Supplementary Online Content

Schönenberger S, Hendén PL, Simonsen CZ, et al. Association of general anesthesia vs procedural sedation with functional outcome among patients with acute ischemic stroke undergoing thrombectomy: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2019.11455

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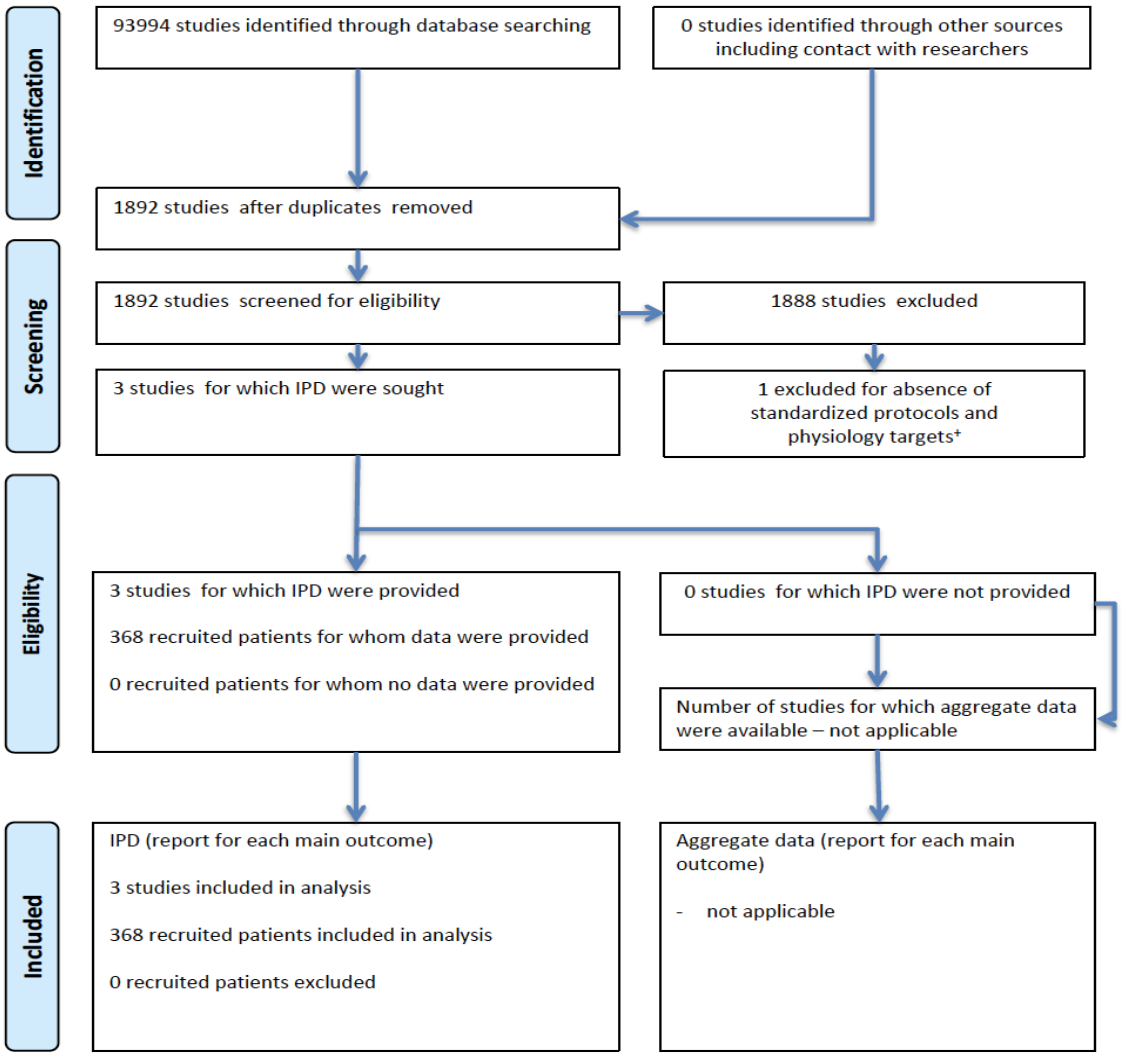
Project outline

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1: PRISMA diagram of the SAGA Meta-Analysis (for SIESTA, ANSTROKE and GOLIATH)



+ The trial executive committee (comprising the lead representatives of 2 each trial) of SIESTA, ANSTROKE and GOLIATH Association (SAGA) decided not to contribute data from the study Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke (CANVAS) pilot trial[1]

Abbrev.: IPD, individual patient data

References for considered and selected studies

1. Sun J, Liang F, Wu Y, et al. Choice of ANesthesia for EndoVAScular Treatment of Acute Ischemic Stroke (CANVAS): Results of the CANVAS Pilot Randomized Controlled Trial. *J Neurosurg Anesthesiol.* Dec 7 2018.
2. Schönenberger S, Uhlmann L, Hacke W, et al. Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. *JAMA.* Nov 15 2016;316(19):1986-1996.
3. Löwhagen Henden P, Rentzos A, Karlsson JE, et al. General Anesthesia Versus Conscious Sedation for Endovascular Treatment of Acute Ischemic Stroke: The AnStroke Trial (Anesthesia During Stroke). *Stroke.* Jun 2017;48(6):1601-1607.
4. Simonsen CZ, Yoo AJ, Sorensen LH, et al. Effect of General Anesthesia and Conscious Sedation During Endovascular Therapy on Infarct Growth and Clinical Outcomes in Acute Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol.* Apr 1 2018;75(4):470-477.

eTable 1: Trial-specific aspects of SIESTA,[2] ANSTROKE[3], and GOLIATH[4]

Trial-specific aspects	SIESTA	ANSTROKE	GOLIATH
Number approached	1808 patients	321 patients	1501 patients
Number randomized	152 patients	106 patients	128 patients
Number analyzed	150 patients	90 patients	128 patients
Baseline characteristics	1. Age 2. Sex 3. Premedication 4. Diabetes mellitus 5. Hyperlipidemia 6. Smoking 7. Congestive heart failure 8. Artrial fibrillation 9. Administration of rtPA 10. Time window of IVT 11. ASPECTS 12. Occlusion type 13. Premorbid mRS 14. NIHSS on admission	1. Age 2. Sex 3. Diabetes mellitus 4. Hyperlipidemia 5. Smoking 6. Congestive heart failure 7. Artrial fibrillation 8. Administration of rtPA 9. ASPECTS 10. Occlusion type 11. Premorbid mRS 12. NIHSS on admission	1. Age 2. Sex 3. Premedication 4. Diabetes mellitus 5. Hyperlipidemia 6. Smoking 7. Congestive heart failure 8. Artrial fibrillation 9. Administration of rtPA 10. Time window of IVT 11. ASPECTS 12. Occlusion type 13. Premorbid mRS 14. NIHSS on admission
Primary endpoint	NIHSS change after 24 h	mRS after 3 months	Infarct growth according to MRI
Secondary endpoints	1. NIHSS after 24 h 2. MRS after 3 months 3. In hospital mortality 4. Cause of death (cerebral y/n) 5. Length of stay ICU 6. Duration of mechanical ventilation 7. Onset-to-door time 8. Groin-puncture-to reperfusion time 9. Door-to-reperfusion 10. Final mTICI 11. Door-to-reperfusion 12. Duration of intervention	1. NIHSS after 24 h 2. NIHSS change after 24 h 3. In-hospital mortality 4. Cause of death (cerebral y/n) 5. Onset-to-door time 6. Groin-puncture-to reperfusion time 7. Door-to-reperfusion 8. Final mTICI 9. Infarct growth according to MRI	1. NIHSS after 24 h 2. NIHSS change after 24 h 3. MRS after 3 months 4. In hospital mortality 5. Cause of death (cerebral y/n) 6. Door-to-reperfusion 7. Final mTICI
Safety	1. Hypotension (< 20% of baseline SBP) 2. Intervention-associated complications, specifications (ICH/SAH / other cerebral / groin / other systemic) 3. Periinterventional hyper- or hypotension (SBP > 180 or < 120 mmHg) 4. Delayed extubation (>2 h after end of intervention)	1. Hypotension (< 20% from baseline SBP) 2.Intervention-associated complications 3. Periinterventional hyper- or hypotension (SBP > 180 or < 120 mmHg) 4. Delayed extubation (>2h after end of intervention) 5. Start of antibiotics within 72h for suspected pneumonia	1. Hypotension (< 20% of baseline SBP) 2. Periinterventional hyper- or hypotension (SBP > 180 or < 120 mmHg) 3. Delayed extubation (>2 h after end of intervention) 4. Start of antibiotics within 72h for suspected pneumonia

	5. Start of antibiotics within 72h for suspected pneumonia		

Abbrev.: NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; h, hours; ICU, intensive care unit; mTICI, modified thrombolysis in cerebral infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; MT, mechanical thrombectomy; SIESTA, Sedation vs Intubation for Endovascular Stroke Treatment; ANSTROKE, ANesthesia during STROKE; GOLIATH, General or Local Anesthesia in Intra Arterial Therapy

eTable 2: List of all prespecified secondary outcomes

Secondary outcomes	
Clinical efficacy outcomes	mRS after 3 months of stroke onset [0-2 (good) vs 3-6 (poor)]
	mRS after 3 months of stroke onset [0-3 (good) vs 4-6 (poor)]
	Early neurological improvement indicated by change of NIHSS Score 24 h after admission [NIHSS after 24 h – NIHSS on admission]
	Intra hospital mortality [yes/no, cause of death (stroke-related/other)]
Imaging efficay outcomes	Final Degree of reperfusion [final mTICI]
	Infarct growth according to respective trial technique [ml]
Care process outcomes	Length of stay in hospital [hours]
	CT to arrival angio [min]
	Arrival angio to puncture [min]
	Groin puncture-to-reperfusion time [min]
	Onset to puncture [min]
	Onset to reperfusion [min]
	Door to puncture [min]
	Door-to-Reperfusion time [min]
	Duration of intervention [min] Reasons for conversion from PS to intubation and GA during MT: Agitation [yes/no], Respiratory problem Aspiration [yes/no],
Adverse events	Hypotension (< 20% of baseline SBP) [yes/no]
	Periinterventional hyper- or hypotension = BP variability (SBP > 180 or < 120 mmHg) [yes/no]
	Intervention-associated complications [yes/no], specifications (ICH/SAH / other cerebral / groin / other systemic)

	Delayed extubation (>2 h after end of intervention)
	Start of Antibiotics within 72h for suspected pneumonia [yes/no]

Abbrev.: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified thrombolysis in cerebral infarction scale; CT, computed tomography; MT, mechanical thrombectomy; SBP, systolic blood pressure; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage

eFigure 2: Risk of bias assessment according to the Cochrane ROB-2 tool from the Cochrane group

Abbrev.: SIESTA, Sedation vs Intubation for Endovascular Stroke Treatment; ANSTROKE, ANesthesia during STROKE; GOLIATH, General or Local Anesthesia in Intra Arterial THerapy

eTable 3: Baseline characteristics of the three single center trials SIESTA, ANSTROKE and GOLIATH

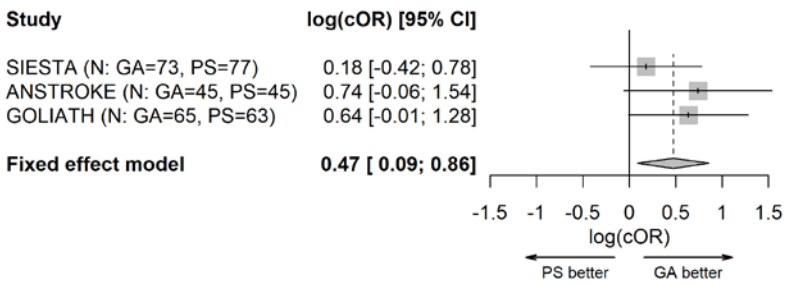
Characteristic	SIESTA (N=150)	ANSTROKE (N=90)	GOLIATH (N=128)
Demographic characteristics			
Age – yr			
Mean (SD)	71.5 (13.8)	71.5 (13.7)	71.4 (11.4)
Male sex – no. (%)	90 (60)	49 (54.4)	66 (51.6)
Female sex – no. (%)	60 (40)	41 (45.6)	62 (48.4)
Vascular risk factors – no. (%)			
Hypertension	107 (71.3)	49 (54.4)	71 (55.9)
Atrial fibrillation	72 (48.0)	36 (40.0)	51 (40.2)
Diabetes mellitus	34 (22.7)	16 (17.8)	18 (14.2)
Hyperlipidemia	44 (29.3)	12 (13.3)	92 (72.4)
Smoking	22 (14.8)	12 (13.3)	40 (31.7)
Pretreatment imaging – no. (%)	N=147	N=90	N=128
ASPECTS* - no. (%) 6-10 < 6	 134 (91.2) 13 (8.8)	 87 (96.7) 3 (3.3)	 101 (78.9) 27 (21.1)
Median (IQR)	8 (7-9)	10 (8-10)	7 (6-8)
Scores on admission – no. (%)			
Premorbid mRS[1]			
0	79 (52.7)	85 (94.4)	101 (78.9)
1	33 (22.0)	1 (1.1)	19 (14.8)
2	23 (15.3)	2 (2.2)	6 (4.7)
> 2	15 (10.0)	2 (2.2)	2 (1.6)
NIHSS on admission[2]			
Median (IQR)	17 (14-20)	18 (15-22)	17.5 (14-21)
Occlusion – no. (%)			
Localization of occlusion			
Single ICA	11 (7.3)	1 (1.1)	8 (6.3)
Single ICA-T	24 (16.0)	16 (17.8)	19 (14.8)
Single MCA	92 (61.3)	52 (57.8)	72 (56.2)
M1	77 (51.3)	47 (52.2)	53 (41.4)
M2	15 (10)	5 (5.6)	19 (14.8)
Tandem	23 (15.3)	21 (23.3)	29 (22.7)
ICA + ICA-T	5 (3.3)	8 (8.9)	9 (7.0)
ICA + M1	16 (10.7)	10 (11.1)	17 (13.3)
ICA + M2	2 (1.3)	3 (3.3)	2 (2.3)
Occlusion side right	63 (42.0)	47 (52.2)	57 (44.5)
Reperfusion treatments (%)			
IV tPA + EST	96 (64.0)	69 (76.7)	96 (75.0)
MT alone	54 (36.0)	21 (23.3)	32 (25.0)
Onset-to-door [min] Mean (SD)	114.9 (78.9)	109.8 (75.3)	173.4 (71.6)

eTable 4: Adjusted analysis for the primary outcome including study treatment interaction term

Characteristics	Odds ratio	95%-CI	p-value
group (GA vs. PS)	1.929	[1.038;3.583]	0.038
Age	0.979	[0.964;0.994]	0.007
Sex	0.773	[0.527;1.133]	0.187
NIHSS on admission	0.880	[0.835;0.927]	<.0001
mRS on admission	0.497	[0.388;0.636]	<.0001
ASPECTS	1.259	[1.117;1.418]	0.0002
Infarction side	1.044	[0.700;1.557]	0.834
ivt	1.195	[0.793;1.801]	0.396
studyID	0.378	[0.203;0.705]	0.002
studyID	0.306	[0.140;0.670]	0.003
studyID*group	0.602	[0.260;1.393]	0.237
studyID*group	1.052	[0.389;2.846]	0.92

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis

eFigure 3: Forest plot of the primary outcome categorical shift of mRS after 3 months in SIESTA, ANSTROKE, and GOLIATH for the intention-to-treat population

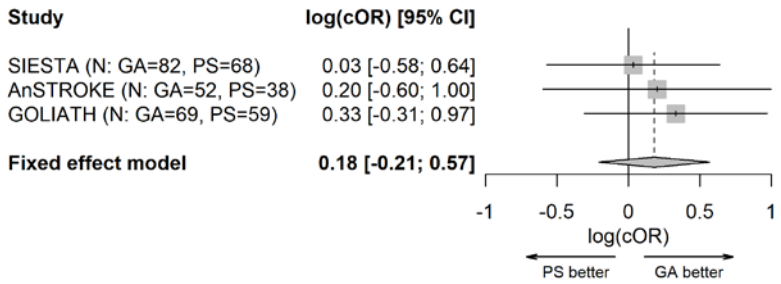


The modified Rankin Scale (mRS) scores range between 0-6; 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not to full extent), 3 moderate disability (requires some help, but able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead. The heterogeneity estimated in the two-stage approach was equal to τ^2=0.

The width of the diamond corresponds to the width of the 95% CI of the estimate.

Abbrev.: mRS, modified Rankin Scale; PS, procedural sedation; GA, general anesthesia; CI, confidence interval; TE, treatment effect; SIESTA, Sedation vs Intubation for Endovascular Stroke Treatment; ANSTROKE, ANesthesia during STROKE; GOLIATH, General or Local Anesthesia in Intra Arterial THerapy

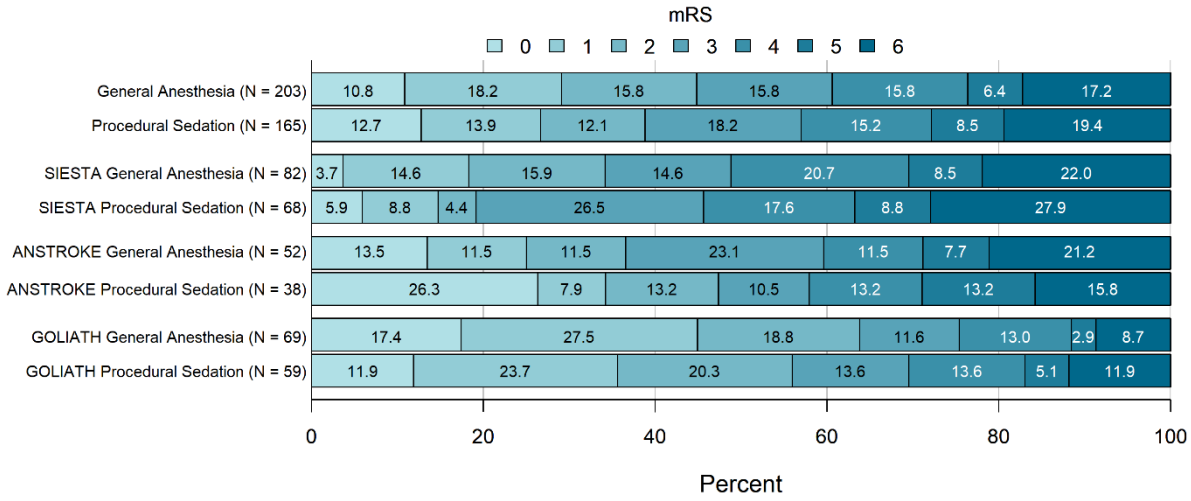
eFigure 4: Forest plot of the primary outcome as the shift of mRS in SIESTA, AnStroke, and GOLIATH for the as-treated population



The modified Rankin Scale (mRS) scores runs between 0-6, 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not in to full extent), 3 moderate disability (requires some help, but able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead.

Abbrev.: mRS, modified Rankin Scale; CS, conscious sedation; GA, general anesthesia; CI, confidence interval; TE, treatment effect; SIESTA, Sedation vs Intubation for Endovascular Stroke Treatment; ANSTROKE, ANesthesia during STROKE; GOLIATH, General or Local Anesthesia in Intra Arterial Therapy

eFigure 5: Functional outcome at 90 days for the as-treated population



Modified Rankin Scale (mRS) scores range at 90 days in both treatment groups. The score runs between 0-6, 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not in to full extent), 3 moderate disability (requires some help, but able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead. Distribution of mRS categories additionally tested by Mann-Whitey-U test (P=0.41).

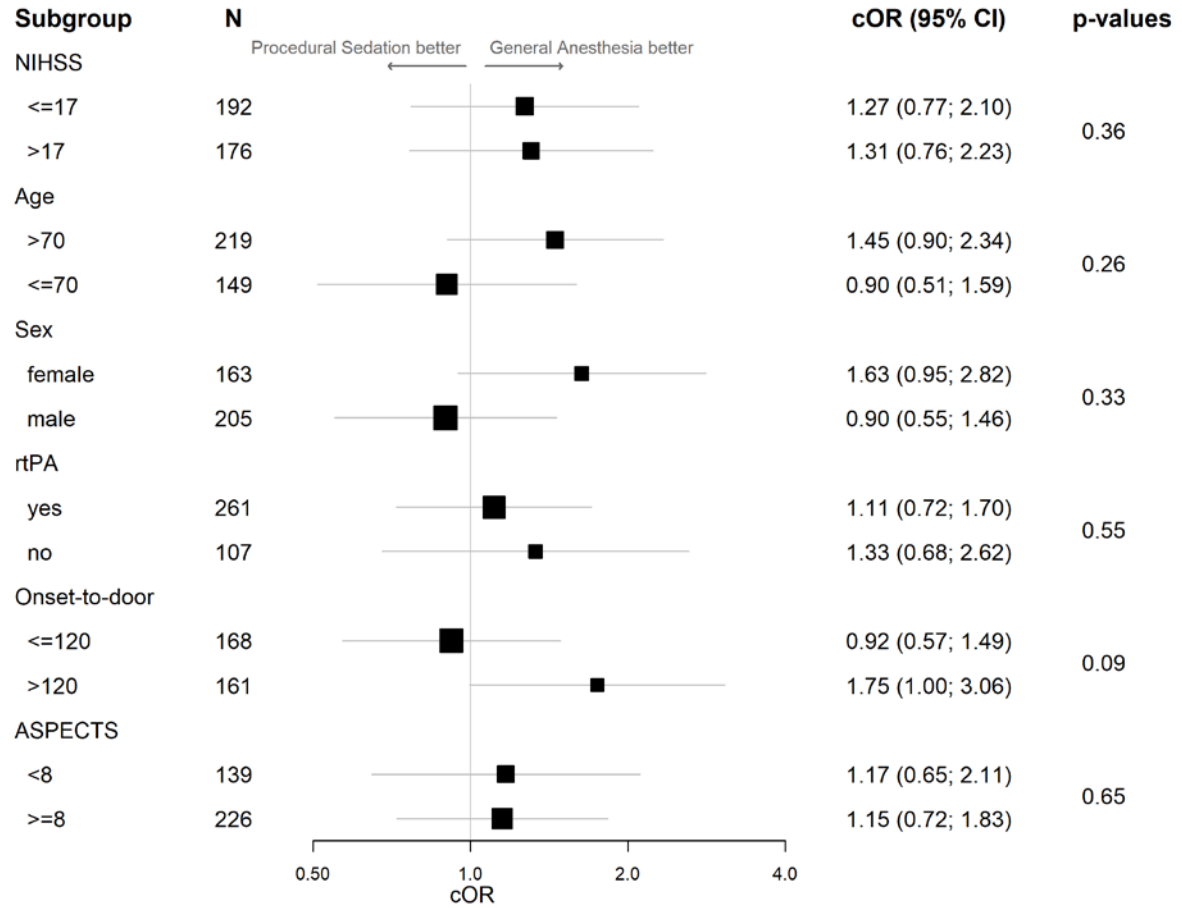
Abbrev.: EST, endovascular stroke treatment; N, number; mRS, modified Rankin Scale; SIESTA, Sedation vs. Intubation for Endovascular Stroke TreAtment; ANSTROKE, Anesthesia for Stroke; GOLIATH, General or Local Anesthesia in Intra Arterial THerapy

eTable 5: Adjusted analysis for the improvement of NIHSS after 24 hours of the intention-to-treat population

Factor	Coefficient	95% CI	p-value
Intercept	5.528	[-2.62;13.67]	0.19
group (GA vs. PS)	-1.11	[-2.90;0.677]	0.22
Age	0.000	[-.073;0.074]	0.99
Sex	1.798	[-.034;3.630]	0.06
NIHSS on admission	-.310	[-.556;-.065]	0.014
mRS on admission	0.863	[-.286;2.012]	0.14
ASPECTS	-.963	[-1.54;-.389]	0.001
Infarction side	0.833	[-1.12;2.787]	0.40
ivt	-.210	[-2.19;1.771]	0.84

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis

eFigure 6: Subgroup analyses for primary outcome for the as-treated population



Size of the data markers is proportional to the precision of the estimates (i.e. the area is proportional to the inverse of the squared standard errors). An interaction term between treatment group and the subgroup variable was included in the model (separately for each subgroup) to calculate p-values.

Abbrev.: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; cOR, common odds ratio; CI, confidence interval

eTable 6: Adjusted analysis for the mRS after 3 months without the patients converted from Procedural Sedation to General Anesthesia

Factor	cOdds ratio	95%-CI	p-value
Group (GA vs. PS)	1.373	[0.934;2.017]	0.11
Age	0.977	[0.961;0.993]	0.005
Sex	0.806	[0.545;1.193]	0.28
NIHSS on admission	0.881	[0.835;0.930]	<.0001
mRS on admission	0.502	[0.385;0.655]	<.0001
ASPECTS	1.258	[1.111;1.423]	0.0003
Infarction side	1.064	[0.701;1.615]	0.77
ivt	1.136	[0.745;1.732]	0.55

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis; cOdds ratio, common Odds ratio

eTable 7: Adjusted analysis for the mRS 5 and 6 after 3 months for Procedural Sedation vs General Anesthesia

Characteristics	Coefficient	95%-CI	p-value
Group (GA vs. PS)	1.768	[1.012;3.090]	0.0459
Age	0.958	[0.934;0.984]	0.0017
Sex	0.499	[0.277;0.897]	0.0208
NIHSS on admission	0.906	[0.838;0.980]	0.0136
mRS on admission	0.441	[0.313;0.622]	<.0001
ASPECTS	1.366	[1.143;1.631]	0.0007
Infarction side	0.847	[0.460;1.559]	0.5939
IVT	1.228	[0.673;2.241]	0.5035

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; IVT, intravenous thrombolysis

eTable 8: Adjusted analysis for in hospital mortality of the intention-to-treat population

Factor	Odds ratio	95% CI	p-value
group (GA vs. PS)	0.751	[0.323;1.748]	0.51
Age	1.016	[0.977;1.057]	0.42
Sex	1.756	[0.719;4.287]	0.22
NIHSS on admission	1.223	[1.072;1.395]	0.002
mRS on admission	1.288	[0.789;2.104]	0.31
ASPECTS	0.798	[0.618;1.029]	0.08
Infarction side	0.964	[0.369;2.519]	0.94
ivt	0.726	[0.284;1.857]	0.50

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis

eTable 9: Adjusted analysis for start of antibiotic treatment with 72 hours because of a suspected pneumonia of the intention-to-treat population

Factor	Odds ratio	95% CI	p-value
group (GA vs. PS)	0.851	[0.496;1.460]	0.66
Age	1.027	[1.002;1.053]	0.28
Sex	1.779	[1.008;3.139]	0.3
NIHSS on admission	1.005	[0.936;1.079]	0.92
mRS on admission	0.844	[0.602;1.182]	0.5
ASPECTS	0.922	[0.794;1.071]	0.48
Infarction side	1.596	[0.882;2.891]	0.37
ivt	1.253	[0.701;2.240]	0.59

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis

eTable 10: Evaluation of crossover from assigned treatment

	GA N=183	**PS N=185**	**Total N=368**
Intubation, no. (%)			
- No	1 (0.5)	164 (88.5)	165 (44.8)
- Yes	182 (99.5)	21 (11.5)	203 (55.2)
Reasons for conversion, no. (%)			
- Severe agitation	0 (0.0)	9 (4.9)	9 (2.4)
- Respiratory failure	0 (0.0)	1 (0.5)	1 (0.3)
- Aspiration	0 (0.0)	1 (0.5)	1 (0.3)
Puncture of internal carotid artery	0 (0.0)	4 (2.2)	4 (1.1)
- Mistakenly treated in PS group	1 (0.5)	0 (0.0)	1 (0.3)
- Reason unknown	0 (0.0)	4 (2.2)	4 (1.1)
- Other	0 (0.0)	2 (1.1)	2 (0.5)
- No conversion	182 (99.5)	164 (88.6)	346 (94.0)

Abbrev: No, number; GA, general anesthesia; PS, procedural sedation

eTable 11: Baseline characteristics of the patients converted from Procedural Sedation to General Anesthesia

Characteristic	Converted patients (N=21)
Demographic characteristics	
Age – yr	
Mean (SD)	74.1 (14.6)
Female sex – no. (%)	11 (52.4)
Vascular risk factors – no. (%)	
Hypertension	12 (57.1)
Diabetes mellitus	5 (23.8)
Hyperlipidemia	3 (14.3)
Smoking	3 (14.3)
Atrial fibrillation	10 (47.6)
Pretreatment imaging – no. (%)	
ASPECTS* - no. (%) 6-10 < 6	 20 (95.2) 1 (4.8)
Median (IQR)	9 (7-10)
Missing	0
Scores on admission – no. (%)	
Premorbid mRS[1]	
0	19 (90.5)
1	0 (0)
2	1(4.8)
> 2	1 (4.8)
NIHSS on admission[2]	
Median (IQR)	19 (16;22)
Occlusion – no. (%)	
Localisation of occlusion	
Single ICA	0 (0)
Single ICA-T	4 (19)
Single MCA	13 (61.9)
M1	13 (61.9)
M2	0 (0)
Tandem	4 (19.0)
ICA + ICA-T	0 (0)
ICA + M1	2 (9.5)
ICA + M2	2 (9.5)
Occlusion side right	9 (42.9)
Reperfusion treatments (%)	
IV tPA + EST	17 (81)
MT alone	4 (19)
Onset-to-door [min] Mean (SD)	97.0 (67.2)

* The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extension of stroke. Score ranges from 0 to 10, higher scores indicating fewer early ischemic changes.

[1] The modified Rankin Scale (mRS) scores runs between 0-6, 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not in to full extent), 3 moderate disability (requires some help, but

able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead.

[2] The NIHSS classifies neurological deficit from 0 (no deficit) to 42 (most severe deficit).

Abbrev.: Yr, years; MRI, Magnetic resonance imaging; CCT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; MT, mechanical thrombectomy; N / no. number; SD, standard deviation; ICA, internal carotid artery; MCA, middle cerebral artery; IQR, interquartile range; IV tPA, intravenous thrombolysis; EST, endovascular stroke treatment

eTable 12: Primary outcome and selected secondary outcomes of the patients converted from Procedural Sedation to General Anesthesia

Variable	**Converted patients (N=21)**
mRS after 3 months[1]: no. **(%)**	
0	0 (0)
1	1 (4.8)
2	0 (0)
3	5 (23.8)
4	7 (33.3)
5	1 (4.8)
6	7 (33.3)
mRS 0-2 after 3 months[1]: no. (%) **mRS 0-3 after 3 months[1]:** no. (%)	1 (4.8) 6 (28.6)
Duration of Intervention [min] (SD)	164.5 (78.1)
Groin-to-reperfusion [min] (SD)	94.8 (51)
Substantial reperfusion (mTICI)[2,3]:	
0-1	3 (14.3)
2a	7 (33.3)
2b	5 (23.8)
3	6 (28.6)

[1] modified Rankin Scale (mRS) scores runs between 0-6, 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not in to full extent), 3 moderate disability (requires some help, but able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead.

[2] reperfusion was defined as mTICI 2b, 2c or 3

[3] modified TICI; range 0 to 3; with 0 no antegrade flow beyond the occlusion, 1 minimal perfusion, 2a perfusion of <50% of the vascular distribution of the occluded artery, 2b perfusion of ≥ 50 of the vascular distribution of the occluded artery, 2c near-complete perfusion except for a few distal cortical vessels or presence of small distal cortical emboli, III complete perfusion

Abbrev.: mRS, modified Rankin Scale; N, number; SD, standard deviation; mTICI, modified thrombolysis in cerebral infarction scale;

eTable 13: Baseline characteristics of the intention-to-treat population without the patients converted from Procedural Sedation to General Anesthesia

Characteristic	**GA (N=183)**	**PS (N=164)**
Demographic characteristics		
Age – yr		
Mean (SD)	71.5 (12.1)	71.1 (13.7)
Female sex – no. (%)	73 (39.9)	79 (48.2)
Vascular risk factors – no. (%)		
Hypertension	119 (65)	96 (58.9)
Diabetes mellitus	35 (19.1)	28 (17.2)
Hyperlipidemia	73/182 (40.1)	72 (43.9)
Smoking	33 (18)	38 (23.6)
Atrial fibrillation	78 (42.6)	71 (43.6)
Pretreatment imaging – no. (%)		
ASPECTS* - no. (%) 6-10 < 6	 163 (89.1) 20 (10.9)	 139 (86.3) 22 (13.7)
Median (IQR)	8 (7-10)	8 (6-10)
Missing	0	3
Scores on admission – no. (%)		
Premorbid mRS[1]		
0	133 (72.7)	113 (68.9)
1	23 (12.6)	30 (18.3)
2	15 (8.2)	15 (9.1)
> 2	12 (6.6)	6 (3.7)
NIHSS on admission[2]		
Mean (SD)	17.7 (4.4)	17.3 (3.8)
Median (IQR)	18 (14;21)	19 (14;20)
Occlusion – no. (%)		
Localisation of occlusion		
Single ICA	8 (4.4)	12 (7.3)
Single ICA-T	27 (14.8)	28 (17.1)
Single MCA	102 (55.8)	101 (61.5)
M1	81 (44.3)	83 (50.6)
M2	21 (11.5)	18 (11)
Tandem	46 (25.1)	23 (14)
ICA + ICA-T	15 (8.2)	7 (4.3)
ICA + M1	29 (15.8)	12 (7.3)

ICA + M2	2 (1.1)	4 (2.4)
Occlusion side right	73 (39.9)	85 (51.8)
Reperfusion treatments (%)		
IV tPA + EST	129 (70.5)	115 (70.1)
MT alone	54 (29.5)	49 (29.9)
Onset-to-door [min] (SD)	141.8 (82.7)	119.0 (67.2)

[*] The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extension of stroke. Score ranges from 0 to 10, higher scores indicating fewer early ischemic changes.

[1] The modified Rankin Scale (mRS) scores runs between 0-6, 0 means no symptoms, 1 no clinically relevant disability, 2 slight disability (able to look after own affairs without assistance, but not in to full extent), 3 moderate disability (requires some help, but able to walk unassisted), 4 moderately severe disability (requires assistance, and unable to walk unassisted), 5 severe disability (requires constant nursing care), 6 dead.

[2] The NIHSS classifies neurological deficit from 0 (no deficit) to 42 (most severe deficit).

Abbrev.: Yr, years; MRI, Magnetic resonance imaging; CCT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; MT, mechanical thrombectomy; PS, procedural sedation; GA, general anesthesia; N / no. number; SD, standard deviation; ICA, internal carotid artery; MCA, middle cerebral artery; IQR, interquartile range; IV tPA, intravenous thrombolysis; EST, endovascular stroke treatment

e**Table 14:** Adjusted subgroup analysis for reperfusion with mTICI ≥ 2b for the mRS after 3 months

Factor	**cOdds ratio**	**95%-CI**	**p-value**
Group (GA vs PS)	1.297	[0.745;2.259]	0.36

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis; cOdds ratio, common Odds ratio

eTable 15: Adjusted subgroup analysis for reperfusion with mTICI < 2b for the mRS after 3 months

Factor	**cOdds ratio**	**95%-CI**	**p-value**
Group (GA vs PS)	1.396	[0.863;2.258]	0.18

Abbrev.: GA, general anesthesia; PS, procedural sedation; mRS, modified Rankin Scale; ASPECTS, Alberta stroke program early CT score; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; ivt, intravenous thrombolysis; cOdds ratio, common Odds ratio

eTable 16: Detailed reperfusion outcome results

Non time-related outcome parameters	General Anesthesia (N=183)	Procedural Sedation (N=185)	General Anesthesia vs. Procedural Sedation OR	95% CI	P-Value
Successful reperfusion (mTICI)[1]:			1.84	(1.12;3.01)	**.016**
0-1	15 (8.2)	24 (13.0)			
2a	35 (19.1)	44 (23.8)			
2b	52 (28.4)	56 (30.3)			
3	81 (44.3)	61 (33.0)			

[1] Modified TICI; range 0 to 3; with 0 no antegrade flow beyond the occlusion, 1 minimal perfusion, 2a perfusion of <50% of the vascular distribution of the occluded artery, 2b perfusion of ≥ 50 of the vascular distribution of the occluded artery, 3 complete perfusion

Abbrev.: N, number; mTICI, thrombolysis in cerebral infarction scale; CI, confidence interval

Project outline (Statistical Analysis Plan) prior to start of any data analysis at July 20th 2018.

Effect of standardized general anesthesia vs conscious sedation on functional outcome in patients with anterior circulation acute ischemic stroke receiving endovascular stroke treatment – an individual patient data meta-analysis from trials randomized for sedation regime

Abstract

Background: In the SIESTA, ANSTROKE, and GOLIATH trials, general anesthesia (GA) was compared with conscious sedation (CS). Primary endpoints were early neurologic recovery (NIHSS difference between baseline and after 24h), mRS after 3 months, and infarct growth, respectively. All trials demonstrated non-inferiority of CS compared to GA, which was in contrast to many previous non-randomized studies.
Objective: The aim of our analysis is to compare CS vs GA based on the data collected in the three trials mentioned above. We will implement a meta-analysis based on individual patient data (IPD meta-analysis). The primary endpoint will be mRS after 3 months. Secondary endpoints will be NIHSS after 24h (and the difference from baseline), the TICI score and others.
Statistical approach: We will carry out an IPD meta-analysis for mRS after 3 months (primary endpoint) and other secondary endpoints to estimate the difference between CS and GA. We will follow recommendations given in the Cochrane handbook (Higgins and Green, 2011) and present the results according to the PRISMA statement (as applicable) (Moher et al., 2009) for meta-analyses based on individual patient data. Covariates such as age, gender, time, ASPECTS, pre-mRS, will be considered in our analysis resulting in a meta-regression model. Fixed and random-effects models will be applied to combine the data sets. The adjusted effect estimates with 95% confidence intervals will be reported. Sensitivity analyses will be applied regarding the covariates included. In a further sensitivity analysis, the primary outcome variable (mRS) will be dichotomized (0-2 vs. 3-6 and 0-3 vs. 4-6). Graphical representations of the results such as forest plots will be provided.
Results: The effect estimates from this meta-analysis are on the highest available evidence level and result from a combination of three single-center trials performed in three different institutions and are, therefore, of high external validity.

Analysis

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Background:	The optimal peri-interventional management of sedation and airway for endovascular stroke treatment (EST) appears to be a crucial factor for treatment success. Non-randomized studies suggested disadvantages for the use of general anesthesia (GA). According to three recent randomized trials that compared GA and conscious sedation (CS), both treatments lead to very similar results. However, long-term function was the primary outcome in only one trial and all three trials were single-center trials and their results therefore not generalizable. In this meta-analysis we will combine the evidence of three single-center randomized trials (SIESTA, GOLIATH and ANSTROKE) to evaluate long-term function (mRS after 3 months) as primary outcome and other secondary outcomes with regard to short- and long-term function, mortality, technical success, feasibility, safety, etc.
Objective/ research question:	This meta-analysis compares GA vs. CS in patients receiving endovascular treatment of acute ischemic anterior circulation stroke.
Study design:	This meta-analysis combines three single-center, prospective, randomized parallel-group, open-label treatment trials with blinded endpoint evaluation (PROBE design). It is based on individual patient data (IPD).

Eligibility criteria:	Inclusion criteria for the three trials: Subjects had to meet all of the following criteria to be considered for inclusion in any of the three trials: 1. Age 18 years or older 2. National Institutes of Health Stroke Scale (NIHSS) >= 10 3. AIS in the anterior circulation 4a. Waiver of consent prior randomization and informed consent by the patient him-/herself or his/her legal representative after EST (SIESTA and GOLIATH) 4b. Oral consent prior to randomization from patient or relative; written consent after treatment from patient or relative (ANSTROKE) 5. Decision for EST according to local protocols for acute recanalizing stroke treatment 6. Could be treated according to standardized in-house protocols for neuro-anesthesia and physiology targets Exclusion criteria: Subjects presenting any of the following criteria were not included in any of the three trials: 1. Radiological ambiguity concerning infarction and vessel occlusion 2. Additional clinical and radiological signs of an occlusion of a vessel other than those listed under inclusion criteria 3. Additional intracerebral hemorrhage 5. Severe agitation on admission (not in GOLIATH) 6. Obvious loss of airway protective reflexes and/or vomiting on admission (not in GOLIATH) 7. Obviously difficult or known difficult airway (not in GOLIATH) 8. Known intolerance of certain medication for sedation and/or analgesia Point 5. – 8. correspond with the exclusion criteria chosen in ANSTROKE (not eligible because of anesthesiological concerns). Additionally, patients were excluded from the ANSTROKE trial if they: 9. Could not receive EST within 8 h from stroke onset 10. Had a NIHSS<14 in left-sided stroke 11. Had an premorbid mRS of >=4 Additionally, patients were excluded from the GOLIATH trial if they: 12. Could not receive EST within 6 h from stroke onset 13. Had a premorbid mRS > 2 14. Had an initial infarct volume on MRI of > 70 ml 15. Had contraindications to MRI

Description of the study population:	Baseline table will be grouped by treatment group (GA or CS) combining the data from all three trials. The study population will be described according to the following characteristics: • Age • Sex • Known vascular risk factors, e.g. hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation • Onset-to-door time • Application of IVT with recombinant tissue-type plasminogen activator (rtPA). • Pretreatment imaging results: Alberta Stroke Program Early CT Score (ASPECTS) in patients, who received a CT imaging prior to treatment; MR-ASPECTS in patients, who received MR imaging prior to treatment; occlusion site according to CT- or MR-angiography; for patients who received both a CT- and an MR-angiography, the results according to the CT-angiography are considered. • occlusion site (left, right) and localization/type (Single ICA / Single ICA-T / Single M1 / Single M2 / Tandem), specification of tandem • Premorbid mRS • NIHSS on admission Furthermore, these variables, their sampling dimensions and their sample frequency will be compared in more detail during data entry between the three trials to evaluate how comparable the patient populations are with regard to the respective parameters. If there are relevant differences, these will be discussed and a compromise be aimed for.
Primary outcome:	• mRS after 3 months of stroke onset [categorical shift].
Secondary outcomes:	Secondary outcomes evaluated: • mRS after 3 months of stroke onset [0-2 (good) vs 3-6 (poor)] • mRS after 3 months of stroke onset [0-3 (good) vs 4-6 (poor)] • Early neurological improvement indicated by change of National Institutes of Health Stroke Scale (NIHSS) Score 24 h after admission [NIHSS after 24 h – NIHSS on admission] • Intrahospital mortality [yes/no, cause of death (stroke-related/other] • Length of stay in hospital [hours] • Duration of ventilation [hours from start of ventilation to extubation and subsequent spontaneous breathing for at least 48 h] • CT to arrival angio [min] • Arrival angio to puncture [min] • Groin puncture-to-reperfusion time [min]

- Onset to puncture [min]
- Onset to reperfusion [min]
- Door to puncture [min]
- Door-to-Reperfusion time [min]
- Duration of intervention [min]
- Final Degree of reperfusion [modified Thrombolysis in Cerebral Infarction Scale (final mTICI)]
- Infarct growth according to respective trial technique [ml]

Safety: Complications

- Hypotension (< 20% of baseline SBP) [yes/no]
- Intervention-associated complications [yes/no], specifications (ICH/SAH / other cerebral / groin / other systemic)
- Periinterventional hyper- or hypotension (SBP > 180 or < 120 mmHg) [yes/no]
- Delayed extubation (>2 h after end of intervention)
- Start of Antibiotics within 72h for suspected pneumonia [yes/no]

- Reasons for conversion from CS to intubation and GA during EST
  1. Agitation [yes/no],
  2. Respiratory problem
  3. Aspiration [yes/no],
  4. Puncture of common carotic artery (ANSTROKE)
  5. Other

Subgroups :

The following subgroups will be considered:

1. Baseline NIHSS ≤ 17/>17
2. Age ≤ 70 years / > 70 years
3. Sex m/f
4. rtPA y/n
5. Onset-to-admission time (median split)
6. ASPECTS <8 / 8-10
7. mTICI 0-2a / 2b-3
8. Potential subgroups resulting from available variables from above

Statistical analysis:

Primary endpoint:

The primary analysis will be done according to the intention-to-treat (ITT) principle with inclusion and treatment group defined by the randomization assignment in each of the three trials. The primary endpoint mRS after 3 months will be evaluated by applying an IPD meta-analysis. The mRS is an ordinally scaled variable. Therefore, a cumulative proportional logit model ("categorical shift-analysis") will

be applied. We will include the following covariates (leading to a meta-regression model): age, sex, NIHSS at baseline, mRS at baseline, ASPECTS, location of occlusion, treatment with intravenous alteplase (yes or no). The odds ratio with the related 95% confidence interval and the p-value will be calculated for the treatment group comparison as well as for each of the included covariates. There are no missing values for the baseline mRS and for mRS after 3 months and, thus, application of related methods is not required.
A per-protocol (PP) analysis excluding those patients of the ITT analysis set without major protocol violations will be performed to assess the robustness of the results of the ITT analysis. A further sensitivity analysis will be performed for the as-treated (AT) population (see definition of analysis sets below).
The meta-regression model will be applied to the IPD of the three trials. We will follow recommendations given in the Cochrane handbook (Higgins and Green, 2011) and present the results according to the PRISMA statement (as applicable) (Moher et al., 2009) for meta-analyses based on individual patient data. Mixed effects models will be applied. The treatment effect will be considered as either fixed or random effect. Both analyses should essentially lead to the same conclusions. If major differences occur, they will be discussed appropriately. We will also assess the heterogeneity between the trials by calculating the intra-class correlation coefficient as well as other measures as the I^2. In case of strong heterogeneity, the results will be discussed. We will also present forest plots to illustrate the results.
Several secondary analyses will be conducted. First, the primary outcome will be dichotomized (0-2 vs. 3-6 as well as 0-3 vs. 4-6). A logistic mixed-effects model will be applied including the same fixed and random effects as in the primary analysis. The secondary endpoints will be analyzed using mixed-effects models adjusted as necessary. Again, the same fixed and random effects will be included.
Definition of analysis sets:
The intention-to-treat (ITT) set includes all patients which were randomized in any of the three trials. In the ITT analysis, all patients are evaluated for the intervention group they have been assigned to. The following explanations and specifications refer to the respective trial.
SIESTA: One patient (patient no. 127) was assigned to the intubation group but actually underwent the intervention in sedation. According to the ITT principle, this patient is counted for the intubation group in the ITT analysis. Therefore, the ITT analysis includes n=150 (sedation: n=77, intubation: n=73) patients.
GOLIATH: The ITT analysis included data 128 patients (sedation: n=63, intubation: n=65).
ANSTROKE: All patients n=91 started in the intervention group that they were assigned for (sedation n=45, intubation n=46). One

patient in the intubation group withdrew the consent. The ITT analysis includes n=90 (sedation: n=45, intubation: n=45) patients. The per-protocol (PP) set includes all patients of the ITT set without major protocol violations.
SIESTA: With exception of patient no. 127, no further major protocol violation occurred. One patient with NIHSS=10 was included (patient no. 142), but this was not seen as a major protocol violation. Therefore, the PP analysis includes n=149 (sedation: n=77, intubation: n=72) patients.
GOLIATH: 2 patients were modified ranking 3 when randomized (both intubation group). One had an infarct > 70ml at randomization (CS). The PP set included n=125 patients (sedation: n=62, intubation: n=63) patients.
ANSTROKE: No protocol violations occurred. PP analysis include n=90 (sedation: n=45, intubation n=45) patients.
Additionally, an as-treated (AT) analysis is performed where patients like no. 127 are evaluated in the group of the intervention she or he actually underwent i.e., although randomized to the intubation group, she or he is evaluated in the sedation group. All patients who started with conscious sedation but crossed over to general anesthesia (intubation) (n=11) are evaluated in the intubation group with one exception (patient no. 90); this patient is evaluated in the sedation group. Therefore, the AT analysis includes n=150 (sedation: n=68, intubation: n=82) patients.
GOLIATH: Four patients crossed over from the sedation group to the intubation group. Hence, 59 in the sedation group and 69 in the intubation group are included in the AT analysis.
ANSTROKE: Seven patients (n=7) crossed over from sedation to intubation group. Therefore, AT analysis includes n=90 (sedation n=38, intubation n=52).
As a further sensitivity analysis, the analysis set that excludes those patients from the PP set who started with conscious sedation but had to change to general anesthesia is performed.

Descriptive analyses:

For the primary and all secondary outcomes, the following descriptive measures of the empirical distribution will be provided for both arms separately as well as for the total sample.
Continuous variables will be described by N, Nmiss, Mean, SD, Median, Q1, Q3, Min, Max. For categorical variables N, Nmiss and percentages will be shown. Tables will be created to summarize the results by the defined interventions. Additionally, further tables will be created by subdividing intervention groups into the defined subgroups.

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Date of the Statistical Analysis Plan 2018-07-20.

