SUPPLEMENTAL MATERIAL

Carotid plaques with high-risk features in embolic stroke of undetermined source: systematic review and meta-analysis

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Contents

Table I: Search strategy

PUBMED		**Number of records**
#1	Stroke OR "transient ischemic attack"	325873
#2	plaque OR atherosclerosis	227905
#3	cryptogenic	6548
#4	#1 AND #2	14250
#5	#3 AND #4	142
Ovid EMBASE		**Number of records**
#1	Stroke.mp. or exp cerebrovascular accident/	464331
#2	transient ischemic attack.mp. or exp transient ischemic attack/	37720
#3	#1 OR #2	475310
#4	cryptogenic.mp.	10600
#5	#3 AND #4	3292
#6	exp atherosclerotic plaque/	31772
#7	#5 AND #6	46
#8	limit #7 to (human and English language)	39

Table II: Risk of bias assessment tool

Risk of bias item	**Response:** Yes = 1, No = 0
External validity	
1. Was the study target population a close representation of the national population (adults, children, or both) in relation to relevant variables? (no restriction on sex/race/profession/marital status or other criteria that would limit the diversity of the sample and therefore its representativeness and the generalizability of the result)	
2. Was the sampling frame a true or close representation of the target population as suggested by the study title and objectives? (e.g. patients presenting with anterior circulation cryptogenic stroke or embolic stroke of undetermined source)	
3. Was some form of random selection used to select the sample, OR, was a census undertaken? (census or consecutive/exhaustive sampling)	
4. Was the likelihood of non-participation bias minimal? (probability that investigators have failed to include subjects that would normally be eligible)	
Internal Validity	
5. Were data collected prospectively directly from the participants (as opposed to mere review of medical records or retrospective data collection)?	
6. Was the process of identifying patients with cryptogenic stroke appropriate and clearly described?	
7. Was the diagnostic method (brain imaging) used to identify high-risk carotid plaque clearly described (type of imaging, *eventually with sequences and qualification of the reader*)?	
8. Was the same assessment protocol used for all the participants?	
9. Were the results of the plaque imaging clearly presented? (adequate reporting of data within each category of lesion/patients + discrete categories/no overlapping + no errors requiring a guess/adjustments)	
10. Were the numerator(s) and denominator(s) for the calculation of the prevalence of high-risk plaque appropriate?	
Interpretation of the score 8 – 10: Low Risk of Bias / High-quality study. Further research is very unlikely to change our confidence in the estimate. 5 – 7: Moderate Risk of Bias / Moderate-quality study. Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. 4 or less: High Risk of Bias / Low-quality study. Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate. Further research is mandatory.	

Adapted from Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934-939, Copyright © 2012, with permission from Elsevier.

Table III: **Specific prevalence of the high-risk features reported in the included studies**

Risk feature	Number of studies*	Number of patients	Prevalence (95% CI) ‡		pooled OR (95% CI) †
			ipsilateral side	contralateral side	
intraplaque haemorrhage	5	162	24.4 (17.9 - 31.5)	0.6 (0.0 - 3.7)	9.4 (2.9 – 30.5)
echolucency	1	44	50.0 (35.8 - 64.2)	31.8 (20.0 - 46.6)	2.1 (0.9 - 5.1)
plaque thickness ≥ 3 mm	1	85	35.3 (26.0 - 45.9)	15.3 (9.2 - 24.4)	3.0 (1.4 - 6.3)
fibrous cap rupture	2	50	23.6 (12.4 - 36.7)	0.0 (0.0 - 3.7)	17.5 (2.2 – 140.1)
thrombus	3	94	6.9 (2.2 - 13.5)	0.0 (0.0 - 2.0)	5.8 (1.0 – 34.3)
ulceration	1	44	0.0 (0.0 - 8.0)	0.0 (0.0 - 8.0)	NA

*One study only provided aggregated data for the high-risk features considered: Bayer-Karpinska A, Schwarz F, Wollenweber FA, Poppert H, Boeckh-Behrens T, Becker A, et al. The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data. BMC Neurol. 2013;13:201.

† The prevalence and odds ratios were pooled using a random effect meta-analysis.

Figure I: Study selection

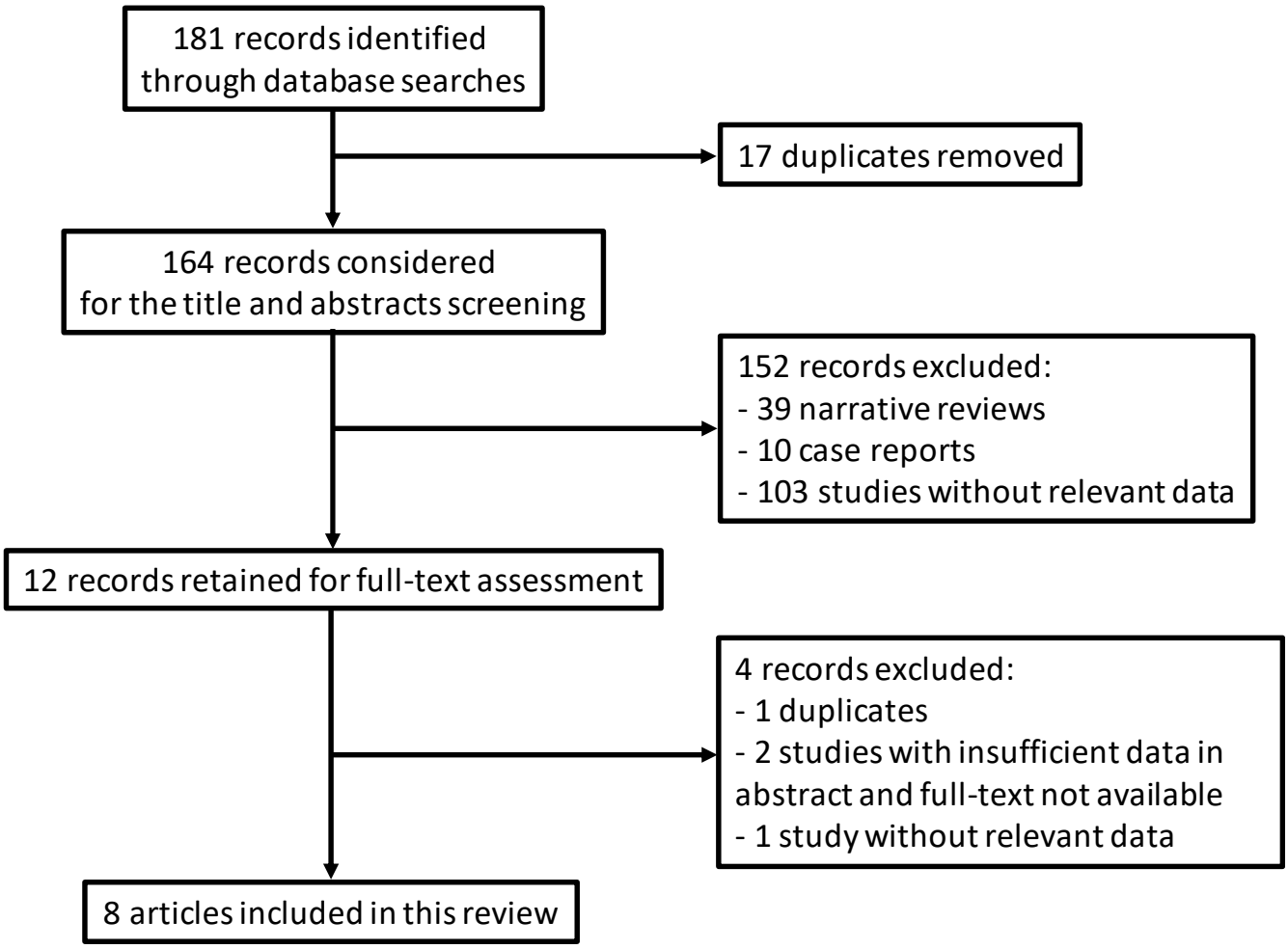
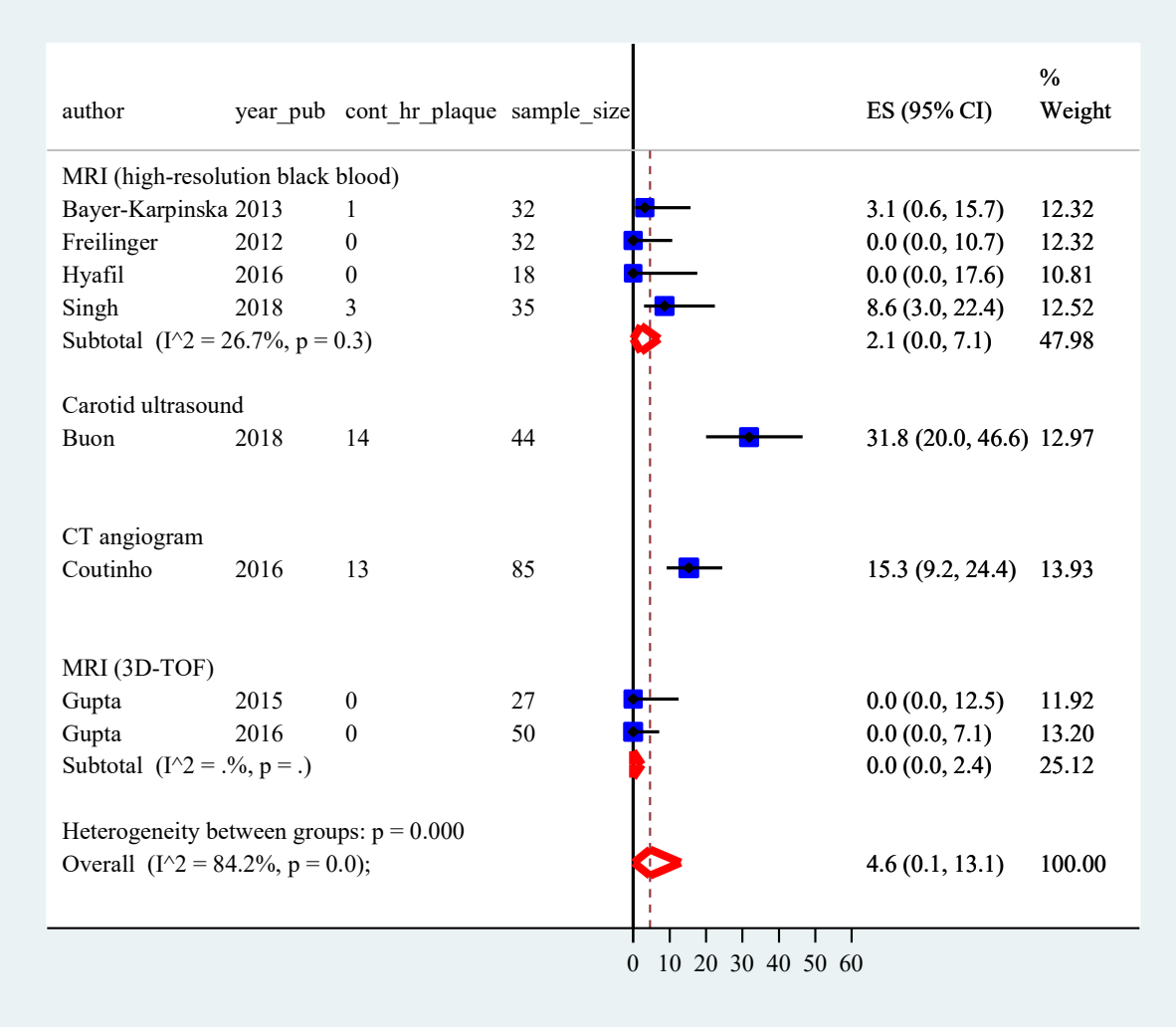
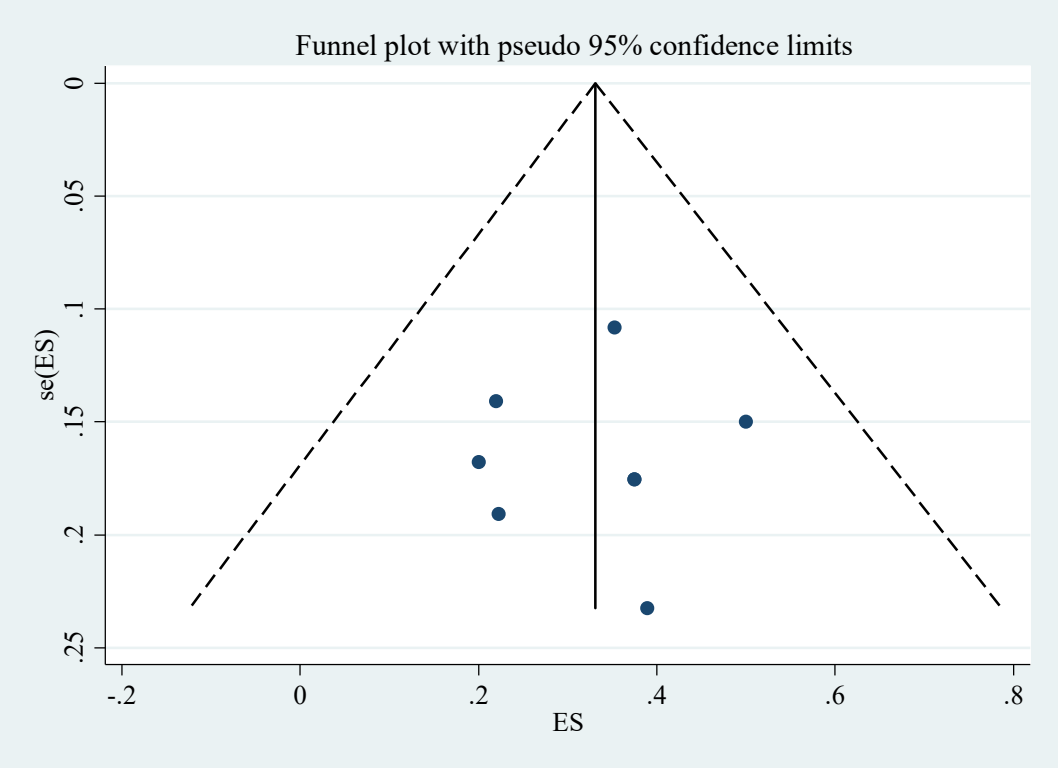


Figure II: Pooled prevalence of contralateral carotid plaque with high-risk features in ESUS



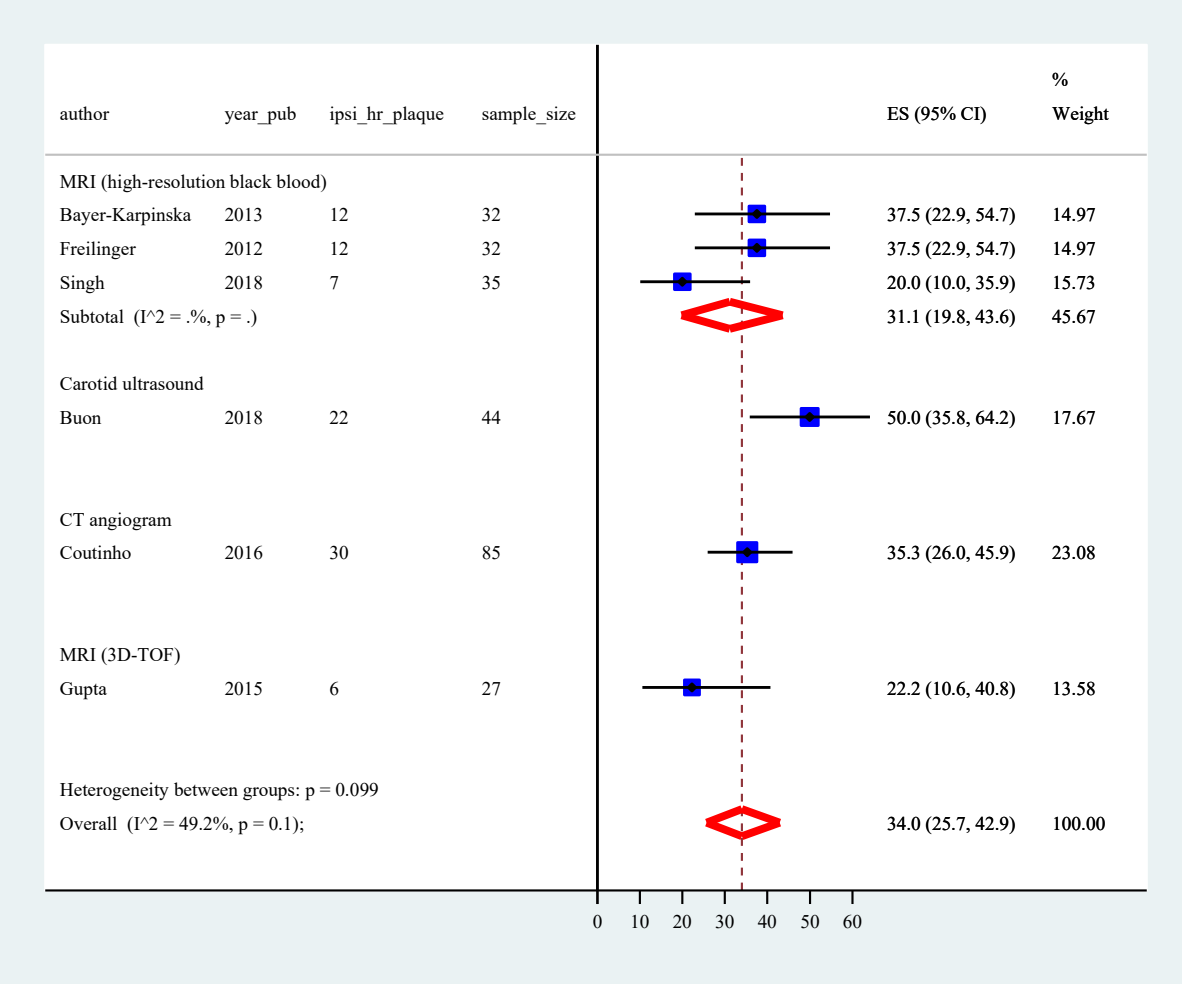
3D-TOF = 3-dimensional time of flight, CI = Confidence interval, CT = Computed tomography, cont_hr_plaque = contralateral carotid plaque with high-risk features, ES = Effect size, MRI = Magnetic resonance imaging, sample_size = number of participants in the study, year_pub = year of publication

Figure III: Funnel plot for the meta-analysis of prevalence of ipsilateral carotid plaque with high-risk features in ESUS



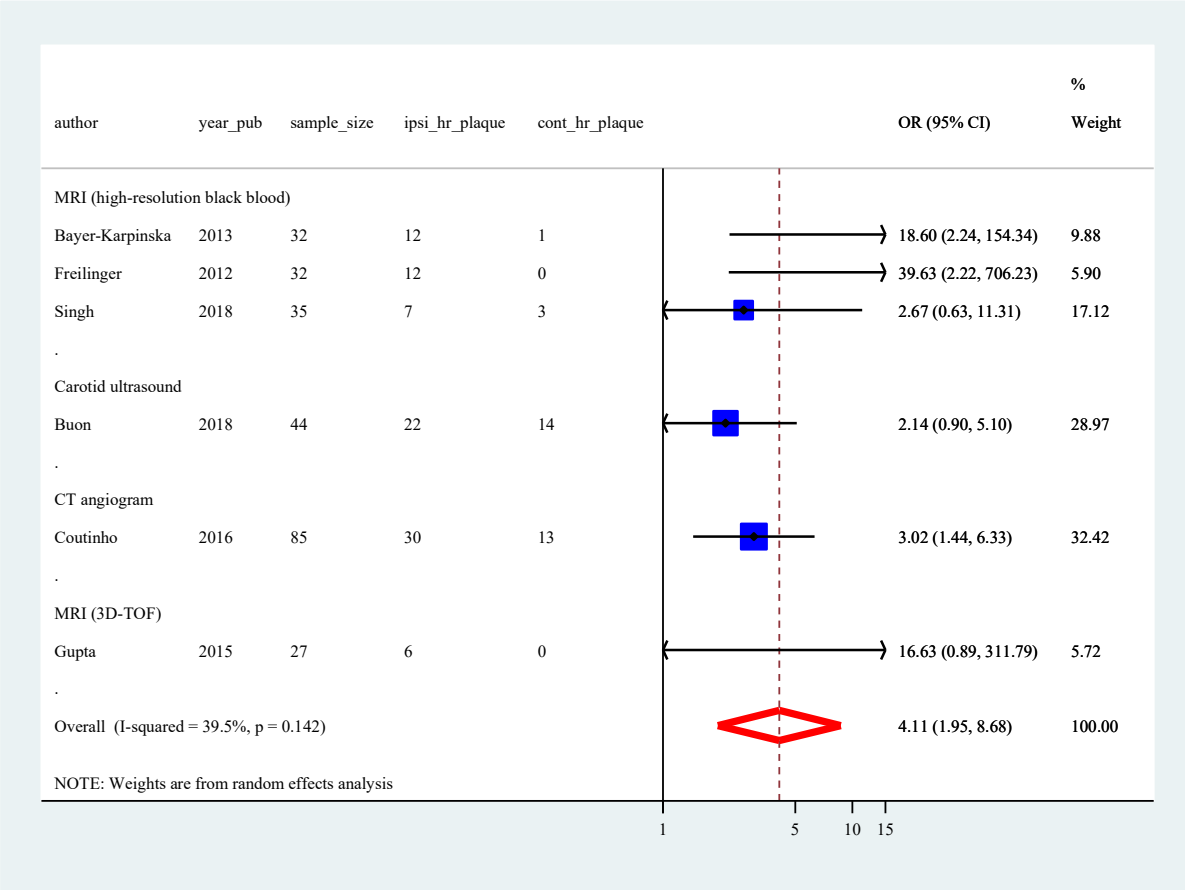
ES = Effect size (prevalence), se (ES) = standard error of effect size
The symmetric distribution of the studies (blue dots) around the average effect size (black vertical line, x = 0.325) supports the absence of small-study effect as confirmed by the Egger's test (p = 0.876). There are only 7 blue dots (instead of 8) because two studies have the same sample size and the same effect size (see Figure 1).

Figure IV: Pooled prevalence of ipsilateral carotid plaque with high-risk features in ESUS after excluding studies with sample size < 20 or with potential population overlap.



3D-TOF = 3-dimensional time of flight, CI = Confidence interval, CT = Computed tomography, ES = Effect size, ipsi_hr_plaque = ipsilateral carotid plaque with high-risk features, MRI = Magnetic resonance imaging, sample_size = number of participants in the study, year_pub = year of publication

Figure V: Odds-ratio of finding plaque with high-risk features in the ipsilateral versus the contralateral carotid in ESUS after excluding studies with sample size < 20 or with potential population overlap.



3D-TOF = 3-dimensional time of flight, CI = Confidence interval, CT = Computed tomography, cont_hr_plaque = contralateral carotid plaque with high-risk features, ipsi_hr_plaque = ipsilateral carotid plaque with high-risk features, MRI = Magnetic resonance imaging, OR = Odds ratio, sample_size = number of participants in the study, year_pub = year of publication