Stroke

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Sonothrombolysis in Patients With Acute Ischemic Stroke With Large Vessel Occlusion

An Individual Patient Data Meta-Analysis

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BACKGROUND AND PURPOSE: Evidence about the utility of ultrasound-enhanced thrombolysis (sonothrombolysis) in patients with acute ischemic stroke (AIS) is conflicting. We aimed to evaluate the safety and efficacy of sonothrombolysis in patients with AIS with large vessel occlusion, by analyzing individual patient data of available randomized-controlled clinical trials.

METHODS: We included all available randomized-controlled clinical trials comparing sonothrombolysis with or without addition of microspheres (treatment group) to intravenous thrombolysis alone (control group) in patients with AIS with large vessel occlusion. The primary outcome measure was the rate of complete recanalization at 1 to 36 hours following intravenous thrombolysis initiation. We present crude odds ratios (ORs) and ORs adjusted for the predefined variables of age, sex, baseline stroke severity, systolic blood pressure, and onset-to-treatment time.

RESULTS: We included 7 randomized controlled clinical trials that enrolled 1102 patients with AIS. A total of 138 and 134 confirmed large vessel occlusion patients were randomized to treatment and control groups respectively. Patients randomized to sonothrombolysis had increased odds of complete recanalization compared with patients receiving intravenous thrombolysis alone (40.3% versus 22.4%; OR, 2.17 [95% CI, 1.03–4.54]; adjusted OR, 2.33 [95% CI, 1.02–5.34]). The likelihood of symptomatic intracranial hemorrhage was not significantly different between the 2 groups (7.3% versus 3.7%; OR, 2.03 [95% CI, 0.68–6.11]; adjusted OR, 2.55 [95% CI, 0.76–8.52]). No differences in the likelihood of asymptomatic intracranial hemorrhage, 3-month favorable functional and 3-month functional independence were documented.

CONCLUSIONS: Sonothrombolysis was associated with a nearly 2-fold increase in the odds of complete recanalization compared with intravenous thrombolysis alone in patients with AIS with large vessel occlusions. Further study of the safety and efficacy of sonothrombolysis is warranted.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: ischemic stroke ■ meta-analysis ■ microsphere ■ odds ratio ■ thrombolysis ■ ultrasonography, Doppler, transcranial

Preliminary evidence has indicated that the addition of pulsed-wave ultrasound to tPA (tissue-type plasminogen activator) may increase the odds of recanalization and favorable functional outcomes in patients with acute ischemic stroke (AIS) with proximal intracranial large vessel occlusions (LVOs).[1–3] These

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Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
CTA	computed tomography angiography
ICH	intracranial hemorrhage
IPD-MA	individual patient data meta-analysis
LVO	large vessel occlusion
MRA	magnetic resonance angiography
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PROSPERO	International Prospective Register of Ongoing Systematic Reviews
RCT	randomized controlled clinical trial
TCD	transcranial Doppler
tPA	tissue-type plasminogen activator
TRUST	Aureva Transcranial Ultrasound Device With tPA in Patients With Acute Ischemic Stroke

findings have been further corroborated by 2 independent aggregated data meta-analyses suggesting the potential utility of ultrasound-enhanced thrombolysis (sonothrombolysis) as an investigational reperfusion therapy for AIS.[4,5]

The largest to date phase 3 randomized-controlled clinical trial (RCT) evaluating the safety and efficacy of sonothrombolysis using an operator-independent ultrasound device compared with intravenous tPA alone reported that delivery of sonothrombolysis was feasible and safe but failed to demonstrate additional clinical benefit in patients with AIS.[6] The lack of efficacy in this trial could partially be explained by the absence of pretreatment imaging documentation of proximal LVO,[7] which has been a prerequisite for the previous sonothrombolysis trials.[8–10] The trial instead included patients based on their admission neurological severity (National Institutes of Health Stroke Scale score [NIHSS] ≥10 points) and could not utilize the imaging documentation of a proximal LVO.[7]

The aim of the present systematic review and individual patient data meta-analysis (IPD-MA) is to systematically assess the safety and efficacy of sonothrombolysis with or without the addition of microspheres against intravenous thrombolysis alone in patients with AIS with LVO by using individual patient data from published RCTs. Using individual patient data, we were also able to assess the utility of sonothrombolysis in different patient subgroups and settings.

METHODS

Our article adheres to the AHA Journals' implementation of the Transparency and Openness Promotion (TOP) Guidelines. Data used in the present IPD-MA will be available from the corresponding author following reasonable requests. This meta-analysis followed the instructions from the Cochrane Handbook for Systematic Reviews, and used a prespecified study protocol that has been published in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO number: CRD42019131848). The results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data guidelines.[11]

Inclusion Criteria of Eligible Participants

An RCT was eligible for inclusion in the present IPD-MA when enrolled patients qualifying the following inclusion criteria:

1. Age >18 years
2. Receiving intravenous tPA treatment within a 4.5-hour treatment window using the standard dose (0.9 mg/kg) in the control treatment arm and intravenous tPA treatment within a 4.5-hour treatment window using the standard dose (0.9 mg/kg) coupled with low-power ultrasound (sonothrombolysis)—with or without the addition of microspheres—in the active treatment arm
3. Confirmation of intracranial vessel occlusion before study enrolment using different available imaging modalities (neurovascular ultrasound, CT or MR angiography [MRA])
4. Premorbid modified Rankin Scale (mRS) score of 0–1
5. Received no treatment with endovascular procedures (eg, direct mechanical thrombectomy or intraarterial thrombolysis) immediately before or during sonothrombolysis/thrombolysis treatment. Patients receiving treatment with endovascular procedures after the administration of sonothrombolysis/ thrombolysis were not excluded from the analysis.

We requested recanalization rates and noncompulsory study characteristics (Table I in the Data Supplement) from the corresponding authors of eligible RCTs that were identified by the literature search.

Risk of Bias Assessment

Risk of bias assessment was performed by 2 independent reviewers (G.T. and A.H.K.) with the Cochrane Risk of Bias assessment tool,[12] and all emerging conflicts were resolved via consensus between the 2 investigators. It was decided that publication bias and small study effects would be assessed if 10 or more studies were included in the present IPD-MA.

Outcome Measures

The primary outcome measure was the rate of complete recanalization at 1 to 36 hours following intravenous tPA bolus. Complete recanalization could be documented by (1) ultrasound, as Thrombolysis in Brain Ischemia scores 4 or 5,[13] (2) computed tomography angiography (CTA), as CTA arterial occlusive lesion scoring of 3,[14] or (3) MRA suggestive of complete recanalization.[7]

Secondary outcomes included:

Efficacy

1. Complete or partial recanalization, according to every available definition,
2. Early clinical recovery, defined as a reduction of 10 points or more on the NIHSS score or a total NIHSS

score of 3 points or less at 2 hours after intravenous tPA bolus,[8]
3. Clinical recovery, defined as a reduction of 10 points or more on the NIHSS score or a total NIHSS score of 3 points or less at 24 hours after intravenous tPA bolus,[8]
4. Favorable functional outcome at 3 months, defined as mRS scores 0 to 1 at 3 months,
5. Functional independence at 3 months (defined as mRS scores of 0–2), and
6. Cumulative functional improvement at 3-months, where we used the whole spectrum of the distribution of 3-month mRS scores. Functional improvement was defined as 1-point decrease in mRS-score across all grades.[6]

Safety

7. Symptomatic intracranial hemorrhage (ICH), according to every available definition,
8. Asymptomatic ICH, and
9. All-cause mortality at 3 months.

Further information on the identification of eligible studies, data transfer and verification process and statistical analysis are provided in the Data Supplement.

RESULTS

Study Selection and Study Characteristics

Systematic search of Medline and Scopus databases yielded 218 and 161 results respectively. After removing duplicates, the titles and abstracts from the remaining 292 studies were screened and 11 potentially eligible studies for the meta-analysis were retained (Figure 1). After retrieving the full-text versions of the aforementioned 11 studies, 4 studies were excluded because they were not RCTs[15–17] or included patients without the diagnosis of AIS.[18] There was no conflict or disagreement between the reviewers (GT, A.K., A.A.V.) who screened the identified studies. The corresponding authors from the 7 studies that met the protocol's inclusion criteria were contacted by e-mail.[6,8,10,19–22]

Risk of bias assessment of included studies disclosed a high risk of performance bias, due to the lack of blinding of participants and personnel in all except for 1 study.[6] The risk of reporting bias was unclear in 4 trials,[10,19–21] due to lack of corresponding study protocols clearly mentioning on all primary and secondary outcomes of interest for each trial. Finally, it should be noted that one of the included studies was not published as a full article at the time of the review,[22] and thus risk of bias was not feasible for this study (Figures I and II in the Data Supplement).

IPD were obtained from all eligible studies. We compared IPD with original publications to assess consistency and applied our predefined inclusion and exclusion criteria as presented in Table II in the Data Supplement. One of the corresponding authors of 2 small RCTs provided a single, merged database with nonoverlapping patient data from the 2 companion reports.[19,20]

Seven studies with 272 patients with AIS with LVO (median age 68 years, 58% men, median baseline NIHSS score 16), 138 in the sonothrombolysis group, and 134 in the control group, were included in the IPD-MA. Together with standard dose (0.9 mg/kg) tPA administration, 3 of the included studies report the use of 2-MHz transcranial Doppler (TCD),[8,20,21] 1 study the use of a 1.8-MHz TCCS,[15] 1 study the use of an operator-independent 2-MHz TCD device,[6] and 2 studies the use of intravenous microspheres coupled with 2-MHz TCD insonation (Table II in the Data Supplement).[10,22] The 2 groups were balanced for all baseline characteristics (Table 1), except for the higher male predominance in the sonothrombolysis group compared with the control group (65.9% versus 50.7%, P=0.011). All baseline characteristics, except for sex, were also well distributed within studies (Figure III in the Data Supplement).

Forest plots of the 2-stage analysis models are presented in Figures IV through XIII in the Data Supplement. In the 1-stage analyses (Table 2), adjusted for the per-protocol confounders, patients receiving treatment with sonothrombolysis had higher likelihood of both complete recanalization (40.3% versus 22.4%; OR, 2.17 [95% CI, 1.03–4.54]; adjusted OR, 2.33 [95% CI, 1.02–5.34]) and any (complete or partial) recanalization (66.4% versus 53.0%; common OR, 1.91 [95% CI, 1.03–3.53]; adjusted common OR, 2.01 [95% CI, 1.03–3.92]). No significant differences between groups were documented on other secondary efficacy outcomes of early clinical recovery (13.5% versus 10.8%; OR, 1.29 [95% CI, 0.54–3.09]; adjusted OR, 0.67 [95% CI, 0.10–4.39]), clinical recovery (22.4% versus 23.5%; OR, 0.94 [95% CI, 0.53–1.66]; adjusted OR, 1.00 [95% CI, 0.55–1.84]), 3-month favorable functional outcome (35.6% versus 27.8%; OR, 1.32 [95% CI, 0.72–2.45]; adjusted OR, 1.43 [95% CI, 0.64–3.19]), 3-month functional independence (48.1% versus 40.5%; OR, 1.37 [95% CI, 0.81–2.30]; adjusted OR, 1.43 [95% CI, 0.77–2.64]), and 3-month functional improvement (common OR, 1.18 [95% CI, 0.68–1.63]; adjusted common OR, 1.05 [95% CI, 0.67–1.65]; Figure 2). About safety outcomes, no significant differences were documented on the probability of symptomatic ICH (7.3% versus 3.7%; OR, 2.03 [95% CI, 0.68–6.11]; adjusted OR, 2.55 [95% CI, 0.76–8.52]), asymptomatic ICH (24.0% versus 25.4%; OR, 0.96 [95% CI, 0.35–2.68]; adjusted OR, 1.30 [95% CI, 0.38–4.39]) or all-cause mortality at 3 months (14.8% versus 15.1%; OR, 0.94 [95% CI, 0.34–2.57]; adjusted OR, 1.23 [95% CI, 0.25–6.05]). Results of the 1-stage IPD-MA adjusting only for the statistically significant covariates according to the ANOVA results were similar and are summarized in Table III in the Data Supplement.

In the subgroup analyses (Figure 3), we detected a moderating effect of age on the association of sonothrombolysis with complete recanalization (<67 years: OR, 4.69 [95% CI, 1.87–11.74] versus ≥67 years:

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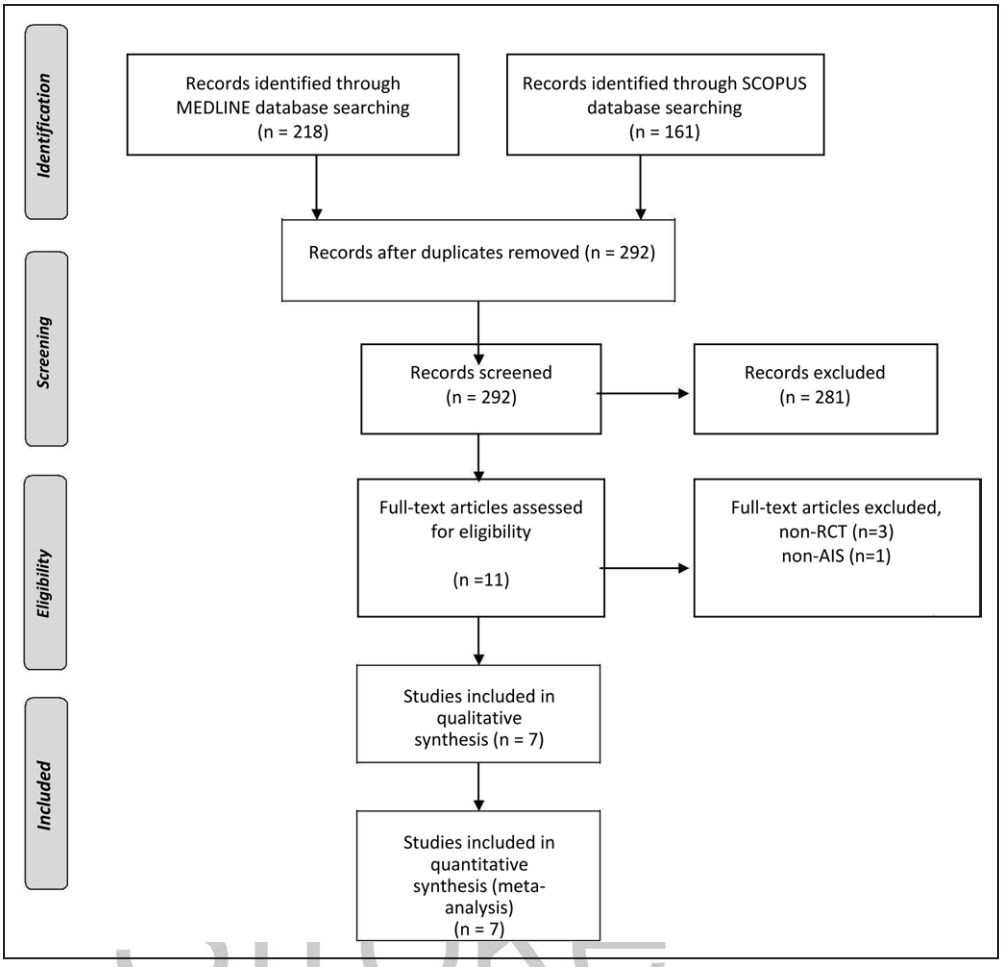

Figure 1. Flow chart on the selection of eligible studies.
AIS indicates acute ischemic stroke; and RCT, randomized controlled clinical trial.

OR, 1.25 [95% CI, 0.40–3.87]; *P* value for interaction: 0.048). We also detected a moderating effect of systolic blood pressure on admission (dichotomized using median value) on the association of sonothrombolysis with complete recanalization (<158 mm Hg: OR, 4.78 [95% CI, 1.77–12.91] versus ≥158 mm Hg: OR, 1.19 [95% CI, 0.27–5.18]; *P* value for interaction: 0.07). No interactions were detected according to the location of occlusion (*P* value for interaction: 0.25), sex (*P* value for interaction: 0.15), baseline NIHSS-score (*P* value for interaction: 0.53), onset-to-tPA bolus (*P* value for interaction: 0.62), and the use of microspheres in combination with sonothrombolysis (*P* value for interaction: 0.53). Likewise, there was no moderating effect of microspheres on the association of sonothrombolysis with 3-month favorable functional outcome (*P* value for interaction: 0.57) or functional independence (*P* value for interaction: 0.60). Finally, we documented that onset to treatment time was linearly and inversely associated with the likelihood of complete recanalization (OR per 10 minute increase: 0.93 [95% CI, 0.90–0.95]) and 3-month favorable functional outcome (OR per 10 minute increase: 0.93 [95% CI, 0.91–0.96]) among patients receiving treatment with sonothrombolysis (Figure XIV in the Data Supplement). After excluding patients from 1 study reporting late recanalization assessment, sonothrombolysis treatment was again associated with a higher probability of complete recanalization compared with intravenous thrombolysis alone (OR, 2.31 [95% CI, 1.09–4.91]; adjusted OR, 2.46 [95% CI, 1.15–5.28]). When restricting the primary analysis to studies that assessed the recanalization outcome with either CTA and/or MRA including a total of 74 total patients (27% of the total meta-analysis population), the association of sonothrombolysis with complete recanalization did not reach statistical significance (OR, 0.87 [95% CI, 0.31–2.48]; adjusted OR, 0.64 [95% CI, 0.18–2.24]). The lack of a significant association in the aforementioned analysis could be attributed to low statistical power, as the outcome of complete recanalization was not found to be associated with the imaging method (TCD/TCCS versus CTA/MRA) used for recanalization assessment (OR, 0.65 [95% CI, 0.25–1.70]).

The primary outcome of complete recanalization was found to be strongly and inversely associated with subsequent endovascular treatment (OR, 0.09 [95% CI, 0.01–0.71]), as endovascular reperfusion procedures were

Table 1. Baseline Characteristics of Included Patients

	Sonothrombolysis group (n=138)	Control group (n=134)	*P* value
Age, median (IQR)	68 (58.25–74.75)	67 (59–75.75)	0.433
Males, %	65.94%	50.75%	0.011
Baseline NIHSS, median (IQR)	16 (12–20)	16 (11–19.75)	0.940
Hypertension, %	61.65%	62.79%	0.849
Atrial fibrillation, %	24.09%	23.13%	0.853
Diabetes, %	21.17%	19.23%	0.694
Current smoking, %	22.31%	24.35%	0.712
Myocardial infarction, %	13.43%	17.89%	0.163
Antiplatelet pretreatment, %	35.45%	47.22%	0.078
Anticoagulant pretreatment, %	8.82%	5.38%	0.276
Systolic blood pressure, mm Hg; median (IQR)	158 (137–171.5)	160 (144–172)	0.330
Diastolic blood pressure, mm Hg; median (IQR)	76 (67.5–89.5)	80.5 (70–90)	0.180
Admission glucose, mg/dL; median (IQR)	116 (106–153)	120.5 (100–148.5)	0.840
Onset-to-tPA bolus time, min; median (IQR)	140 (113–163)	134 (110–166)	0.690
Occluded vessel, %			0.586
M1-MCA	73.91%	72.39%	
M2-MCA	22.46%	21.64%	
ICA (intracranial)	2.90%	2.99%	
other	0.72%	2.99%	
Proximal occlusion, %*	76.81%	75.37%	0.781
ICA stenosis, %	27.41%	28.70%	0.828
EVT, %	7.83%	9.02%	0.742

EVT indicates endovascular treatment; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; and NIHSS, National Institutes of Health Stroke Scale.

*Defined as intracranial ICA or M1-MCA occlusion.

performed at the time of the conduction of included trials only as rescue procedures for patients with unsuccessful recanalization following the end of the sonothrombolysis or thrombolysis. In other worlds, a limited number of patients (8% in the sonothrombolysis group and 9% in the control group) with documented unsuccessful recanalization on TCD or angiography following the termination of alteplase infusion or following the end of real-time TCD monitoring were transferred to the angio suite to undergo endovascular treatment. Consequently, there was a selection bias leading to a strong negative correlation between complete recanalization and endovascular treatment that occurred following the assessment of recanalization status.

DISCUSSION

Our IPD-MA showed that sonothrombolysis produced a nearly 2-fold increase in the odds of complete recanalization compared with intravenous tPA alone in patients with AIS with LVO. This association was independent of potential confounders including demographics, location of occlusion, baseline stroke severity, onset to treatment time, and baseline blood pressure levels. This relationship was found to be more pronounced in younger patients and in patients presenting with normal or mildly elevated systolic blood pressure values. Patients in the sonothrombolysis group were found to have higher rates of symptomatic intracranial hemorrhage compared with the control group; however, the difference between the 2 groups did not reach statistical significance in either unadjusted or adjusted analyses. No association of sonothrombolysis with other efficacy or safety outcomes was uncovered. There was no interaction of microspheres on the association of sonothrombolysis with complete recanalization and clinical outcomes.

Our results are in accordance with 2 very recently published aggregate-data meta-analyses, also suggesting a 2-fold increase in the likelihood of complete recanalization with sonothrombolysis after 60 to 120 minutes from tPA bolus and no difference in clinical or safety outcomes.[23,24] One of the aforementioned meta-analyses reported also an almost 2-fold increase in the likelihood of complete or partial recanalization (risk ratio, 1.90 [95% CI, 1.26–2.88]), with no improvement of ≥4 points in NIHSS score (risk ratio, 1.43 [95% CI, 0.99–2.07]).[24] Interestingly, both meta-analyses reported a potential benefit for patients under 65 years of age randomized to treatment with sonothrombolysis (risk ratio, 1.20 [95% CI, 0.92–1.57]).[23,24] This observation is in line with the

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Table 2. Overview of the One-Step Approach Analyses on Efficacy and Safety Outcomes

Outcomes	Intervention population	Control population	Absolute risk difference (%)	Risk ratio (95% CI)	Odds ratio (95% CI)	Adjusted risk ratio (95% CI)	Adjusted odds ratio (95% CI)
Efficacy outcomes							
Complete recanalization	40.3% (54/134)	22.4% (30/134)	17.9	1.59 (1.02–2.15)	2.17 (1.03–4.54)	1.67 (1.13–2.20)	2.33 (1.02–5.34)
Any recanalization	66.4% (91/137)	53% (71/134)	13.4	…	1.91 (1.03–3.53)	…	2.01 (1.03–3.92)*
Early clinical recovery	13.5% (12/89)	10.8% (11/102)	2.7	1.25 (0.57–2.47)	1.29 (0.54–3.09)	0.70 (0.12–3.06)	0.67 (0.10–4.39)
Clinical recovery	22.4% (30/134)	23.5% (31/132)	1.1	0.95 (0.59–1.44)	0.94 (0.53–1.66)	1.00 (0.61–1.54)	1.00 (0.55–1.84)
Favorable functional outcome at 3 mo	35.6% (48/135)	27.8% (35/126)	7.8	1.20 (0.79–1.68)	1.32 (0.72–2.45)	1.21 (0.72–1.78)	1.43 (0.64–3.19)
Functional independence at 3 mo	48.1% (65/135)	40.5 (51/126)	7.6	1.18 (0.89–1.46)	1.37 (0.81–2.30)	1.20 (0.86–1.52)	1.43 (0.77–2.64)
Functional improvement at 3 mo	…	…	…	…	1.18 (0.68–1.63)*	…	1.05 (0.67–1.65)*
Safety outcomes							
Symptomatic intracranial hemorrhage	7.3% (10/137)	3.7% (5/134)	3.6	1.92 (0.69–4.76)	2.03 (0.68–6.11)	2.29 (0.76–5.76)	2.55 (0.76–8.52)
Asymptomatic intracranial hemorrhage	24% (18/75)	25.4% (18/71)	1.4	0.97 (0.41–1.89)	0.96 (0.35–2.68)	1.14 (0.41–2.37)	1.30 (0.38–4.39)
Mortality at 3 mo	14.8% (20/135)	15.1% (19/126)	0.3	0.98 (0.54–1.70)	0.94 (0.34–2.57)	1.17 (0.28–3.40)	1.23 (0.25–6.05)

*Common odds ratio.

interaction that we had uncovered in the present analyses showing that the beneficial effect of sonothrombolysis on complete recanalization was more pronounced (approximately 4-fold higher) in patients aged <67 years.

Similarly, the interaction of higher pretreatment systolic blood pressure on the association of sonothrombolysis with complete recanalization is also intriguing. Our international collaborative group has previously reported that increasing admission systolic blood pressure levels were associated with lower odds of complete recanalization in patients with AIS with proximal intracranial occlusions treated with intravenous thrombolysis.[25] This association has been reproduced in a recent meta-analysis evaluating the association of pretreatment blood pressure levels with different outcomes in patients with AIS including tPA-induced recanalization.[26] The inverse relationship between increased pretreatment systolic blood pressure levels and vessel patency might be attributed to the potential association of elevated pretreatment systolic blood pressure with both increased baseline thrombus burden and impaired endogenous capacity for fibrinolysis.[27] Nevertheless, our findings provide rationale in favor of stratifying randomization in future sonothrombolysis trials based on age and pretreatment systolic blood pressure levels.

The recanalization rates of the intravenous tPA (control) group in the present IPD-MA are 2× higher (22%) compared with the successful recanalization rates reported after tPA treatment and before endovascular procedures in mechanical thrombectomy trials (11%)[28] and in the tPA treatment (control) group before mechanical thrombectomy (10%) in the Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTEND-IA TNK) trial.[29] The difference in percentages of tPA-induced recanalization in our IPDMA and the previous reports[26,27] could be attributed to the imaging modality used for the assessment of successful recanalization (ultrasound, CTA, or MRA in sonothrombolysis trials as noninterventional imaging modalities [Table II in the Data Supplement] versus interventional digital subtraction angiography in mechanical thrombectomy trials[28,29]) and the timing of recanalization assessment (1–36 hours after tPA bolus in sonothrombolysis trials versus immediately after the end of tPA administration in the aforementioned mechanical thrombectomy trials).

Certain strengths of the present report need to be acknowledged. To the best of our knowledge, this is the first to date IPD-MA evaluating the safety and efficacy of sonothrombolysis in AIS with LVO compared with intravenous thrombolysis alone. The present dataset included previously unpublished data from 3 RCTs,[6,21,22] while our statistical analysis plan was prespecified and published in the PROSPERO database. Finally, all analyses were conducted by an independent group of statisticians (D.M., G.S., A.A.V.) that were not involved in any of the sonothrombolysis RCTs.

Nevertheless, several methodological shortcomings need to be taken into account when interpreting our results. First, it should be noted that despite the

Figure 2. Distribution of 3-mo modified Rankin Scale (mRS) scores in patients with acute ischemic stroke with large vessel occlusion receiving treatment with sonothrombolysis or intravenous thrombolysis alone.

lack of important heterogeneity between studies in the analyses of all outcomes (Figures IV through XIII in the Data Supplement), there were significant differences in some of the outcome definitions (complete recanalization, complete or partial recanalization, symptomatic ICH) between trials. All these outcomes have been dichotomised within the trials and this can also lead to loss of power and important information. Specifically, it should be highlighted that data on the time of recanalization assessment varied across the protocols of included studies ranging between 1 hour from tPA-bolus in the German study[19,20] and 22 to 36 hours following symptom onset in the Norwegian study[22] (Table II in the Data Supplement). In addition, it should be noted that we did not include the exact time of recanalization assessment from individual patients in our individual patient data meta-analysis protocol. Thus, we cannot assess whether delayed recanalization was a reason for the lack of clinical improvement despite the significantly higher recanalization rates of patients receiving sonothrombolysis treatment. Nevertheless, it should be kept in mind that the timing of recanalization was identical in the active and control groups of the individual studies (Table II in the Data Supplement).

Second, no central adjudication of the imaging outcomes of successful recanalization and ICH were performed, while these outcomes were prospectively documented by local investigators and were extracted as provided by authors of the corresponding RCTs. Moreover, it should be noted that different imaging modalities both within and across studies were used to detect the presence of an LVO at baseline assessment (Table II in the Data Supplement). Third, it should be highlighted that the subgroup analyses were neither expected to have significant power, nor to be free of residual confounding. Therefore, the reported findings on the potential modifying role of age and admission blood pressure on the effect of sonothrombolysis on recanalization should be interpreted with caution and as hypothesis generating only. Likewise, the lack of significant difference in the likelihood of recanalization translating into clinical outcomes could potentially be attributed to the lack of power rather than the absence of a true association. A notable characteristic in all forest plots (Figures IV through XIII in the Data Supplement) is that the prediction intervals are quite wide, suggesting that results are far from conclusive and the summary estimates are likely to change considerably when future trials are added. Additionally, it should be noted that there is a high risk of performance bias and effect overestimation due to the lack of blinding of participants and personnel in all except for 1 study.[6] Finally, we should highlight that the vast majority of patients in the

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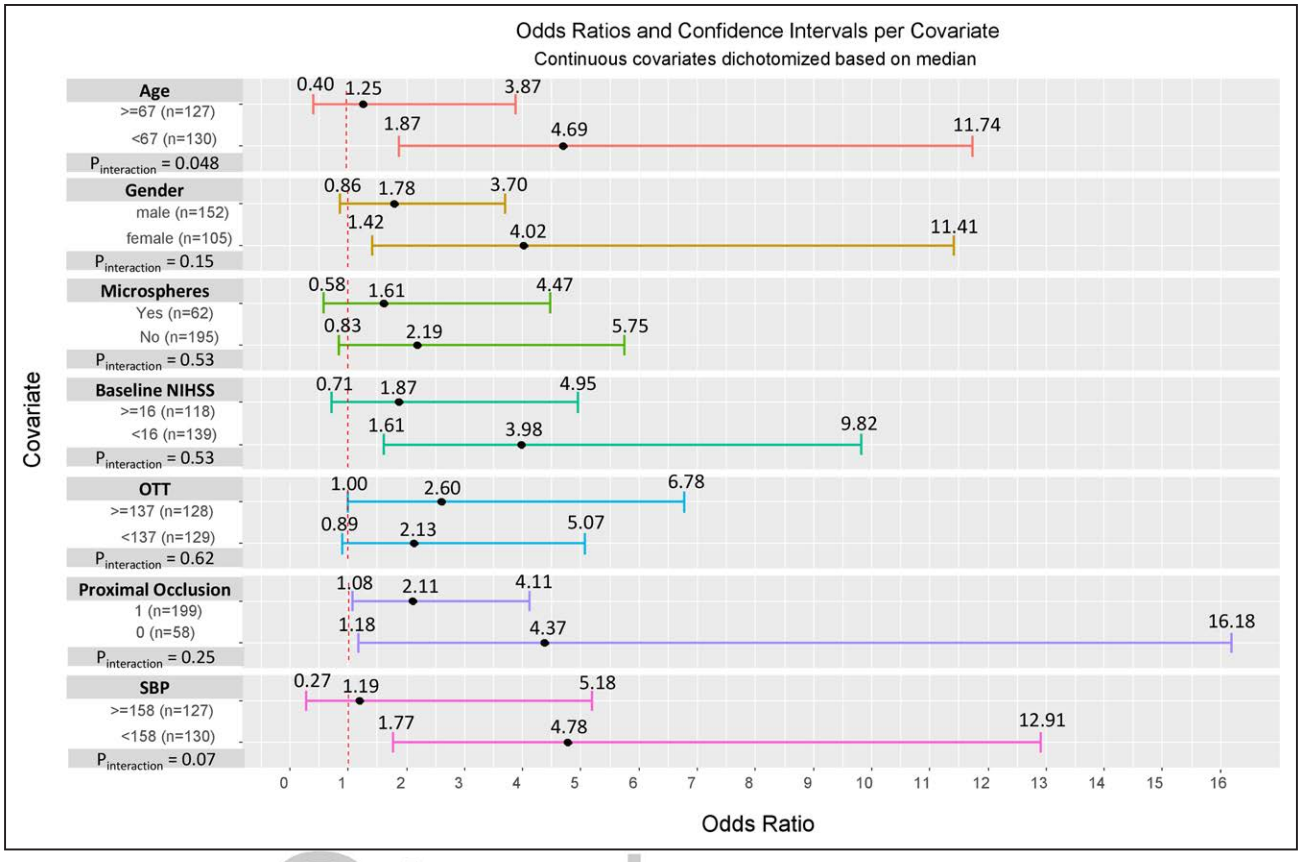

Figure 3. Subgroup analyses on the effect of sonothrombolysis on the primary outcome of complete recanalization (15 patients were excluded from the analyses due to missing data).
NIHSS indicates National Institutes of Health Stroke Scale; OTT, onset to tPA (tissue-type plasminogen activator) bolus time; and SBP, systolic blood pressure.

present IPD-MA had distal internal carotid artery and/or middle cerebral artery occlusions (Table 1) and therefore our findings cannot be extrapolated to patients presenting with acute occlusions in other intracranial vessels.

In conclusion, the present IPD-MA provides preliminary evidence that sonothrombolysis nearly doubles the odds of complete recanalization when compared with intravenous thrombolysis alone in patients with AIS with LVO. Contrary to the results of mechanical thrombectomy RCTs and in spite of the higher recanalization rates no difference in clinical outcomes was uncovered.[30] These findings may serve for sample size estimation in the TRUST trial (Aureva Transcranial Ultrasound Device With tPA in Patients With Acute Ischemic Stroke; REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT 03519737) that aims to randomize patients with LVO who meet standard tPA criteria and are being transferred from primary to comprehensive stroke centres ("drip-and-ship") to pulsed-wave ultrasound exposure or no ultrasound.[31] TRUST will introduce a new transcranial ultrasound therapeutic device with 2 possible insonation positions (right temporal or left temporal), with the aim to target LVO occlusions identified by CTA. Complete recanalization at receiving hospitals on digital subtraction angiography before mechanical thrombectomy will be the primary end point of this trial.[31] The results of the TRUST trial will provide a critical additional datapoint about the efficacy of sonothrombolysis for improving tPA-induced recanalization rates in patients with AIS with LVO.

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Supplemental Materials

Complete search algorithm used in MEDLINE search
Online Tables I–III
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REFERENCES

1. Alexandrov AV. Ultrasound enhancement of fibrinolysis. *Stroke*. 2009;40(3 suppl):S107–S110. doi: 10.1161/STROKEAHA.108.530931
2. Tsivgoulis G, Alexandrov AV. Ultrasound-enhanced thrombolysis in acute ischemic stroke: potential, failures, and safety. *Neurotherapeutics*. 2007;4:420–427. doi: 10.1016/j.nurt.2007.05.012
3. Tsivgoulis G, Culp WC, Alexandrov AV. Ultrasound enhanced thrombolysis in acute arterial ischemia. *Ultrasonics*. 2008;48:303–311. doi: 10.1016/j.ultras.2007.11.008
4. Tsivgoulis G, Eggers J, Ribo M, Perren F, Saqqur M, Rubiera M, Sergentanis TN, Vadikolias K, Larrue V, Molina CA, et al. Safety and efficacy of ultrasound-enhanced thrombolysis: a comprehensive review and meta-analysis of randomized and nonrandomized studies. *Stroke*. 2010;41:280–287. doi: 10.1161/STROKEAHA.109.563304
5. Ricci S, Dinia L, Del Sette M, Anzola P, Mazzoli T, Cenciarelli S, Gandolfo C. Sonothrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2012;10:CD008348. doi: 10.1002/14651858.CD008348.pub3
6. Alexandrov AV, Köhrmann M, Soinne L, Tsivgoulis G, Barreto AD, Demchuk AM, Sharma VK, Mikulik R, Muir KW, Brandt G, et al; CLOTBUST-ER Trial Investigators. Safety and efficacy of sonothrombolysis for acute ischaemic stroke: a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Neurol*. 2019;18:338–347. doi: 10.1016/S1474-4422(19)30026-2
7. Schellinger PD, Alexandrov AV, Barreto AD, Demchuk AM, Tsivgoulis G, Kohrmann M, Alleman J, Howard V, Howard G, Alexandrov AW, et al; CLOTBUSTER Investigators. Combined lysis of thrombus with ultrasound and systemic tissue plasminogen activator for emergent revascularization in acute ischemic stroke (CLOTBUST-ER): design and methodology of a multinational phase 3 trial. *Int J Stroke*. 2015;10:1141–1148. doi: 10.1111/ijs.12536
8. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moyé LA, et al; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med*. 2004;351:2170–2178. doi: 10.1056/NEJMoa041175
9. Alexandrov AV, Mikulik R, Ribo M, Sharma VK, Lao AY, Tsivgoulis G, Sugg RM, Barreto A, Sierzenski P, Malkoff MD, et al. A pilot randomized clinical safety study of sonothrombolysis augmentation with ultrasound-activated perflutren-lipid microspheres for acute ischemic stroke. *Stroke*. 2008;39:1464–1469. doi: 10.1161/STROKEAHA.107.505727
10. Molina CA, Barreto AD, Tsivgoulis G, Sierzenski P, Malkoff MD, Rubiera M, Gonzales N, Mikulik R, Pate G, Ostrem J, et al. Transcranial ultrasound in clinical sonothrombolysis (TUCSON) trial. *Ann Neurol*. 2009;66:28–38. doi: 10.1002/ana.21723
11. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–1665. doi: 10.1001/jama.2015.3656
12. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928
13. Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke*. 2001;32:89–93. doi: 10.1161/01.str.32.1.89
14. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Saver JL, Marks MP, Prabhakaran S, Kallmes DF, Fitzsimmons BF, et al; Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; STIR Thrombolysis in Cerebral Infarction (TICI) Task Force. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke*. 2013;44:2650–2663. doi: 10.1161/STROKEAHA.113.001972
15. Bardon P, Kuliha M, Herzig R, Kanovsky P, Skoloudik D. Safety and efficacy of sonothrombolysis using bilateral TCD monitoring by diagnostic 2 MHz probes - a pilot study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2014;158:233–237. doi: 10.5507/bp.2012.064
16. Perren F, Loulidi J, Poglia D, Landis T, Sztajzel R. Microbubble potentiated transcranial duplex ultrasound enhances IV thrombolysis in acute stroke. *J Thromb Thrombolysis*. 2008;25:219–223. doi: 10.1007/s11239-007-0044-6
17. Reinhard M, Taschner CA, Hörsch N, Allignol A, Maurer CJ, Niesen WD, Lambeck J, Wallesch CW, Urbach H, Weiller C, et al. Endovascular Treatment versus Sonothrombolysis for Acute Ischemic Stroke. *Cerebrovasc Dis*. 2015;40:205–214. doi: 10.1159/000439142
18. Školoudík D, Kuliha M, Hrbáč T, Jonszta T, Herzig R; SONOBUSTER Trial Group. Sonolysis in Prevention of Brain Infarction During Carotid Endarterectomy and Stenting (SONOBUSTER): a randomized, controlled trial. *Eur Heart J*. 2016;37:3096–3102. doi: 10.1093/eurheartj/ehv492
19. Eggers J, Koch B, Meyer K, König I, Seidel G. Effect of ultrasound on thrombolysis of middle cerebral artery occlusion. *Ann Neurol*. 2003;53:797–800. doi: 10.1002/ana.10590
20. Eggers J, König IR, Koch B, Händler G, Seidel G. Sonothrombolysis with transcranial color-coded sonography and recombinant tissue-type plasminogen activator in acute middle cerebral artery main stem occlusion: results from a randomized study. *Stroke*. 2008;39:1470–1475. doi: 10.1161/STROKEAHA.107.503870
21. Larrue V, Viguier A, Arnaud C, Cognard C, Petit R, Rigal M, Cristini C. Transcranial ultrasound combined with intravenous microbubbles and tissue plasminogen activator for acute ischemic stroke: a randomized controlled study. *Stroke*. 2007;38:472.
22. Nacu A, Kvistad CE, Naess H, Øygarden H, Logallo N, Assmus J, Waje-Andreassen U, Kurz KD, Neckelmann G, Thomassen L. NOR-SASS

(Norwegian Sonothrombolysis in Acute Stroke Study): randomized controlled contrast-enhanced sonothrombolysis in an unselected acute ischemic stroke population. *Stroke*. 2017;48:335–341. doi: 10.1161/STROKEAHA.116.014644
23. Zafar M, Memon RS, Mussa M, Merchant R, Khurshid A, Khosa F. Does the administration of sonothrombolysis along with tissue plasminogen activator improve outcomes in acute ischemic stroke? A systematic review and meta-analysis. *J Thromb Thrombolysis*. 2019;48:203–208. doi: 10.1007/s11239-019-01899-6
24. Chen Z, Xue T, Huang H, Xu J, Shankar S, Yu H, Wang Z. Efficacy and safety of sonothombolysis versus non-sonothombolysis in patients with acute ischemic stroke: a meta-analysis of randomized controlled trials. *PLoS One*. 2019;14:e0210516. doi: 10.1371/journal.pone.0210516
25. Tsivgoulis G, Saqqur M, Sharma VK, Lao AY, Hill MD, Alexandrov AV; CLOTBUST Investigators. Association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. *Stroke*. 2007;38:961–966. doi: 10.1161/01.STR.0000257314.74853.2b
26. Malhotra K, Ahmed N, Filippatou A, Katsanos AH, Goyal N, Tsioufis K, Manios E, Pikilidou M, Schellinger PD, Alexandrov AW, et al. Association of elevated blood pressure levels with outcomes in acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Stroke*. 2019;21:78–90. doi: 10.5853/jos.2018.02369
27. Hrafnkelsdóttir T, Ottosson P, Gudnason T, Samuelsson O, Jern S. Impaired endothelial release of tissue-type plasminogen activator in patients with chronic kidney disease and hypertension. *Hypertension*. 2004;44:300–304. doi: 10.1161/01.HYP.0000137380.91476.fb
28. Tsivgoulis G, Katsanos AH, Schellinger PD, Köhrmann M, Varelas P, Magoufis G, Paciaroni M, Caso V, Alexandrov AW, Gurol E, et al. Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions. *Stroke*. 2018;49:232–235. doi: 10.1161/STROKEAHA.117.019261
29. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, Yan B, Bush SJ, Dewey HM, Thijs V, et al; EXTEND-IA TNK Investigators. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *N Engl J Med*. 2018;378:1573–1582. doi: 10.1056/NEJMoa1716405
30. Katsanos AH, Malhotra K, Goyal N, Palaiodimou L, Schellinger PD, Caso V, Cordonnier C, Turc G, Magoufis G, Arthur A, et al. Mortality risk in acute ischemic stroke patients with large vessel occlusion treated with mechanical thrombectomy. *J Am Heart Assoc*. 2019;8:e014425. doi: 10.1161/JAHA.119.014425
31. Aureva Transcranial Ultrasound Device With tPA in Patients With Acute Ischemic Stroke (TRUST). Last accessed: September 2, 2019. https://clinicaltrials.gov/ct2/show/NCT03519737.