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Title: Different mismatch concepts for MRI-guided thrombolysis in unknown onset stroke

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Abstract

Objective: To explore the prevalence of the perfusion-weighted imaging (PWI) - diffusion-weighted imaging (DWI) mismatch and response to intravenous thrombolysis in the WAKE-UP trial.

Methods: We performed a prespecified post-hoc analysis of ischemic stroke patients screened for DWI - fluid-attenuated inversion recovery (FLAIR) mismatch in WAKE-UP who underwent PWI. We defined PWI-DWI mismatch as ischemic core volume <70 ml, mismatch volume >10 ml and mismatch ratio >1.2. Primary efficacy endpoint was a modified Rankin Scale score of 0-1 at 90 days, adjusted for age and symptom severity.

Results: Of 1,362 magnetic resonance imaging (MRI) screened patients, 431 underwent PWI. Of these, 57 (13%) had a double mismatch, 151 (35%) only a DWI-FLAIR mismatch and 54 (13%) only a PWI-DWI mismatch. DWI-FLAIR mismatch was more prevalent than PWI-DWI mismatch (48%; 95% CI 43%-53% vs 26%; 95% CI 22%-30%, p<0.0001). Screening for either one of the mismatch profiles resulted in a yield of 61% (95% CI 56%-65%). Prevalence of PWI-DWI

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mismatch was similar in patients with (27%) or without (24%) DWI-FLAIR mismatch (p= 0.52). In an exploratory analysis in the small subgroup of 208 randomized patients with PWI, PWI-DWI mismatch status did not modify the treatment response (p for interaction= 0.73).

Interpretation: Evaluating both the DWI-FLAIR and PWI-DWI mismatch pattern in patients with unknown time of stroke onset will result in the highest yield of thrombolysis treatment. The treatment benefit of alteplase in patients with a DWI-FLAIR mismatch seems not merely driven by the presence of a PWI-DWI mismatch, although this analysis was underpowered.

Introduction

Advanced neuroimaging techniques identify patients who benefit from intravenous reperfusion therapy in the extended time window after stroke onset and when onset time is unknown. Magnetic resonance imaging (MRI) provides more insights into the parenchymal and perfusion status in comparison to computed tomography (CT), although MRI is less accessible in stroke centers worldwide.

The presence of a diffusion-weighted imaging (DWI) – fluid-attenuated inversion recovery (FLAIR) mismatch is an imaging pattern revealed in patients who present in the 4.5 hour time window after stroke onset. Determining this mismatch in patients with unknown time of stroke onset is an interesting approach to increase the amount of thrombolysis eligible patients.[1] *The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke* (WAKE-UP) trial randomized

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patients with a DWI-FLAIR mismatch to placebo or alteplase, and indeed showed a treatment response similar to that observed in previous clinical trials within the therapeutic time window in patients with known stroke onset times. [2] DWI and perfusion-weighted imaging (PWI) offer an alternative mismatch paradigm that distinguishes ischemic from potentially salvageable tissue. [3] Since almost 20% of stroke patients present with unknown time of stroke onset [4, 5], imaging identification of potential responders to reperfusion treatment is of great importance. It is unknown whether the two different mismatch patterns identify different patient groups or signify different magnitude of treatment response to intravenous thrombolysis. To explore this question, we conducted a prespecified post-hoc analysis of the WAKE-UP trial. We analyzed the individual and combined yield of each mismatch paradigm and investigated whether an association between both mismatch profiles exists. We also studied the interaction between the presence of a PWI-DWI mismatch and treatment with alteplase in patients randomized in WAKE-UP.

Methods

Study design and patients

In this post-hoc analysis, we analyzed clinical and neuroimaging data from the subset of ischemic stroke patients screened in the WAKE-UP trial with PWI at baseline. The WAKE-UP trial was an investigator-initiated, multicenter, randomized, double blind, placebo-controlled clinical trial. A detailed description can be found in the original publication. [2] Main inclusion criteria were age between 18 and 80 years of age, independency before the stroke, unknown onset of stroke symptoms and time from last seen well >4.5 hours. Treatment had to be initiated within 4.5 hours

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of symptom recognition. Patients eligible for thrombectomy, with severe stroke defined as National Institute of Health Stroke Scale (NIHSS) >25, with contraindications to alteplase (except for the time criterion) and with insufficient imaging quality were excluded. Patients fulfilling these criteria were screened with MRI between September 2012 and June 2017 (**screened patients**) (Fig 1, panel A). If a DWI lesion was present in the absence of a FLAIR hyperintense signal in the corresponding region, patients were randomized to alteplase or placebo (**randomized patients**). Patients without DWI-FLAIR mismatch were not randomized. The other main imaging exclusion criteria were the absence of a DWI lesion, DWI lesions larger than one third of the middle cerebral artery territory, diagnosis of hemorrhagic stroke or severe motion artefacts. Centers could decide whether they used MRI as first imaging modality or CT followed by MRI. National or local ethics committees or institutional review boards approved the trial. Informed consent was signed by patients or their legal representatives, according to national and local regulations.

Image analysis

In the original trial, imaging was performed at baseline and 22-36 hours after randomization. The standard MRI protocol consisted of DWI, FLAIR, time-of-flight magnetic resonance angiography (TOF-MRA) and gradient echo (GE) or susceptibility-weighted imaging (SWI). In a subset of patients, PWI (echoplanar T2* weighted sequence with gadolinium contrast bolus) was added to the protocol. Performing PWI was left to the discretion of the local investigator. In the WAKE-UP trial, local investigators visually rated the DWI-FLAIR mismatch. PWI was not used to guide randomization in the WAKE-UP trial. In the current analysis, we focused on patients with available

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PWI at baseline. Automated analysis and calculation of DWI and PWI lesion volumes was performed using the RAPID software (iSchemaView, Menlo Park, CA, version 4.9 and 5.0), which identifies ischemic core based on a threshold $<620*10^{-6}mm^2/s$ on the apparent diffusion coefficient (ADC) and the PWI lesion volume by the time to maximum of the residue function (Tmax) with a threshold of > 6s (Fig 2). We defined PWI-DWI mismatch according to the imaging criteria used in the EXTEND trial [3]: core (DWI) lesion volume < 70 ml, absolute mismatch volume > 10 ml (PWI lesion - DWI lesion) and mismatch ratio >1.2 (PWI lesion/DWI lesion). After automated RAPID analysis, we manually adjusted the outputs if the selection of the arterial input function (AIF) or venous output function (VOF) was suboptimal based on visual inspection of the AIF and VOF curve generated by RAPID. Artifacts on the core or hypoperfusion map were manually removed after visual inspection of all generated maps. On baseline imaging, we manually delineated the DWI lesion volume with Horos software [6] if a lesion was not correctly identified by RAPID. Adjustment of AIF or VOF, removal of artifacts and manual delineation was done by L.S., blinded to clinical information. Double mismatch refers to the presence of both a DWI-FLAIR and PWI-DWI mismatch.

Outcome measures

The primary efficacy end point was defined as a modified Rankin Scale (mRS) score of 0 or 1 at 90 days. This scale ranges from 0 (no symptoms) to 6 (dead), with values of 0 or 1 representing patients with a favorable functional outcome.[7] Secondary efficacy end points were the ordinal score

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on the mRS at 90 days. Safety end points were death or dependency (mRS 4-6) at 90 days and death at 90 days.

Statistical analysis

We used a McNemar test to compare the diagnostic yield of the DWI-FLAIR and PWI-DWI mismatch in screened patients. The proportions of PWI-DWI mismatch patients with or without a DWI-FLAIR mismatch were compared using a chi-square test. We compared baseline characteristics between randomized patients with and without PWI at baseline, between patients with a double mismatch versus only a DWI-FLAIR mismatch and between treatment arms in patients with a double mismatch and with only a DWI-FLAIR mismatch. Statistical analysis of treatment effect was performed in the intention-to-treat population for all patients with available information on clinical endpoints. We studied the interaction between the presence of the PWI-DWI mismatch and treatment with alteplase on the primary end point using an unconditional logistic regression analysis, adjusted for age and NIHSS score (similar as in the original paper [2]), fitted to estimate the odds ratio and its 95% confidence interval. We performed subgroup analyses on the stratification variable PWI-DWI mismatch. We analyzed the categorical shift in the distribution of the modified Rankin scale towards a better outcome by fitting a proportional-odds logistic regression model, resulting in a common odds ratio. Safety endpoints were analyzed with an unconditional logistic regression model, adjusted for age and NIHSS score, fitted to estimate the odds ratio and its 95% confidence interval. Statistical analyses were conducted in SAS software version 9.4 (SAS Institute) and R.[8] A p-value of <0.05 was considered significant.

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Results

Of 1,362 screened patients, 227/503 (45%) randomized patients and 245/859 (29%) non-randomized patients underwent PWI. In total, 41 patients were excluded from the analysis because of insufficient PWI or DWI quality, resulting in successful mismatch analysis in 208 of the randomized and in 223 of the non-randomized patients (Fig 1 panel A). We manually adjusted arterial input or venous output function in 12 subjects and removed artifacts in 87 subjects.

Diagnostic yield

Of all 431 screened patients with PWI at baseline, a DWI-FLAIR mismatch was identified in 208 (48%; 95% confidence interval [CI], 43%-53%) patients. Of these, 57 presented with a double mismatch and 151 with only a DWI-FLAIR mismatch. A total of 54 patients (13%) presented with only a PWI-DWI mismatch and were consequently not randomized in WAKE-UP. Fewer patients had a PWI-DWI mismatch (n=111; 26%; 95% CI, 22%-30%) than a DWI-FLAIR mismatch ($p<0.0001$). MRI-based selection of patients by any of the mismatch paradigms would have identified 262 patients as potentially eligible (61%; 95% CI,56%-65%) (Fig 1 panel A, B and C).

Relationship between DWI-FLAIR and PWI-DWI mismatch

We did not identify an association between the DWI-FLAIR and PWI-DWI mismatch since the frequency of a PWI-DWI mismatch was similar in randomized patients with DWI-FLAIR

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mismatch and non-randomized patients without DWI-FLAIR mismatch (57/208, 27% vs 54/223, 24%, p=0.52).

Characteristics of randomized patients

Baseline characteristics of randomized patients with versus without available PWI and baseline characteristics of randomized patients with a double mismatch versus only a DWI-FLAIR mismatch can be found in the supplementary data. The median NIHSS score was higher in patients with a double mismatch compared to those with only a DWI-FLAIR mismatch (8; IQR, 5-13 vs 5; IQR, 3-8, p<0.0001). RAPID analysis identified larger DWI (8 ml; IQR, 0-18 vs 0 ml; IQR, 0-8, p=0.007) and PWI lesion volumes (50 ml; IQR, 26-89 vs 0 ml; IQR,0-7, p<0.0001) in patients with a double mismatch. Any (80% vs 19%, p<0.0001) and large (59% vs 9%, p<0.0001) vessel occlusions were more frequent in patients with a double mismatch. Baseline characteristics per treatment arm of randomized patients with only a DWI-FLAIR mismatch and with a double mismatch are described in table 1 and 2. Of 57 patients with a double mismatch, 32 patients were assigned to alteplase and 25 to placebo. Patients in the alteplase group were older compared to patients in the placebo group (mean age 68.25; Standard deviation (SD) 11.31 versus 64.68; SD 8.91, p=0.045). There were no significant differences in baseline characteristics in patients with only a DWI-FLAIR mismatch treated with alteplase versus placebo. Of 208 randomized patients, 8 were lost to follow up (6 treated with alteplase and 2 treated with placebo).

Efficacy and safety outcomes

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Information on the primary efficacy end point was available for 200 randomized patients (145/151 with only a DWI-FLAIR mismatch, 55/57 with a double mismatch). In an exploratory analysis, the presence of a PWI-DWI mismatch in addition to a DWI-FLAIR mismatch did not modify the treatment response in the small subgroup of 200 patients of the WAKE-UP trial (p for interaction= 0.73). In patients with only a DWI-FLAIR mismatch, 45/76 (59%) receiving alteplase and 35/69 (51%) receiving placebo achieved a favorable outcome at 90 days (odds ratio 1.44; 95% CI 0.71-2.91). In patients with a double mismatch, 14/30 (47%) treated with alteplase versus 9/25 (36%) receiving placebo reached a favorable outcome at 90 days (odds ratio 1.86; 95% CI 0.54-6.44) (table 3).

In addition, we explored the clinical outcomes over the total range of the modified Rankin Scale. In randomized patients with a DWI-FLAIR mismatch, there was no interaction between the presence of a PWI-DWI mismatch and treatment with alteplase (p for interaction=0.69). The median mRS score at 90 days in patients with a double mismatch was 2 (IQR, 1-4) in the alteplase group and 3 (IQR, 1-3) in the placebo group (common odds ratio 1.83; 95% CI 0.68-4.93, p=0.23; Fig 2 panel A, table 3). In patients with only a DWI-FLAIR mismatch, the median mRS score at 90 days was 1 (IQR, 1-2) in both treatment groups (common odds ratio 1.45; 95% CI 0.80-2.62, p=0.22; Fig 2 panel B.).

Death at 90 days and death or dependency (mRS 4-6) at 90 days did not differ between patients treated with alteplase or placebo (table 3).

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Discussion

In this prespecified post hoc analysis of the WAKE-UP trial, we evaluated the percentage of patients with unknown stroke onset still eligible for thrombolysis based on findings on MRI. We identified up to 61% of ischemic stroke patients fulfilling imaging criteria for acute intravenous treatment by the DWI-FLAIR and/or PWI-DWI mismatch pattern. In a relatively small sample size, the presence of a PWI-DWI in addition to a DWI-FLAIR mismatch did not modify the effect of treatment with alteplase.

The yield of the DWI-FLAIR mismatch to select patients eligible for thrombolysis in the unknown time window was double that of the PWI-DWI mismatch pattern. However, a substantial proportion of patients (13%) presented with a PWI-DWI mismatch in the absence of a DWI-FLAIR mismatch. Few trials investigating the PWI-DWI or perfusion lesion-ischemic core mismatch have reported the frequency of mismatch patterns among screened patients who were otherwise eligible for thrombolysis. Previously, studies investigating the PWI-DWI mismatch in patients with known stroke onset times in the 0-6 hour time window after stroke onset reported rates of 54% [9] and 88%.[10] The PRE-FLAIR study revealed a DWI-FLAIR mismatch in 38% of patients with known stroke onset times between 0-12 hours. [1] A post-hoc analysis of data from the AXIS2 trial found a similar yield of 44% for the DWI-FLAIR mismatch, but a higher yield of 72% for the PWI-DWI mismatch, resulting in a yield of 80% when screening for both mismatch profiles.[11] The high proportion of the PWI-DWI mismatch probably resulted from the inclusion of patients with a DWI lesion of at least 15 ml, excluding small lesion strokes that are less likely to reveal a penumbral pattern. In

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contrast, the WAKE-UP trial revealed very small core lesion volumes in a large proportion of screened patients.[2]

We found no difference in the proportions of a PWI-DWI mismatch in patients with or without DWI-FLAIR mismatch. The presence of an association would suggest a mutual underlying disease mechanism [11] in which collaterals could play a role. In patients with good collaterals the association between time and development of a FLAIR hyperintense signal within the DWI lesion was less pronounced compared to patients with poor collateral status. [12] Good collaterals can be assumed in patients with a PWI-DWI mismatch, resulting in an association between the two mismatch patterns.[13] However, other studies could not confirm the association between the severity of hypoperfusion and development of a FLAIR hyperintense signal over time. [14,15] The lack of association between both mismatch profiles in our study population might be due to the fact that only one third of patients had a visible vessel occlusion and stroke severity was rather moderate.

We explored the modifying role of the presence of a PWI-DWI mismatch on treatment related outcome in patients with a DWI-FLAIR mismatch. Unfortunately the sample size for this subanalysis was rather small which is a limitation of this study. However, we found no interaction between the presence of a PWI-DWI mismatch and treatment. Since we lack power in our population, the presence of a synergistic effect of both mismatches on treatment response compared to the presence of either one of the mismatch profiles needs further study. In addition, half of the patients encountered with a PWI-DWI mismatch were not randomized based on the absence of a DWI-FLAIR mismatch and therefore their response to treatment could not be assessed.

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Since around 20% of patients present with unknown stroke onset time [4, 5], implementing MRI-guided patient selection has a great relevance for treating ischemic stroke. In contrast to the PWI-DWI mismatch, which can also be appreciated on CT perfusion as perfusion lesion-ischemic core mismatch, the DWI-FLAIR mismatch can only be evaluated using MRI. An approach using MRI may be more inclusive than one based on CT perfusion, given the high yield of the DWI-FLAIR mismatch. Multimodal MRI with DWI, FLAIR, PWI, GE or SWI and TOF-MRA is a feasible and probably the most inclusive approach to identify thrombolysis eligible patients in the unknown time window. We cannot extrapolate our findings to thrombectomy eligible patients in the unknown or extended time window, in which there is only evidence for the perfusion lesion-ischemic core or clinical-core mismatch, but not the DWI-FLAIR mismatch.[16, 17]

In conclusion, given their high combined yield, screening for the presence of both mismatch profiles by MRI with PWI, DWI and FLAIR is likely the most inclusive approach to identify ischemic stroke patients still eligible for intravenous thrombolysis in the unknown time window.

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Robin Lemmens is a senior clinical investigator of FWO Flanders.

Author contributions

LS, AW, FB, PD, SC, GT and RL were responsible for acquisition and analysis of data.

LS, PD, VT, GT and RL were responsible for drafting of manuscript and figures.

AW, FB, BC, MEb, MEn, JBF, CG, KWM, NN, SP, CZS, VT, GT and RL were responsible for conception and design of the study.

Potential conflicts of interest

SC reports equity interest in Ischemaview.

MEn reports lecture and seminar fees paid to the Charité from Boehringer-Ingelheim.

CG received honoraria as speaker or consultant from Boehringer-Ingelheim.

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KWM has participated in advisory boards for Boehringer-Ingelheim and receives research support from Boehringer-Ingelheim for the ATTEST-2 trial.

GT reports lecture fees from Boehringer-Ingelheim,

RL has no personal disclosures, but reports consultancy fees paid to KU Leuven from Ischemaview.LS, AW, FB, PD, BC, MEb, JBF, NN, SP, CZS and VT have nothing to report.

Boehringer-Ingelheim owns patent rights to Actilyse (alteplase), but had no involvement in the WAKE-UP trial. Imaging analyses described in this manuscript were performed by Ischemaview software (RAPID).

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Figure Legends

Figure 1

Figure 1. (A) Schematic overview of patients screened and/or randomized in the original WAKE-UP trial and those included in the current post-hoc analysis. (B) Prevalence of each mismatch type in screened and/or randomized patients with available PWI. Numbers in the bars indicate the percentage of all screened patients with PWI with a certain mismatch type. (C) 2 by 2 table with DWI-FLAIR and PWI-DWI mismatch as classifiers, showing the number of patients per group. Double mismatch refers to the presence of both the PWI-DWI and DWI-FLAIR mismatch. *PWI: perfusion-weighted imaging; DWI: diffusion-weighted imaging; FLAIR: fluid attenuated inversion recovery.*

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Figure 2

Figure 2. Imaging examples (left) and distributions of scores on the modified Rankin Scale at 90 days (right) in patients with a double mismatch and DWI-FLAIR mismatch only. (A) Double mismatch refers to the presence of both the PWI-DWI and DWI-FLAIR mismatch. Automated RAPID analysis shows a PWI-DWI mismatch (core < 70 ml, mismatch ratio > 1.2, mismatch volume > 10 ml). The core lesion is delineated on DWI (magenta) and the time to maximum (Tmax) > 6s volume on PWI (green). The distribution of scores on the modified Rankin Scale (mRS) at 90 days shows no significant difference in patients treated with alteplase versus placebo in the subgroup of patients with a double mismatch (common odds ratio 1.83; 95% CI, 0.68-4.93; p=0.23). Numbers in the bars indicate the percentage of patients for each score on the mRS. (B) In patients with only a DWI-FLAIR mismatch, automated RAPID analysis reveals no PWI-DWI mismatch. The core lesion is delineated on DWI (magenta) and the time to maximum (Tmax) > 6s volume on PWI (green). The distribution of scores on the modified Rankin Scale (mRS) at 90 days shows no significant difference in patients treated with alteplase versus placebo in the subgroup of patients with only a DWI-FLAIR mismatch (common odds ratio 1.45; 95% CI 0.80-2.62; p=0.22). Numbers in the bars indicate the absolute number of patients for each score on the mRS. *PWI: perfusion-weighted imaging; DWI: diffusion-weighted imaging; FLAIR: fluid attenuated inversion recovery.*

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Table 1. Baseline demographic characteristics of randomized patients with a double mismatch and only DWI-FLAIR mismatch allocated to alteplase versus placebo

	Only DWI-FLAIR mismatch	Double mismatch

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	N = 151			N = 57		
	Alteplase N = 80	**Placebo N = 71**	**p-value**	**Alteplase N=32**	**Placebo N = 25**	**p-value**
Age, mean (SD), years	63.74 (11.92)	63.73 (13.90)	0.60	68.25 (11.31)	64.68 (8.91)	0.05
Male Gender, No. (%)	56 (70)	49 (69)	1.0	17 (53)	15 (60)	0.79
Medical history or risk factors						
Arterial hypertension No. (%)[a]	40 (50)	34 (48)	0.74	16 (50)	14 (56)	0.79
Diabetes mellitus No. (%)[b]	9 (11)	15 (21)	0.12	6 (19)	5 (20)	0.66
Hypercholesterolemia No. (%)[c]	33 (41)	22 (31)	0.38	9 (28)	13 (52)	0.17
Atrial fibrillation No. (%)[d]	6 (8)	6 (8)	1.0	6 (19)	6 (24)	0.75
History of ischemic stroke No. (%)[e]	13 (16)	7 (10)	0.34	4 (13)	2 (8)	0.69

[a]Data on arterial hypertension were missing for 1 patient treated with placebo with only DWI-FLAIR mismatch.

[b]Data on diabetes mellitus were missing for 1 patient treated with alteplase with only DWI-FLAIR mismatch and 2 patients treated with alteplase.with double mismatch.

[c]Data on hypercholesterolemia were missing for 2 patients treated with alteplase and 1 with placebo with only DWI-FLAIR mismatch and in 5 patients treated with alteplase and 1 with placebo with double mismatch.

[d]Data on atrial fibrillation were missing for 2 patients treated with alteplase and 1 with placebo with only DWI-FLAIR mismatch.

[e]Data on history of ischemic stroke were missing for 1 patient treated with alteplase with only DWI-FLAIR mismatch.

SD: standard deviation; No: Number; IQR: interquartile range

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Table 2: Baseline stroke, imaging and treatment characteristics of randomized patients with a double mismatch and only DWI-FLAIR mismatch allocated to alteplase versus placebo

	Only DWI-FLAIR mismatch N = 151			Double mismatch N = 57		
	Alteplase N = 80	**Placebo N = 71**	**p-value**	**Alteplase N=32**	**Placebo N = 25**	**p-value**
Reason for unknown time of symptom onset			0.94			0.48
Night sleep, No. (%)	74 (93)	64 (90)		28 (88)	24 (96)	
Day sleep, Aphasia or other, No. (%)	6 (8)	7 (10)		4 (13)	1 (4)	
Time between LSW point and symptom recognition, median (IQR), hours[a]	7.00 (4.50-8.50	7.00 (5.00-8.50)	0.60	6.50 (4.50-8.67)	8.13 (5.96-10.13)	0.15
NIHSS sum score, median (IQR)	5 (3-8)	5 (3-8)	0.48	7.5 (5-13)	9 (5-12)	0.64
DWI lesion volume at baseline, median (IQR), ml	0 (0-10)	0 (0-7)	0.45	8 (0-17)	3 (0-28)	0.83
PWI lesion volume at baseline, median (IQR), ml	0 (0-8)	0 (0-5)	0.24	50 (28-75)	50 (21-109)	0.74
Time from symptom recognition to MRI median (IQR), hours	2.62 (1.98-3.17)	2.43 (1.87-3.12)	0.31	2.47 (1.87-3.38)	2.33 (2.08-3.42)	0.79
Time from symptom recognition to treatment initiation median (IQR), hours[b]	3.05 (2.52-3.62)	2.97 (2.33-3.53)	0.42	2.90 (2.20-3.75)	2.92 (2.50-3.87)	0.96
Time between LSW and treatment initiation median (IQR), hours[c]	10.18 (7.12-12.00)	10.27 (8.08-12.08)	0.89	9.47 (7.76-12.04)	11.12 (8.30-13.25)	0.16
Vessel occlusion on time-of-flight MRA[d]						
Any, No. (%)	17 (22)	11 (16)	0.40	26 (84)	19 (76)	0.51
Large vessel occlusion, No. (%)	9 (12)	4 (6)	0.25	18 (58)	15 (60)	1.0

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[a]Time between last seen well point and symptom recognition was missing for 4 patients treated with alteplase and 3 patients treated with placebo with only DWI-FLAIR mismatch and 3 patients treated with alteplase.and 1 patient treated with placebo with double mismatch.

[b]Time from symptom recognition to treatment was missing for 2 patients treated with alteplase and 1 patient treated with placebo with only DWI-FLAIR mismatch and 1 patient treated with alteplase.with double mismatch.

[c]Time between last seen well point and treatment initiation was missing for 5 patients treated with alteplase and 4 patients treated with placebo with only DWI-FLAIR mismatch and 4 patients treated with alteplase and 1 patient treated with placebo with double mismatch

[d]Any vessel occlusion and large vessel occlusion was missing for 2 patients treated with alteplase and 1 with placebo with only DWI-FLAIR mismatch and for 1 patient treated with alteplase with double mismatch. Large vessel occlusion was defined as an occlusion of the intracranial internal carotid artery or main stem of the middle cerebral artery.

No: Number; LSW: last seen well; IQR: interquartile range; NIHSS: national Institutes of Health Stroke Scale; DWI: diffusion-weighted imaging; PWI: perfusion-weighted imaging; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography.

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Table 3: Efficacy and Safety outcomes in patients with a double mismatch treated with alteplase versus placebo

	Alteplase N=32	**Placebo N = 25**	**Effect Variable[a]**	**Adjusted Effect Variable value (95% CI)**	**P-value**
Efficacy outcomes					
mRS score 0 or 1, No. (%)[b]	14 (47)	9 (36)	OR	1.86 (0.54-6.44)	0.33
Median mRS score (IQR)[c]	2 (1-4)	3(1-3)	cOR	1.83 (0.68-4.93)	0.23
Safety Outcome					
Death at 90 days, No. (%)[f]	3 (9)	0 (0)	OR	$<1.0\ 10^{-3}$ ($<1.0\ 10^{-3}$ - $> 9.9\ 10^{2}$)	0.95
Death or dependency at 90 days, No. (%)[g]	8 (27)	5 (20)	OR	0.87 (0.20-3.85)	0.86

[a]Odds Ratio's (OR) and common Odds Ratio's (cOR) were adjusted for the stratification variables age and symptom severity.

[b]Modified Rankin Scale (mRS) scores of 0 or 1 were considered the favorable outcomes. The primary efficacy outcome was analyzed in 30 patients in the alteplase group and 25 patients in the placebo group. Two patients in the alteplase group were lost to follow up.

[c]Categorical shift in the distribution of mRS scores between the two treatment groups was analyzed in 30 patients in the alteplase group and 25 patients in the placebo group. Two patients in the alteplase group were lost to follow up.

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[f]Primary safety outcome death at 90 days was analyzed in 32 patients in the alteplase group and 25 patients in the placebo group.

[g]Primary safety outcome death or mRS score 4-6 at 90 days was analyzed in 30 patients in the alteplase group and 25 patients in the placebo group. Two patients in the alteplase group were lost to follow up.

IQR: interquartile range.

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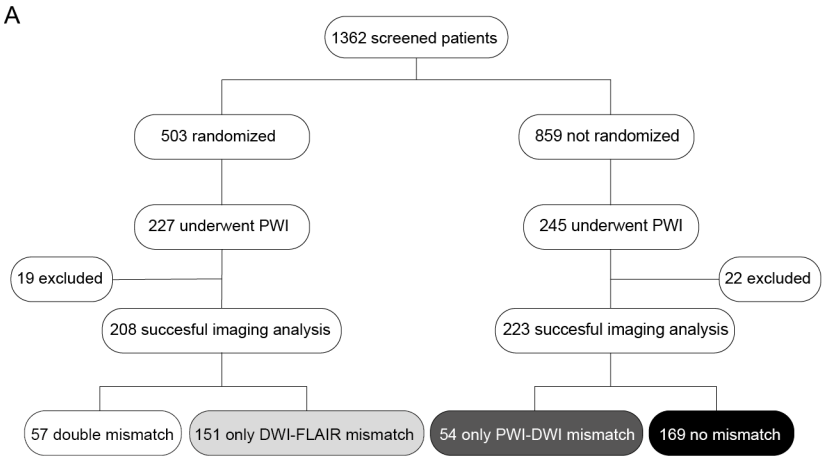

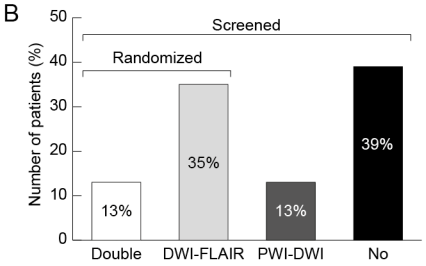

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	DWI-FLAIR	No DWI-FLAIR	Total
PWI-DWI	57 (13%)	54 (13%)	111 (26%)
No PWI-DWI	151 (35%)	169 (39%)	320 (74%)
Total	208 (48%)	223 (52%)	

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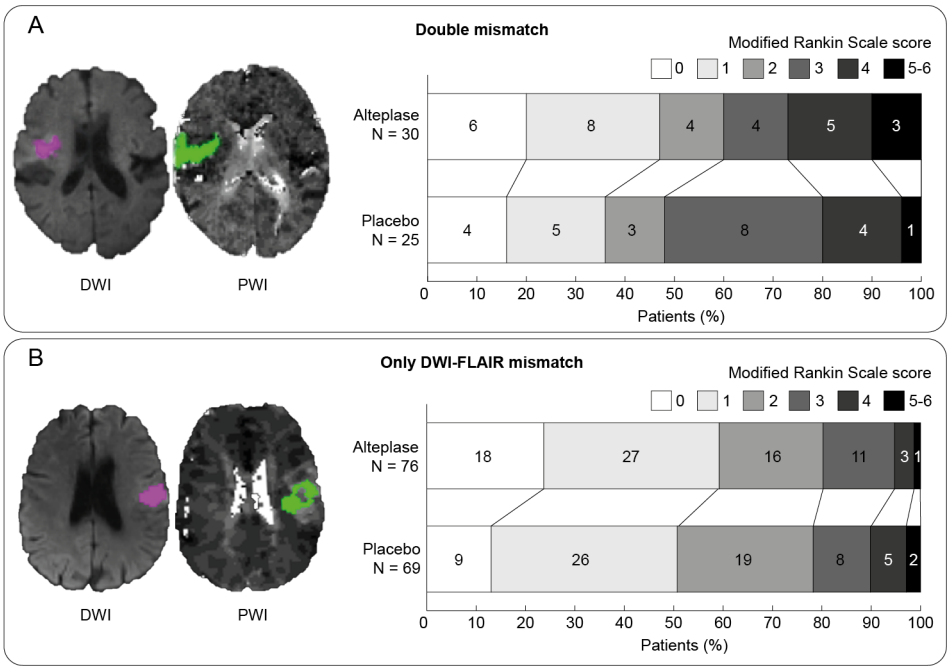

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