

Supplementary Online Content

Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden: a meta-analysis. *JAMA Neurol*. Published online April 18, 2016. doi:10.1001/jamaneurol.2016.0292.

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eReferences.

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

eMethods

Complete algorithm used in the MEDLINE database search

(("cerebrum"[MeSH Terms] OR "cerebrum"[All Fields] OR "cerebral"[All Fields] OR "brain"[MeSH Terms] OR "brain"[All Fields]) AND microbleeds[All Fields]) AND (thrombolysis[All Fields] OR ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields] OR "alteplase"[All Fields]) OR tPA[All Fields])

eTable 1. Excluded studies with reasons for exclusion

Study name	Reason for exclusion
Kidwell et al ¹	IA thrombolysis administration
Kim et al ²	Both IV and IA thrombolysis administration
Moriya et al ³	Study not reporting sICH rates
Yan et al ⁴	MRI performed before or after IV thrombolysis

IA: intra-arterial, IV: intravenous, sICH: symptomatic intracerebral hemorrhage

eTable 2. Baseline characteristics of the studies included in the meta-analysis

Author s	Stud y name	Countr y	Patie nts (N)	Age (years)	Ma les	HT N	DM	AF	HC L	Prio r IS/T IA	Smok ing	NIHS S admis sion	OTT (min)	Admiss ion SBP (mmHg)	Admis sion DBP (mmH g)	Admis sion Glucos e (mg/dl)	CMB s Imag ing Meth od
Dannen berg et al ⁵	-	German y	326	74.8± 12.2	48. 8%	85. 0%	22. 7%	39. 3%	52. 5%	24.5 %	16.9 %	9.6±6. 1	139.8± 52.5	156.7±2 6.1	85.4±1 7.8	132.8± 41.6	GRE (3.0 T)
Dere x et al ⁶	-	France	44	63.2± 14.1	52. 3%	- -	- -	- -	- -	- -	- -	14±5.8 4	263±7 4	- -	- -	- -	GRE (1.5 T)
Fiehler et al ⁷	BRA SIL	Internat ional	570	69 (59- 77)	59. 8%	- -	- -	- -	- -	- -	- -	13 (8- 17)	- -	- -	- -	- -	GRE (1.5 T)
Goyal et al ⁸	-	USA	21	58.9± 14.6	61. 9%	80. 9%	23. 8%	14. 3%	23. 8%	33.3 %	6.2% 05	6.2±5. 05	- 2.7	169.2±2 13.5	104.1± 73.3	139.7± 73.3	GRE (1.5T /3.0 T)
Gratz et al ⁹	-	Switzerl and	174	69.6± 12.8	35. 6%	71. 3%	19. 5%	31. 0%	62. 1%	- -	13.2 %	8±6.1 60.6	196.7± 60.6	161.6±2 9.6	88.2±1 9.7	124.2± 34.2	SWI (1.5 T/ 3.0 T)
Kakuda et al ¹⁰	DEF USE study	USA, Canada, Belgiu m	70	70.9± 29.3	44. 3%	61. 4%	27. 1%	- -	24. 3%	- -	42.9 %	12.6±1 0.0	320.8± 74.5	168.4±6 2.7	83.2±3 4.3	- -	GRE (1.5 T)
Kimura et al ¹¹	-	Japan	224	76.2± 10.6	54. 0%	70. 5%	25 %	49. 1%	24. 1%	- -	33.0 %	13.4±7 .1	146.3± 33.2	156.6±1 03.3	82.3±3 4.4	148.9± 53.9	GRE (1.5 T)
Turc et al ¹²	-	France	717	74 (60- 83)	48. 9%	63. 0%	15. 8%	23. 1%	- -	9.9 %	17.8 %	11 (6- 8)	152 (120- 195)	154.9±2 1.4	82.3±1 5.2	126±3 6	GRE (1.5 T)
Yan et al ¹³	-	China	333	66.1± 13.0	67. 0%	68. 2%	20. 1%	37. 2%	47, 7%	- -	- -	- 2	234±9 2	- -	- -	- -	SWI (3.0 T)

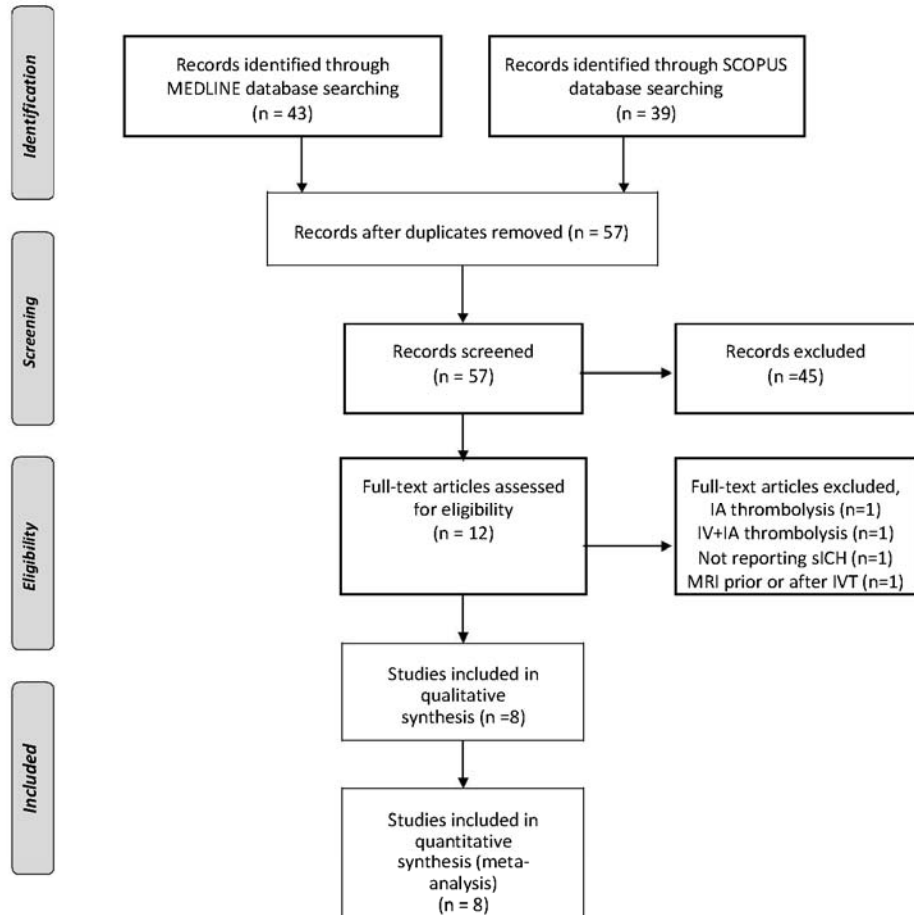
N: Number, HTN: hypertension, DM: diabetes mellitus, AF: atrial fibrillation, HCL: hypercholesterolemia, IS: ischemic stroke, TIA: transient ischemic attack, NIHSS: National Institutes of Health Stroke Scale, OTT: onset-to-treatment time, min: minutes, SBP: systolic blood pressure, DBP: diastolic blood pressure, Glu: glucose on admission, T: Tesla

eTable 3. Sensitivity analyses, after excluding the unpublished study data by Goyal et al.⁸

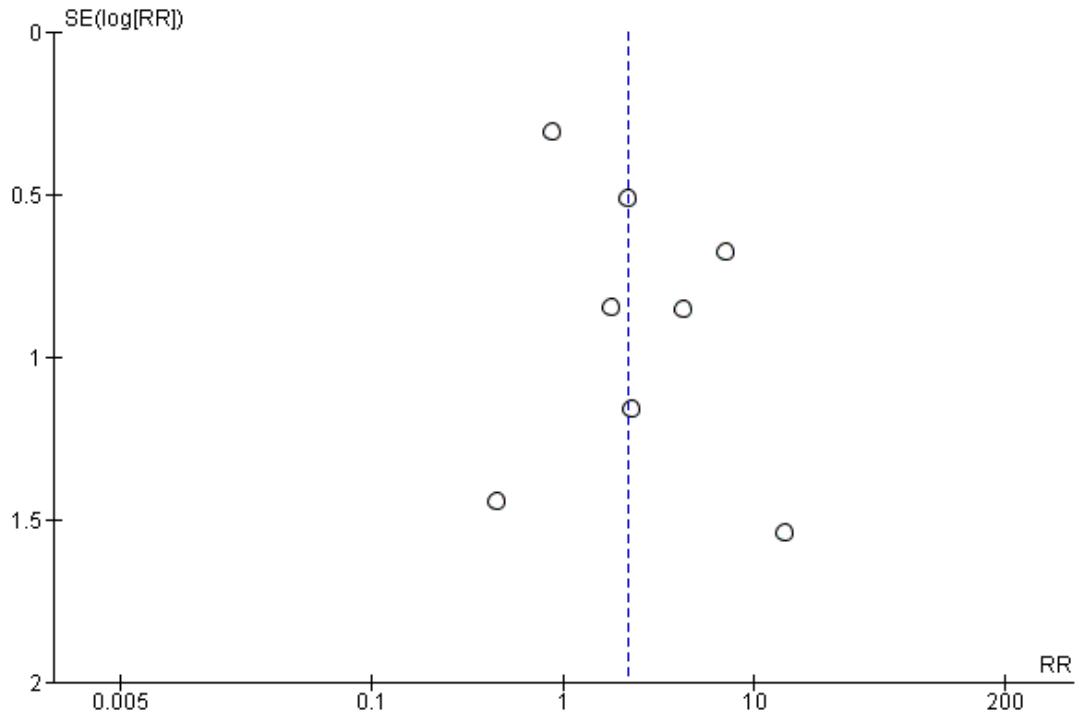
Analysis	All studies	After excluding data by Goyal et al⁸
risk of sICH following IVT in AIS patients with and without CMBs	RR=2.36 (1.21-4.61)	RR=2.17 (1.12-4.21)
risk of sICH following IVT in AIS patients with >10 CMBs compared to AIS patients with 0-10 CMBs	RR=12.10 (4.36-33.57)	RR=10.41 (3.20-33.87)
risk of sICH following IVT in AIS patients with >10 CMBs compared to AIS patients with 1-10 CMBs	RR=7.01 (3.20-15.38)	RR=7.32 (3.21-16.65)
Subgroup analysis on the risk of sICH following IVT in AIS patients with CMBs compared to AIS patients without CMBs, according to the imaging protocol used	RR=2.31 (1.02-5.24) (GRE) Subgroup difference: p=0.71	RR=2.04 (0.90-4.62) (GRE) Subgroup difference: p=0.63
Subgroup analysis on the risk of sICH following IVT in AIS patients with >10 CMBs compared to AIS patients with 1-10 CMBs, according to the imaging protocol used	RR=7.67 (3.38-17.38) (GRE) Subgroup difference: p=0.45	RR=8.11 (3.43-19.17) (GRE) Subgroup difference: p=0.43
Subgroup analysis on the risk of sICH following IVT in AIS patients with >10 CMBs compared to AIS patients with 0-10 CMBs, according to the imaging protocol used	RR=13.65 (4.36-42.75) (GRE) Subgroup difference: p=0.44	RR=11.72 (2.98-46.07) (GRE) Subgroup difference: p=0.52

sICH: symptomatic intracerebral hemorrhage, IVT: intravenous thrombolysis, AIS: acute ischemic stroke, CMB: cerebral microbleed, RR: risk ratio, GRE: gradient recalled echo magnetic resonance imaging

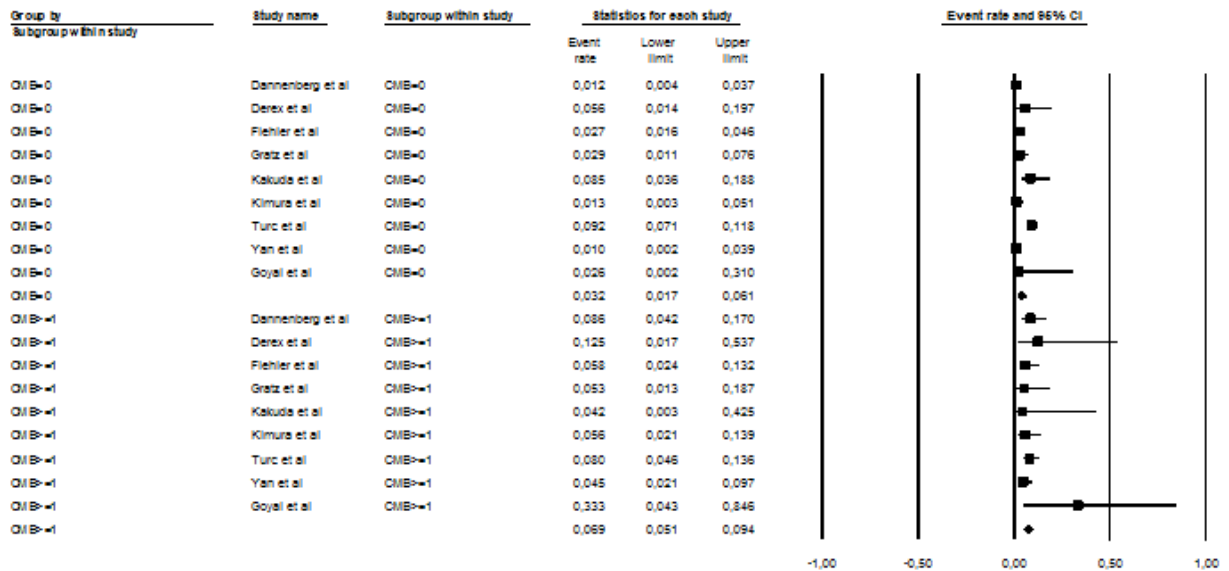
eFigure 1. Flow chart presenting the selection of eligible studies



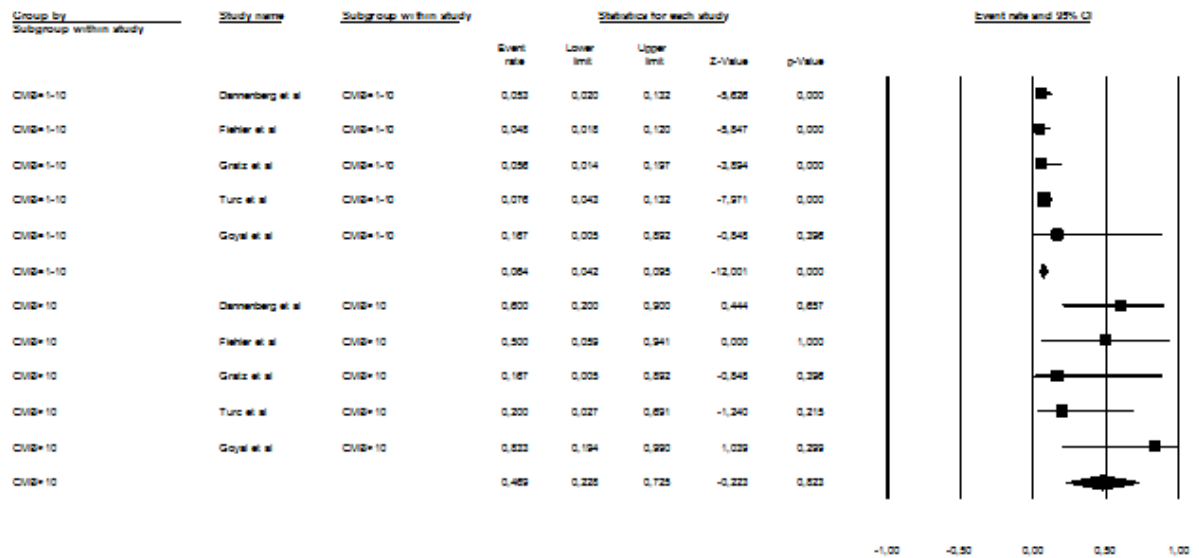
eFigure 2. Funnel plot of the included studies



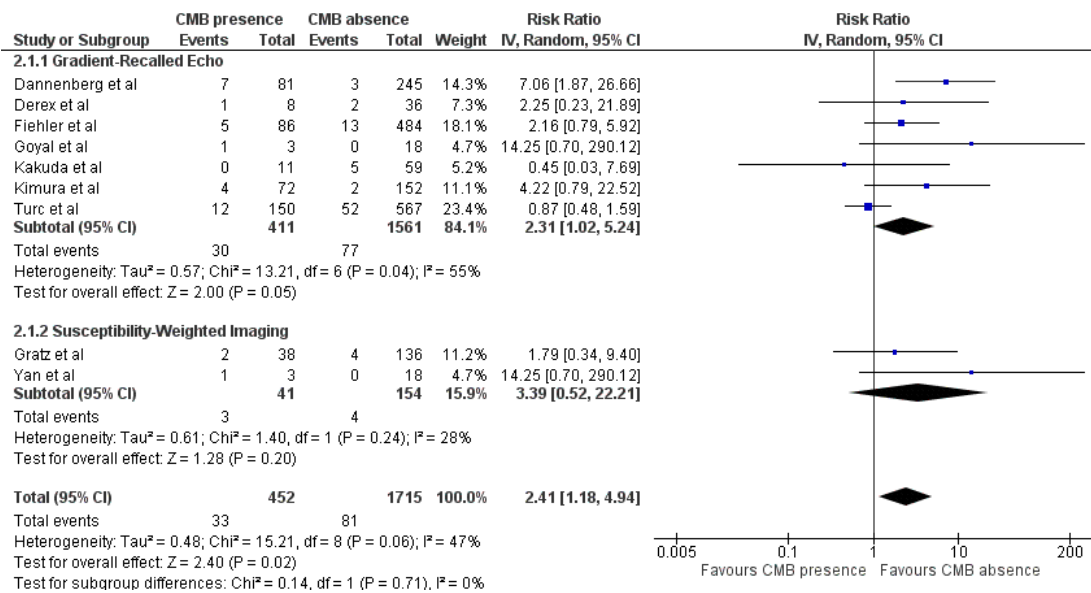
eFigure 3. Pooled incidence rates of symptomatic intracerebral hemorrhage for patients with cerebral microbleed absence and one or more cerebral microbleeds present on MRI screening before the administration of intravenous thrombolysis.



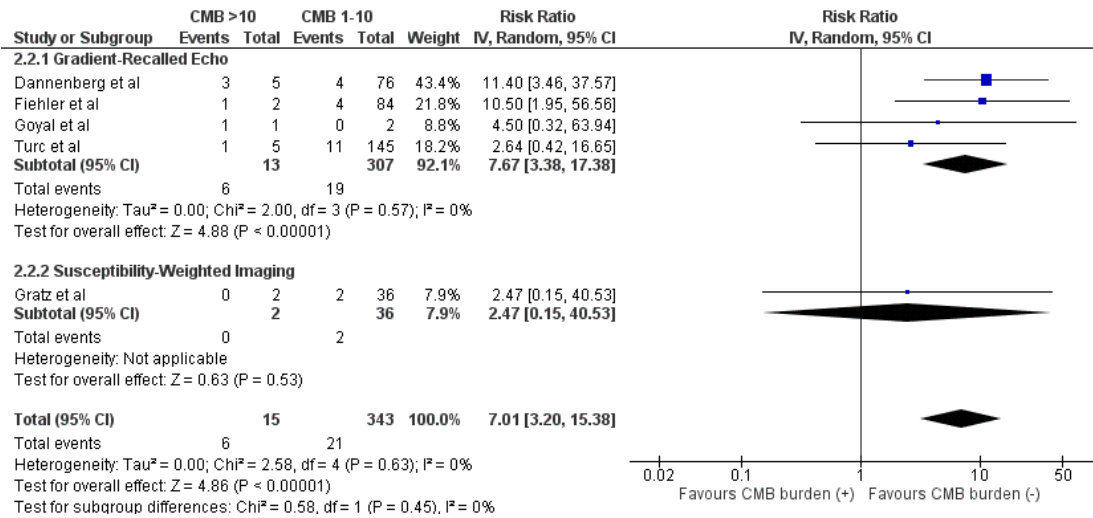
eFigure 4. Pooled incidence rates of symptomatic intracerebral hemorrhage for patients with low to moderate cerebral microbleed burden (1-10 cerebral microbleeds) and high cerebral microbleed burden (>10 cerebral microbleeds) present on MRI screening before the administration of intravenous thrombolysis.



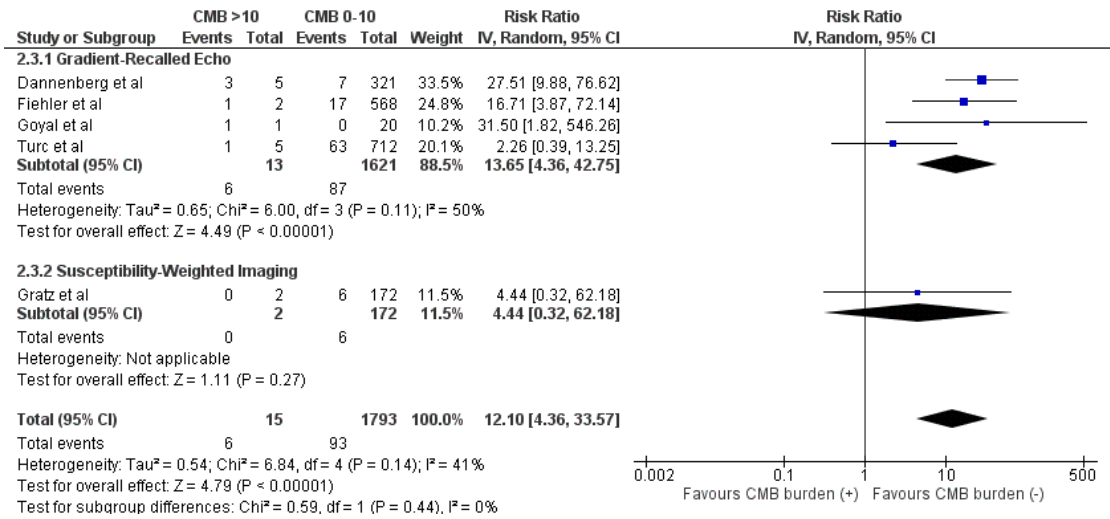
eFigure 5. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed presence when compared to patients with cerebral microbleed absence, according to the imaging protocol used for the detection of cerebral microbleeds.



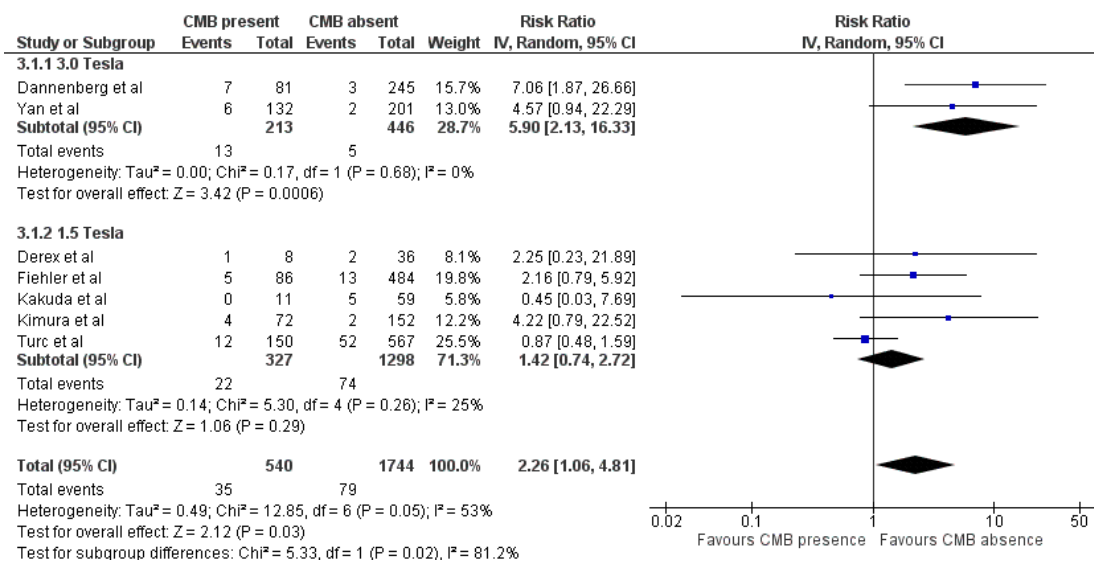
eFigure 6. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed burden (>10 cerebral microbleeds) when compared to patients with 1-10 cerebral microbleeds, according to the imaging protocol used for the detection of cerebral microbleeds.



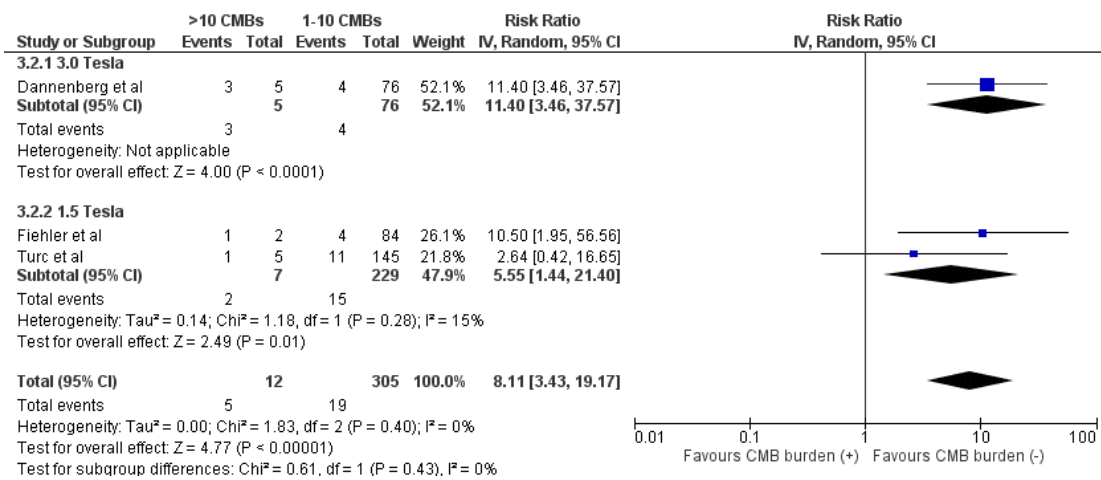
eFigure 7. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed burden (>10 cerebral microbleeds) when compared to patients with 0-10 cerebral microbleeds, according to the imaging protocol used for the detection of cerebral microbleeds.



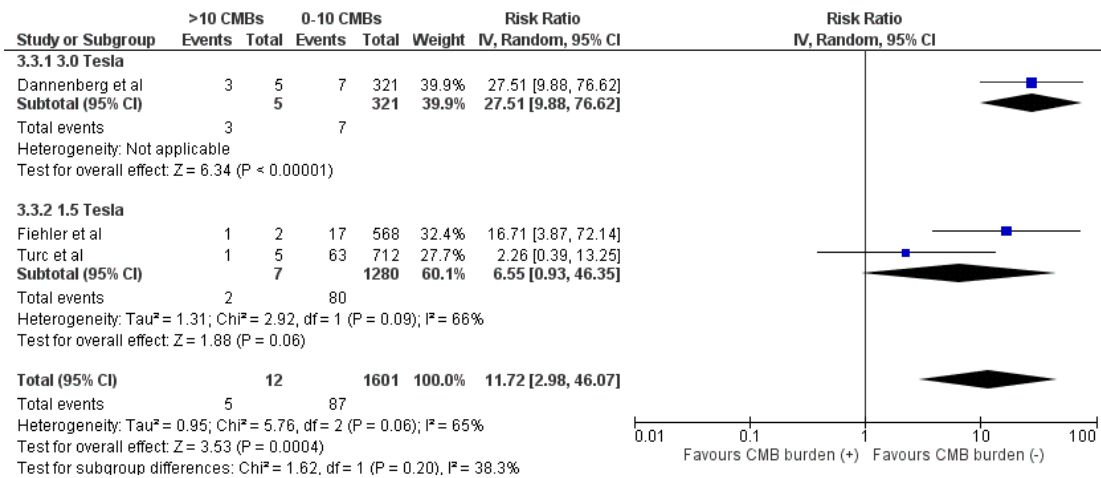
eFigure 8. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed presence when compared to patients with cerebral microbleed absence, according to the strength of the magnetic field used in the study protocols.



eFigure 9. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed burden (>10 cerebral microbleeds) when compared to patients with 1-10 cerebral microbleeds, according to the strength of the magnetic field used in the study protocols.



eFigure 10. Subgroup analysis on the risk of symptomatic intracranial hemorrhage following intravenous thrombolysis in acute ischemic stroke patients with evidence of cerebral microbleed burden (>10 cerebral microbleeds) when compared to patients with 0-10 cerebral microbleeds, according to the strength of the magnetic field used in the study protocols.



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