Supplemental Online Content

Turc G, Hadziahmetovic M, Walter S, et al. Comparison of mobile stroke unit with usual care for acute ischemic stroke management: a systematic review and meta-analysis. *JAMA Neurol*. Published online February 7, 2022. doi:10.1001/jamaneurol.2021.5321

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

eMethods.

Search strategy (Pubmed)

We searched Medline, Cochrane Library and Embase for articles published in English language between January 1st, 1960 and September 11th, 2021, using the following combination of keywords and the Boolean operators ‘‘and’’ and ‘‘or’’: “Mobile”, “Stroke”, “Unit”, “Treatment”, “Ambulance” and “Prehospital”. The following search strategy was used for Pubmed:

(((("mobile"[All Fields] OR "mobiles"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) AND "Unit"[All Fields]) OR (("mobile"[All Fields] OR "mobiles"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND "Unit"[All Fields]) OR (("ambulance s"[All Fields] OR "ambulances"[MeSH Terms] OR "ambulances"[All Fields] OR "ambulance"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields])) OR (("prehospital"[All Fields] OR "pre-hospital"[All Fields]) AND "stroke"[All Fields])) AND "English"[Language] AND 1960/01/01:3000/12/31[Date - Entry]

On-board computed tomographic angiography capability

All MSUs in included studies were equipped with a CT scanner allowing for angiography (CTA). However, specific criteria for performing CTA in the MSU were unfortunately not detailed, may not have been standardized and are likely to slightly differ across studies. It is likely that CTA was very rarely performed on board before the demonstration of the benefit of mechanical thrombectomy for large vessel occlusion-related acute ischemic stroke in 2015. To our knowledge, two MSU teams did not perform CTAs during the included study period (Larsen et al.[1] and Kummer et al.[2]). Furthermore, In BEST-MSU, on-board CTA was only carried out by Memphis, Houston, and Los Angeles teams during the trial. It was done routinely only in Memphis, and rarely in Houston and Los Angeles. Therefore, the results of BEST-MSU do not reflect routine on-board CTA use since the majority of MT cases were enrolled in Houston.

Three-month mRS in RCTs

In two of the three randomized controlled trials, 90-day mRS outcomes were either not assessed (Walter et al[7]) or only assessed in a minority of control-group patients (Ebinger et al[8]) and therefore not included in the specific meta-analyses of functional outcomes.

eTable 1. Key features of included studies

	Design and setting	Number of patients	Main inclusion criteria	Primary outcome (MSU vs. control)	Other salient results
Walter et al, Lancet Neurol 2012[7]	- RCT - Homburg (Germany) - 2008 to 2011	- Total: 100 - AIS: 54 - IVT: 20	-18-80 y.o. - Stroke symptoms (ROSIER scale) - Onset ≤2.5hrs	Alarm to therapy decision time: 35 (31–39) vs. 76 (63–94), p<0.0001	Alarm-to-IVT time: 38 (34–42) vs. 73 (60–93) p<0.0001
Ebinger et al, JAMA 2014[8] (PHANTOM-S)	- RCT - Berlin (Germany) - 2011 to 2014	- Total: 6182 - AIS: 2111 - IVT: 530	- Age ≥18 y.o. - Stroke symptoms - Onset ≤4 hrs or unknown	Alarm-to-IVT: mean (95%CI) 51.8 (49.0-54.6) vs. 76.3 (73.2-79.3) p<0.001	IVT rates: 33% vs. 21% p<0.001
Ebinger et al, JAMA Neurol 2015 (PHANTOM-S)	Same as above, provides additional results regarding "Golden Hour"-IVT				
Helwig et al, JAMA Neurol 2019[9]	- RCT - Saarland (Germany) - 2015 to 2017	- Total: 116 - AIS: 71 - IVT: 30 - MT: 9	- Age ≥18 y.o. - Stroke symptoms (cl-FAST scale) - Onset ≤8 hrs or unknown	Proportion of patients accurately triaged with MSU vs. LAMS score: 100% vs. 69.8%, p<0.001	Alarm-to-IVT time: mean (SD): 50.1 (10.1) vs 84.9 (30.2), p<0.001
Ebinger et al, JAMA 2021[10] (B_PROUD)	- Large prospective controlled study (3 MSUs) - Berlin (Germany) - 2017 to 2019	- Total: 1543 (confirmed AIS or TIA) - AIS: 1288 - IVT: 833 - MT: 216	- Age ≥18 y.o. - Stroke symptoms - Onset ≤4 hrs - mRS score ≤3 before index event	mRS at 90 days: Adjusted common OR for worse outcome: 0.71 (95%CI: 0.58-0.86), p<0.001	90-day co-primary endpoint: common OR for worse outcome 0.73 (0.54-0.99), p= 0.04
Grotta JC et al, New Engl J Med 2021[11] (BEST-MSU)	- Large prospective controlled study - USA (7 cities) - 2014 to 2020	- Total: 1515 - AIS: 1103 - IVT: 941 - MT: 262	- Age ≥18 y.o. - Stroke symptoms - Last known normal ≤4.5 hrs - Suspected stroke on scene (including physical examination) - No obvious contraindication to IVT	Mean utility-weighted mRS score at 90 days in patients eligible for IVT (n=1047): adjusted difference 0.08 (95%CI 0.04-0.13)	Adjusted pooled OR for mRS 0-1 for all enrolled patients: 1.82 (95% CI 1.39-2.37), p<0.001
Weber et al, Neurology 2013[12]	- Observational - Berlin (Germany) - 2011 (MSU group), 2010 (historical control group of	- Total: 77 (+50 historical controls) - AIS: 45 - IVT: 23	- Age ≥18 y.o. - Stroke symptoms (DIASE algorithm) - Onset ≤4 hrs or unknown - No obvious non-stroke disease after	Feasibility and technical reliability	Alarm-to-IVT time: 58 (50–63) vs. 92 (79-112)

	IVT-treated patients)		on-scene examination		
Kunz et al, Lancet Neurol 2016[13]	- Observational - Berlin (Germany) - 2011-2015 - Control group: contemporary in-hospital IVT registry	- Total: 658 - AIS: 658 - IVT: 658 - MT: 82	- Age ≥18 y.o. - Treated with IVT for AIS - Lived at home without assistance before stroke	mRS 0-1 at 90 days :53% vs. 47% adjusted OR 1.40 (95%CI 1.00-1.97), p=0·052	Alarm-to-IVT time : 46 (39-53) vs. 76 (64-93), p<0.0005
Taqui et al, Neurology 2017[14]	- Observational - Cleveland (US) - 2014 - Control group: ED patients (same year, retrospective control group)	- Total: 100 (+53 controls) - AIS: 63 - IVT: 16	- Suspected stroke (including on-scene evaluation by EMS with CPSS) - Time from symptom onset was not a selection criterion	Not specified	Alarm-to-IVT time 55.5 (46–65) vs 94 (78–105) p=0.0006
Nolte et al, Stroke 2018[15]	- Observational - Berlin (Germany) - 2011-2015 - Control group: contemporary in-hospital IVT registry	- Total: 264 - AIS: 264 - IVT: 264 - MT: 10	- Age ≥18 y.o. - Treated with IVT for AIS - Patients with pre-stroke dependency	mRS 0-3 at 90 days : 39% vs. 25%, p=0.01 Adjusted OR 1.99 (95%CI 1.02–3.87), p=0.04	Onset-to-IVT time 97 (69–159) vs. 135 (98–184), p<0.001
Kummer et al, J Am Heart Assoc 2019[2]	- Observational - New York (US) - 2016-2017 - Control group: contemporary (conventional ambulance)	- Total: 85 - AIS: 40 - IVT: 38	- Suspected stroke	Alarm-to-IVT time Mean (SD): 61.2 (15.3) vs. 91.6 (39.2) p=0.001	Adjusted mean decrease in alarm-to-IVT time: 29.7 (95%CI 6.9–52.5)
Zhao et al, Stroke 2020[16]	- Observational - Melbourne (Australia) - 2017-2019 (MSU group) -2 historical control groups: IVT-treated (2016-2017) and MT-treated (2017-2018)	- Total: 939 (+133 controls) - AIS: 311 - IVT: 100 - MT: 41	- Suspected stroke - Onset ≤12 hrs - No obvious non-stroke disease after on-scene examination by paramedic crew	Alarm-to-IVT time saving: 42.5 (95% CI 36.0–49.0) Alarm-to-MT time saving: 51 (95%CI 30.1-71.9], p<0.001	Modelization: median DALY saved through earlier provision of reperfusion therapies: 20.9 for IVT and 24.6 for MT
Zhou et al, Cerebrovasc Dis 2021[17]	- Observational - Xingyang (China) - 2018-2019 - Control group: contemporary stroke patients admitted by conventional ambulances	- Total: 203 (+24 IVT-treated controls) - AIS: 134 - IVT: 14 - MT: 3 (4 in control group)	- Suspected stroke - No obvious non-stroke disease after on-scene examination by emergency physician - Main analysis: patients treated with IVT for AIS	Alarm-to-IVT time: 59.5 (42–75) vs. 89 (32–164), p=0.001	mRS 0-2 at 90 days (IVT-treated patients): 79 vs. 67%, p=0.49

Larsen et al, Eur J Neurol 2021[1]	- Observational (prospective, controlled intervention study) - Østfold county (Norway) - 2017-2020	- Total: 440 - AIS: 159 - IVT: 199 (including 50 stroke mimics) - MT: 16	- Age ≥18 y.o. - Stroke symptoms - Onset ≤4 hrs	Onset-to-IVT time 101 (71–155) vs. 118 (90–176), p=0.007	MSU patients more often discharged home (adjusted OR 2.36 95%CI 1.11–5.03)

Time metrics are described as median (IQR) unless specified otherwise.

Abbreviations: AIS: acute ischemic stroke; CPSS: Cincinnati Prehospital Stroke Scale; cl-FAST: consciousness, leg, face, arm, speech, time; DALY: disability-adjusted life years ; DIASE: dispatcher identification algorithm for stroke emergencies; ED: emergency department; mRS: modified Rankin Scale; MSU: Mobile Stroke Unit; MT: mechanical thrombectomy; IVT: intravenous thrombolysis; LAMS: Los Angeles Motor Scale; OR: odds ratio; RCT: randomized controlled clinical trial; ROSIER: recognition of stroke in the emergency room; SD: standard deviation; TIA: transient ischemic attack.

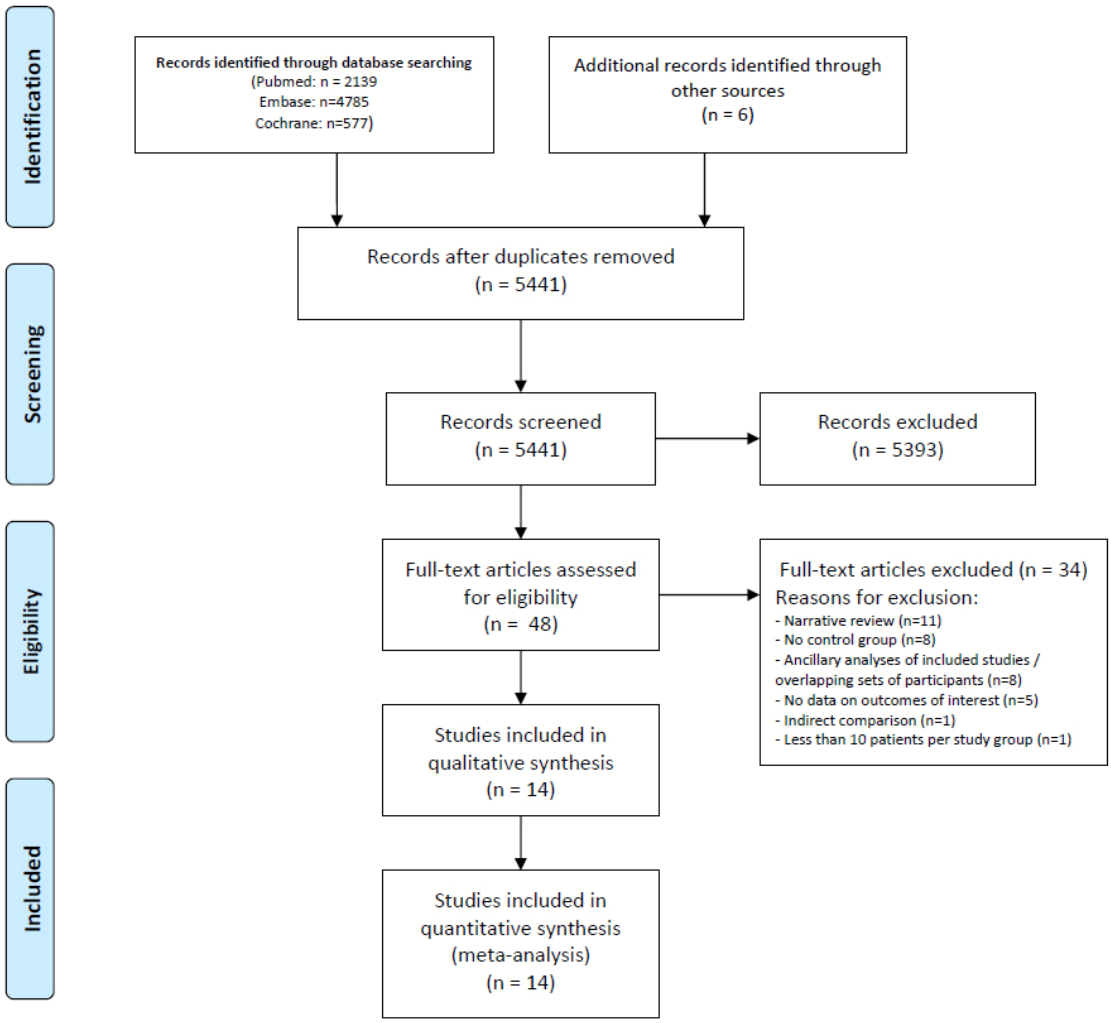
eTable 2. Adjustment variables in each study reporting adjusted results for excellent outcome or reduced disability

	B_PROUD[10]	BEST_MSU[11]	Kunz et al[13]	Larsen et al[1]	Helwig et al[9]*
Age	X	X	X	X	X
Sex	X		X	X	
Hypertension	X				
Diabetes mellitus	X		X		
Atrial fibrillation	X		X	X	
Previous stroke or TIA		X			
Initial stroke severity	X	X	X	X	X
Dependency before stroke	X	X		X	
Mechanical thrombectomy			X		
Study center	X	X	NA	NA	NA

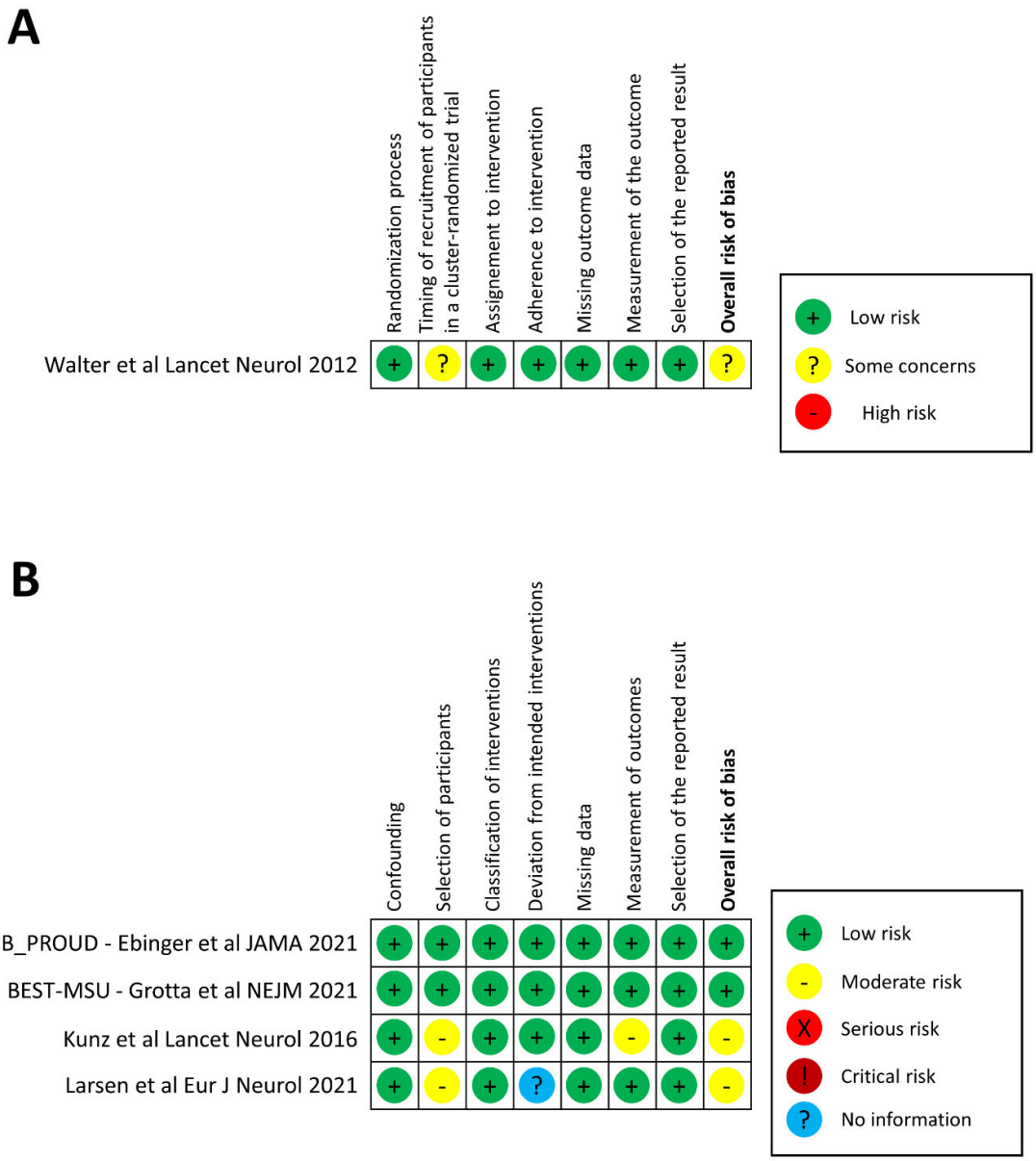
Abbreviations: NA: not applicable (single-center study); TIA: transient ischemic attack

*Post-hoc analysis based on individual participant data.

eFigure 1. PRISMA flow chart



eFigure 2. Risk of bias of each included study for excellent functional outcome (mRS score of 0-1 at 90 days), according to the RoB2 tool for cluster-randomized trials (panel A) and the ROBINS-I tool for nonrandomized studies (panel B)



Justification:

Panel A :

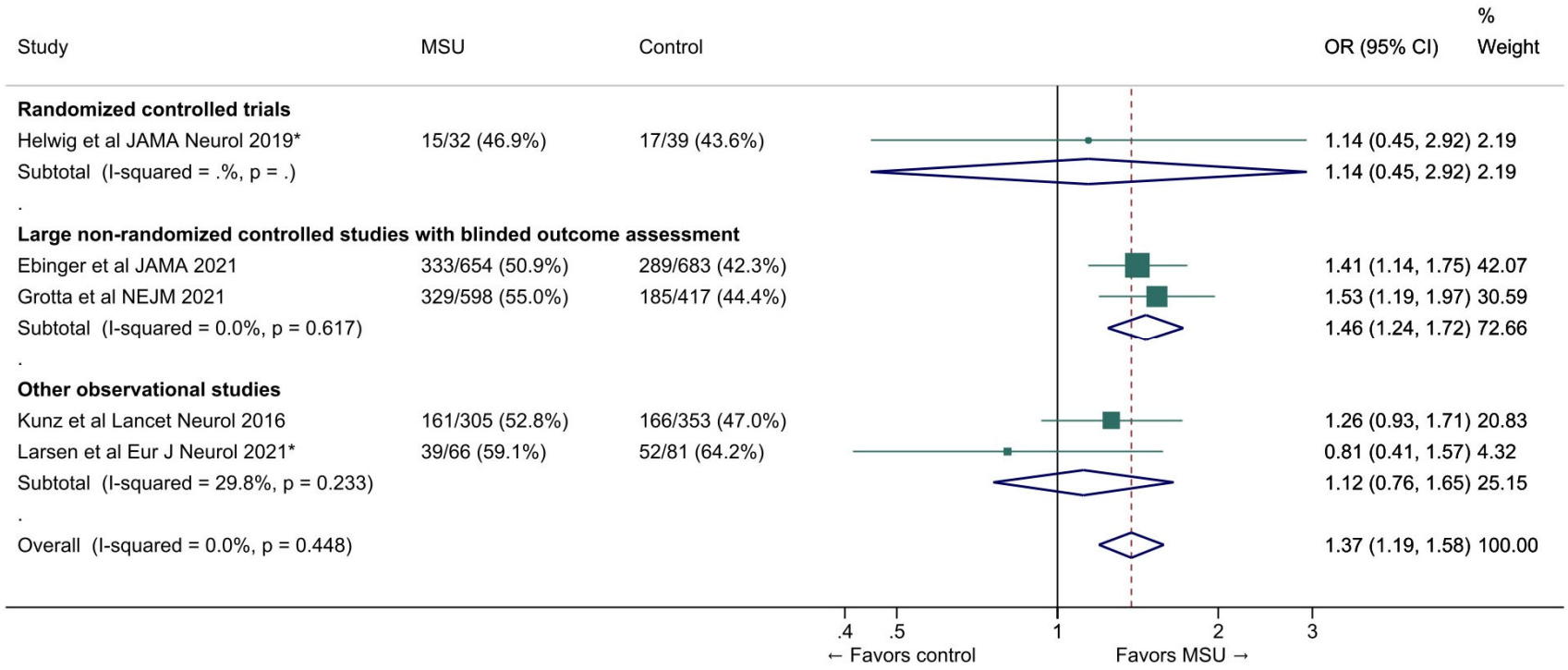
- Those identifying actual participants were aware of cluster allocation before recruitment. Therefore, it cannot be excluded that this could have affected recruitment differentially between the intervention groups, consciously or subconsciously. However, this seems to be unlikely provided the screening logs. The modest sample sizes do not allow to really judge whether the observed baseline imbalances are solely due to chance or not. The proportion of

excellent outcome in each treatment arm was not reported in the original publication and was therefore calculated post-hoc, based on individual participant data.

Panel B:

B_PROUD and BEST-MSU were considered at low risk of bias for all domains, taking into account the fact that the ROBINS-I tool has been designed for non-randomized studies. The two remaining studies were rated at overall moderate risk of bias due to unblinded assessment of functional outcome (Kunz et al) and possible selection bias.

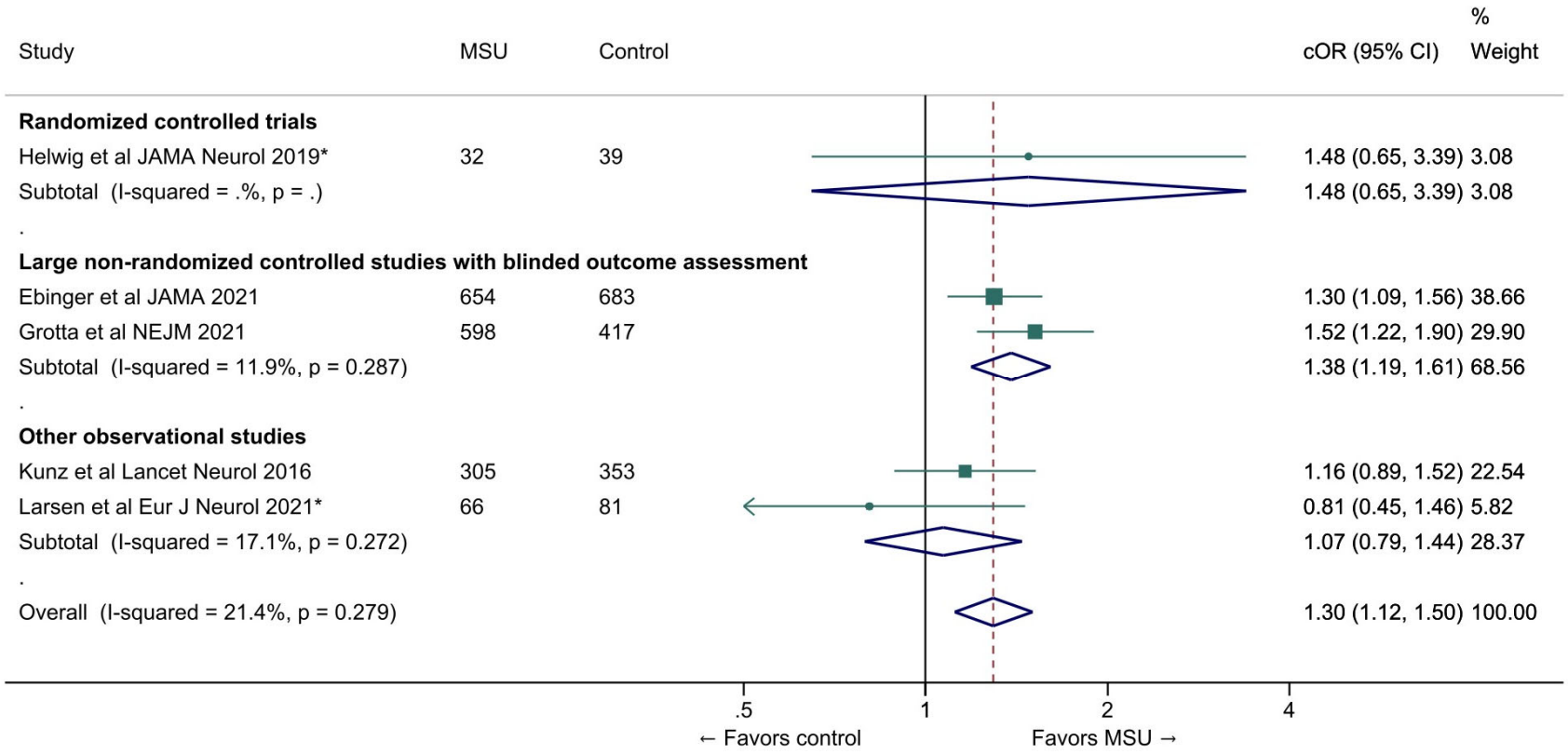
eFigure 3. Pooled odds ratio for excellent outcome (mRS score of 0-1 at 90 days) in patients with MSU deployment vs usual care (random-effects meta-analysis, crude ORs)



Test for heterogeneity between subgroups: P=0.36

* Previously unpublished data, excluding stroke mimics in the study by Larsen et al. When including stroke mimics, the crude OR for excellent outcome in the study by Larsen et al. was 0.92 (95%CI: 0.51 to 1.67).
Results are expressed as number of patients with mRS 0-1 divided by the total number of patients, in each treatment group. MSU denotes Mobile Stroke Unit.

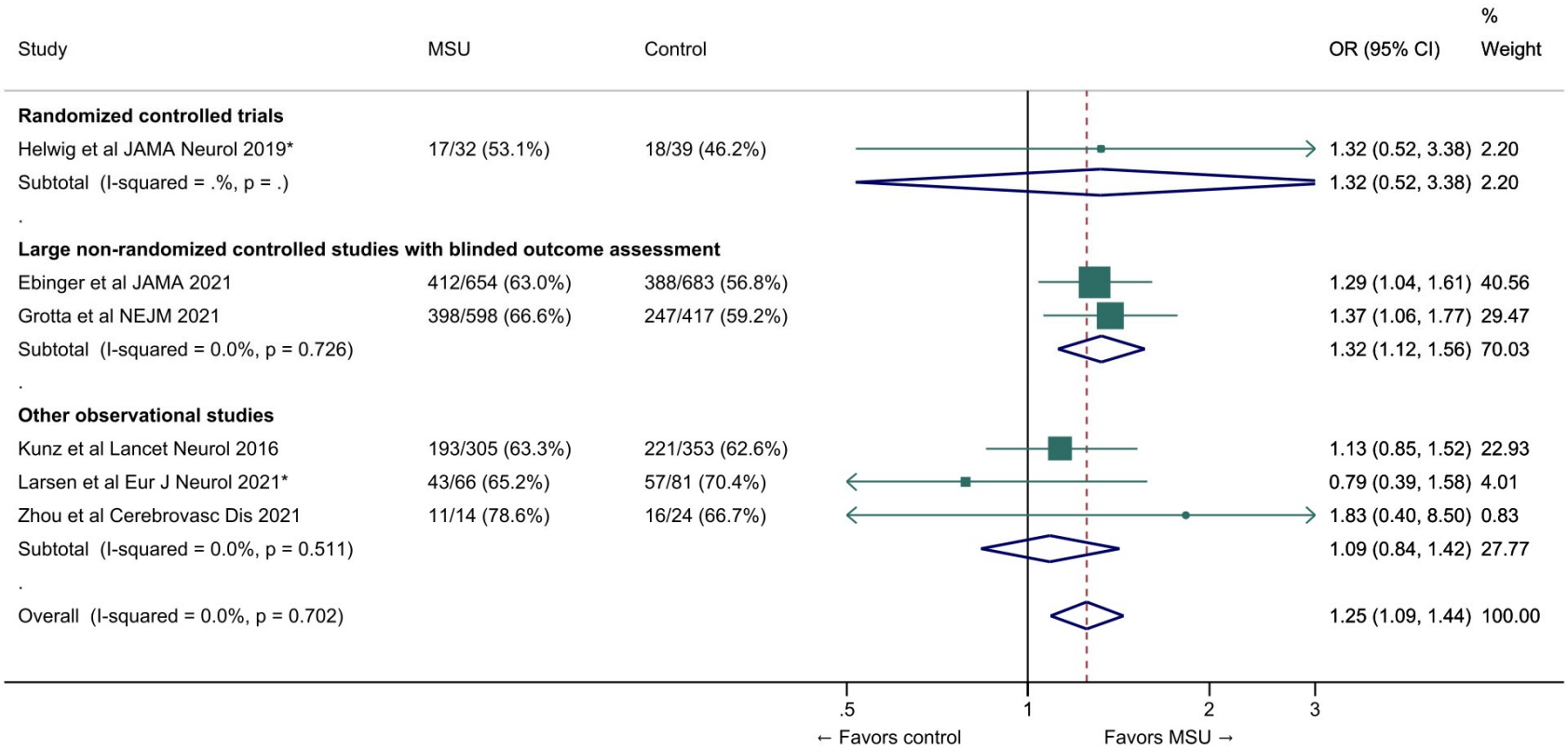
eFigure 4. Pooled odds[10,16] ratio for reduced disability (shift analysis over the whole range of the mRS scores at 90 days) in patients with MSU deployment vs usual care (random-effects meta-analysis, crude ORs)



Test for heterogeneity between subgroups: P=0.25

* Previously unpublished data, excluding stroke mimics in the study by Larsen et al. When including stroke mimics, the crude cOR for reduced disability in the study by Larsen et al. was 0.85 (95%CI: 0.51 to 1.44).
Abbreviations: cOR: common odds ratio, MSU: Mobile Stroke Unit.

eFigure 5. Pooled odds ratio for good outcome (mRS score of 0-2 at 90 days) in patients with MSU deployment vs usual care (random-effects meta-analysis, crude ORs)

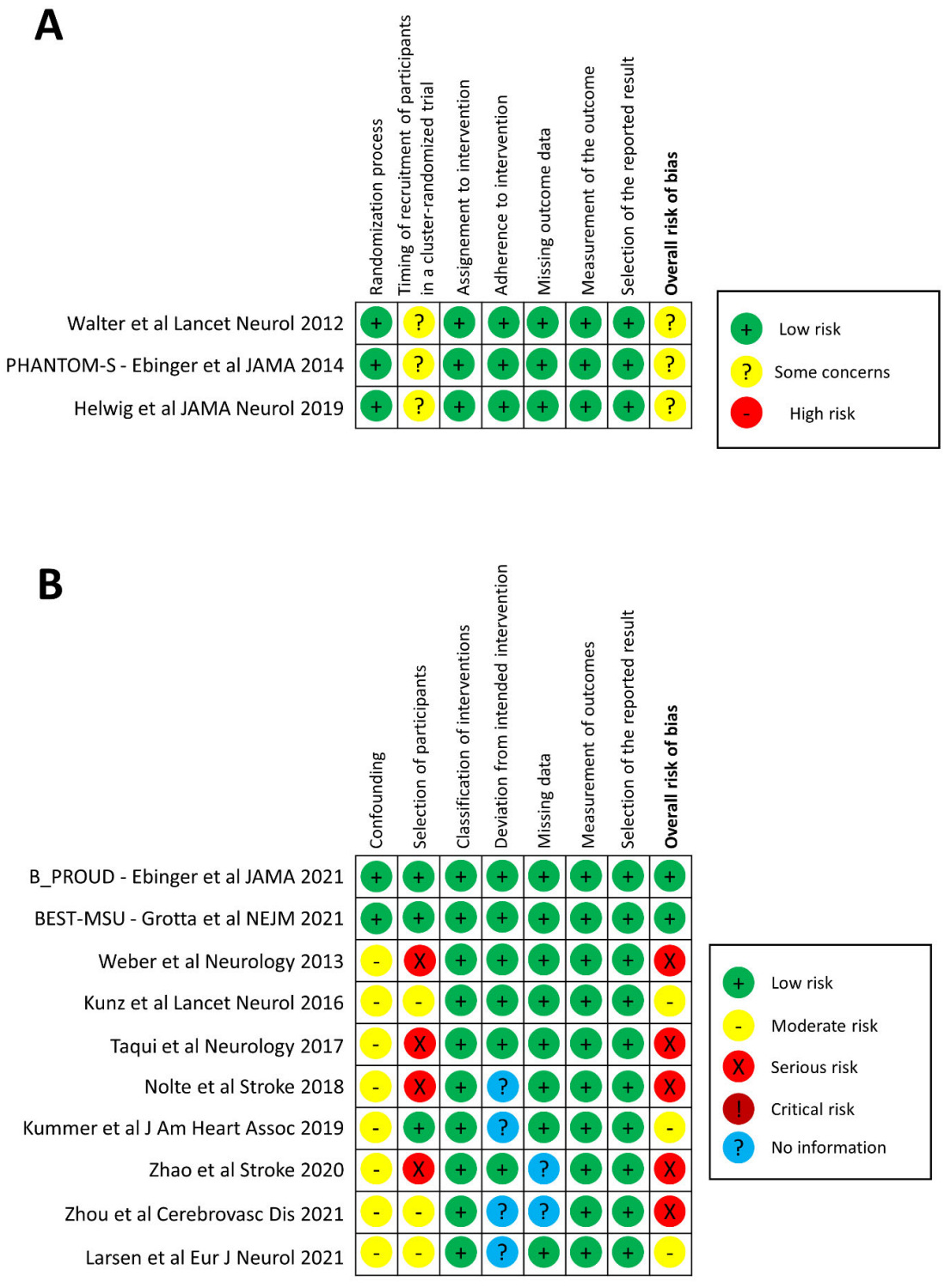


Test for heterogeneity between subgroups: P=0.47

* Previously unpublished data, excluding stroke mimics in the study by Larsen et al. When including stroke mimics, the crude OR for good outcome in the study by Larsen et al. was 0.82 (95%CI: 0.44 to 1.54).

Results are expressed as number of patients with mRS 0-2 divided by the total number of patients, in each treatment group. MSU denotes Mobile Stroke Unit.

eFigure 6. Risk of bias of each included study for alarm-to-IVT time, according to the RoB2 tool for cluster-randomized trials (panel A) and the ROBINS-I tool for nonrandomized studies (panel B)



Justification :

Panel A :

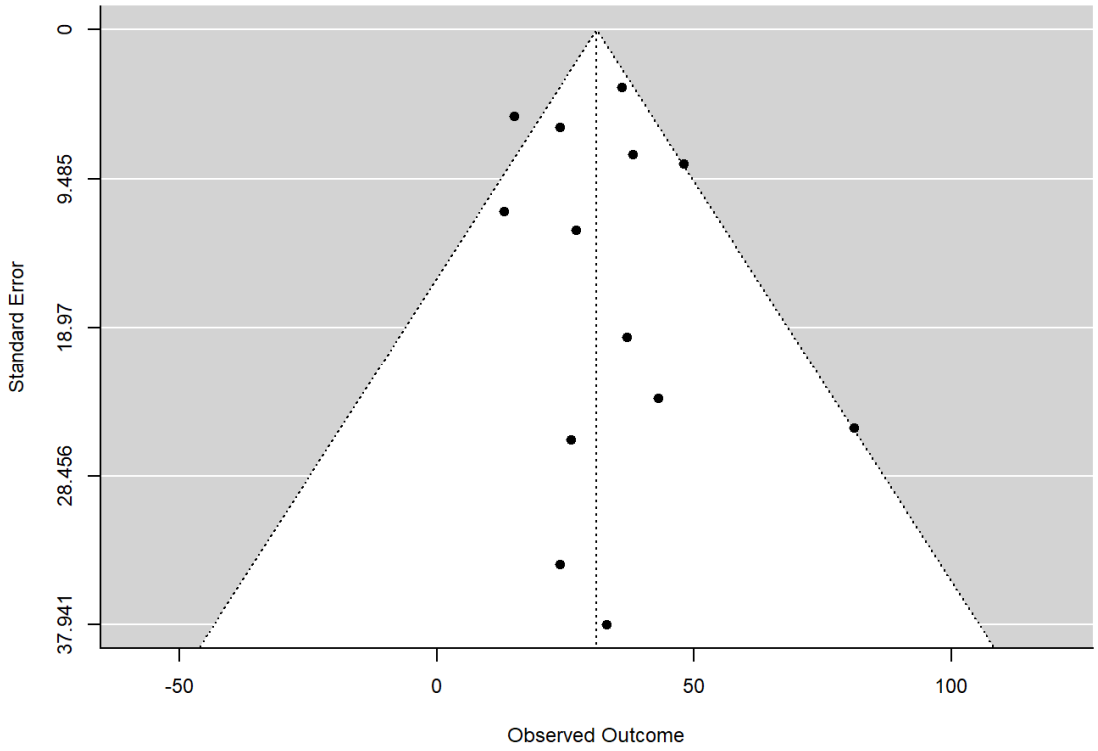
- Walter et al & Helwig et al: those identifying actual participants were aware of cluster allocation before recruitment. Therefore, it cannot be excluded that this could have affected recruitment differentially between the intervention groups, consciously or subconsciously. However, this seems to be unlikely provided the screening logs. The modest sample sizes do not allow to really judge whether the observed baseline imbalances are solely due to chance or not.

- PHANTOM-S: those identifying actual participants were aware of cluster allocation before recruitment. Therefore, it cannot be excluded that this could have affected recruitment differentially between the intervention groups, consciously or subconsciously (e.g., a conventional ambulance might have been dispatched instead of the MSU during MSU weeks). However, there was no imbalance in baseline characteristics between the two groups.

Panel B:

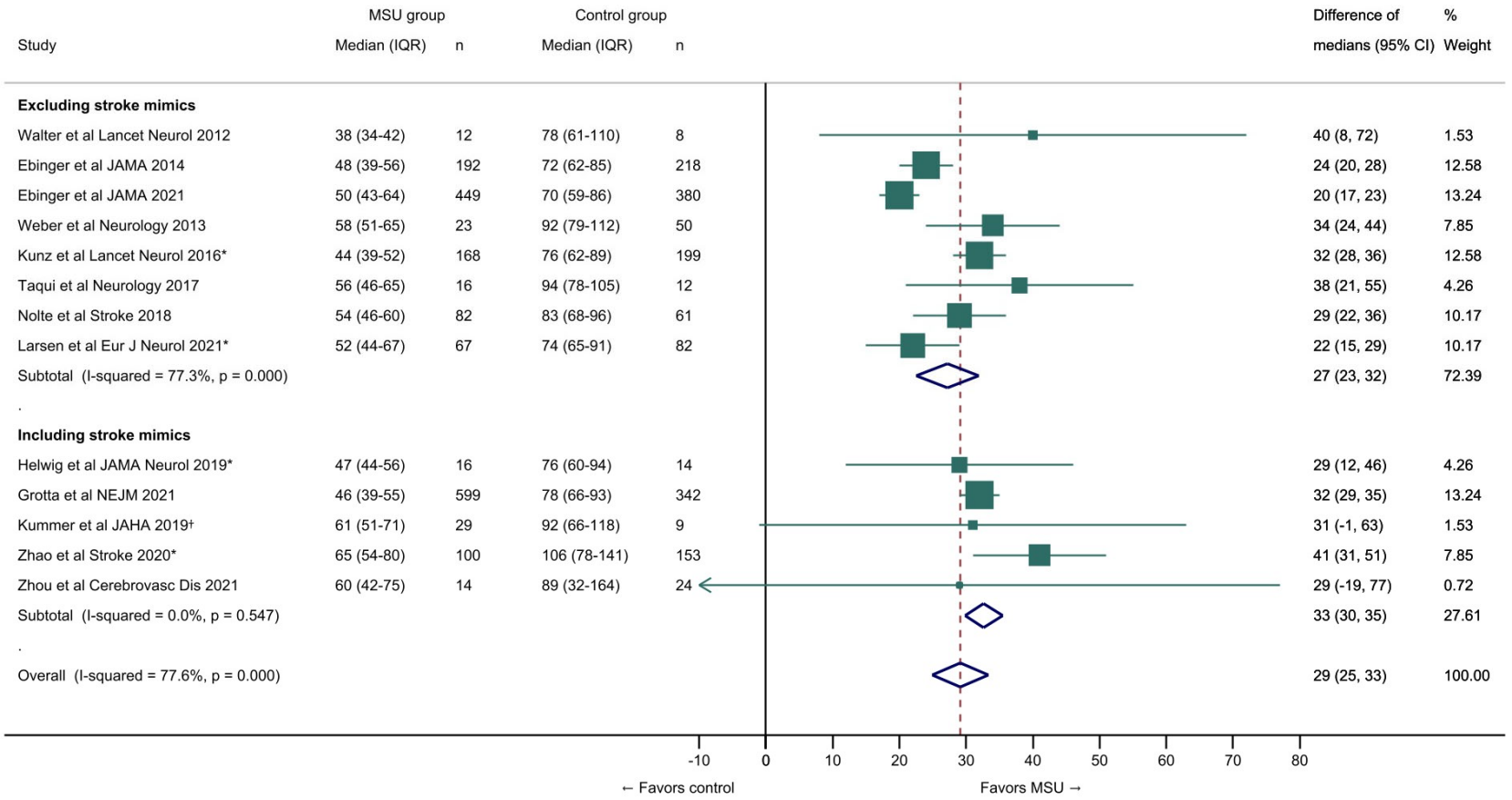
- Three studies were considered at serious risk of selection bias because the control group was historical.[12,14,16] The study by Nolte et al. was considered at serious risk of selection bias because of a major imbalance at baseline between MSU patients and controls regarding the proportion of institutionalization before stroke (36% vs. 64%, respectively, $P<0.0001$).[15]

eFigure 7. Funnel plot of studies included in the meta-analysis of the median reduction of symptom onset or last known well to IVT time in patients with MSU deployment vs usual care



Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p=0.77 and p=0.44, respectively).

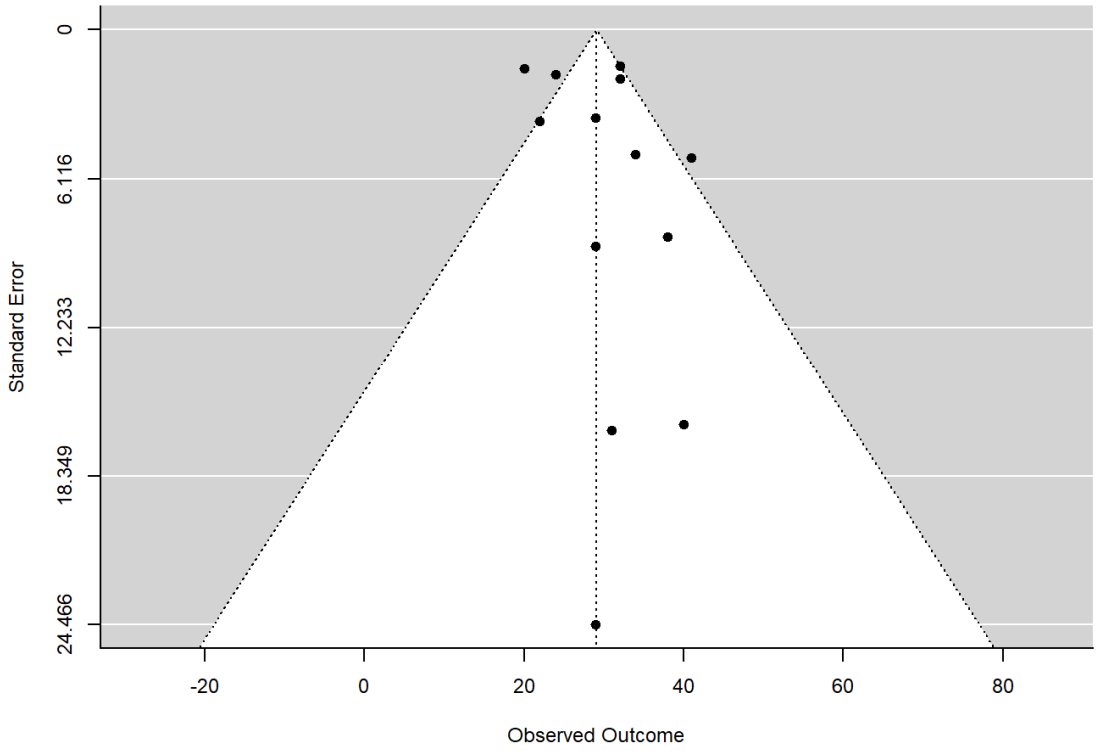
eFigure 8. Pooled difference of medians of alarm (ambulance dispatch)-to-IVT time in patients with MSU deployment vs usual care (random-effects meta-analysis)



Test for heterogeneity between subgroups: P<0.0001

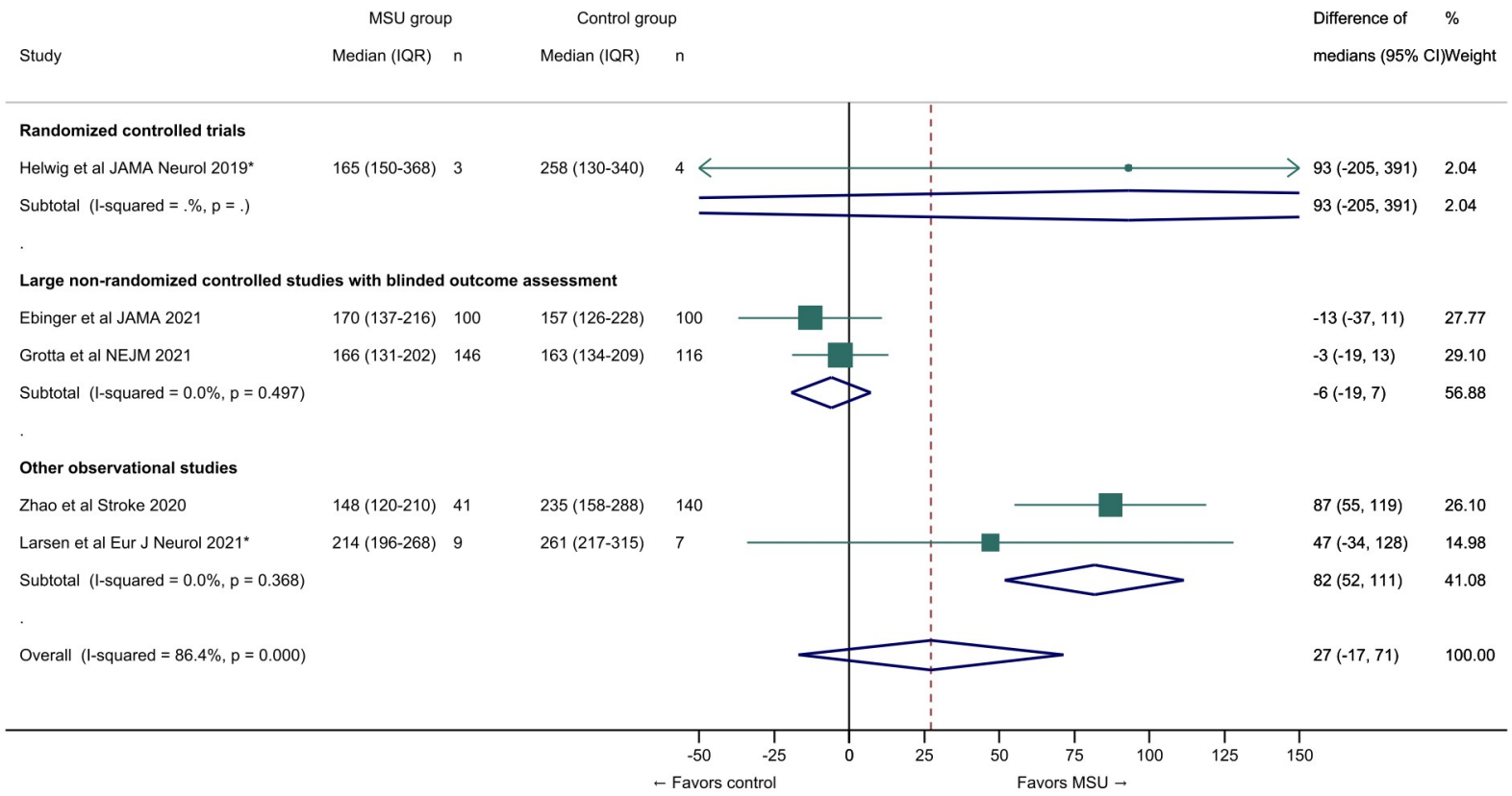
* Previously unpublished (disentangled) data. There was partial overlap in participants between the PHANTOM-S study and the study by Kunz et al.
†Estimated from published means and standard deviations (61 ±15 vs. 92 ±39 min),[2] assuming normal distribution.
Abbreviations: IVT: intravenous thrombolysis, MSU: Mobile Stroke Unit.

eFigure 9. Funnel plot of studies included in the meta-analysis of the median reduction of alarm (ambulance dispatch)-to-IVT time in patients with MSU deployment vs usual care



Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p=0.77 and p=0.23, respectively).

eFigure 10. Pooled difference of medians of symptom onset/last known well-to-MT time in patients with MSU deployment vs usual care (random-effects meta-analysis)

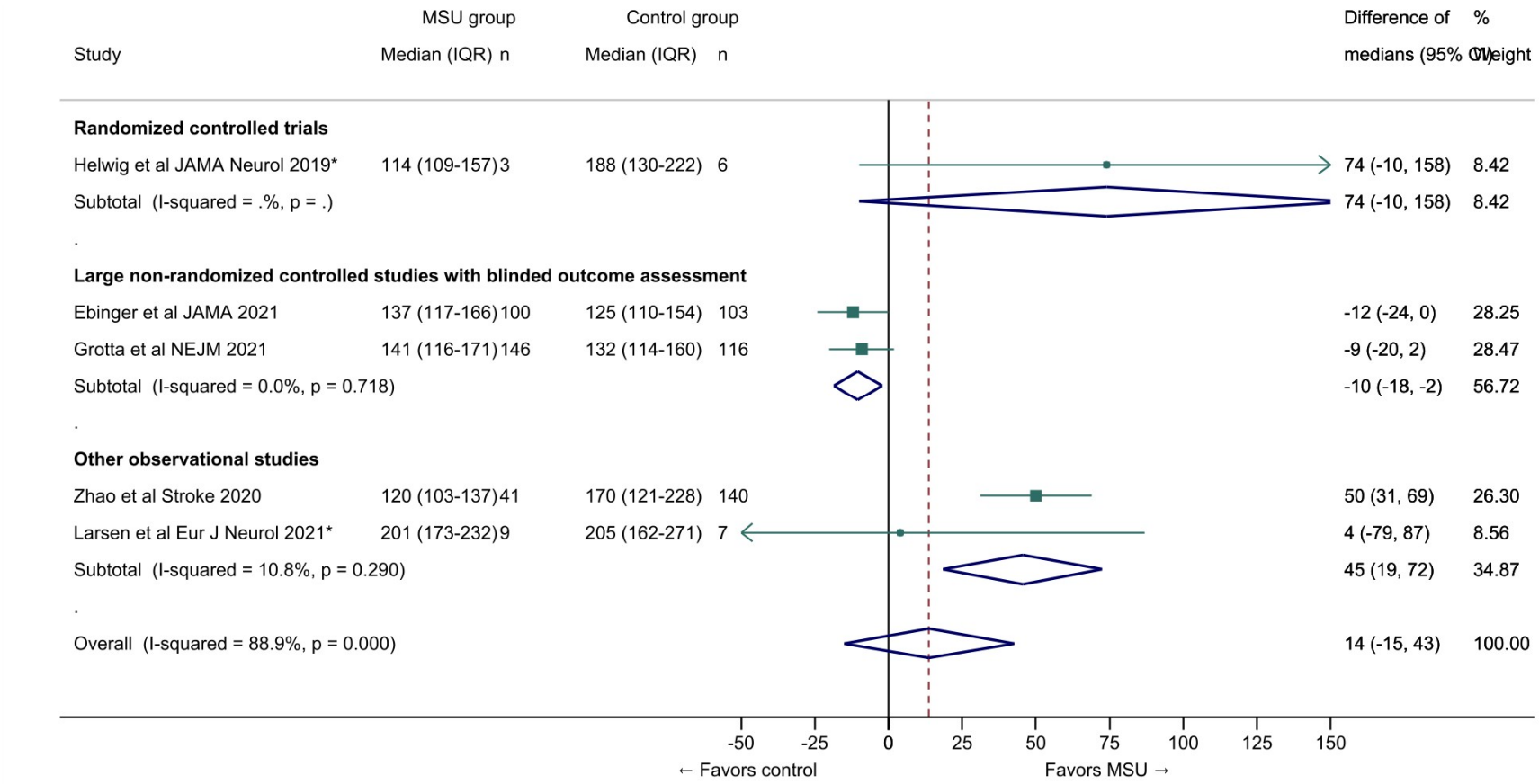


Test for heterogeneity between subgroups: P<0.0001

* Previously unpublished data.

Abbreviations: MSU: Mobile Stroke Unit, MT: mechanical thrombectomy.

eFigure 11. Pooled difference of medians of alarm (ambulance dispatch)-to-MT time in patients with MSU deployment vs usual care (random-effects meta-analysis)

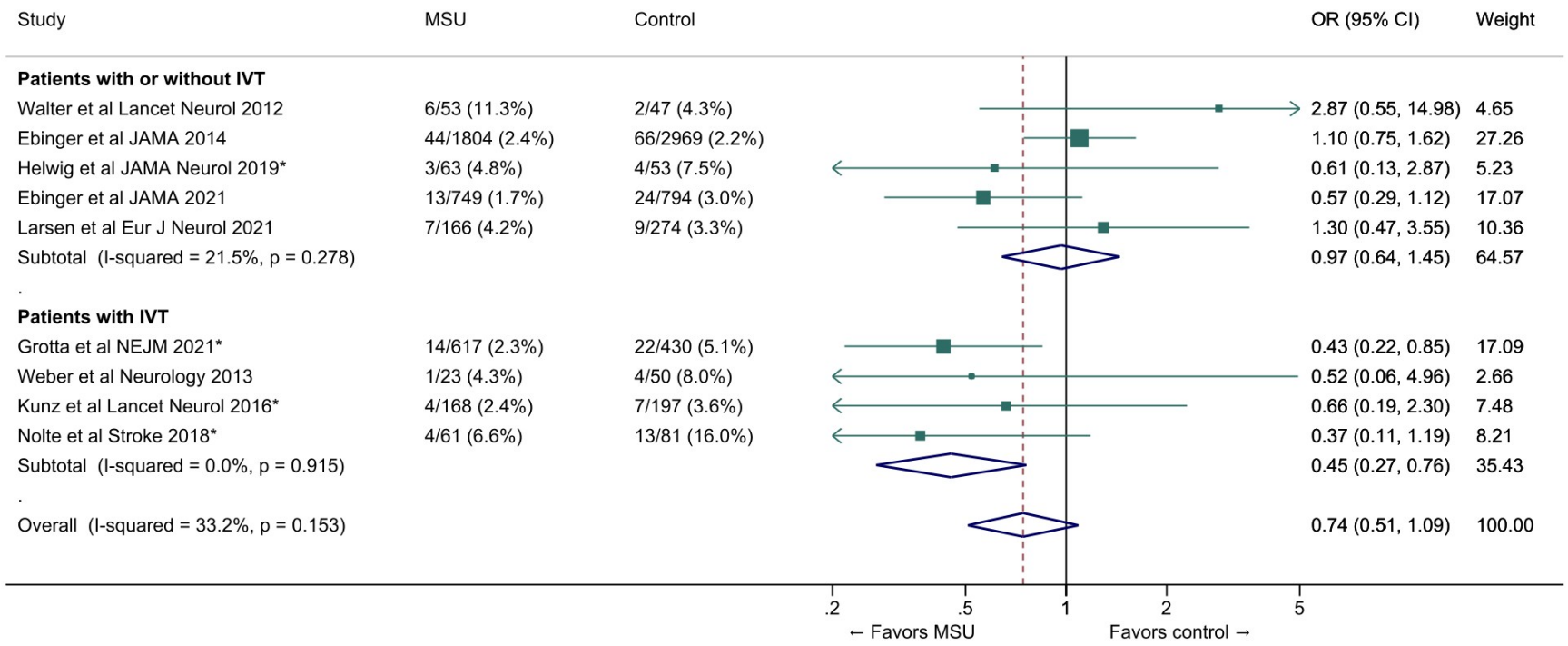


Test for heterogeneity between subgroups: P<0.0001

* Previously unpublished data.

Abbreviations: MSU: Mobile Stroke Unit, MT: mechanical thrombectomy.

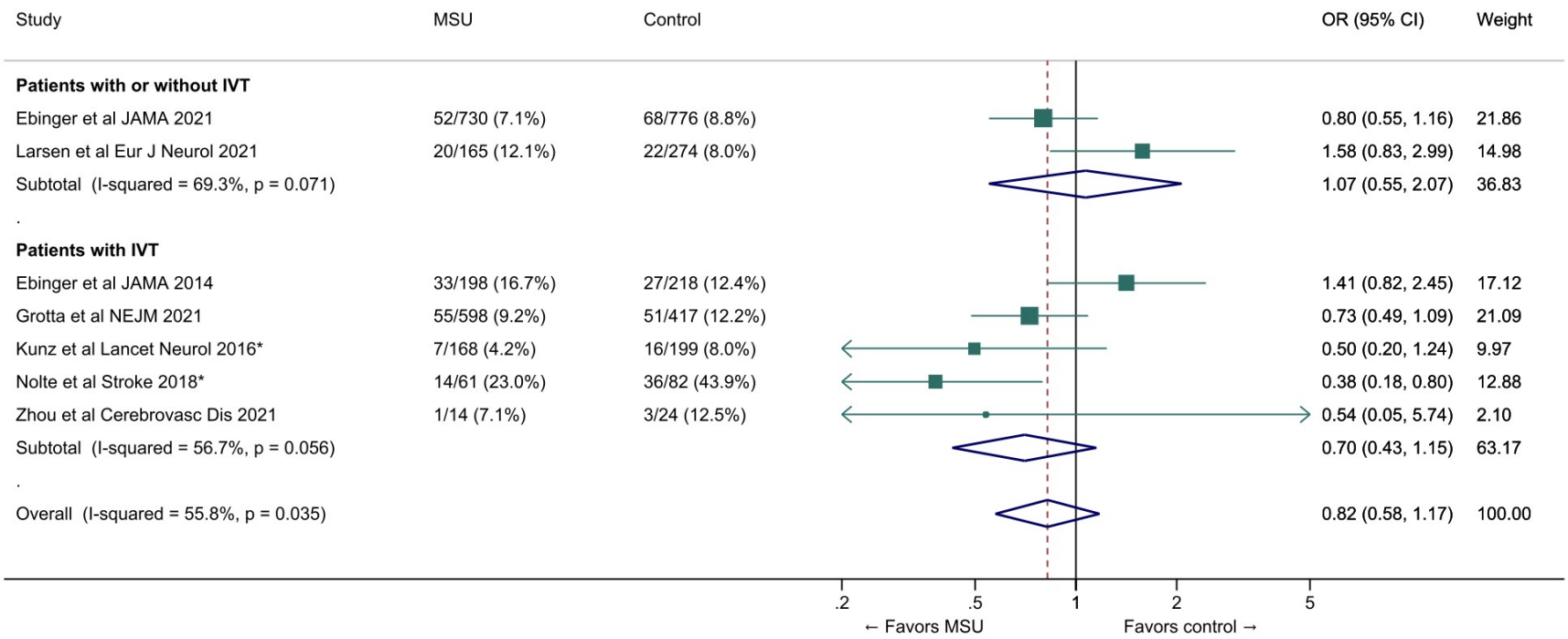
eFigure 12. Pooled odds ratio for all-cause mortality 7 days after MSU deployment vs usual care (random-effects meta-analysis, crude ORs)



Test for heterogeneity between subgroups: P=0.01

*Previously unpublished data. There was partial overlap in participants between the PHANTOM-S study and the study by Kunz et al.
Results are expressed as number of patients dead at 7 days divided by total number of patients, in each treatment group.
Abbreviations: MSU: Mobile Stroke Unit.

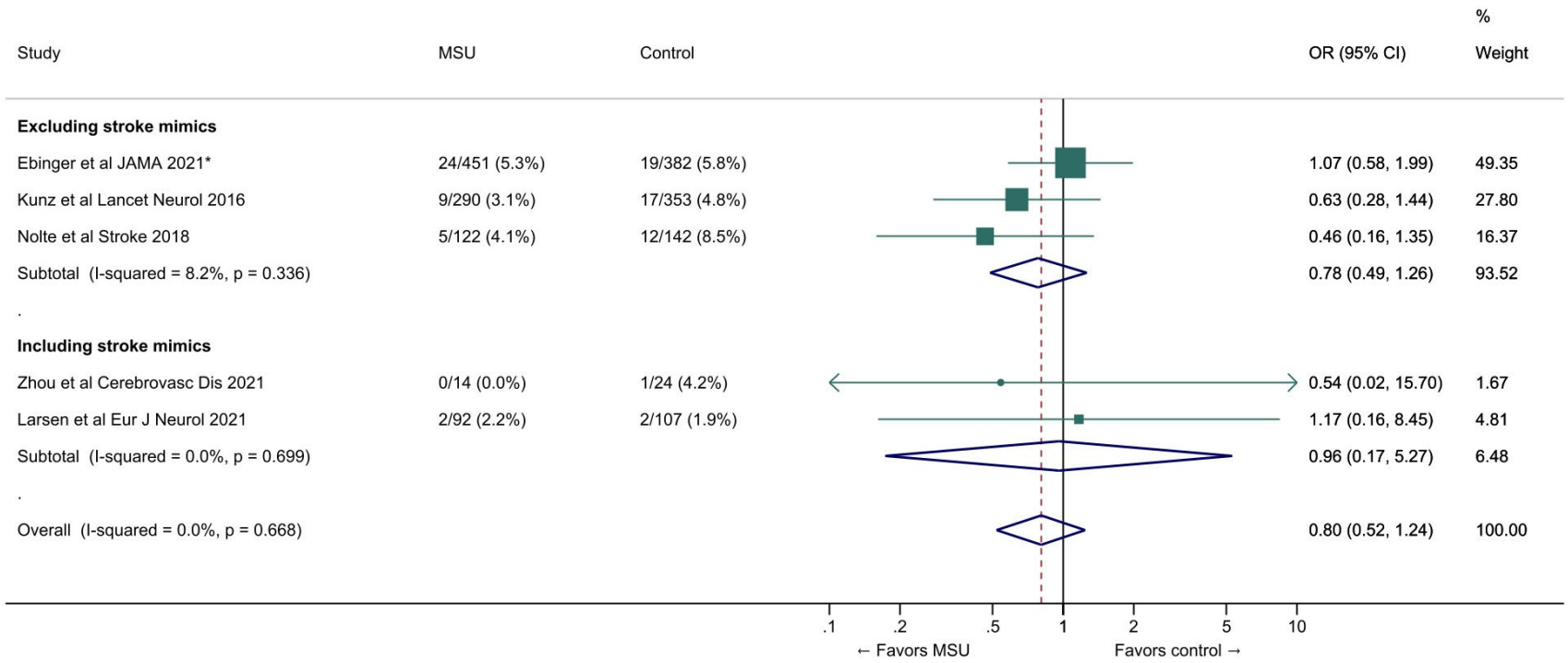
eFigure 13. Pooled odds ratio for all-cause mortality 90 days after MSU deployment vs usual care (random-effects meta-analysis, crude ORs)



Test for heterogeneity between subgroups: P=0.59

*Previously unpublished (disentangled) data. There was partial overlap in participants between the PHANTOM-S study and the study by Kunz et al.
Results are expressed as number of patients dead at 90 days divided by total number of patients, in each treatment group.
Abbreviations: MSU: Mobile Stroke Unit.

eFigure 14. Pooled odds ratio for symptomatic intracerebral hemorrhage in patients with MSU deployment vs usual care (random-effects meta-analysis, crude ORs)

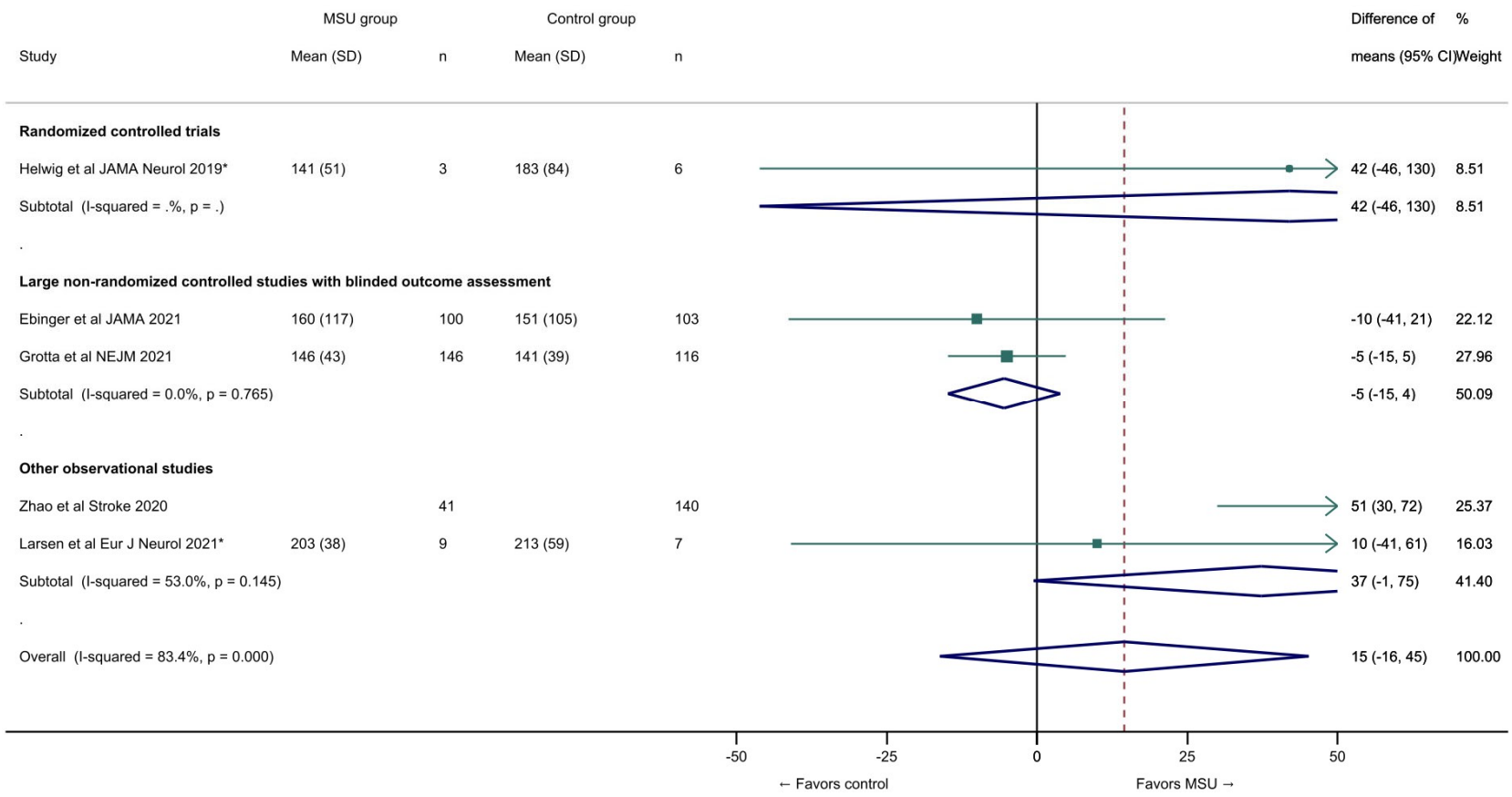


Test for heterogeneity between subgroups: P=0.83

*Previously unpublished data.

Results are expressed as number of patients with symptomatic intracerebral hemorrhage (according to each study's definition) divided by number of patients treated with IVT, in each treatment group. Definition of sICH varied across studies.
Abbreviations: MSU: Mobile Stroke Unit.

eFigure 15. Pooled difference of means of alarm (ambulance dispatch)-to-MT time in patients with MSU deployment vs usual care (post-hoc analysis; random-effects model)



* Previously unpublished data.
Abbreviations: MSU: Mobile Stroke Unit; SD: standard deviation.

eReferences.

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