Validation of the ability of ESER score to predict recurrent stroke: a meta-analysis

Type

Research paper

Keywords

meta-analysis, ischaemic stroke, recurrent stroke, risk prediction, ESER

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Introduction
A risk stratification model is pretty important to prevent the recurrent stroke for ischemic stroke patients. The present study aimed to meta-analysis the ability of Essen Stroke Risk Score (ESRS) to accurately predict recurrence of ischemic stroke.

Material and methods
Studies on the diagnostic performance of Essen Stroke Risk Score in predicting recurrent stroke were searched by electronic and manual methods. Quality pooled C-statistics, and 95% confidence intervals (95% CI) were evaluated.

Results
Fifteen studies with a total of 94,052 patients were included in the meta-analysis. The pooled C-statistics of ESER for patients without atrial fibrillation (AF) experiencing recurring strokes at 90-day or one-year were 0.65 (95% CI: 0.58-0.73) and 0.57 (95% CI: 0.53-0.60), and the heterogeneity was weak. The average ratio of one-year recurrent stroke in the low-risk and high-risk groups classified according to ESRS is 5.6%(range 1.4 to 12.1%) and 9.2%(range 3.2 to 20.1%), respectively. And the calibration analysis showed the pooled RR in the low-risk group is 0.88 (95%CI: 0.24-3.19) and 0.88 (0.24-3.31) with wide confidence intervals and high levels of heterogeneity, indicating the calibration ability was low.

Conclusions
ESRS had low to moderate ability to predict recurrence of stroke in patients with ischemic stroke and low calibration ability, which need to be further improved.

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Key words: ESRS; Ischaemic stroke; Meta-analysis; Recurrent stroke; Risk prediction

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Introduction

Stroke is a disabling disease that imposes social burdens. Patients who have experienced cerebral ischemic events are at high risk for recurrent stroke[1,2,3]. Since the introduction of antihypertensive, lipid lowering, and antiplatelet therapies over 20 years ago, the rate of recurrence has been declining [4,5]. Therefore, identifying those at highest risk should help to optimize secondary prevention, So an effective risk stratification model for recurrent stroke is essential for ischemic stroke patients.

The Essen Stroke Risk Score (ESRS) was developed for use in the CAPRIE study and validated externally[6,7], and is now widely used in clinical practice. The ESRS takes into account predictors such as age, hypertension, diabetes mellitus, previous myocardial infarction (MI), other cardiovascular diseases, atrial fibrillation (AF), peripheral artery disease (PAD), smoking, and previous TIA or stroke. The ESRS identifies two risk categories: low (score 0–2) and high (score 3 or greater). Many studies have demonstrated the capability of the ESRS to predict recurrent stroke in ischemic stroke patients[8,9,10].

However, studies on the effectiveness of the ESRS were restricted with differences in study endpoint, follow-up time, region, and populations, and demonstrated that the ESRS had different predictive accuracy in different situations. Therefore, the scope and predictive ability of ESRS needs further research. The aim of our meta-analysis was to determine the accuracy of ESRS for predicting recurrent stroke in ischemic stroke patients.

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Methods

Study selection

Inclusion criteria were: i) research aimed at the predictive or calibration abilities of the ESRS scoring system; ii) cohort study; iii) patients with ischemic stroke; v) primary endpoint was recurrent stroke; and vi) C-statistics and 95% confidence intervals were available.

Exclusion criteria were: i) patients had cardioembolic stroke aetiology; ii) primary endpoint was cardiovascular event; iii) study focused on self-evaluation of the ESRS; iv) paper was a review or repeated data; and v) data were incomplete and the researchers could not be contacted.

Literature search

We searched the Cochrane Library Search databases, PubMed and Embase for studies published between January 1, 2009 and March 30, 2019 using the key words “ESRS” or “Essen stroke risk score”.

Data extraction and quality assessment

The quality of selected studies was independently assessed by two researchers. Any disagreements were resolved by consensus or another reviewer. The quality assessment was based on the method proposed by McGinn et al.[11]. The basic line of included studies, the C-statistics, and 95% CIs were collected. C-statistics revealed the score’s ability to discriminate between experimental variables; a C-statistic > 0.5 was considered statistically significant; a score of 0.5–0.7 = low value, 0.7–0.9 = medium, and > 0.9 = high[12,13]. We then summarized the number of recurrent strokes in different risk stratifications as categorized by ESRS.

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Consistency test

The heterogeneity between the studies was examined by the I^2 value; I^2 < 25% means low heterogeneity, 25–50% means intermediate, and > 50% means high. A fixed effects model was applied when two or more studies showed homogeneity (I^2 < 50%), otherwise, a random effects model was used, the Consistency test based on the method proposed by Wang L et al[14]. Consistency testing was performed by STATA 15.1 software.

Discrimination of ESRS

STATA 15.1 was performed to pooled the C-statistics of the ESRS scores. 90-day, one-year and five-year follow-up results were analyzed.

Calibration of the ESRS

The observed number of recurrent strokes in different ESRS stratifications in the selected studies were compared to the predicted number. The predicted number of recurrent strokes for each stratum was calculated by the observed number of each stratum of the validation study, multiplied by the recurrent stroke risk rate which derived in the original ESRS trial. Result is presented as relative risk(RR) with a 95% CI for each stratum of the ESRS score. RR= 1 indicates a good calibration between the observed and predicted result, RR >1 indicates the ESRS under-predicts the risk of endpoint, RR < 1 indicates the ESRS over-predicts the risk of endpoint[15]. Calibration analysis was performed by Review Manager 5.2 software (Oxford, England).

A sensitivity analysis was performed by comparing the fixed and random effects models. The degree of asymmetry was tested by an Egger's test to evaluate the publication bias.

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Results

Literature selection

135 articles were initially selected, 32 publications were remained after screening for titles and abstracts. 15 of these 32 articles were included after reviewing the full-text (Figure 1). Tables 1 & 2 show the basic information and quality assessment of included studies.

Predicting ability

Table 3 summarized of C-statistics for different study populations and follow-up times. The heterogeneity test showed I^2 in most of the groups was < 50% (Table 4). The pooled C-statistic of ESER or 90-day and one-year recurrent stroke for patients without atrial fibrillation (AF) were 0.65 (95% CI: 0.58-0.73) and 0.57 (95% CI: 0.53-0.60), respectively. For studies including patients with AF, the pooled C-statistics of ESER score for 90-day and one-year recurrent stroke were 0.56 (95% confidence interval [CI]: 0.48-0.64 and 0.61 (95% CI: 0.59- 0.63). The one-year pooled C-statistic of ESRS scores in studies excluding AF was similar to that of studies including AF (P=0.07)

Calibration ability

For studies without patients with AF, the average ratio of one-year recurrent stroke in the low-risk and high-risk group based on ESRS was 5.6% (ranging from 3.1 - 12.4%) and 9.2% (from 3.2 - 20.1%), which were similar to the figures in the original ESRS study. In studies without AF, the average ratio of recurrent stroke based on ESRS score stratum was similar to studies containing AF. The calibration analysis result showed ESER did not significantly under

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or overestimate the observed risk of one-year recurrent stroke in each stratum; the pooled RR in the low-risk group is 0.88 (95%CI: 0.24-3.19) and 0.88 (0.24-3.31) for the high-risk group (RR=0.88, P > 0.05) (Figure 2). However, the results should be interpreted cautiously due to wide confidence intervals of the RRs value and high levels of heterogeneity.

Sensitivity and bias analysis

The fixed and random effects models in each group showed similar results without significant differences (data not shown), which meant good stability. Egger's tests showed there was no publication bias (Table 3).

Discussion

Predictive capability of ESRS

Recurrent stroke is an independent risk factor for poor prognosis[25]. In order to reduce recurrence of strokes, it is necessary to identify high-risk patients and make appropriate therapeutic decisions. At present, many clinical scoring models, including ESRS, ABCD2 and Stroke Prognosis Instrument SPI-II, are used to assess the risk of recurrence. ABCD2 has shown good predictive ability for recurrent stroke in the short-term for TIA patients[26,27]. Compared with ABCD2，ESER is more easy to calculate and more widely apply in clinical practices, for which do not consist any of imaging data such as brain MRI or carotid ultrasound. The components of SPI-II risk score are similar to ESER, but SPI-II is mainly aimed at predicting recurrent stroke or death within two-years in stroke patients, ESRS is primarily used to predict in one-year follow up[28,29,30]. However, our analysis showed ESRS score was capable of predicting recurrent stroke, but the pooled C-statistics for one-year recurrence was 0.57, indicating low accuracy. In addition, we found that the ESRS was more accurate at the 90-day

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follow-up compared to one-year follow-up, possibly because recurrent stroke occurred more in the first 90 days follow-up.

However, because there are too many potential confounding factors, the predictive ability of a score model based on clinical characteristics will not be highly accurate. Ling et al. reported that by including points for hypertension>15 years, diabetes>10 years, IS/TIA, and the stroke subtype by large artery atherosclerosis, the ability of the original ESRS to predict recurrent stroke within one year was improved; C-statistics of ESRS and modified ESRS were 0.58 and 0.70[24]. Stahrenberg et al. showed that hsTropT increased the C-statistic of ESRS score from 0.695 (ESRS) to 0.747 (ESRS+hsTropT) in patients with acute cerebral ischemia[31]. Sumi et al. showed it could improve the discriminatory ability of the modified ESRS by adding a few more variables such as gender, waist circumference, and stroke subtype[17]. However, it is suitable to incorporate too many clinical factors into a scoring system, otherwise, it is too complicated to use widely in clinical practice.

Atrial fibrillation (AF) was not included in the original ESRS and it is recommended patients with AF not use ESRS to predict recurrence[6]. However, we found that the one-year pooled C-statistic of ESRS score in studies without AF was even slightly higher than that of studies containing AF, which meant some patients in the study had AF and some did not have AF. The average incidence of recurrence in ESRS score stratum in studies excluding patients with AF was similar to that of studies containing patients with AF. Previous studies have shown that atrial fibrillation has not been identified as an independent risk factor [32,33], so we believe that the ESRS system may be extended to stroke patients with a history of AF.

Calibration capability of ESRS score

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A excellent score model not only shows good predictive ability, but also good calibration ability, which means the predictive result can be repeated. The present study showed that the scope of prevalence of one-year recurrent stroke in included studies without AF was a wide of range, specially the incidence in Meng 2010' study was significantly higher than Weimar 2009' and Chen 2016' study. For the reason that, Meng 2010' study was carried out in China, in contrast that Weimar 2009' study validated in western population. It has been proved that the overall proportion of ischemic stroke appeared higher in Chinese than white populations owing to race and region[34]. In other way, Chen 2016' study also came from China, but which focused on outpatients in Beijing(capital of China), so the incidence was lower than Meng 2010' study owing to social, economic and environmental conditions[35].The incidence of recurrence in one-year follow-up ranged from 3.1 - 12.4% for the low-risk ESRS score group and 3.2 - 20.1% for the high-risk group. However, our results showed the incidence of the endpoints by ESRS score increased with the risk stratification in each included study. The calibration analysis showed a certain calibration accuracy between the predicted and observed rate of recurrence in each risk strata of the ESRS score. However, the calibration analysis also showed wide confidence intervals of the pooled RRs and high levels of heterogeneity between the included studies, so the results should be interpreted cautiously.

Limitations

Firstly, most of the included studies were retrospective (although original data were acquired prospectively), and many selected studies failed to specify whether blinding procedure was taken appropriately. Secondly, the total numbers of the included studies are low and the analysis of calibration capability showed high levels of heterogeneity, so the results of calibrating ability

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should be interpreted very cautiously. A large-scale prospective research focusing on calibration ability is thus warranted.

Conclusion

Our results demonstrated that ESRS had minimal discrimination ability in predicting recurrent stroke in patients with ischemic stroke and it seemed the ESRS was also suitable to predict for patients with AF. The calibration ability of ESRS needs further verification.

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Disclosure statement

The authors declare no conflict of interest.

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Not applicable.

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Figure legend

Figure 1. Flow diagram of the process of study selection.

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Figure 2. The forest plot of the calibration analysis

Note: RR = 1 indicates a good calibration between the observed and predicted result. A relative risk (RR) >1 indicates the ESRS under-predicts the risk of endpoint, RR < 1 indicates the ESRS over-predicts the risk of endpoint.

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Table 1. The basic characteristics of included studies

Study	Country or region	Type of study P/R	Data original	Sample size	Age (yr)	Males (%)	Follow-up time	Endpoint	Excluding AF	randomized	Population
Weimar 2008[7]	Germany	P	SCALA	852	67.1	57	17.5 m	RS	No	No	IS /TIA
Weimar 2009[8]	Germany	P	REACH	15605	68.9	59.6	1 yr	RS	No	No	IS /TIA
Weimar 2010[9]	Germany	P	-	1897	56	67.7	1 yr	RS	No	No	IS/TIA
Fitzek 2010[13]	Germany	P	-	730	73.1	49.1	1 yr	RS	No	No	IS /TIA
Ay 2010 [14]	USA	R	-	1458	72-74	53.7	90 d	RS	No	No	IS /TIA
Chandrathera 2011 [15]	UK	R	Oxford vascular study	1247	73	54	90 d	RS	Yes	No	IS /TIA
Meng 2011[16]	China	P	CNSR	11384	-	63.4	1 yr	RS	Yes	No	IS /TIA
Sumi 2012 [17]	Japan	P	EVEREST registry	3292	70-71	67.2	1 yr	RS	No	No	IS
Weimar 2012 [18]	Germany	P	INSIGHT	1163	66.3	57.5	13 m	RS	No	No	IS /TIA
Liu 2013 [19]	China	P	CHANCE	167	61.1	71.3	90 d	RS	Yes	No	minor IS / TIA
Andersen 2015[20]	Danish	R	Nationwide Danish cohort	42182	70.1	54.3	1yr,5yr	RS	Yes	No	IS /TIA
Chen 2016[21]	China	P	ROOTS	3316	64.8	59.6	3,6,12 m	RS	Yes	No	IS/TIA(outpatients)
Liu 2017 [22]	China	P	BOSS	1699	62	69.2	1 yr	RS	Yes	No	IS
Li 2017[23]	China	P	CNSR	8287	63.2	63.1	1 yr	RS	No	No	IS /TIA
Ling 2018 [24]	China	P	-	773	66	69.7	1 yr	RS	No	No	IS

Abbreviations: RS=recurrent stroke; IS=ischemic stroke; TIA= transient ischemic attack; AF=atrial fibrillation;NA = not available; P = prospective; R = retrospective;

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Table 2. Quality assessment of all included studies

Study	Q1	Q2	Q3	Q4	Q5
Weimar et al. 2008[7]	Y	N	Y	Y	U
Weimar et al 2009[8]	Y	N	Y	Y	U
Weimar et al 2010[9]	Y	N	Y	Y	U
Fitzek et al 2010[13]	Y	N	Y	Y	U
Ay et al 2010 [14]	Y	N	Y	U	U
Chandrathera 2011 [15]	Y	N	Y	U	U
Meng et al 2011[16]	Y	N	Y	Y	U
Sumi et al 2012 [17]	Y	N	Y	Y	U
Weimar et al 2012 [18]	Y	N	Y	Y	U
Liu et al 2013 [19]	N	N	U	Y	U
Andersen et al 2015[20]	Y	N	Y	U	U
Chen et al 2016[21]	N	N	Y	Y	U
Liu et al 2017 [22]	Y	N	N	Y	U
Li et al 2017[23]	Y	N	Y	Y	U
Ling et al 2018 [24]	Y	N	Y	Y	U

Note: Q1: Did the included patients have different disease severities?

Q2: Did the patient selection process exhibit bias? Internal authenticity

Q3: Was the dropout rate lower than 20%?

Q4: Was the predictor to be evaluated blinded to the endpoint events?

Q5: Were the endpoint events blinded to predictors?

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Y: Yes; N: No; U: unclear.

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Table 3. Pooled C-statistics of ESSR score according to ninety-day and one-year follow-up time

Follow-up time	Study	ESSR
Ninety-day recurrent stroke with patient excluding AF	Liu 2013[19]	0.68(0.56-0.80)
	Chen 2016[21]	0.63(0.53-0.72)
	Pooled C-statistic	**0.65(0.58-0.73)**
Ninety-day recurrent stroke with patient including AF	Ay 2010[14]	0.59 (0.53-0.66)
	Chandrathera 2011[15]	0.51(0.42-0.59)
	Pooled C-statistic	**0.56(0.48-0.64)**
One-year recurrent stroke With patient excluding AF	Weimar 2009[8]	0.56(0.53-0.58)
	Meng 2011[16]	0.60(0.57-0.61)
	Andersen 2015[20]	0.54(0.53 – 0.55)
	Liu 2017[22]	0.58(0.52-0.64)
	Pooled C-statistic	**0.57(0.53-0.60)**
One-year recurrent stroke With patient including AF	Fitzek 2010[13]	0.59(NA)
	Weimar 2010[9]	0.62(0.57-0.67)
	Sumi 2012[17]	0.60(0.55-0.65)
	Weimar 2012[18]	0.62(0.59-0.65)
	Chen 2016[21]	0.62(0.56-0.68)
	Li 2017[23]	0.57(NA)
	Ling 2018[24]	0.58(0.54-0.61)
	Pooled C-statistic	**0.61(0.59- 0.63)**
17.5 months recurrent stroke	Weimar 2008[7]	0.56
Five-year recurrent stroke	Andersen 2015[20]	0.56 (0.55–0.57)

Abbreviations: ESRS= the Essen stroke risk score, AF=atrial fibrillation, CI = confidence interval NA=not available.

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Table 4. Meta-analysis of the discrimination ability of ESRS scores

Endpoint time	Pooled C-statictis (95% CI)	No.	Heterogeneity test			Egger's test	
			χ^2	*P*	I^2 (%)	Bias	*P*
Ninety-day recurrent stroke with AF exclusion	0.65(0.58-0.73)	2	0.41	0.52	0.00	5.95	-
Ninety-day recurrent stroke with AF inclusion	0.56(0.48-0.64)	2	1.99	0.158	49.8	-4.73	-
One-year recurrent stroke with AF exclusion	0.57(0.53-0.60)	4	29.54	0.00	89.80*	3.14	0.43
One-year recurrent stroke with AF inclusion	0.61(0.59- 0.63)	7	3.4	0.49	0.00	-0.047	0.98

Abbreviations: ESRS= the Essen stroke risk score, AF=atrial fibrillation, CI = confidence interval;

*Note: *：a random effects model was applied（I^2>50%）*

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Table 5. Recurrent stroke events in ninety-day and one-year follow-up for ischaemic stroke with or without AF, n (%)

Follow-up time	Study	Patient(%)	
		Low risk	High risk
Ninety-day recurrent stroke	Ay 2010[14]	39/1316 (1.3)	21/142 (17.9)
	Chandrathera 2011[15]	21/236 (1.6)	28/284 (2.5)
	Liu 2013[19]	4/61(6.6)	17/106(16.0)
	Average (%)	3.1	12.1
One-year recurrent stroke With patient with AF exclusion	Weimar 2009[8]	142/4556(3.1)	482/11049(4.4)
	Meng 2011[16]	727/5845(12.4)	1112/5539(20.1)
	Chen 2016[21]	18/1326(1.4)	64/1990(3.2)
	Average.	5.6	9.2
One-year recurrent stroke With patient including AF	Weimar 2008[7]	11/296(3.7)	28/404(6.9)
	Weimar 2010[9]	33/947(3.5)	74/950(7.8)
	Fitzek 2010[13]	19/269(7.1)	57/454(12.6)
	Weimar 2012[18]	27/500(5.4)	31/356(8.7)
	Average (%)	4.9	9.0

Abbreviations: AF= atrial fibrillation

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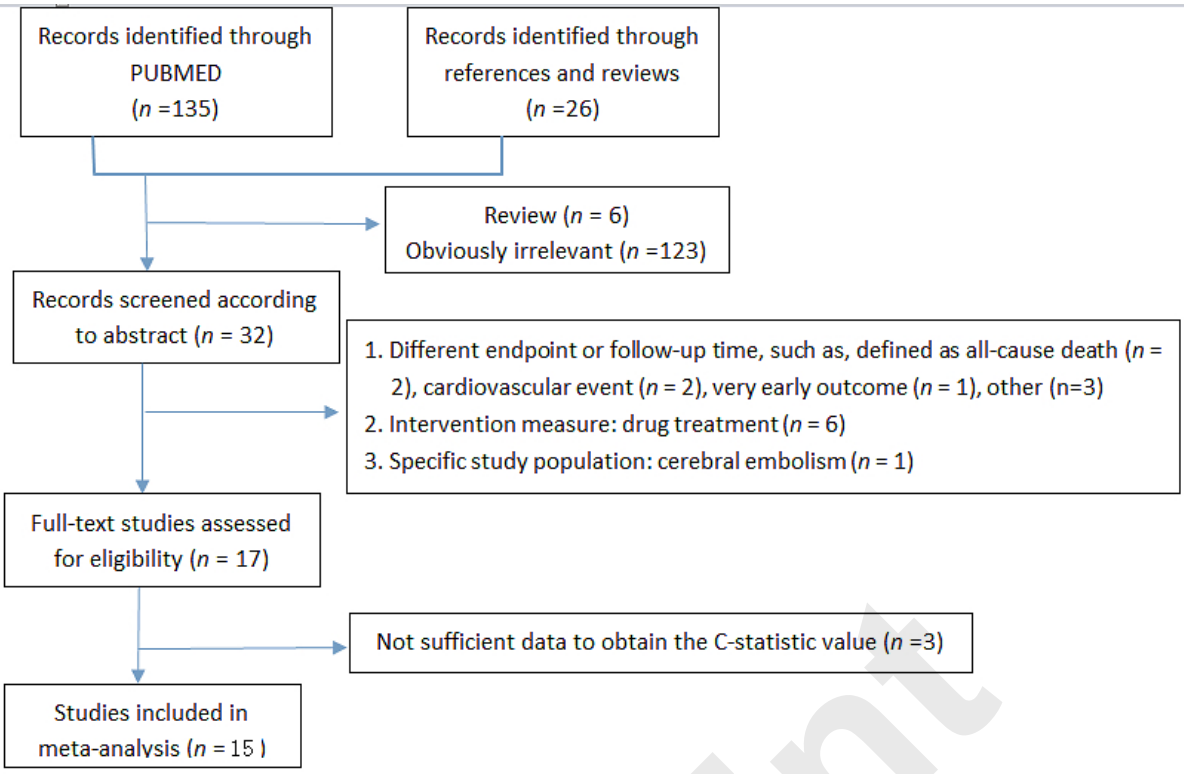
Records identified through PUBMED (n =135)
Records identified through references and reviews (n =26)
Review (n = 6)
Obviously irrelevant (n =123)
Records screened according to abstract (n = 32)
1. Different endpoint or follow-up time, such as, defined as all-cause death (n = 2), cardiovascular event (n = 2), very early outcome (n = 1), other (n=3)
2. Intervention measure: drug treatment (n = 6)
3. Specific study population: cerebral embolism (n = 1)
Full-text studies assessed for eligibility (n = 17)
Not sufficient data to obtain the C-statistic value (n =3)
Studies included in meta-analysis (n = 15)

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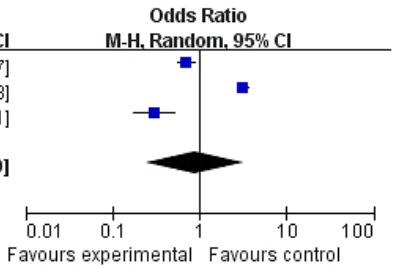
low risk strata

Study or Subgroup	observed Events	Total	predictived Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2016	142	4556	200	4556	33.8%	0.70 [0.56, 0.87]
Meng 2011	727	5845	257	5845	34.0%	3.09 [2.67, 3.58]
Wermar 2009	18	1326	58	1326	32.2%	0.30 [0.18, 0.51]
Total (95% CI)		**11727**		**11727**	**100.0%**	**0.88 [0.24, 3.19]**
Total events	887		515			

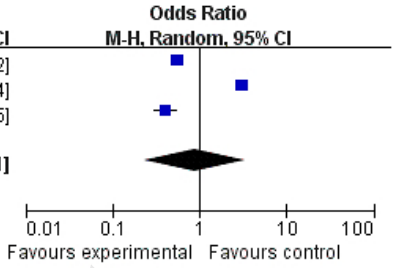
Heterogeneity: Tau² = 1.26; Chi² = 165.90, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.19 (P = 0.85)



High risk strata

Study or Subgroup	observed Events	Total	predictived Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2016	482	11049	840	11049	33.5%	0.55 [0.49, 0.62]
Meng 2011	1112	5539	421	5539	33.5%	3.05 [2.71, 3.44]
Wermar 2009	64	1990	151	1990	33.0%	0.40 [0.30, 0.55]
Total (95% CI)		**18578**		**18578**	**100.0%**	**0.88 [0.24, 3.31]**
Total events	1658		1412			

Heterogeneity: Tau² = 1.35; Chi² = 458.97, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.18 (P = 0.86)



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