

# Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute

## Stroke – An Analysis of the WAKE-UP Randomized Clinical Trial

### Supplemental material

**eTable 1** Sensitivity analysis: Association between presence of at least 1 cerebral microbleed and functional and safety outcomes at 90 days. Model adjusted for presence of arterial hypertension and atrial fibrillation in addition to age and NIHSS score.

Populat ion	Subgroup	Functional outcome <sup>a</sup>				Safety outcomes <sup>b</sup>			
		Excellent (mRS ≤1)		Good (mRS ≤2)		sICH		Any ICH	
		OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>
All patients	All	1.07 (0.64-1.80)	.790	0.91 (0.50-1.67)	.764	2.57 (1.07-6.16)	<b>.035</b>	1.52 (0.79-2.92)	.208
	Placebo	1.34 (0.63-2.86)		0.81 (0.35-1.88)		3.59 (0.82-15.74)		1.21 (0.42-3.48)	
	Alteplase	0.88 (0.44-1.78)	.424	1.04 (0.44-2.46)	.683	2.17 (0.74-6.32)	.584	1.76 (0.77-4.02)	.585
Strictly lobar	All	0.79 (0.40-1.59)	.513	0.70 (0.32-1.53)	.369	1.88 (0.59-5.98)	.285	1.81 (0.82-4.00)	.145
	Placebo	0.65 (0.22-1.95)		0.39 (0.12-1.23)		3.12 (0.49-20.01)		1.59 (0.41-6.17)	
	Alteplase	0.91 (0.37-2.23)	.651	1.14 (0.39-3.35)	.178	1.45 (0.35-6.09)	.514	1.93 (0.73-5.06)	.820
Non-strictly-lobar	All	1.44 (0.71-2.90)	.313	1.20 (0.51-2.81)	.681	4.23 (1.41-12.72)	<b>.010</b>	1.25 (0.48-3.24)	.650
	Placebo	2.50 (0.91-6.90)		1.62 (0.50-5.29)		4.62 (0.72-29.40)		0.85 (0.19-3.73)	
	Alteplase	0.83 (0.32-2.19)	.126	0.84 (0.25-2.84)	.450	4.03 (1.01-16.04)	.909	1.73 (0.49-6.11)	.479

<sup>a</sup>Point estimates below 1 indicate worse functional outcome in patients with one or more CMBs. <sup>b</sup>Point estimates above 1 indicate higher risk of hemorrhage with in patients with one or more CMBs. <sup>c</sup>First P value per group corresponds to the hypothesis that across all patients, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients that received either alteplase or placebo, the odds ratio is identical (no interaction). For absolute percentages per group, see Figures 1 and 2 in the main text.

# Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke – An Analysis of the WAKE-UP Randomized Clinical Trial

## Supplemental material

**eTable 2** Sensitivity analysis: Association between alteplase treatment and functional and safety outcomes according to presence and spatial distribution of cerebral microbleeds. Model adjusted for presence of arterial hypertension and atrial fibrillation in addition to age and NIHSS score.

Population	Subgroup	Functional outcome <sup>a</sup>				Safety outcomes <sup>b</sup>			
		Excellent (mRS ≤1)		Good (mRS ≤2)		sICH		Any ICH	
		OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>	OR (95% CI)	P <sup>c</sup>
All patients	All	1.61 (1.06-2.44)	<b>.024</b>	1.75 (1.06-2.90)	<b>.030</b>	2.13 (0.88-5.18)	.096	1.68 (0.94-3.01)	.082
	≥1 CMBs	1.15 (0.46-2.88)	.424	2.13 (0.73-6.17)	.683	1.59 (0.41-6.16)	.584	2.21 (0.70-6.93)	.585
	No CMBs	1.75 (1.10-2.79)		1.65 (0.93-2.93)		2.63 (0.80-8.66)		1.52 (0.77-3.00)	
Strictly lobar	All	1.81 (1.17-2.81)	<b>.008</b>	1.90 (1.12-3.25)	<b>.018</b>	2.17 (0.79-5.96)	.134	1.57 (0.85-2.90)	.149
	≥1 CMBs	2.42 (0.64-9.21)	.651	4.90 (1.11-21.52)	.178	1.22 (0.17-8.71)	.514	1.84 (0.41-8.22)	.820
	No CMBs	1.75 (1.10-2.78)		1.66 (0.94-2.93)		2.62 (0.80-8.62)		1.52 (0.78-2.98)	
Non-strictly-lobar	All	1.55 (1.00-2.40)	<b>.048</b>	1.55 (0.91-2.64)	.111	2.55 (0.92-7.07)	.072	1.66 (0.87-3.16)	.125
	≥1 CMBs	0.58 (0.15-2.20)	.126	0.86 (0.17-4.30)	.450	2.31 (0.32-16.51)	.909	3.10 (0.49-19.67)	.479
	No CMBs	1.75 (1.10-2.79)		1.66 (0.94-2.95)		2.65 (0.79-8.85)		1.52 (0.76-3.02)	

<sup>a</sup>Point estimates above 1 indicate better functional outcome with alteplase treatment. <sup>b</sup>Point estimates above 1 indicate higher risk of hemorrhage with alteplase treatment. <sup>c</sup>First P value per group corresponds to the hypothesis that across patients with any number of CMBs, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients with no CMBs and at ≥1 CMBs, the odds ratio is identical (no interaction). For absolute percentages per group, see Figures 3 and 4 in the main text.

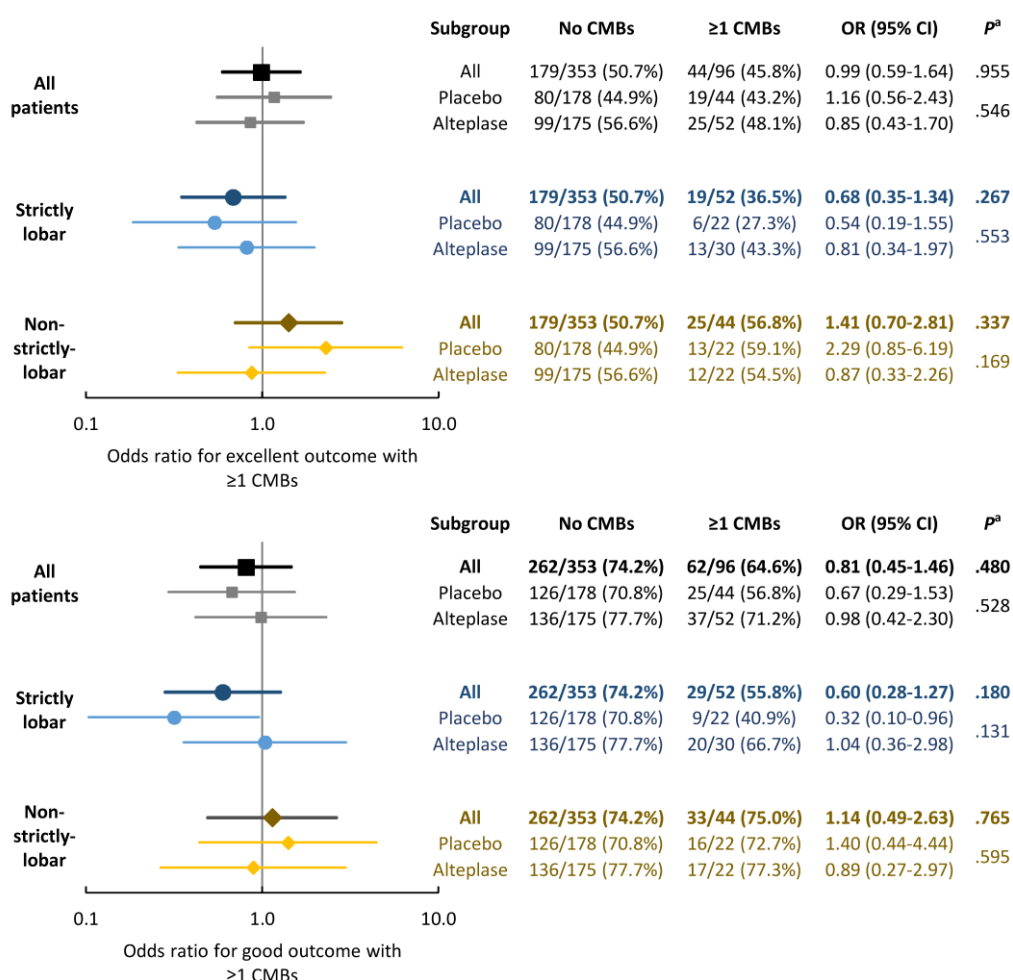
## Supplemental material

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# Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke – An Analysis of the WAKE-UP Randomized Clinical Trial

## Supplemental material

eFigure 1



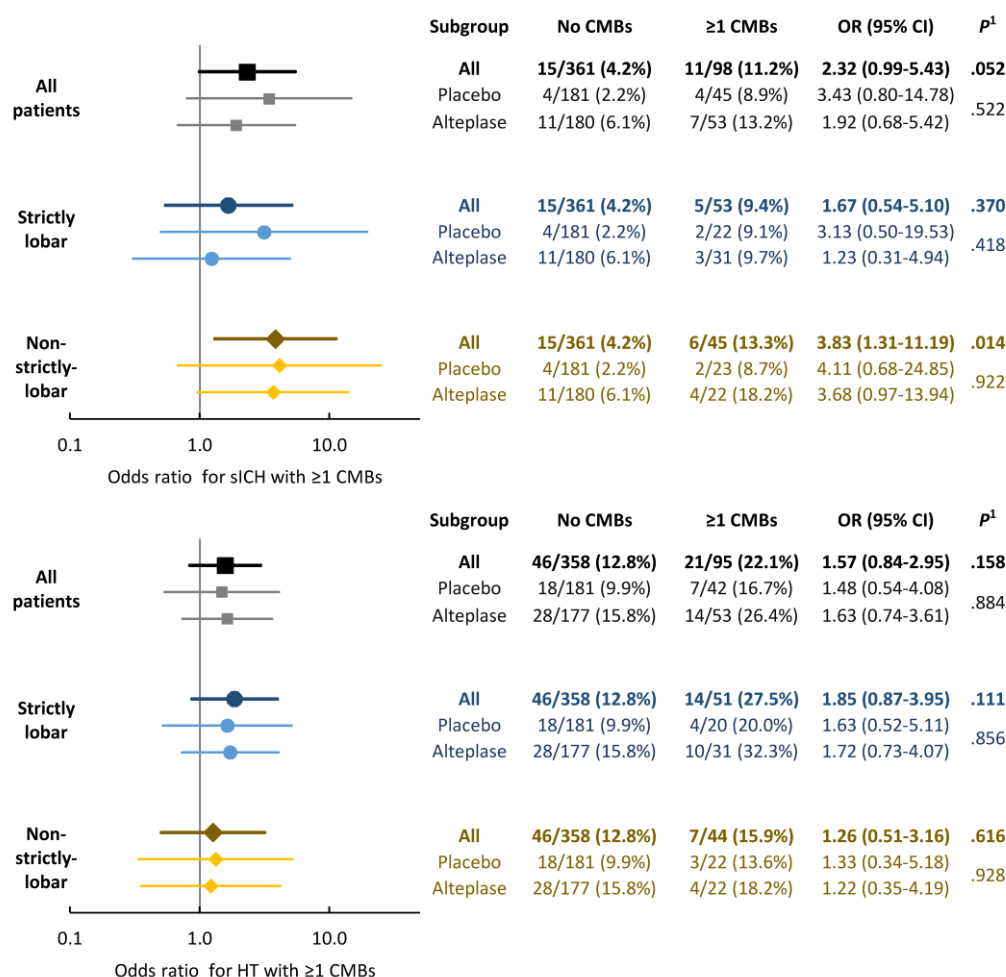
**eFigure 1 Association between presence of at least 1 cerebral microbleed and functional outcome at 90 days.** Point estimates below 1 indicate worse functional outcome in patients with one or more CMBs. <sup>a</sup>First P value corresponds to the hypothesis that across all patients, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients that received either alteplase or placebo, the odds ratio is identical (no interaction).

CMBs indicates cerebral microbleeds; OR, odds ratio; CI, confidence interval.

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## Supplemental material

eFigure 2



**eFigure 2 Association between presence of at least 1 cerebral microbleed and hemorrhagic complications.**

Point estimates above 1 indicate higher risk of hemorrhage with in patients with one or more CMBs. <sup>a</sup>First P value per group corresponds to the hypothesis that across all patients, the odds ratio is equal to 1 (no effect); second P value corresponds to the hypothesis that within strata of patients that received either alteplase or placebo, the odds ratio is identical (no interaction).

CMBs indicates cerebral microbleeds; OR, odds ratio; CI, confidence interval; sICH, symptomatic intracranial hemorrhage; HT, hemorrhagic transformation.

# Cerebral Microbleeds and Treatment Effect of Intravenous Thrombolysis in Acute Stroke – An Analysis of the WAKE-UP Randomized Clinical Trial

Supplemental material

eFigure 3



**eFigure 3** Relative frequencies of symptomatic intracerebral hemorrhage according to SITS-MOST and ECASS II/ECASS III criteria by treatment group and presence of cerebral microbleeds. CMBs indicate cerebral microbleeds.