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Mismatch-Based Delayed Thrombolysis

A Meta-Analysis

Nishant K. Mishra, MBBS; Gregory W. Albers, MD; Stephen M. Davis, MD, FRACP;
Geoffrey A. Donnan, MD, FRACP; Anthony J. Furlan, MD;
Werner Hacke, MD; Kennedy R. Lees, MD, FRCP

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 principal 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

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From the Acute Stroke Unit (N.K.M., K.R.L.), University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, and Faculty of Medicine, University of Glasgow, Glasgow, Scotland; Stanford Stroke Center (G.W.A.), Stanford University Medical Center, Stanford, Calif; Royal Melbourne Hospital (S.M.D.), University of Melbourne, Parkville, and National Stroke Research Institute (G.A.D.), University of Melbourne, Melbourne, Australia; Neurological Institute (A.J.F.), Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio; and University of Heidelberg (W.H.), Heidelberg, Germany.

Correspondence to Kennedy R. Lees, MD, FRCP, University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary and Faculty of Medicine, University of Glasgow, Glasgow, G11 6NT, UK. E-mail k.r.lees@clinmed.gla.ac.uk

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vs placebo 1:1; median time for administration of alteplase=3 hours, 59 minutes) confirmed clinical benefit within 4.5 hours of stroke onset. (OR=1.34; 95% CI, 1.02 to 1.76; $P=0.04$).⁴ However, the wider 95% CI at 6 hours (0.9 to 1.5 for 271 to 360 minutes in the meta-analysis⁴) have suggested that there may still be patients able to benefit from 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.”^{5,6} 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.⁷ 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.⁸ 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 desmoteplase together because both are thrombolytic agents.⁹ 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.^{9–15} Alteplase is already a proven therapy for treating stroke patients within the early hours after stroke onset (NINDS¹⁶ and ECASS III³).¹⁷ Doses that have acceptable safety and efficacy have been identified.^{18–20} 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.¹⁸ 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.¹⁸

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 thrombolized and nonthrombolized 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 underline 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.²¹ 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 $\mu\text{g}/\text{kg}$ 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]²¹) 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 I^2 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, $N=97^{20}$; the DEDAS trial, $N=34^{19}$; the EPITHET trial, $N=77$ [“good neurological outcome” for patients with $\{n=30\}$ and without $\{n=47\}$ reperfusion in mismatch patients only]²²; and the DEFUSE trial, $N=34$, in mismatch patients with $\{n=18\}$ and without $\{n=16\}$ early reperfusion²³). Corresponding information was not reported in the DIAS II trial.¹⁸ Similarly, to answer whether a favorable clinical outcome occurred more frequently in the thrombolized group of patients, information on 410 patients was available (DIAS I, $N=102^{20}$; DIAS II, $N=186^{18}$; DEDAS, $N=37^{19}$; and EPITHET,

N=85; mismatch patients with and without good neurological outcome in the thrombolysis group, n=42, and the placebo group, n=43²²) 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 thrombolized, 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 thrombolized and non-thrombolized 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 thrombolized and nonthrombolized 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 thrombolized within 3 to 6 hours of stroke onset versus those who were thrombolized 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 trial^{20,30}, 9 on the EPITHET trial (8 articles^{20,22,33–36}), 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 Thrombolized?

The data from 211 patients showed greater individual odds for reperfusion and/or recanalization amongst those who

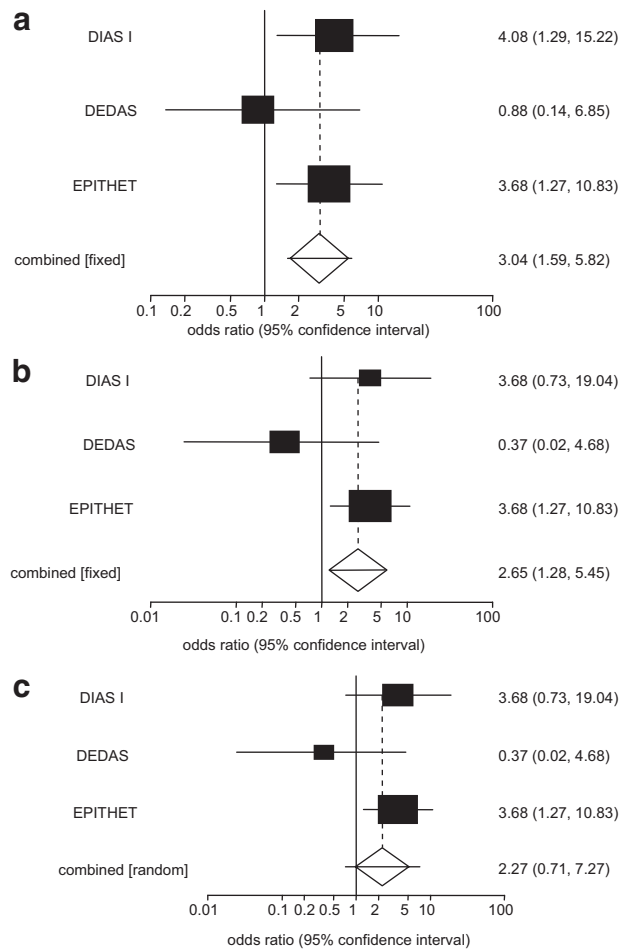


Figure 1. Did reperfusion or recanalization occur more frequently in patients who were thrombolized? Findings are shown from the fixed-method analysis of combined data (a) after exclusion of abandoned doses by fixed (b) and random-method (c) analyses.

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 $I^2=25.7%$; Figure 1a).

We repeated our analysis after excluding desmoteplase doses that were abandoned for clinical development; the subanalysis restricted to 90 $\mu\text{g}/\text{kg}$ 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 $I^2=50.5%$). 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

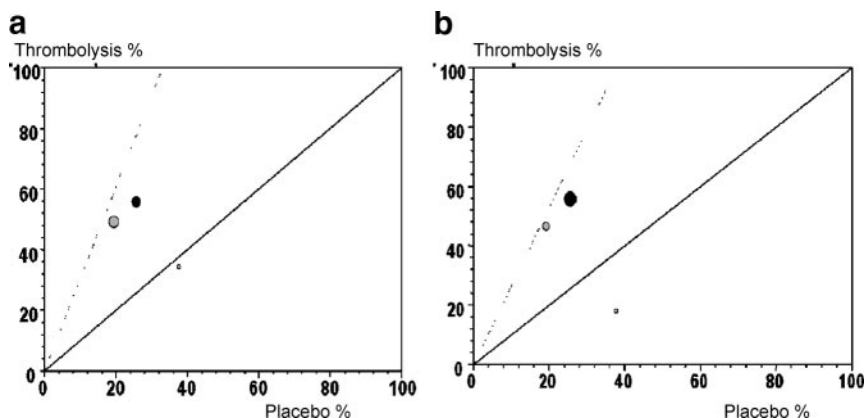


Figure 2. Did reperfusion or recanalization occur more frequently in patients who were thrombolized? L'Abbé plot examining (a) the complete data set and (b) the abandoned doses excluded for heterogeneity. The circle size denotes the sample size; DIAS, gray circles; DEDAS open circles; and EPITHET, black circles.

(DIAS I²⁰ OR=3.4; 95% CI, 1.3 to 8.8; DEDAS¹⁹ OR=9.6; 95% CI, 1.5 to 64.6; EPITHET²² OR=7.2; 95% CI, 2.3 to 23.2; and DEFUSE²³ 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; I²=0%; Figure 3a).

In a sensitivity analyses in which DEFUSE²³ trial data were excluded (as DEFUSE,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; I²=0%; Figure 3b).

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

With the exception of DIAS II,¹⁸ all trials reported nonsignificantly improved odds of a favorable clinical outcome in

the thrombolysis group of patients: DIAS I²⁰ OR=2.2; 95% CI, 0.7 to 7.4; DEDAS¹⁹ OR=2.4; 95% CI, 0.4 to 28.0; EPITHET²² OR=1.7; 95% CI, 0.7 to 4.4; and DIAS II¹⁸ 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; I²=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, I² was 0% and *P* was 0.89 (Figure 4b).

We repeated our analysis after excluding desmoteplase doses that were abandoned for clinical development: with 90 μg/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 I²=0%. After exclusion of DIAS II data, OR=1.88; 95% CI, 0.95 to 3.72, and heterogeneity

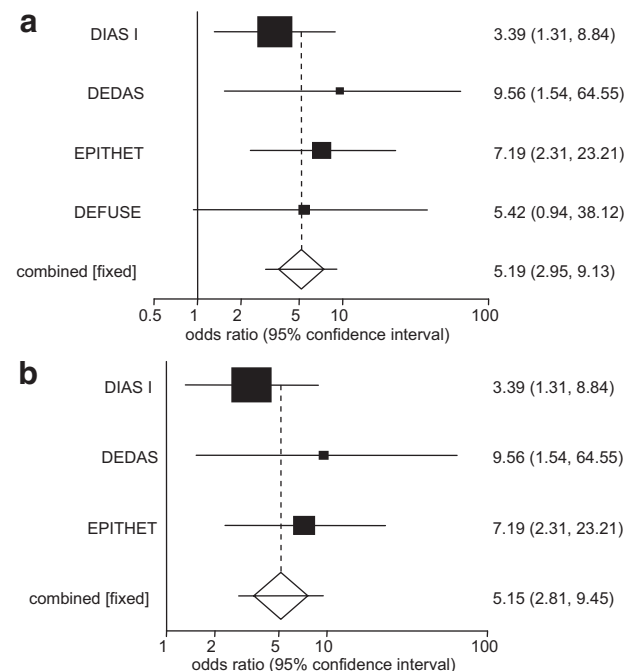


Figure 3. Are favorable outcomes more common in patients who underwent reperfusion? Findings are shown from the fixed-method analysis of combined data (a) and after excluding DEFUSE data (b).

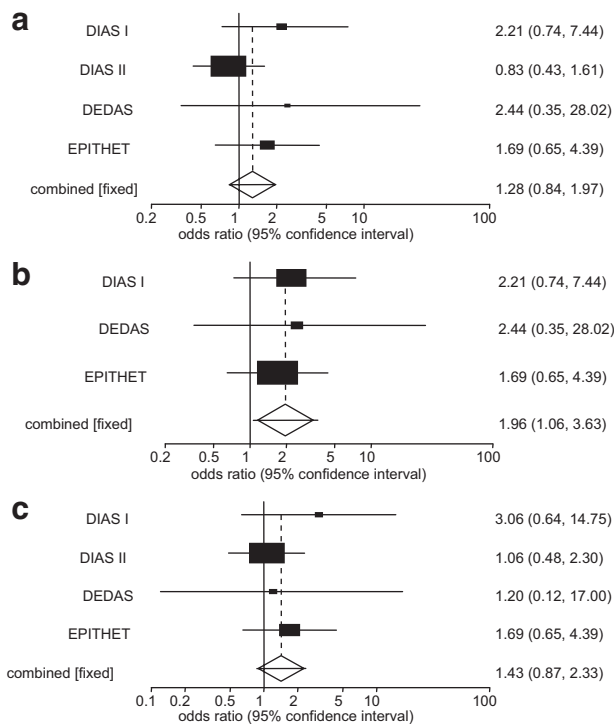


Figure 4. Did a favorable clinical outcome occur more frequently in the thrombolized group of patients? Findings are shown from the fixed-method analysis of combined data (a), after exclusion of DIAS II data (b), and after exclusion of abandoned DEFUSE data (c).

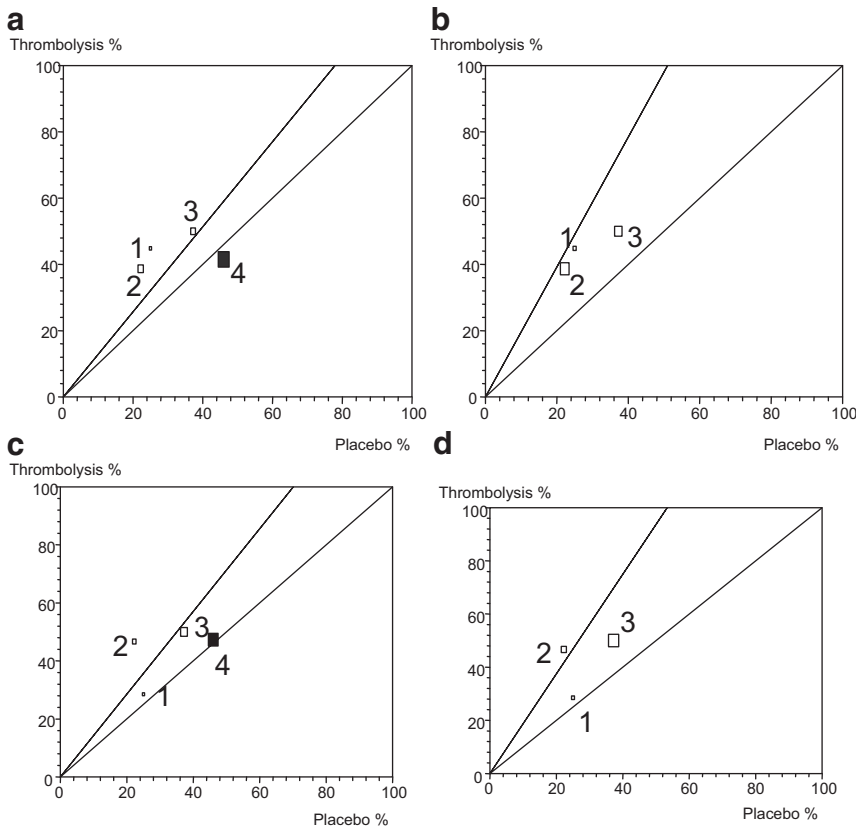


Figure 5. Did a favorable clinical outcome occur more frequently in the thrombolysed group of patients? L'Abbé plot examining heterogeneity in the analysis (a) for complete data, (b) for DIAS II data excluded, (c) for complete data but abandoned doses excluded, and (d) for DIAS II data and abandoned-dose data excluded. The size of the square denotes the sample size. 1 indicates DEDAS; 2, DIAS I; 3, EPITHET; and 4, DIAS II (black rectangle).

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 Mortality in Thrombolysed Compared With Nonthrombolysed Patients?

Here, the individual odds for mortality were nonsignificant in the thrombolysis group: DIAS II¹⁸ $OR=2.4$; 95% CI, 0.7 to 10.1; DIAS I $OR=3.6$; 95% CI, 0.5 to 161.3; EPITHET²² $OR=2.7$; 95% CI, 0.8 to 10.9; and DEDAS¹⁹ $OR=0.5$; 95% CI, 0.0 to 34.9. 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 patients treated with 90 $\mu\text{g}/\text{kg}$ 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 I²⁰ nor DIAS II individually suggested significantly greater odds (DIAS I $OR=1.07$; 95% CI, 0.4 to 2.9; $P=0.9$;

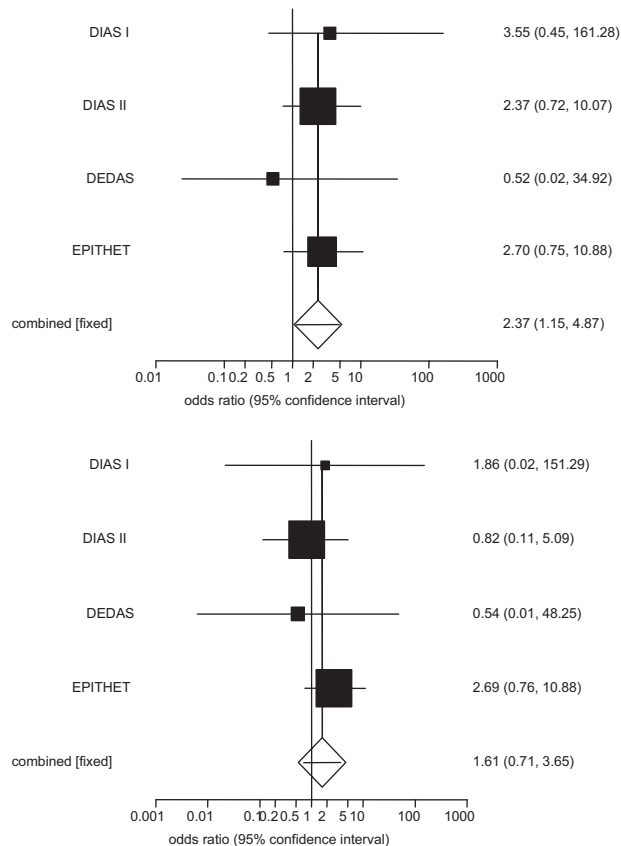


Figure 6. Was there a greater probability of mortality in thrombolized patients compared with those not thrombolized? Findings are shown from the fixed-method analysis of combined data (a) and after exclusion of the abandoned-dose data (b).

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 $\mu\text{g}/\text{kg}$ group and 3 of 14 deaths in the 125 $\mu\text{g}/\text{kg}$ group were considered related to the trial medication. In the DEDAS trial, the sole death in the 90 $\mu\text{g}/\text{kg}$ group was due to aspiration pneumonia, whereas that in the 125 $\mu\text{g}/\text{kg}$ 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

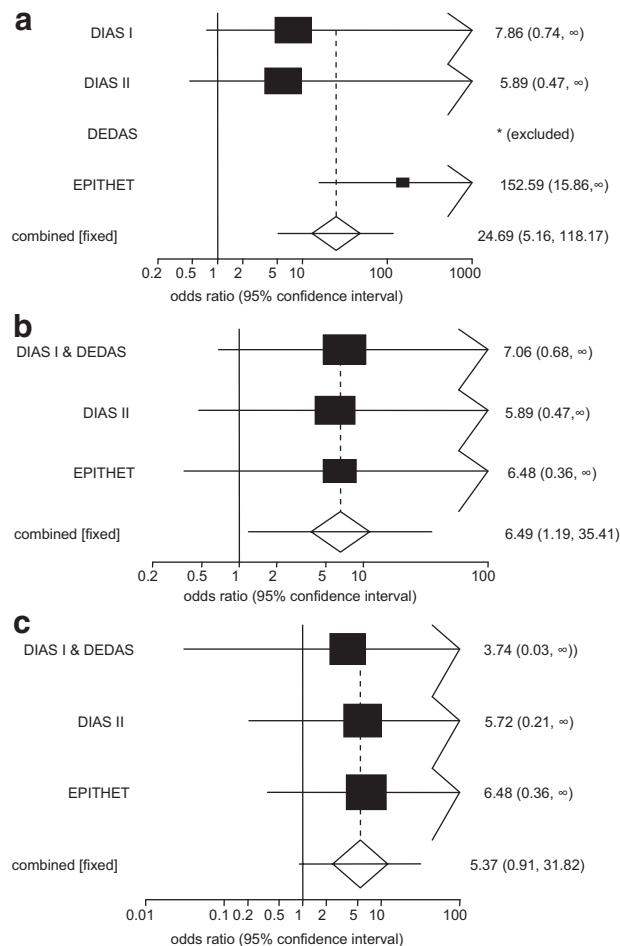


Figure 7. Was there a greater probability of SICH in thrombolized patients compared with those not thrombolized? Findings are shown from the fixed-method analysis for all studies combined but with DEDAS data excluded (a), DIAS I & DEDAS combined (b), and after exclusion of the abandoned-dose data (c).

mismatch hypothesis to select and thrombolize 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/revascularization 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

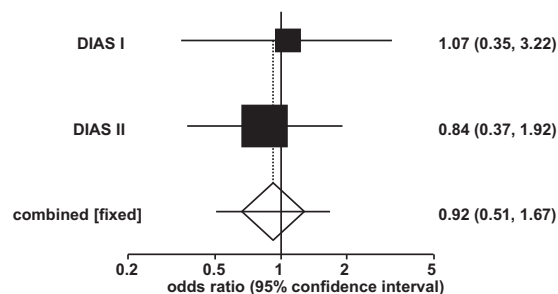


Figure 8. Were there better clinical findings (outcomes or reperfusion) when treatment was commenced within 3 to 6 hours vs 6 to 9 hours?

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 trial²³ data. The DIAS II trial¹⁸ 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 trial³ and have been regarded as sufficient to influence national and European stroke treatment guidelines (SIGN⁴⁴ and ESO⁴⁵).

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,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,^{18–20,22–23} of which DEFUSE²³ could be considered only in the analysis of a favorable clinical outcome among patients with reperfusion versus no reperfusion. DIAS II¹⁸ did not report reperfusion findings and had to be excluded where these data were needed. The L'Abbé plot^{46,47} suggested that DIAS II¹⁸ 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 ≈14.³ When treatment with alteplase is started within 6 hours OTT, the number needed to treat rises to 25.⁴⁸ 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.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.²⁹ The EPITHET investigators reported similar findings.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 (Tmax, 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 weaken 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 for the steering committee for DIAS I–IV. S.M.D. was coprincipal investigator of the EPITHET trial, is on the advisory board of Servier Australia, and has received honoraria from Boehringer Ingelheim for lectures. G.A.D. was coprincipal investigator of the EPITHET trial, is a member of advisory boards for Servier Australia and Boehringer Ingelheim, and has received honoraria from both companies. A.J.F. is a consultant to Paion and to Forest Laboratories. W.H. was chairman of the steering committee of DIAS and cochair of the steering committees of DEDAS and DIAS II trials, sponsored by Paion and Forest, and received honoraria for his activities in the conduct and development of the trial. K.R.L. was chairman of the data monitoring committees for DIAS I–IV, DEDAS, and ECASS III trials of thrombolysis in acute ischemic stroke, sponsored by Paion, Forest Laboratories, Lundbeck, and Boehringer Ingelheim.

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Correction

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 Thrombolized 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>.

¹[Correction for Vol 41, Number 1, January 2010. Pages e25-e33.]
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