the title and abstract, we selected for further examination all relevant articles describing the original findings of studies that used the mismatch hypotheses and selected patients for thrombolysis despite delay beyond 3 hours of stroke onset. We checked whether any later article or abstract offered supplemental data. Once selected, each article was read completely and the relevant data extracted. We also searched the bibliography of each of these articles for additional articles.

Statistical Analysis

For this meta-analysis, we retrieved “estimate(s) of effect” from the abstract(s). When relevant data were missing, we searched the full text and any supplementary articles. Primarily, we wished to analyze data derived from the patients with a mismatch profile on an intention-to-treat basis, but when intention-to-treat data were unavailable, we accepted “per protocol” data and described the underlying limitations. Our comparisons were mainly planned between patients offered any dose of any thrombolytic agent and the corresponding placebo-treated patients.

We performed subgroup analyses amongst patients who were treated with thrombolytics at doses approved or still under clinical investigation, ie, 90 μg/kg desmoteplase or 0.9 mg/kg rt-PA. Comparisons (summary estimates) are expressed as ORs and their 95% CIs. Whereas we applied both fixed (inverse-variance weighting method) and random (adjusted OR [a-OR]) methods to calculate the summary estimate, we reported only the findings of the fixed method but have indicated the instances where the results diverged.

We assessed the heterogeneity with the test statistics for heterogeneity and I² for inconsistency supported by examination of L’Abbé plots.

Our analysis included data derived from those patients who were selected (or could have been selected) on the basis of their mismatch profile. To assess whether favorable outcomes (clinical outcomes at day 90) were more common amongst patients who had successful reperfusion, we retrieved data on 242 patients for whom the reperfusion findings were available (the DIAS I trial, N = 97; the DEDAS trial, N = 34; the EPITHET trial, N = 77 [“good neurological outcome” for patients with n = 30 and without n = 47] reperfusion in mismatch patients only]; and the DEFUSE trial, N = 34, in mismatch patients with n = 18 and without n = 16) early reperfusion). Corresponding information was not reported in the DIAS II trial. Similarly, to answer whether a favorable clinical outcome occurred more frequently in the thrombolysed group of patients, information on 410 patients was available (DIAS I, N = 102; DIAS II, N = 186; DEDAS, N = 37; and EPITHET,
N=85; mismatch patients with and without good neurological outcome in the thrombolysis group, n=42, and the placebo group, n=43)23 for those patients who received any thrombolytic agent at any dosage. Next, to answer whether reperfusion or recanalization occurred more frequently amongst those who were thrombolyzed, we retrieved data on 211 patients who received thrombolytic therapy at any dose (DIAS I, 97 patients20; DEDAS, intention to treat 37 patients19 and target population 23 patients; and EPITHET, 77 patients22). To assess mortality between thrombolyzed and non-thrombolyzed patients, we extracted data on 410 patients (DIAS I, 102 patients20; DIAS II, 186 patients18; DEDAS, 37 patients19; and EPITHET, 85 mismatch only patients22). To assess SICH between thrombolyzed and nonthrombolyzed patients, we extracted data on 405 patients (DIAS I, 102 patients20; DIAS II, 186 patients18; DEDAS, 37 patients19; and EPITHET, 80 mismatch patients only22). Owing to mathematical difficulties involved in calculating OR when the numerator is zero, we combined the DEDAS data with DIAS I data for mortality analysis.

We undertook sensitivity (subgroup) analyses in which we compared the data after excluding the data for those who received doses of desmoteplase that were abandoned for further evaluation. We also analyzed differences in clinical outcome between the patients who were thrombolyzed within 3 to 6 hours of stroke onset versus those who were thrombolyzed beyond 6 hours. Finally, we compared and contrasted the attributes of the studies and assessed their quality on the basis of the manner in which patients were enrolled and the resulting baseline characteristics.

Results

Literature Search

The literature search led to 13 citations on the DEFUSE trial (10 articles)23–32, 2 on the DEDAS trial (1 article19), 6 on the DIAS trial20,30, 9 on the EPITHET trial (8 articles20,22,33–36), and 2 on DIAS II (1 article).37 Information on 502 patients was obtained from the 5 main articles describing the relevant trials (DIAS, 104 patients20; DIAS II, 186 patients18; DEDAS, 37 patients19; DEFUSE, 74 patients23; and EPITHET, 101 patients22), and the data corresponding to patients with a mismatch profile were retrieved for subsequent analysis.

Comparative Analysis of the Mismatch Trials

We compared the attributes that differed between trials to highlight the underlying heterogeneity in the manner in which the selected trials were conducted (Supplemental Table I available online at http://stroke.ahajournals.org). DIAS II18 enrolled the least severely affected stroke patients (median NIHSS score=9) and EPITHET,22 the most severely affected (median NIHSS score=14 in the treatment arm and 10 in the placebo arm). Median baseline NIHSS scores were 11.5 and 12, respectively, in the DEFUSE23 and DIAS I20 trials. We also compared the time since stroke onset until thrombolysis (OTT), and we assessed qualitatively the proportion of patients treated in each trial after 4.5 hours (Supplemental Table II, available online at http://stroke.ahajournals.org). Detailed analysis of OTT could not be undertaken without raw data.

Findings From Statistical Analyses

**Did Reperfusion or Recanalization Occur More Frequently in Patients Who Were Thrombolyzed?**

The data from 211 patients showed greater individual odds for reperfusion and/or recanalization amongst those who received thrombolytic therapy in: DIAS I20 (OR=4.1; 95% CI, 1.3 to 15.2) and EPITHET (OR=3.7; 95% CI, 1.3 to 10.8). Odds were nonsignificant in the DEDAS trial19 (OR=0.9; 95% CI, 0.1 to 6.9). The combined data gave a greater adjusted odds for reperfusion/recanalization for the patients who had thrombolytic therapy at any dosage (a-OR=3.0; 95% CI, 1.6 to 5.8; P<0.05, P for heterogeneity=0.26, and I²=25.7%; Figure 1a).

We repeated our analysis after excluding desmoteplase doses that were abandoned for clinical development; the subanalysis restricted to 90 μg/kg desmoteplase or rt-PA gave an a-OR=2.65 and a 95% CI of 1.3 to 5.5 (P=0.007 fixed method; Figure 1b) and an a-OR=2.28 and a 95% CI of 0.7 to 7.3 (P=0.17 random method; Figure 1c) (P for clinical heterogeneity=0.13, and I²=50.5%). We also examined the underlying heterogeneity by L’Abbé plot (Figures 2a and 2b).

**Are Favorable Outcomes More Common in Patients Who Underwent Reperfusion?**

The individual odds for a favorable clinical outcome in the 4 studies reporting this end point were greater in patients who underwent reperfusion compared with those who did not
(DIAS I\textsuperscript{20} OR=3.4; 95% CI, 1.3 to 8.8; DEDAS\textsuperscript{19} OR=9.6; 95% CI, 1.5 to 64.6; EPITHET\textsuperscript{22} OR=7.2; 95% CI, 2.3 to 23.2; and DEFUSE\textsuperscript{23} OR=5.4; 95% CI, 0.94 to 38.1). For all trials combined, the a-ORs were greater for patients who had successful reperfusion compared with those who did not (a-OR=5.2; 95% CI, 3 to 9.1; \(P\) for clinical heterogeneity=0.60; \(I^2\)=0%; Figure 3a).

In a sensitivity analyses in which DEFUSE\textsuperscript{23} trial data were excluded (as DEFUSE,\textsuperscript{23} unlike others, was a nonrandomized, prospectively conducted study), the a-OR remained greater among patients with successful reperfusion (a-OR=5.2; 95% CI, 2.8 to 9.5; \(P\)=0.00; heterogeneity statistics \(P\)=0.4; \(I^2\)=0%; Figure 3b).

**Did a Favorable Clinical Outcome Occur More Frequently in the Thrombolysed Group of Patients?**

With the exception of DIAS II\textsuperscript{18} all trials reported nonsignificantly improved odds of a favorable clinical outcome in the thrombolysis group of patients: DIAS I\textsuperscript{20} OR=2.2; 95% CI, 0.7 to 7.4; DEDAS\textsuperscript{19} OR=2.4; 95% CI, 0.4 to 28.0; EPITHET\textsuperscript{22} OR=1.7; 95% CI, 0.7 to 4.4; and DIAS II\textsuperscript{18} OR=0.8; 95% CI, 0.4 to 1.6. The combined data analysis failed to show a significant benefit (a-OR=1.28; 95% CI, 0.84 to 1.97; \(P\) for clinical heterogeneity=0.28; \(I^2\)=20.9%; Figure 4a). After exclusion of DIAS II data, a-OR was 1.96, 95% CI was 1.06 to 3.63, and for clinical heterogeneity, \(I^2\)=0% and \(P\)=0.89 (Figure 4b).

We repeated our analysis after excluding desmoteplase doses that were abandoned for clinical development: with 90 \(\mu\)g/kg desmoteplase and rt-PA 0.9 mg/kg data alone, we found a-OR=1.4; 95% CI, 0.9 to 2.3, \(P\)=0.16; for clinical heterogeneity, \(P\)=0.56 and \(I^2\)=0%. After exclusion of DIAS II data, OR=1.88; 95% CI, 0.95 to 3.72, and heterogeneity...
statistics $I^2=0\%$ and $P=0.69$ (Figure 4c). L’Abbé plots were examined for underlying heterogeneity in these analyses (Figure 5). Under sensitivity analysis, no differential effect of desmoteplase versus alteplase was found, with the ratio of OR $0.7$ (95% CI, 0.24 to 1.92; $P=0.46$).

**Was There a Greater Probability of SICH in Thrombolysed Compared With Nonthrombolysed Patients?**

Here, the individual odds for SICH were nonsignificant in the thrombolysis group: DIAS I OR $1.6$; 95% CI, 0.7 to 3.7; and DEDAS OR $0.5$; 95% CI, 0.0 to 3.4. The combined data analysis found a significant increase in mortality in the thrombolysis group of patients compared with the placebo group (a-OR $2.4$; 95% CI, 1.2 to 4.9; $P=0.02$; P for heterogeneity $0.67$; and $I^2=0\%$; Figure 6a).

Repeating our analysis after excluding data from the abandoned desmoteplase doses, ie, restricting the analysis to treated with 90 μg/kg desmoteplase or 0.9 mg/kg rt-PA, we found a-OR $1.6$; 95% CI, 0.7 to 3.7; $P=0.28$; P for heterogeneity $0.56$; and $I^2=0\%$ (Figure 6b). Under sensitivity analysis, no differential effect of desmoteplase versus alteplase was found, with the OR $0.8$ (95% CI, 0.2 to 3.5; $P=0.8$).

**Was There a Greater Probability of SICH in Thrombolysed Compared With Nonthrombolysed Patients?**

The individual odds for SICH were nonsignificant: DIAS I OR $7.9$; 95% CI, 0.7 to infinity; DIAS II OR $5.9$; 95% CI, 0.5 to infinity; and EPITHET OR $152.6$; 95% CI, 15.9 to infinity; but the combined odds for SICH were significantly greater for the group that underwent thrombolytic therapy (a-OR $24.7$; 95% CI, 5.2 to 118.2; heterogeneity statistics $I^2=35.4\%$ and $P=0.2$; Figure 7a). After we combined data from DEDAS with DIAS I, the findings remained nonsignificant for the individual odds (DIAS I+DEDAS OR $7.1$; 95% CI, 0.7 to infinity) but were significant for the combined analysis (a-OR $6.5$; 95% CI, 1.2 to 35.4, and for clinical heterogeneity, $P=1.0$ and $I^2=0\%$; Figure 7b).

Repeating the analysis by excluding the data associated with abandoned thrombolytic doses, the findings were nonsignificant for both individual odds (DIAS I+DEDAS OR $3.7$; 95% CI, 0.03 to infinity; DIAS II OR $5.7$; 95% CI, 0.2 to infinity; and EPITHET OR $6.5$; 95% CI, 0.4 to infinity) and in combination a-OR $5.4$; 95% CI, 0.9 to 31.8; $P$ for heterogeneity $0.97$; and $I^2=0\%$ (Figure 7c) but attained marginal significance of the adjusted odds derived by considering the DIAS I and DEDAS data separately (a-OR $6.0$; 95% CI, 1.00 to 35.8; heterogeneity statistics $P=1.00$ and $I^2=0\%$). There were no SICH occurrences in the placebo arms, and therefore, a sensitivity analysis to assess any differential effect of desmoteplase versus alteplase could not be undertaken.

**Were There Better Clinical Findings (Outcomes or Reperfusion) When Treatment Was Commenced Within 3 to 6 Hours Versus 6 to 9 Hours?**

Limited data were available to examine OTT, and neither DIAS I nor DIAS II individually suggested significantly greater odds (DIAS I OR $1.07$; 95% CI, 0.4 to 2.9; $P=0.9$;
DIAS II OR = 0.8; 95% CI, 0.4 to 1.8; P = 0.7). With the data from both trials combined, the a-OR = 0.9; 95% CI, 0.5 to 1.7, and P = 0.8 (Figure 8).

Analysis of Mortality
In DIAS I, 1 placebo and 2 desmoteplase deaths occurred due to cardiac causes. In the DIAS II trial, only 1 of 3 deaths in the 90 μg/kg group and 3 of 14 deaths in the 125 μg/kg group were considered related to the trial medication. In the DEDAS trial, the sole death in the 90 μg/kg group was due to aspiration pneumonia, whereas that in the 125 μg/kg groups was due to evolving neurologic deterioration of a left middle cerebral artery infarct, leading to pneumonia.

Discussion
We undertook a meta-analysis of all previous studies that evaluated the principle of physiologic selection for delayed thrombolysis, based on the presence of potentially viable tissue in the ischemic penumbra.38,39 These trials used the mismatch hypothesis with either MRI (perfusion/diffusion mismatch) or CT (perfusion/cerebral blood volume mismatch) as a signature of the putative penumbra.19,20,22,24,25,40–43 Apart from the recent DIAS II trial,18 these trials had supported the physiologic basis of the mismatch concept. The disappointing findings of the DIAS II trial have been attributed to limitations of the study and to chance.37 To test for consistency, we undertook a meta-analysis of the studies that studied the mismatch hypothesis to select and thrombolyze patients despite delays beyond 3 hours. Five trials, DIAS I,20 DIAS II,18 EPITHET,22 DEFUSE,23 and DEDAS,19 were available for inclusion. Our results indicate that reperfusion/recanalization is more common with thrombolysis when all doses are considered together, but the significance was lost with the exclusion of data for abandoned doses, which reduced the power of our analysis through effects on sample size. Furthermore, a favorable clinical outcome was more common
amongst patients with successful reperfusion of the ischemic parenchyma, despite delays beyond 3 hours from stroke onset. This conclusion was not influenced by inclusion of the nonrandomized DEFUSE trial\textsuperscript{23} data. The DIAS II trial\textsuperscript{18} did not report reperfusion findings.

However, we did not find evidence that a favorable clinical outcome was significantly improved in the group that underwent thrombolysis. Neither did we find a significant benefit when we excluded doses of desmoteplase that were abandoned for clinical development. The CI around our estimate of effect remains wide and would be consistent with a doubling of odds for a favorable outcome, although in this respect, DIAS II suggests that the likely upper limit may be 1.6. Even so, odds of 1.6 remain greater than those achieved in unselected patients treated with rt-PA in the ECASS III trial\textsuperscript{17} and have been regarded as sufficient to influence national and European stroke treatment guidelines (SIGN\textsuperscript{44} and ESO\textsuperscript{45}).

Late treatment, even amongst selected patients, may carry some risk. We found a marginally significant increase in the odds of death among all treated patients, with a point estimate of 2.4. When we restricted the analysis to 0.9 mg/kg rt-PA and to the dose of desmoteplase that remains under development (90 μg/kg), the OR for mortality fell to 1.6 and the risk was nonsignificant. Higher doses of desmoteplase were clearly linked to excessive SICH and were abandoned for this reason. Our analysis did not take into account the attributed cause of death. Many deaths in DIAS II and EPITHET were considered unrelated to treatment. The attribution may be important for understanding the mechanism of effect, but caution is required when drawing conclusions from subjective assessments such as these. Treatment failure can contribute to late death, just as unrecognized excitotoxic damage may represent a potential mechanism. Regardless, if mortality is increased, this may be mediated via hemorrhagic transformation.

Despite a lack of significance in the individual odds for SICH in patients given thrombolytic therapy, the a-OR indicated a statistically significant increase in SICH after delayed thrombolysis. Similarly, an increased risk of SICH has long been recognized for time-based t-PA in the established clinical windows, but this is offset by the improved clinical outcomes in treated patients. After exclusion of doses of desmoteplase that were abandoned for clinical development,\textsuperscript{20} the adjusted odds for SICH again lost significance.

Caution is required in interpreting these post hoc subgroup analyses. Although the inclusion of data from all doses may give a falsely pessimistic view of the risk/benefit profile after mismatch-based thrombolysis, post hoc exclusion of doses that were abandoned in clinical development is a data-driven decision and raises statistical concerns of bias that can only be assuaged by further prospective trials. We found no evidence that relatively earlier (3- to 6-hour) versus later (6- to 9-hour) treatment influenced our findings. This is particularly relevant, because ECASS III has recently shown that unselected patients benefit from alteplase given within 4.5 hours of stroke onset, and a small proportion of patients in the mismatch trials would now be considered eligible for such treatment. We cannot exclude the possibility that some of the potential benefit among mismatch patients may be time dependent, but it appears unlikely that this is sufficient to explain all effects. Now that the ECASS III results have been presented, another meta-analysis of individual patient data from the trials studied herein should be undertaken to assess clinical and radiologic outcomes for patients who were thrombolized beyond 4.5 hours of stroke onset. Similarly, an additional analysis comparing outcomes in patients with mismatch versus those without mismatch is desirable but was beyond the scope of our meta-analysis.

Our meta-analysis included data from 5 different trials,\textsuperscript{18,20,22–23} of which DEFUSE\textsuperscript{23} could be considered only in the analysis of a favorable clinical outcome among patients with reperfusion versus no reperfusion. DIAS II\textsuperscript{18} did not report reperfusion findings and had to be excluded where these data were needed. The L’Abbé plot\textsuperscript{46,47} suggested that DIAS II\textsuperscript{18} contributed to the heterogeneity in the combined analysis of favorable outcomes in all thrombolized patients, and the DEDAS trial contributed to the heterogeneity in the analysis of reperfusion and recanalization in patients thrombolized with the abandoned doses excluded. Both sources of heterogeneity appeared to affect the results by virtue of the effects of sample size on the power of a study.

We know that the number needed to treat to achieve an enhanced favorable outcome with alteplase may be as few as 7 within 3 hours, but this number has risen by 3 to 4.5 hours to \textasciitilde 14.\textsuperscript{3} When treatment with alteplase is started within 6 hours OTT, the number needed to treat rises to 25.\textsuperscript{48} Hence, our challenge is to identify those patients most likely to benefit from delayed thrombolysis. The use of either MRI to identify perfusion/diffusion mismatch or a CT-based alternative is attractive. It is clear from our data that delayed thrombolysis among patients selected according to mismatch imaging is associated with increased reperfusion/recanalization and that recanalization/reperfusion is associated with improved outcomes. At present, although the data remain consistent with improved functional outcome from delayed thrombolysis among mismatch patients, a statistically significant benefit on functional outcomes has not been confirmed. Although our pooled results suggest that mortality may be higher, the retention of excessive doses of desmoteplase in the analysis is likely to lead to overestimation of any risk.

We note that existing methods for defining mismatch may be optimized in the future, resulting in greater power of the mismatch-based thrombolysis studies. For example, we considered 1.2 as the cutoff for defining a mismatch profile. However, a post hoc analysis of the DEFUSE study has recently shown that the highest sensitivity and specificity occurred at a mismatch ratio of 2.6, suggesting that the previous studies were probably underpowered and lacked a sufficiently rigorous definition for the mismatch ratio.\textsuperscript{27} Furthermore, the 2-second threshold for Tmax is likely also suboptimal, as a posthoc analyses of DEFUSE data showed a significantly better correlation between infarct growth and penumbra salvage volume for perfusion-weighted imaging lesions defined by Tmax >6 seconds.\textsuperscript{29} The EPITHET investigators reported similar findings.\textsuperscript{33} It is now clear that both trials included significant volumes of benign oligemia in their mismatch assessments. Recently, automated online anal-
ysis of MR mismatch has been described that facilitates rapid selection of patients for delayed treatment. In summary, continued refinement in the definitions of different perfusion parameters may result in a better choice of the best measure of perfusion (Tnax, time to peak, mean transit time, cerebral blood volume, or cerebral blood flow) and correction for arterial input functions.

Thus, the definitions used in the trials published to date have been generous and have included many patients who had limited penumbral tissue and limited prospects of clinical improvement in response to thrombolysis. The recently formed STIR collaboration is initiating a detailed examination of this topic. The diversity of mismatch definitions and large number of investigators involved in these studies weakens conclusions about the potential value of mismatch in the future clinical management of patients with stroke. However, these weaknesses do not extend to our conclusions about the status of existing evidence for use of thrombolysis among mismatch patients: patients were selected according to the best intentions of the investigators under protocols that were state of the art when written, although they have already been superseded. Prospective phase III trials are required to test whether thrombolysis is associated with a favorable risk/benefit ratio when used under modified circumstances. In Australia, the EXTEND trial, which will use a phase III design and randomization of patients 4.5 to 9 hours after stroke onset to alteplase or placebo and automated mismatch selection, will test this hypothesis. Meanwhile, although the concept of selection of patients based on individual pathophysiology rather than a rigid time window remains attractive, delayed treatment according to mismatch selection cannot be recommended as part of routine care until or unless further trials show benefit.

Disclosures

N.K.M. is supported by a University of Glasgow scholarship. G.W.A. was the principal investigator of the DEFUSE trial, is a consultant to Genentech and to Lundbeck, and was cochair of the EPITHET trial, is on the advisory board of Servier and a consultant to Genentech and to Lundbeck, and was cochair for the EXPERT trial. N.K.M. is supported by a University of Glasgow scholarship. A.J.F. is chairman of the steering committee of DIAS and cochair of the EXTEND trial, which will use a phase III design and randomization of patients 4.5 to 9 hours after stroke onset to alteplase or placebo and automated mismatch selection, will test this hypothesis. Meanwhile, although the concept of selection of patients based on individual pathophysiology rather than a rigid time window remains attractive, delayed treatment according to mismatch selection cannot be recommended as part of routine care until or unless further trials show benefit.

References


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In the article “Mismatch-Based Delayed Thrombolysis: A Meta-Analysis” by Mishra et al,1 two sentences had incorrect reference citations. The corrections are listed below.

1. On page e27, under Results in the subsection “Literature Search,” 6th line: “(DIAS, 104 patients8; DIAS II, 186 patients18; DEDAS, 37 patients9; DEFUSE, 74 patients10; and EPITHET, 101 patients11)” should be replaced with “(DIAS, 104 patients20; DIAS II, 186 patients18; DEDAS, 37 patients19; DEFUSE, 74 patients23; and EPITHET, 101 patients22).”

2. On page e28, under the subsection entitled “Did a Favorable Clinical Outcome Occur More Frequently in the Thrombolyzed Group of Patients?,” 1st line, “With the exception of DIAS II,24” should be replaced with “With the exception of DIAS II,18.”

The authors and publisher regret these errors.

The corrected version can be viewed online at http://stroke.ahajournals.org.
Stroke January 2010

Original Contributions

Mismatch-Based Delayed Thrombolysis: A Meta-Analysis

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背景与目的:卒中发生后,随着发病时间到接受治疗的时间间隔延长,患者从溶栓治疗中的临床获益将会下降。目前在临床病例研究及临床试验中已开始使用影像学上的“错配”模型来识别可以进行扩大时间窗溶栓治疗的患者,该方法具有一定的表面效度。我们此次对相关的临床试验进行荟萃分析就是为了检验目前所获得的证据是否支持“错配”模型指导下的扩大时间窗的溶栓治疗。

方法:我们收集了在卒中发生3小时以后接受溶栓治疗研究患者的结局数据,其溶栓治疗前影像检查提示存在“错配”。该荟萃分析所参考的临床试验均通过对Web of Knowledge网站进行系统检索得到。我们比较了溶栓患者与非溶栓患者在良好结局、再灌注或血管再通、死亡率、症状性颅内出血方面存在的差异,同时还比较了卒中后3-6小时溶栓组与6-9小时溶栓组实现成功再灌注及临床症状改善患者良好结局的可能性。结果以调整的OR值及95% CI来表示。通过临床异质性、I²(不一致性)以及L’Abbé点的统计变量来检验其异质性。

结果:我们检索到了DIAS、DIASII、DEDAS、DEFUSE以及EPITHET试验的相关文章,共获得502例发病3小时后接受溶栓治疗的患者。成功再灌注的患者其发生良好结局的调整OR值大于未实现再灌注患者的调整OR值(调整OR=5.2;95% CI: 3.9-8.0;I²=0%)。接受溶栓治疗患者的再灌注/血管再通的比值比有所增加(调整OR=3.0;95% CI: 1.6-5.8;I²=25.7%)。联合数据分析显示溶栓后患者死亡率显著增加(调整OR=2.4;95% CI: 1.2-4.9;I²=0%)。溶栓后患者发生症状性颅内出血的风险显著增加(调整OR=6.5;95% CI: 1.2-35.4;I²=0%)。但是当剔除了临床已废弃的去氨普酶剂量的数据后并未重复得到上述结果(调整OR=1.6;95% CI: 0.7-3.7;I²=0%)。

结论:依据影像学的错配模型对患者进行扩大溶栓时间窗的筛选可使溶栓患者的再灌注/血管再通常与临床结局改善有关。尽管患者临床仍有可能获益,但此荟萃分析结果却显示扩大时间窗的溶栓治疗并未使患者的临床结局得到改善。扩大时间窗的溶栓治疗使症状性颅内出血的风险显著增加,还有可能导致死亡率增加。目前关于错配模型的诊断标准仍在不断演变发展,需要通过III期临床试验进一步验证。

关键词:溶栓,错配,灌注,去氨普酶

(Stroke. 2010;41:e25-e33. 王春娟 译 刘丽萍 秦海强 校)
大时间窗的溶栓治疗而增加风险。因此，人们提出了通过影像学检查的方法来筛选那些存在可挽救脑组织的患者，使其能从扩大时间窗的溶栓治疗中获益。这些方法中最为重要的就是通过磁共振灌注相 (PWI) 与弥散相 (DWI) 之间的“错配”来筛选患者 [5,6]。目前，已经有几个试验通过磁共振的方法来筛选患者并进行溶栓治疗，甚至有些中心还将影像的错配和扩大时间窗的溶栓治疗应用于常规的临床工作 [7]。我们此研究的目的就是通过对已发表的数据进行荟萃分析来明确通过错配模型筛选患者进行溶栓治疗是否能够在临床中常规推荐。

方法

试验的选择

该荟萃分析只入选了描述相关试验结果的文章，这些试验可以是通过既定的错配模型来前瞻性连续入组扩大时间窗的溶栓患者（在卒中发病后 3 小时之外），也可以是以错配为基础进行的随机对照研究。该研究排除了个案报道、病例系列报道以及局限于特定解剖部位的研究报道 [8]。其对入选试验中相关概念的定义如下：(1)“错配”模型指的是灌注异常的体积应至少是梗死核心的 1.2 倍，且该影像检查方法在指定的临床研究中心可以开展；(2)“症状性颅内出血”(SICH) 应是在溶栓治疗后经过放射检查证实的脑出血，同时伴有临床症状的加重（对于重组组织型纤溶酶原激活物 [rt-PA] 治疗的患者其发生的时间应在 36 小时之内，而对于去氨普酶治疗的患者其发生的时间应在 72 小时之内）；(3) 再灌注和 / 或血管再通均分别按照各种研究的定义执行；(4) 良好的临床结局定义为国立卫生研究院卒中量表 (NIHSS) 评分较基线改善大于等于 8 分或 NIHSS 达到 0 分或 1 分同时 / 或者改良 Rankin 量表 (mRS) 评分为 0 分或 1 分；(5) 死亡率指的是在溶栓治疗后 90 天内发生的死亡 (mRS=6)。因为 rt-PA 和去氨普酶均为溶栓治疗药物，故在荟萃分析中将二者放在一起进行研究 [9]。但是二者在某些方面仍有不同：去氨普酶的分子结构中缺乏第二个环状结构，不需要被纤溶酶断开，它在整个环结构时具有生物活性，神经毒性较 rt-PA 降低且只有有限的数量能通过血脑屏障。理论上去氨普酶比 rt-PA 具有优越性，因为在没有纤维蛋白的情况下去氨普酶几乎没有生物学活性 [9-15]。但阿替普酶是已经经过临床试验在卒中早期使用有效的溶栓药物 (NINDS [16] 和 ECASS III [17])。其可接受的安全和有效剂量也已经被证实 [18-20]。但是对于扩大溶栓时间窗后的有效性来说，二者尚需要进一步的研究证明。不过，我们还对所有关于去氨普酶与阿替普酶疗效差异的研究进行了敏感度分析。

文献检索

首先，我们在 Web of Knowledge 网站上以“clinical trial”、“prospective study”、“stroke trail*”、“thrombolytic agent”、“desmoteplase”、“tissue plasminogen activator”、“recanalization in stroke”、“reperfusion therapy in stroke”、“penumbra in stroke” 和“mismatch hypothesis” 10 个广义词条进行检索。然后，对这些文献进行精确定义，提炼出以“错配假说”和“溶栓”为主要侧重点的研究。该研究最后一次检索的时间是 2009 年 3 月 1 日。通过对这些文献的题目和摘要进行复习，我们挑选出那些提供了研究原始数据并应用错配假说筛选患者实施扩大 3 小时时间窗进行溶栓治疗的研究，并对其进行深入分析研究。对于挑选出来的每一篇文章我们都会通读全文并提取出相关的数据。另外，我们还检索了上述文章的参考文献作为分析的附件参考资料。

统计分析

在 DIAS II 研究之前，所有对缺血半暗带的识别都是通过磁共振灌注加权成像与弥散加权成像之间的错配来实现 [18]。而 DIAS II 研究获得允许首次将 CT 灌注成像显示错配用于患者筛选，可依据各研究中心的实际情况作为磁共振灌注研究的替代选择。所有将错配模型定义为灌注异常区至少是梗死核心区 1.2 倍的试验均纳入了此项研究。我们并没有限定上述研究中如何对灌注进行测量。例如，在 DIAS II 中，不同研究中心可根据实际情况选择 CT 灌注成像显示错配人群。而 DEFUSE 和 EPITHET 试验中对 CT 灌注的计算则是基于对灌注加权像进行后处理所得的数据，这些后处理数据已经对动脉输入的数值及灌注异常的阈值进行了校正。与之相反，在一系列的去氨普酶的研究中，错配是以“实时”生成的数据进行定义而不需要后处理的程序，这一过程主要通过研究者的“肉眼观察技术”来实现。
但是，ITT 分析所需要的数据无法得到，故最终选择进行“按方案分析 (PP 分析)”并对统计分析的潜在局限性进行了描述。我们的研究主要计划在溶栓患者与对应的未溶栓患者之间进行，无论溶栓患者接受的是何种剂量的何种溶栓药物。

我们对已批准的溶栓药物或者尚在临床试验阶段的溶栓药物（比如采用 90 μg/kg 的去氨普酶或者 0.9 mg/kg 的 rt-PA）实施溶栓治疗的患者进行了亚组分析。比较的结果（概要估计）以 OR 值及其 95% CI 表示。鉴于在概要估计时使用了固定效应模型（逆变换量加权方法）和随机效应模型（调整 OR 值 [a-OR] [21]）两种方法。在这里我们仅报告了固定效应模型方法的计算结果，但在数据结果离散的地方给出了图解。我们通过异质性检验的统计方法对数据的异质性进行检验，同时通过 L’Abbé 曲线检验产生的 I² 值来检测数据的不一致性。


在这些研究中有部分患者是因接受某一剂量的去氨普酶而被放弃再进行深入分析，在此次分析中，我们也同样排除了这一部分数据，其余入组的数据在对比后进行敏感性分析（亚组分析）。我们同样还分析了在发病后 3-6 小时之间溶栓的患者与发病 6 小时后接受溶栓的患者在临床结局上的不同。最后，我们比较并对比了这些研究在属性上的差别，评估了这些研究在患者入组方式上存在的质量问题以及由此所导致的基线特征。

### 结果

文献检索

文献检索出的相关引文分别为：DEFUSE 13 篇 (10 篇文章) [23-32]，DEDAS 试验 2 篇 (1 篇文章 [19])，DIAS 试验 6 篇 [20,30]，EPITHET 试验 9 篇 (8 篇文
章 [20,22,33-36]，DIAS II 2 篇（1 篇文章）[37]。从上述 5 篇主要描述相关试验的文章中提取了 502 名患者的信息 (DIAS, 104 名患者 [20]；DIAS II, 186 名患者 [18]；DEDAS, 37 名患者 [39]；DEFUSE, 74 名患者 [23]；EPITHET, 101 名患者 [22])，同时还提取了与错配模型相关的数据以进行后续分析。

错配模型试验的比较分析

我们比较了各项试验的不同属性，强调入选的这些试验在实施方法方面存在潜在的异质性 (补充表 I，来自网页 http://stroke.ahajournals.org)。DIAS II[18] 入选人群为受累最轻的卒中患者 (NIHSS 得分中位数 =9)，而 EPITHET[22] 入选人群为严重受累的卒中患者 (NIHSS 得分中位数在治疗组 =14，安慰剂组

=10)。DEFUSE[23] 和 DIAS II[20] 基线的 NIHSS 评分的中位数分别为 11.5 和 12。我们还比较了卒中发病至溶栓治疗的时间间隔 (OTT)，我们还从质量上对发病 4.5 小时以后接受治疗患者的比例进行评估 (补充表 II，来自网页 http://stroke.ahajournals.org)。但因文章中缺乏原始数据，无法对 OTT 进行详细分析。

统计分析中的发现

接受溶栓治疗的患者发生再灌注或血管再通的比例更高吗？

来自 211 名患者的数据显示，在以下这两个研究中，接受溶栓治疗的患者实现再通和 / 或再灌注有更大的个体优势：DIAS II[20] (OR=4.1 : 95% CI, 图 2 是否溶栓的患者更容易发生再灌注或血管再通呢？使用 L’Abbé 曲线分析完整数据结果如图 a；在因异质性剔除了一部分研究数据后分析结果如图 b。圆圈的大小表明样本量的多少；DIAS — 灰色圆圈；DE-DAS — 开放的圆圈；EPITHET — 黑色圆圈。

图 3 实现再灌注的患者更易产生良好的临床结局吗？使用固定效应模型对联合数据分析得出的结果如图 a；排除了 DEFUSE 数据后得出的结果如图 b；排除了已经剔除剂量的数据后得出的结果如图 c。
1.3-15.2)，EPITHET(OR=3.7, 95% CI, 1.3-10.8)。在 DEDAS 试验[19](OR=0.9; 95% CI, 0.1-6.9) 中，此优势却并不明显。联合分析数据显示接受任一剂量溶栓治疗的患者有更高的再灌注/血管再通的校正优势 (a-OR=3.0; 95% CI, 1.6-5.8; P<0.05, 异质性 P=0.26, I²=25.7%; 见图 1a)。

我们剔除一部分不再进行临床分析的去氨普酶的研究数据后再进行分析；该分析限定于使用90 μg/kg 去氨普酶或正常 rt-PA 剂量的患者, a-OR=2.65; 95% CI, 1.3-5.5; 使用固定效应模型 P=0.007; 见图 1b); a-OR=2.28, 95% CI, 0.7-7.3(使用随机效应模型 P=0.17; 见图 1c)。临床异质性 P=0.13, I²=50.5%)。我们还通过 L’Abbé 曲线检验了潜在的异质性 (见图 2a 和 2b)。

实现再灌注的患者更易产生良好的临床结局吗？

下面的四项研究中均报道了这一结局终点，相较于未实现再灌注的患者，良好临床结局的个体优势在实现再灌注患者中更为明显 (DIAS I[20] OR=3.4; 95% CI, 1.3-8.8; DEDAS[19] OR=9.6; 95% CI, 1.5-64.6; EPITHET[22] OR=7.2; 95% CI, 2.3-23.2; DEFUSE[23] OR=5.4; 95% CI, 0.94-38.1)。将上述所有试验数据进行联合分析后发现，对于成功实现再通的患者其调整的 OR 值要明显高于那些未实现再通的患者 (a-OR=5.2; 95% CI, 3.9-9.1; 临床异质性 P=0.60; 见图 3a)。

在排除 DEFUSE[23] 试验数据 (DEFUSE[23] 不同于其他试验，它是一项非随机的前瞻性试验) 后进行的敏感性分析，在成功实现再灌注的患者中其调整 OR 值仍高于未实现再灌注的患者 (a-OR=5.2; 95% CI, 2.8-9.5; P=0.00; 异质性统计 P=0.4; I²=0%; 见图 3b)。

溶栓患者更易产生良好的临床结局吗?

除 DIAS II 外[18]，其他试验均报道溶栓组与非溶栓组患者相比发生良好临床结局的优势并不显著：DIAS II[20] OR=2.2; 95% CI, 0.7-7.4; DEDAS[19] OR=2.4; 95% CI, 0.4-28.0; EPITHET[22] OR=1.7; 95% CI, 0.7-4.4; DEDAS II[19] OR=0.8; 95% CI, 0.4-1.6。联合分析的数据亦未表明溶栓组可有显著获益 (a-OR=1.28; 95% CI, 0.84-1.97; 临床异质性 P=0.28; I²=20.9%; 见图 4a)。在排除 DIAS II 试验数据后，a-OR=1.96; 95% CI, 1.06-3.63, 临床异质性分析 I²=0%, P=0.89(见图 4b)。

我们剔除一部分不再进行临床分析的去氨普酶的研究数据后再进行分析：仅选择 90 μg/kg 的去氨普酶组和 0.9 mg/kg 的 rt-PA 组数据，结果发现 a-OR=1.4; 95% CI, 0.9-2.3, P=0.16；临床异
质性 $P=0.56, I^2=0\%$。在排除 DIAS II 的数据后，OR=1.88 ; 95% CI, 0.95-3.72, 临床异质性 $P=0.69, I^2=0\%$（见图 4c）。我们使用了 L’Abbé 曲线来检测上述试验潜在的异质性 (见图 5)。在敏感性分析中，去氨普酶相较于阿替普酶无显著的效应差异，OR=0.7(95% CI, 0.24-1.92 ; $P=0.46$)。

接受溶栓治疗的患者较未接受溶栓治疗的患者死亡率更高吗？

溶栓治疗组患者死亡率无显著的个体差异：DIAS I[18] OR=2.4; 95% CI, 0.7-10.1; DIAS I OR=3.6; 95% CI, 0.5-161.3 ; EPITHET[22] OR=2.7; 95% CI, 0.8-10.9 ; DEDAS[19] OR=0.5; 95% CI, 0.0-34.9。联合数据分析发现溶栓组患者相较于安慰剂组患者死亡率显著增加 (a-OR=2.4; 95% CI, 1.2-4.9; $P=0.02$ ; 异质性 $P=0.67; I^2=0\%$ ; 见图 6a)。

剔除一部分不再进行临床分析的去氨普酶剂量的研究数据，比如将数据分析限定于接受 90 $\mu$g/kg 去氨普酶或 0.9 mg/kg rt-PA 溶栓治疗的患者，结果发现 a-OR=1.6; 95% CI, 0.7-3.7; $P=0.28$ ; 异质性 $P=0.56$; $I^2=0\%$ (见图 6b)。在敏感性分析中，去氨普酶和阿替普酶无效应差异，OR=0.8(95% CI, 0.2-3.5 ; $P=0.8$)。

接受溶栓治疗的患者较未溶栓患者发生症状性颅内出血 (SICH) 的可能性更大吗？

在下述的试验中，发生 SICH 无显著的个体差异：DIAS I OR=7.9; 95% CI, 0.7-无穷大; DIAS II OR=5.9; 95% CI, 0.5-无穷大; EPITHET OR=152.6; 95% CI, 0.5-无穷大 (见图 7a)。联合数据分析发现溶栓组患者相较于安慰剂组患者死亡率显著增加 (a-OR=2.4; 95% CI, 1.2-4.9; $P=0.02$ ; 异质性 $P=0.67; I^2=0\%$ ; 见图 6a)。

图 6 接受溶栓治疗的患者较未接受溶栓治疗的患者死亡率更高吗？采用固定效应模型对联合数据进行分析得出的结果如图 a；排除了已经剔除剂量的数据后得出的结果如图 b。

图 7 接受溶栓治疗的患者较未接受溶栓治疗的患者死亡率更高吗？采用固定效应模型对联合数据进行分析得出的结果如图 a；DEDAS 联合 DIAS I 数据分析后得出的结果如图 b；排除了已经剔除剂量的数据后得出的结果如图 c。

图 8 平衡后 3-6 小时内的溶栓治疗比 6-9 小时内的溶栓治疗临床表现 (临床结局或再灌注情况) 更好吗？
15.9-无穷大；但是联合数据分析结果显示溶栓治疗组发生SICH的联合比值明显高于未接受溶栓治疗患者（a-OR=24.7；95% CI，5.2-118.2；异质性分析I²=35.4%；P=0.2；见图7a）。我们将DEDAS和DIAS I的数据联合分析后，发生SICH的可能性仍无显著个体差异（DIAS I+DEDAS OR=7.1；95% CI，0.7-无穷大），但将所有数据进行联合分析后却发现结果有显著统计学差异（a-OR=6.5；95% CI，1.2-35.4；临床异质性P=1.0；I²=0%；见图7b）。

剔除弃用的溶栓药物剂量相关数据后再次分析，结果显示个体数据及联合数据分析均无显著差异（DIAS I+DEDAS OR=3.7；95% CI，0.03-无穷大；DIAS II OR=5.7；95% CI，0.2-无穷大；EPITHET OR=6.5；95% CI，0.4-无穷大），联合数据分析结果：a-OR=5.4；95% CI，0.9-31.8，异质性P=0.97；I²=0%（见图7c），但分别处理DIAS I和DEDAS数据后得到的校正比值存在微小差异（a-OR=6.0；95% CI，1.00-35.8；异质性统计P=1.00；I²=0%）。在安慰剂组无SICH发生，因此无法对去氨普酶和阿替普酶效应差异进行敏感性分析。

卒中后3-6小时内的溶栓治疗比6-9小时内的溶栓治疗临床表现（临床结局或再灌注情况）更好吗？计算OTT所获得的数据非常有限。DIAS I[20]和DIAS II均未提示有显著的试验个体优势（DIAS I OR=1.07；95% CI，0.4-2.9；P=0.9；DIAS II OR=0.8；95% CI，0.4-1.8；P=0.7）。二者数据联合分析得出调整OR=0.9；95% CI，0.5-1.7；P=0.8(见图8)。

死亡率分析

在DIAS I试验中，安慰剂组1例及去氨普酶组2例均死于心脏疾病。在DIAS II中，90 μg/kg组中，3例死亡，125 μg/kg组中14例死亡，其中90 μg/kg组中1例和125 μg/kg组中3例死亡原因与试验药物有关。在DEDAS试验中，90 μg/kg组唯一1例死亡归因于吸入性肺炎，而125 μg/kg组中的死亡归因于左侧大脑中动脉梗死使神经功能恶化，导致肺炎发生。

讨论

依据缺血半暗带内存在潜在可挽救的脑组织的理论，我国对既往进行的评估扩大时间窗的生理学选择策略的研究进行了荟萃分析[38,39]。这些研究均采用了错配假说，主要通过磁共振（灌注/弥散错配）或CT(灌注/脑血容量错配)检查手段来显示假说存在的缺血半暗带[19,20,22,24,25,40-43]。除了最近发表的DIAS II试验[18]之外，所有相关的试验均支持错配概念存在生理学基础。DIAS II试验令人失望的结果主要归结于研究设计的局限性以及偶然机遇[37]。为了验证结果的一致性，我们对采用错配模型来筛选患者进行溶栓（尽管超过了3小时时间窗）治疗的所有研究进行了荟萃分析。入选的试验共5个：DIAS I[20]，DIAS II[18]，EPITHET[22]，DEFUSE[23]及DEDAS[19]。荟萃分析结果表明，如果将所有数据联合起来分析，溶栓患者发生再灌注/血管再通的可能性要大于未溶栓患者，但是如果将已经剔除剂量的数据排除在外，上述差异则无显著统计学意义，这主要是因为剔除剂量的数据通过样本量的作用形成了统计的把握度。此外，尽管在超过3小时时间窗后实施扩大时间窗溶栓治疗，成功实现缺血半暗带再灌注的患者其发生良好临床结局的可能性要显著高于未实现再灌注的患者。这一结论并不受非随机的DEFUSE试验数据[23]的影响。而DIAS II试验在再灌注方面未发现上述差异。

但是，在溶栓治疗组中，我们并没有发现其临床结局显著优于对照组的证据，同样也未发现在排除去氨普酶试验中放弃了进行进一步研究的剂量组之后，溶栓组较对照组有显著获益。我们荟萃分析得出的效应估计的可信区间过宽，欲得到良好临床结局，其比值比就需要加倍才行，即使这样，DIAS II试验表明其可信区间的可能上限仅为1.6。即使K.6这样的比值比，也要大于在ECASS III中从未筛选即给予rt-PA治疗患者的比值比。这足以影响英国国家以及欧洲卒中治疗指南（SIGN[44]和ESO[45]）。

扩大时间窗的溶栓治疗，即使是经过筛选的患者，仍有可能存在一些治疗的风险。我们发现，在所有接受溶栓治疗的患者中，其死亡比值比的显著性较对照组稍有增加，处于边缘状态，点估计值为2.4。而如果将分析的数据限定在采用0.9 mg/kg rt-PA以及采用仍处于研究阶段的去氨普酶（90 μg/kg）治疗的患者，其OR值则降至1.6。治疗的风险则无明显统计学差异。较高剂量的去氨普酶与严重的症状性颅内出血明确相关，放弃对该剂量组的研究也是基于此原因。在我们的荟萃分析中并没有将其他可引起死亡的原因考虑在内。在DIAS II和EPITHET试验中，许多死亡是与溶栓治疗不相关的。这些贡献死亡的原因可能对于作用机制的理解很重要，但是如果通过主观评估来得出结论，那这样的结论一定要慎重。药物治疗的失败可以导致后期死亡，这正以前未识别的兴奋性毒性损伤一样，它可能就代表了一种潜在的作用机制。无论如何，如果溶栓治疗后死亡率增加，则很可能是通过出血转换导致的。

对于接受溶栓治疗的患者来说，单个试验发生的症状性颅内出血的比值比没有显著统计学差异，但是对所有数据进行联合分析后，其调整OR值提示扩
大时间窗溶栓后患者发生症状性颅内出血的风险显著增加。与之结论相同的是，很早以前人们就认识到即使在3小时内, 随着时间延长，应用 t-PA 发生症状性颅内出血的风险也是逐渐增加，但是这与接受溶栓患者的临床结局改善相抵消。如果将已经放弃临床剂量研究的去氨普酶数据排除在外, 则症状性颅内出血的调整 OR 值又将具有统计学差异。对于上述事后亚组分析的结论在解读时应格外慎重。荟萃分析时将所有剂量的数据均纳入在内进行分析或许会让人对基于错配模型的溶栓治疗的风险/获益比报以一种错误的悲观的看法，但是将放弃进一步剂量研究的数据排除在外的事后分析是由后来的数据结果所驱动的，这必然会导致统计学上的偏倚，只有通过更进一步的前瞻性试验来证实。目前我们尚未发现证据能够证明相对早期溶栓（3-6小时）治疗与相对晚期溶栓（6-9小时）会对我们研究的结论有何影响。但是时间窗与治疗结论还是显著相关的，因为 ECASS III 试验最近已经表明, 即使未经过筛选，患者在发病后4.5小时内接受阿替普酶溶栓仍可从中获益, 而上述试验中经过错配模型筛选的一小部分患者也应该适合于此种治疗方式。目前我们尚无法得出结论是否存在错配的患者其潜在获益一定是时间依赖性的, 但是这似乎并不能完全解释扩大时间窗溶栓治疗的作用。既然现在 ECASS III 已经发表, 那么就应再进行一项荟萃分析, 对本篇所提到的所有研究中患者个体的数据进行分析, 来评估4.5小时之外溶栓的患者其临床及影像结局如何。同样地, 对于存在错配的患者与不存在错配患者的临床结局进行额外的比较分析也同样具有重要价值, 但这并不在我们此次荟萃分析的范围之内。我们此项荟萃分析共入选了5个不同的试验研究[18-22,23], 其中只有 DEFUSE[23] 试验表明获得再灌注与未获得再灌注的溶栓患者其良好预后的结局有显著不同。DIAS II[24] 试验并未报道溶栓与未溶栓对患者是否再灌注的影响, 因此如果要分析溶栓后再灌注情况, 该项研究应排除在外。L’Abbé 曲线表明[46,47], 在对所有溶栓患者良好临床结局情况进行联合分析时, DIAS II 试验导致了其异质性的产生, 而DEDAS 试验则使溶栓治疗后再灌注和再通方面存在异质性。这两项异质性会因为样本量对研究把握度的干扰而影响研究结果。我们研究中采用的错配识别方法无论是用磁共振灌注/弥散, 还是用 CT 作为替代, 都具有很好的研究前景。从我们分析得出的数据很清楚地知道, 通过影像学的错配模型来筛选患者进行扩大时间窗的溶栓治疗与患者再灌注 /血管再通比例增加紧密相关，而再灌注 /血管再通则与临床结局改善相关。但是，尽管目前各试验研究关于错配患者扩大时间窗溶栓后临床功能结局改善的结果是一致的, 但在统计学方面的显著差异还有待进一步确证。在我们此项荟萃分析中, 扩大时间窗溶栓患者的死亡率增加, 这可能主要与剂量过大的去氨普酶的数据分析产生的重要影响, 导致过高估计了溶栓治疗的风险。我们还注意到, 现有错配模型的定义有可能在将来会进一步得到完善, 从而使以错配为基础的溶栓研究的把握度更大。例如, 我们将 1.2 作为错配模型定义的截断值, 但是最近发表的 DEFUSE 研究的事后分析已经表明, 能产生最高敏感度和特异度的错配比应是 2.6, 这说明以前研究的把握度有可能不足, 同时对错配比的定义也不够精确[27]。此外, Tmax 为 2 秒的阈值也同样不够理想, DEFUSE 研究的事后分析显示了梗死核心与可挽救的缺血半暗带之间显著改善的相关性, 其中对 PWI 损伤的定义为 Tmax>6 秒[28]。在 EPITHET 研究中也报道了同样的发现[30]。目前我们清楚的是, 上述两项研究在错配评估方面都包括了良性灌注不足的区域。目前, 网络上已经有自动进行磁共振错配识别的软件, 这能推动扩大时间窗溶栓患者的筛选加快。总而言之, 对灌注参数的不断更新可为人们产生最佳的灌注测量方式(Tmax、达峰时间, 平均通过时间, 脑血容量以及脑血流), 同时不断纠正动脉的输入功能。因此, 到目前为止发表的各项试验研究中对错配的定义都相对较为宽泛, 这无疑会入选一些只有很少一点半暗带、溶栓后临床结局改善不显著的患者。最近成立的 STIR 联盟正在发起一项针对此课题的详细检查。错配模型定义的多样性以及众多研究参与其中, 无疑会削弱错配模型将来在卒中患者中应用的潜在价值的结论。但是, 这种削弱并不会影响错配患者接受溶栓治疗的证据级别：此类患者是研究者依据设计良好的研究方案精心挑选出的患者。为了在改良后的错配筛选环境下进一步验证溶栓治疗与良好的风险/获益比相关, 还需要开展前瞻性的 III 期临床试验来证实。目前在澳大利亚，已经开始的 EXTEND 试验将按照临床 III 期设计并入组卒中发病4.5-9 小时的患者, 随机分配到阿替普酶组与安慰剂组, 同时采用错配自动计算方式, 来验证上述假说。另外, 尽管患者的筛选理念是基于个体化的病理生理学而不是僵化的 Trigger时间窗概念，这对
于研究者来说会很有吸引力，但是，根据缺乏匹配
对患者进行扩大实验的治疗仍然不能作为一项临
床常规来推荐，除非未来的某项试验能够证实其可
使患者临床获益。