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Review Article

CT perfusion guided intravenous thrombolytic therapy for acute ischemic stroke: a systematic review and meta-analysis

Jiantong Shen[1*], Xiaodong Wang[2*], Guihua Tian[3], Xianglian Li[4], Fang Fu[5], Xuhui Shen[1], Jinlan Yao[1], Peng Qiao[1]

[1]School of Medicine, Huzhou University, Huzhou Central Hospital, 759 Erhuan Rd, Huzhou 313000, Zhejiang, PR China; [2]Institute of Hospital Management, West China Hospital, Sichuan University, Chengdu 610041, PR China; [3]Dongzhimen Hospital Beijing University of Chinese Medicine, Beijing 100700, PR China; [4]Nephrology Department, Chengdu Military General Hospital, Chengdu 610083, PR China; [5]Ophthalmology Department, Chengdu Aviation Medical Center, Chengdu 610202, PR China. [*]Co-first authors.

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Abstract: Background: The effectiveness of CT perfusion guided to select acute ischemic stroke patients who are eligible for thrombolytic therapy is unclear. This meta-analysis studied the effect of CT perfusion guided intravenous thrombolytic therapy for acute ischemic stroke on clinical outcomes. Methods: PubMed, EMBASE, CENTRAL, Cochrane Library, Health Technology Assessment database were searched in June 2017 and screened reference lists of included studies. The Mantel-Haenszel method were used in pooled Odds Ratio of favorable outcome, which were used random effects model, while the SICH, ICH and mortality data were pooled by using Peto's methods. Additionally, the random effects model was used in pooled adjusted estimates. Results: Eight experimental and observational studies with 9900 samples were included. The pooled OR of favorable outcome (mRS score ≤ 2) in patients who received CTP guided thrombolysis versus time guided thrombolysis was 1.12 (95% CI, 0.79-1.58). The pooled Peto ORs of SICH, ICH and Mortality were 0.81 (0.39-1.68), 1.28 (0.76-2.17) and 1.07 (0.89-1.28) respectively. Conclusions: Functional outcome, SICH, and mortality following thrombolysis of AIS patients beyond time window using CTP are comparable to those for patient thrombolysed at time window using NCCT alone. However, because of the limited number of the studies and low level evidences, these estimates should be regarded with caution.

Keywords: Systematic review, CT perfusion, intravenous thrombolytic, stroke

Background

Stroke is the leading cause of death and disability in the world [1, 2]. There were *11* 931.1 thousands incident stroke cases, 104 178.7 thousands prevalent stroke cases, 6167.3 thousands stroke deaths, caused 113 million DALYs lost in 2017 [2, 3]. The estimated global lifetime risk of stroke from the age of 25 years onward is 24.9% [4]. According to American Heart Association reporting, about 87% of strokes were ischemic strokes [5]. In the early stage of ischemic change, based on non-contrast CT (NCCT), intravenous thrombolysis is recommended by current clinical guidelines. However, it only had a short time window. Intravenous administration of tissue plasminogen activator (tPA) was approved for use within 3 hours of symptom onset, and newer evidence show a potential benefit to 4.5 h [6]. The proportion of patients treated within time window was low and one of the most important approaches to solve this problem was to extend the thrombolysis time. CT perfusion could determine a patient's eligibility for thrombolysis according to extent of salvageable brain tissue or ischemic penumbra from symptom onset regardless of the time, which may be useful to select acute ischemic stroke patients who were beyond approved time window or unknown symptom onset time to get intravenous thrombolysis. However, the benefit of this approach in clinical outcome remains debate [7, 8]. The goal of this study was to systematically review the evidence for the effectiveness of CT perfusion versus time guided selection of acute ischemic

stroke patients if they are eligible for thrombolytic therapy.

Methods

Criteria for considering studies for this review

A study was eligible if it was a randomized controlled trial (RCT), non-randomized controlled clinical trial, cohort study, or case-control study that compared CTP guided intravenous thrombolysis for acute ischemic stroke against time guided intravenous thrombolysis. The eligible study was also required to have explicitly reported the outcome of favorable outcome (mRS score ≤ 2) at 90 days, symptomatic intracerebral haemorrhage (SICH), intracerebral haemorrhage (ICH) or mortality (either reported as raw data or adjusted effect estimates with 95% confidence intervals).

Literature search

A literature search of PubMed, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register Database of Reviews of Effectiveness, Health Technology Assessment database was undertaken in June 2017. The references of all articles selected for the review for potentially relevant articles were also scanned.

Study process

In order to select articles that met the inclusion criteria, two reviewers (S.J.T. and L.X.L.), were trained in research methods, screened all titles/abstracts and full texts independently. They assessed risk of bias and extracted information for each included study independently too. Disagreements were resolved by consensus.

Assessment of methodological quality

The Cochrane risk of bias tool for RCTs have been used in assessed risk of bias of included RCTs [9]. These items included random sequence generation, allocation concealment, blinding of participants and personnel, adjudication of the outcomes, incomplete outcome data, selective reporting and prognostic balance between treatment groups.

Newcastle-Ottawa Quality Assessment Scale have been used to assess the risk of bias of cohort studies [10, 11]. These items included representativeness of the exposed cohort, ascertainment of exposure, selection of the non-exposed cohort, demonstration that outcome of interest was not present at start of study, comparability of study controls for important factors, assessment of outcome, follow-up time, incomplete outcome data. According to Cochrane risk of bias tool, the risk of bias have been classed to low risk, unclear risk and high risk during assessment.

Data collection

The information was extracted from each included study including general study characteristics (author name, year of publication, total number of participants, study design), patient characteristics (baseline NIHSS, time from symptom onset to treatment, age), treatment (CT scanner type, CT perfusion color maps, dose of rtPA). Furthermore, information on data source (e.g. claims data, electronic medical records), and methods used to control confounding (e.g. logistic or cox regression, and control variables) were also documented by researcher. Except raw event data, the adjusted estimates and their associated 95% CIs, as well as the factors adjusted were also collected by researcher.

Statistical analysis and data synthesis

The date of study design were analyzed separately (i.e. trials and observational studies). RevMan5.3 software was used to analyze the data. A random effects model with Mantel-Haenszel method was used to calculate pooled Odds Ratio (OR) (and 95% confidence interval [CI]) of favorable outcome. Because of the very low event rate, Peto's methods have been used to pooled the SICH, ICH and mortality data and pooled Peto ORs and associated 95% CIs are reported [12, 13]. Additionally, random effects model has been used to pool the adjusted estimates (adjusted OR and 95% CI). Cochran chi-square test and the I-squared statistic were used to examine the heterogeneity among studies. Alternative effect measures (OR *vs.* risk ratio (RR)), pooling methods (Peto *vs.* Mantel-Hanszel method), and statistical models regarding heterogeneity (random *vs.* fixed effects) were used to carried out sensitivity analyses.

The standards set by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Sy-

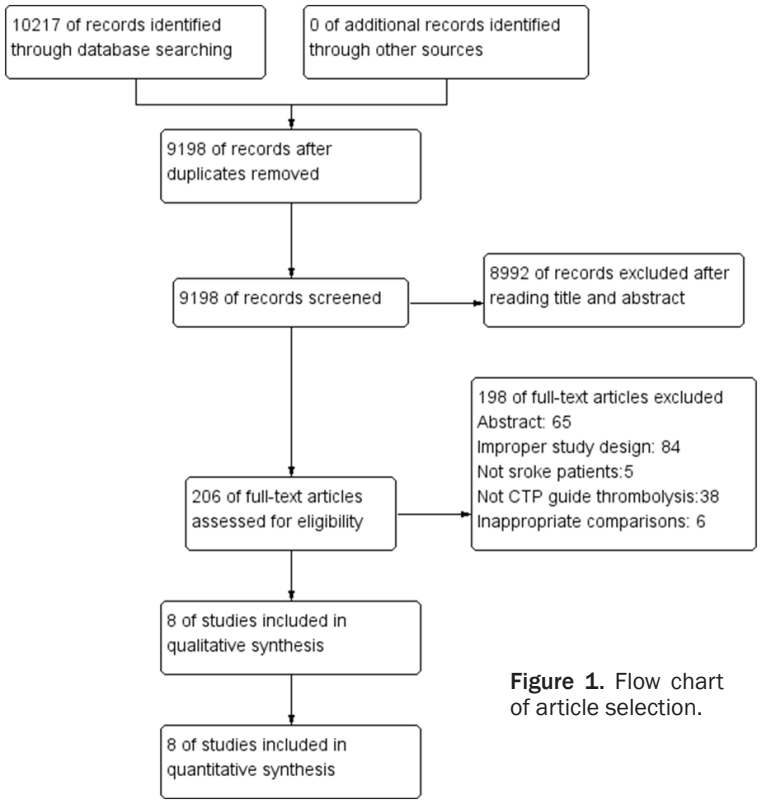

Figure 1. Flow chart of article selection.

stematic Reviews and Meta-Analyses (PRISMA) for the conduct and reporting of the study were been strictly followed [14, 15].

Results

A total of 10217 potentially relevant reports were identified. After a title and abstract screening, there were 206 reports potentially eligible; ultimately, eight reports including five prospectively cohort studies, two retrospective cohort studies and one quasi-randomized controlled trial are included (**Figure 1**).

The eight included studies were published between 2011 and 2015 with 9900 samples. These studies were conducted in the US (Gentile 2012 [16], McDonald 2014 [17]), Spain (Obach 2011 [18], García-Bermejo 2012 [19]), UK (Sztriha 2011 [20]), Australia (Bivard 2015 [21]), Germany (Eyding 2011 [22]) and China (Huang 2013 [23]). The characteristics of included studies are shown in **Table 1**.

Methodological quality of included studies

All studies (except McDonald) were performed in tertiary care centers, patients were thrombolysed according to a standard clinical protocol, so that patients didn't have any intracerebral hemorrhage at the start of the study. Two studies (García-Bermejo, Bivard) drew control groups from different sources. Confounders were adjusted in four studies (Obach, Sztriha, García-Bermejo and McDonald), these groups were considered to be comparable. Three studies (Obach, Sztriha, Bivard) assessed outcomes blindly. However, the remaining studies were assessed as being low risk, because these outcomes were objective. Three studies (Eyding, Gentile, McDonald) unclearly reported follow-up time was classified as unclear risk.

The random sequence of study by Huang generated based on date of admission. We assessed the study as being at low risk, although the blinding of participants and personnel was incomplete, because outcomes were objective, which were not likely to be influenced by lack of blinding (**Table 2**).

Favorable outcome

Four cohort studies and one quasi-randomized controlled trial have reported favorable outcome (mRS score ≤ 2), and the unadjusted rate of favorable outcome in perfusion CT selected thrombolysis was similar to NCCT selected thrombolysis in time window. As shown in **Figure 2**, four cohort studies with 1581 patients were combined, and unadjusted odds of favorable outcome was not statistically significant (unadjusted OR = 1.12; 95% CI, 0.79-1.58). These studies also reported adjusted rate of favorable outcome, and showed a more benefit result than unadjusted even without significant (adjusted OR=1.55; 95% CI, 0.91-2.65), as seen in **Figure 3**.

The quasi-randomized controlled trial also showed no statistically significant different in favorable outcome between perfusion CT selected thrombolysis and time guide thrombolysis (OR = 1.41; 95% CI, 0.52-3.84).

Table 1. Characteristic of included studies

Studies	Design	Sample size	CT scanner type	CT perfusion Colour maps	CT perfusion group			NCCT group			RtPA (alteplase)
					Time to treatment (h)	Age (y)	NIHSS	Time to treatment (h)	Age (y)	NIHSS	
Obach 2011	Prospectively cohort	368	64 row, Siemens	CBF, CBV, TPP	> 3 h (28%)	73	9	> 3 h (16%)	73	10	0.9 mg/kg
Sztriha 2011	Prospectively cohort	254	16-slice, GE	CBF, CBV, MTT	3-6	74	13	0-3	74	14	0.9 mg/kg
Eyding 2012	Retrospective cohort	57	64-slice, Siemens	CBF, CBV, TTP	3-4.5	71	11	< 3	73	7	0.9 mg/kg
Gentile 2012	Prospectively cohort	25	16/64-slice, Siemens	CBF, CBV, TPP	< 5	62	NR	< 5	64	NR	0.9 mg/kg
García-Bermejo 2012	Prospectively cohort	215	64 rows, GE; 32 rows, Toshiba	CBF, CBV, MTT	> 4.5	69	9	< 4.5	72	11	mg/kg
Huang 2013	Quasi-randomized controlled trial	66	64 rows, GE	MTT, CBV	3-6	58	9	< 4.5	64	10	0.6-0.9mg/kg
McDonald 2014	Retrospective cohort	8153	NR	NR	NR	73	NR	NR	73	NR	NR
Bivard 2015	Prospectively cohort	762	64/320 slice, Toshiba	NR	< 4.5	73	14	< 4.5	74	12	NR

Note. NCCT: non-contrast CT; NIHSS = National Institutes of Health Stroke Scale; MTT = mean transit time; CBV = cerebral blood volume; CBF = cerebral blood flow; TTP = time to peak; NR = not report.

Table 2. Risk bias of included studies

Author (year)	Representativeness of the exposed cohort	Ascertainment of exposure	Selection of the non-exposed cohort	Demonstration that outcome of interest was not present at start of study	Comparability of study controls for important factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Obach (2011)	+	+	+	+	+	+	+	+
Sztriha (2011)	+	+	+	+	+	+	+	+
Eyding (2012)	+	+	+	+	-	+	?	+
Gentile (2012)	+	+	+	+	-	+	?	+
García-Bermejo (2012)	+	+	-	+	+	+	+	+
McDonald (2014)	+	+	+	+	+	+	?	+
Bivard (2015)	+	+	-	+	-	+	+	+

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Huang (2013)	-	-	+	+	+	+	+

Note. + = low risk, ? = unclear risk, - = high risk.

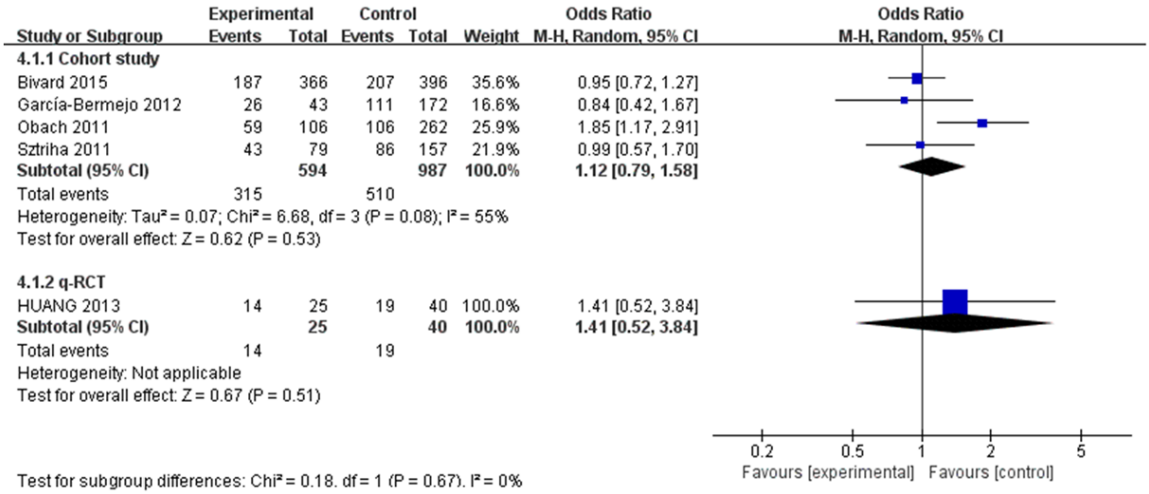

Figure 2. Rate of favorable outcome (mRS score ≤ 2) in patients who received CTP guided thrombolysis versus time guided thrombolysis based on raw data.

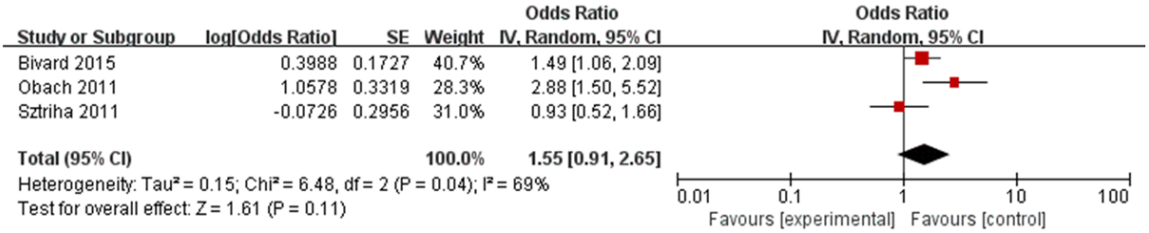

Figure 3. Rate of favorable outcome (mRS score v2) in patients who received CTP guided thrombolysis versus time guided thrombolysis based on adjusted data.

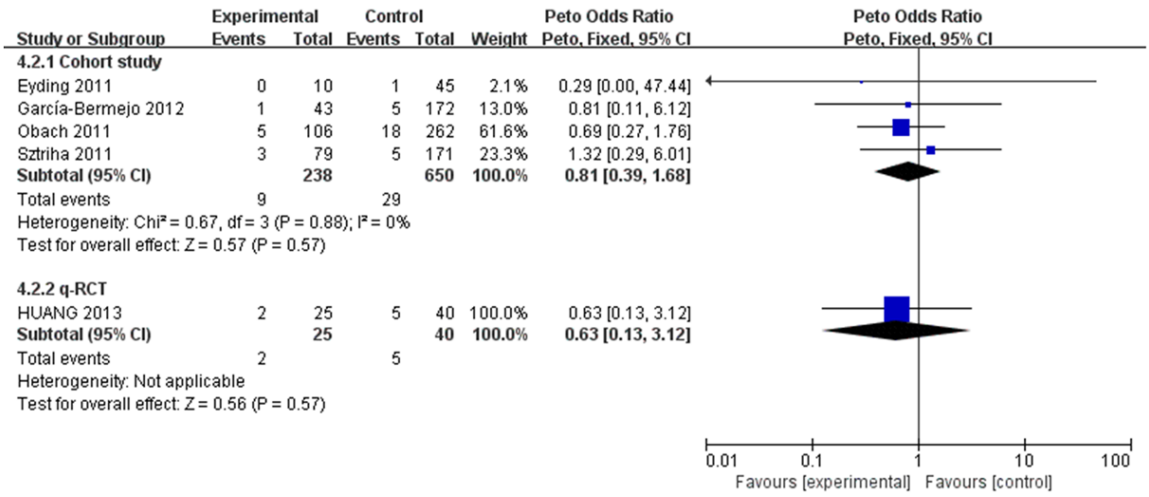

Figure 4. Risk of SICH in patients who received CTP guide thrombolysis versus time guide thrombolysis based on raw data.

SICH

As seen in **Figure 4**, four cohort studies with 888 patients were included to perform meta-analyses, which demonstrated that the no significant differences in outcome of SICH between CTP group and control group (unadjusted OR = 0.81; 95% CI, 0.39-1.68). One study

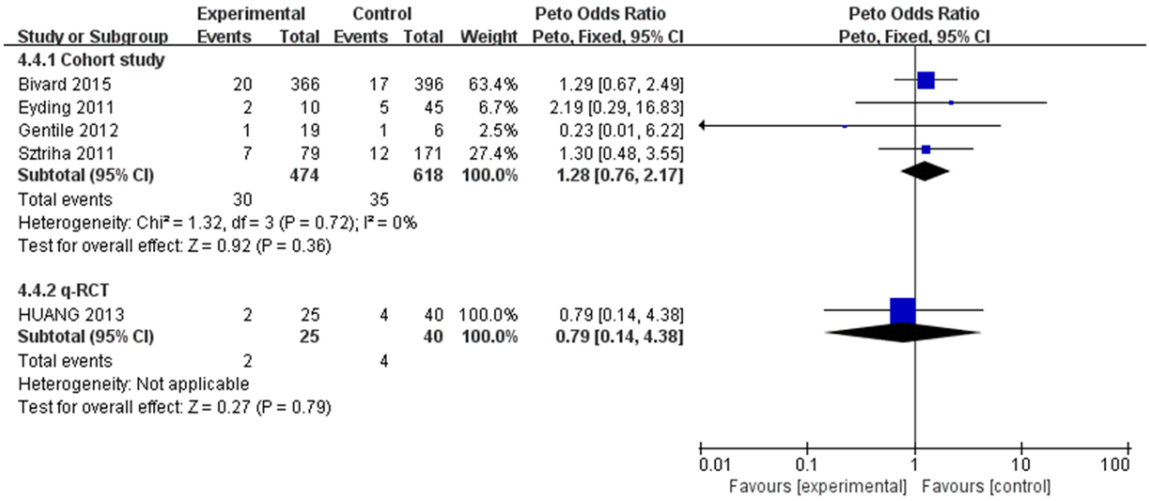

Figure 5. Risk of ICH in patients who received CTP guide thrombolysis versus time guide thrombolysis based on raw data.

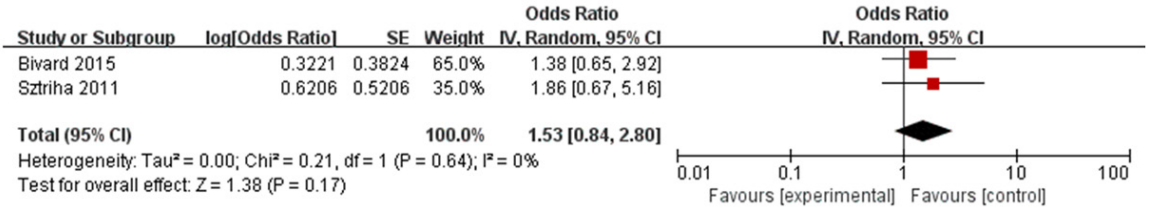

Figure 6. Risk of ICH in patients who received CTP guide thrombolysis versus time guided thrombolysis based on adjusted data.

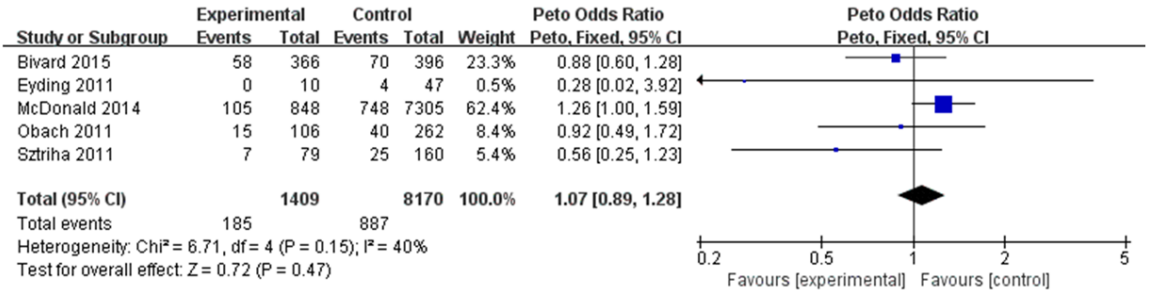

Figure 7. Risk of mortality in patients who received CTP guide thrombolysis versus time guide thrombolysis based on raw data.

(Sztriha 2014) reported adjusted rate of SICH (unadjusted OR = 0.63; 95% CI, 0.13-3.12) and one quasi-randomized controlled trial (adjusted OR = 3.0; 95% CI, 0.59-15.21) are both demonstrated the same result.

ICH

Four cohort studies with 1092 patients were included to perform mete analysis, there showed no significant difference in outcome of ICH between perfusion CT guided thrombolysis and NCCT guided thrombolysis in time window (unadjusted OR = 1.28; 95% CI, 0.76-2.17), as shown in **Figure 5**. The pooled result of adjusted ICH rate was similar (adjusted OR = 1.53; 95% CI, 0.84-2.80), as shown in **Figure 6**.

No significant difference was found in the quasi-randomized controlled trial (unadjusted OR = 0.79; 95% CI, 0.14-4.38).

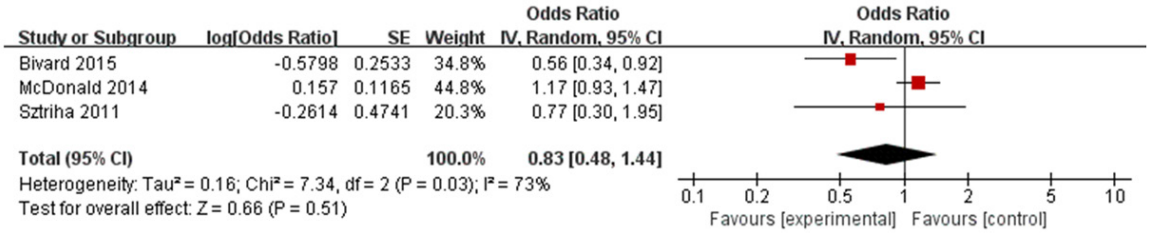

Figure 8. Risk of mortality in patients who received CTP guide thrombolysis versus time guide thrombolysis based on adjusted data.

Table 3. Results of CTP guided thrombolysis versus thrombolysis in 3 hour based on NCCT

Outcome or subgroup	Studies	Participants	Effect estimate (OR)	I^2
Favorable outcome*	4			
Cohort study	3	1248	1.14 [0.75, 1.74]	52%
q-RCT	1	38	1.09 [0.28, 4.19]	-
ICH$^{\Delta}$	4			
Cohort study	3	1067	1.34 [0.79, 2.28]	0%
q-RCT	1	38	1.04 [0.09, 12.11]	-
SICH$^{\Delta}$	4			
Cohort study	3	555	0.83 [0.29, 2.40]	0%
q-RCT	1	38	0.47 [0.05, 4.02]	-
Mortality$^{\Delta}$	4	1308	0.78 [0.56, 1.08]	0%

NOTE: *Odds Ratio (M-H, Random, 95% CI); $^{\Delta}$Peto Odds Ratio (Peto, Fixed, 95% CI).

Mortality

Five cohort studies with 9579 patients were included to perform meta-analysis. There were similar unadjusted mortality between perfusion CT selected thrombolysis and NCCT selected thrombolysis in time window (OR = 1.07; 95% CI, 0.89-1.28), as shown in **Figure 7**. Except the study by McDonald, there was a benefit trend on outcome of mortality in CTP group. The mortality was decreased after adjustment (adjusted OR = 0.83; 95% CI, 0.48-1.44), as shown in **Figure 8**.

Sensitivity analysis

Five studies (Bivard 2015, Obach 2011, Sztriha 2011, McDonald 2014 and Huang 2013) reported the comparison results of CTP guided thrombolysis beyond time window to NCCT guided thrombolysis in three hours. Compared to NCCT guided thrombolysis in three hours, CTP guided thrombolysis had similar results in favorable outcome and ICH, while benefit in SICH and morality, but without statistically significant different (**Table 3**).

The sensitivity analysis using alternative effect measures, statistical methods, and analysis models did not show any important changes in the pooled effects (Supplemental Figures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11).

Discussion

This systematic review and meta-analysis estimated the pooled outcomes from studies where CT perfusion guided thrombolysis was compared to time guided thrombolysis. It was found that patients treated beyond time window based on CTP had higher rates of favorable outcome and ICH, and lower rate of SICH than patients treated within time window based on NCCT. Although these differences were small and have no statistically significant different, but these results were similar to adjusted results. Patients treated beyond time window based on CTP had lower rates of adjusted mortality than patients treated within time window based on NCCT, although the difference have no statistically significant different. Compared to patients thrombolysis within 3 hours based on NCCT, patients treated beyond 3 hour based on CTP also had higher rates of favorable outcome and ICH, but had a lower rates of SICH and mortality, although the difference have no statistically significant different too. Therefore, the results of review were robust. The outcomes of mRS ≤ 2 at 90 days, SICH and mortality in CTP guided thrombolysis group in this review were 53%, 3.8% and 13% respectively, which were similar to the results

of recent mete analysis with results as 59.4%, 3.6% and 10% respectively [24].

Compared with NCCT, CTP is increasingly being used to discriminate extent of salvageable brain tissue to optimize acute therapy and predict clinical outcomes. Acute ischemic stroke patients were still get intravenous thrombolysis treatment even they were not meet the traditional thrombolysis criteria (e.g. beyond time window, unknown onset time). Some studies showed that there were no differences in SICH or functional outcome between patients thrombolysed within 4.5 hours or beyond 4.5 hours [20, 25]. The study by Obach showed that CTP guided thrombolysis yielded superior benefits (adjusted OR = 4.48; 95% CI, 1.68-11.98), and lower rate of SICH (RR = 0.65; 95% CI, 0.09-4.75) and mortality (RR = 0.84; 95% CI, 0.43-1.67) in patients treated beyond 3 hours than treated within 3 hours [18]. The small randomized control trial show that patients with stroke of unknown onset who get CTP guided thrombolysis had higher rates of recanalization and favorable functional outcome than patients in placebo group [26]. A high proportion of acute stroke patients with SITS-MOST and ECASS-3 exclusion criteria can be safely and efficaciously treated with intravenous thrombolysis using a CTP selection protocol [27].

Findings may be influenced by many factors, such as CTP penumbra and mismatch parameters, CT scanners as well as varied brain coverage, those were important determinants of stroke treatment risk and the validation and standardization of CTP methods. Two included studies restricted their samples to middle cerebral artery territory patients and the results were similar to other studies. These demonstrated that the results were not influenced by type of artery involved in the stroke, which contrasts with the conclusions of previous research.

Two disadvantages of CTP were renal damage from iodinated contrast administration and radiation exposure. However, none of the studies in this review reported these. The risk for contrast induced nephropathy (CIN) in patients with stroke receiving CTP was low, and the long term effects of radiation from CTP stroke imaging were not entirely clear yet. Compared to NCCT, CTP was less cost and more incremental benefits used to select patient for thrombolysis, because CTP was better able to exclude patients who were at higher risk of secondary intracranial hemorrhage (ICH) and better include patients who could benefit from thrombolysis beyond 4.5 hours post symptom onset [28-30].

To the best of our knowledge, this is the first review to systematically assess the effectiveness of CT perfusion versus NCCT guided selection of acute ischemic stroke patients who are eligible for thrombolytic therapy. The literature search strategy was thorough, and all relevant evidences have been captured. The analysis of data was thorough and careful. Instead of using grand pooling of the data, several pre specified subgroup analyses were used to explore sources of heterogeneity and both raw data and adjusted data were used in analyses. Although our assessment was low to moderate risk of bias, it was limited by the nature of the observe study which was considered as low quality evidence, and this view's studies were all observed research. Thus, our study does not provide level 1 evidence whether perfusion CT selection leads to better outcomes with rtPA treatment than non-contrast CT selection. RCTs needed to be done in the future.

Conclusions

Functional outcome, SICH and mortality following thrombolysis of AIS patients beyond the time window using CTP are comparable to those for patient thrombolysed at time window using NCCT alone. However, because of the limited number of the studies and low level evidences, these estimates should be regarded with caution.

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Disclosure of conflict of interest

None.

Abbreviations

AIS, acute ischemic stroke; NCCT, non-contrast CT; SICH, symptomatic intracerebral haemorrhage; ICH, intracerebral haemorrhage; DALY, Disability Adjusted of Life Years; CIN, contrast induced nephropathy.

Address correspondence to: Jinlan Yao, School of Medicine, Huzhou University, Huzhou Central Hospital, 759 Erhuan Road, Huzhou 313000, Zhejiang, PR China. E-mail: cebm_atong@qq.com

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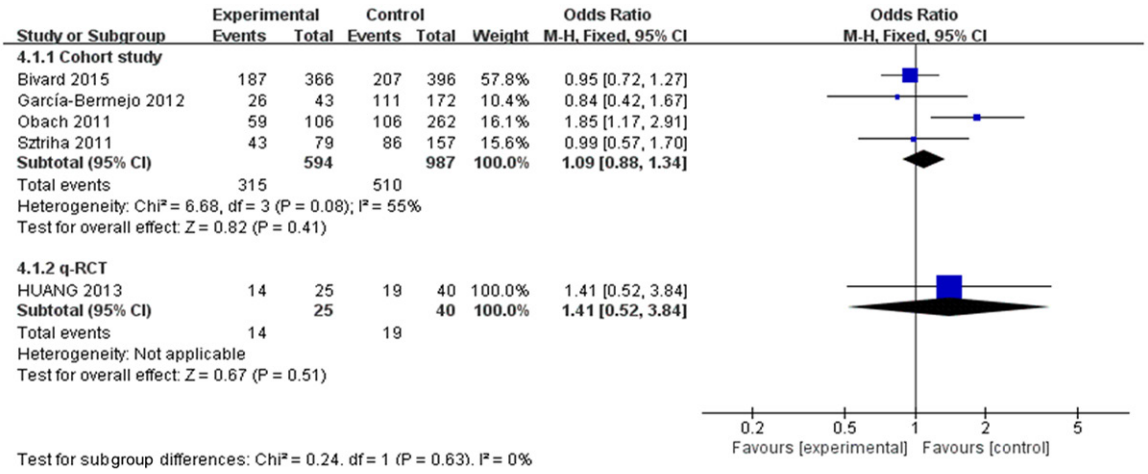
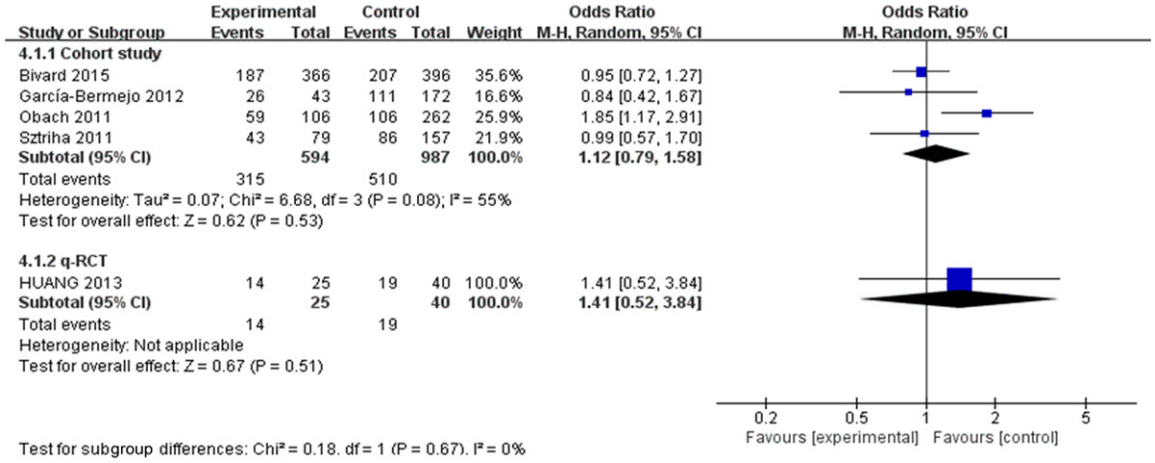
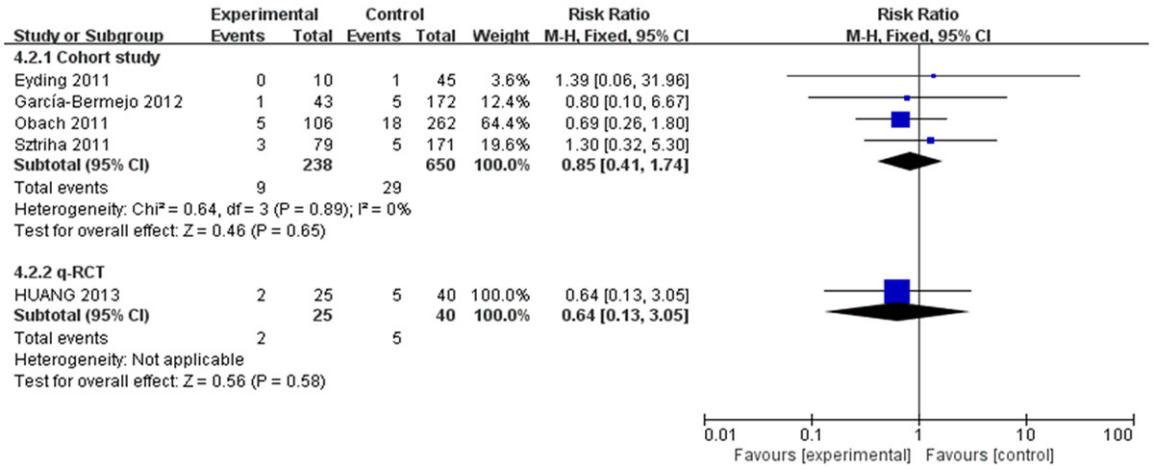


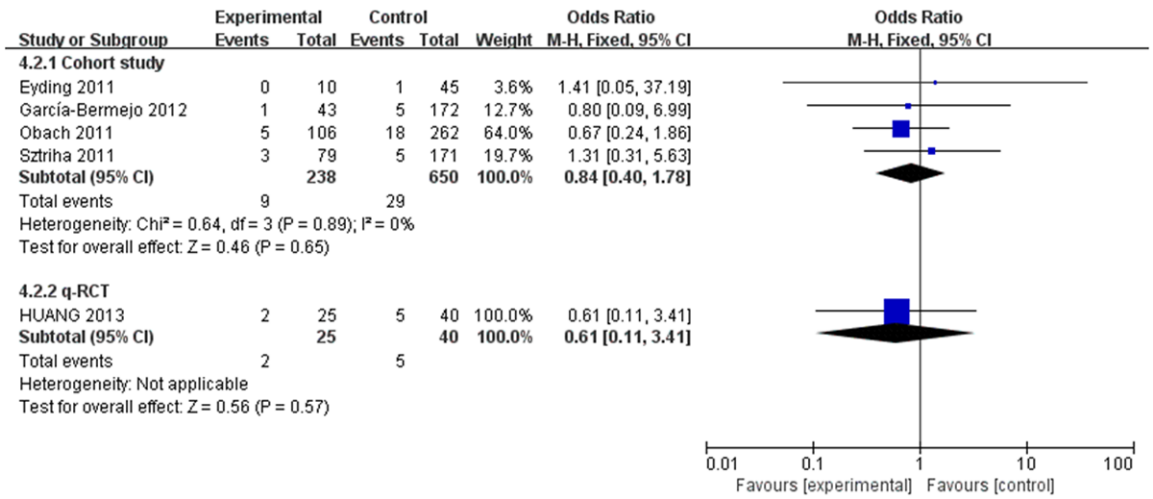
Supplemental Figure 1. Sensitivity analysis of favorable outcome (mRS score ≤ 2) by using fixed Mantel-Hanszel statistical model based on raw data.



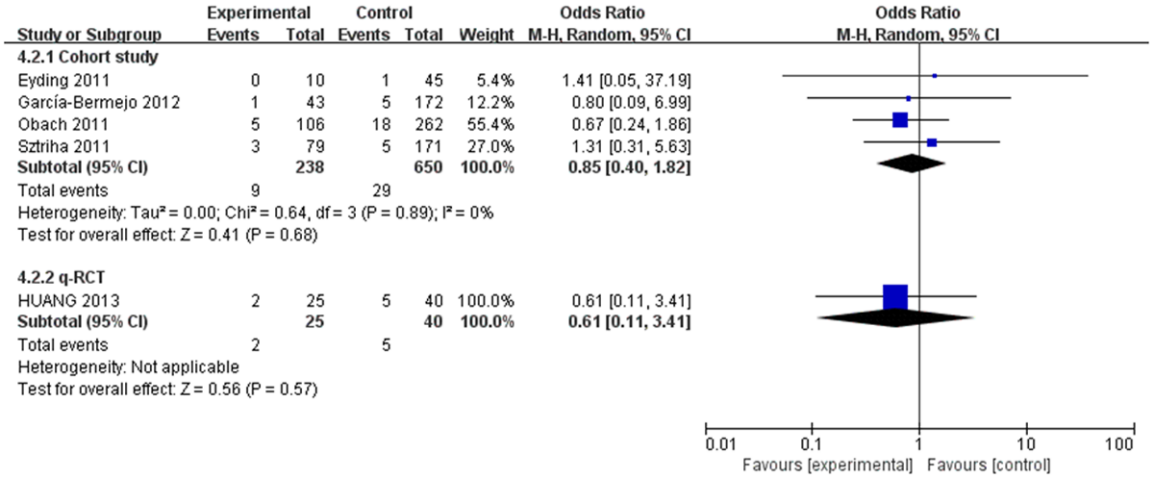
Supplemental Figure 2. Sensitivity analysis of favorable outcome (mRS score ≤ 2) by using alternative effect measure risk ratio based on raw data.



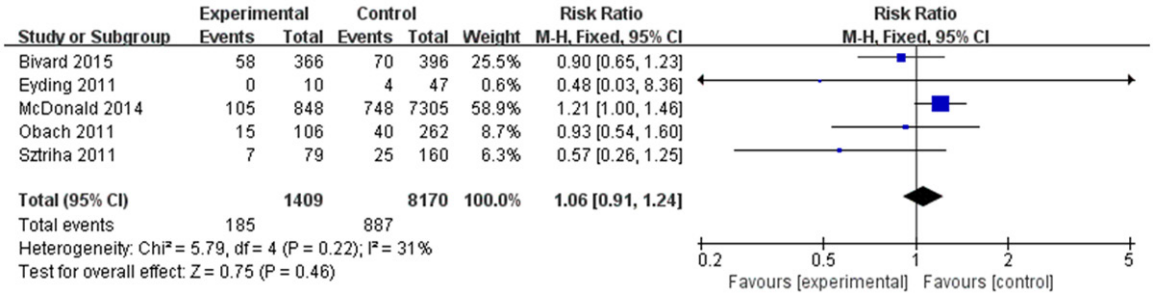
Supplemental Figure 3. Sensitivity analysis of SICH by using alternative effect measure risk ratio based on raw data.



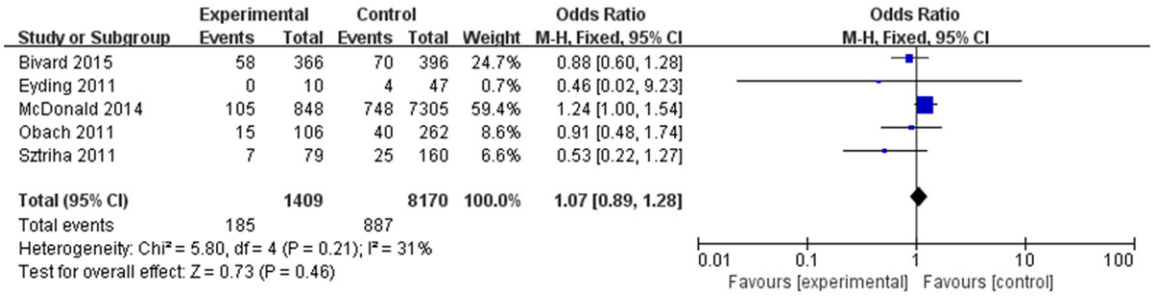
Supplemental Figure 4. Sensitivity analysis of SICH by using fixed Mantel-Hanszel statistical model based on raw data.



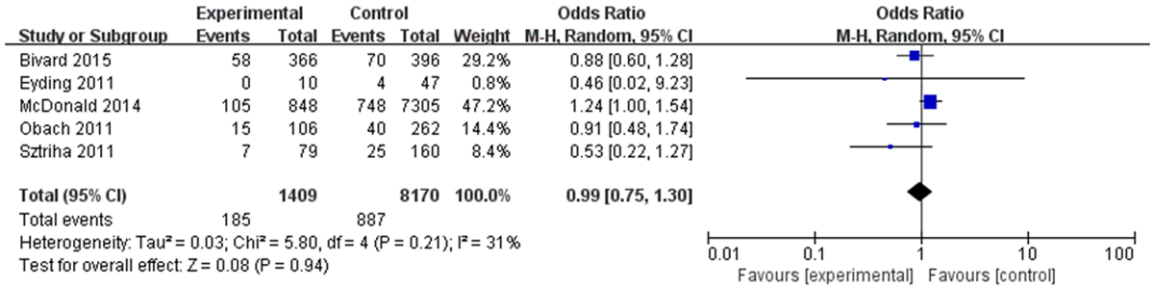
Supplemental Figure 5. Sensitivity analysis of SICH by using random effects model based on raw data.



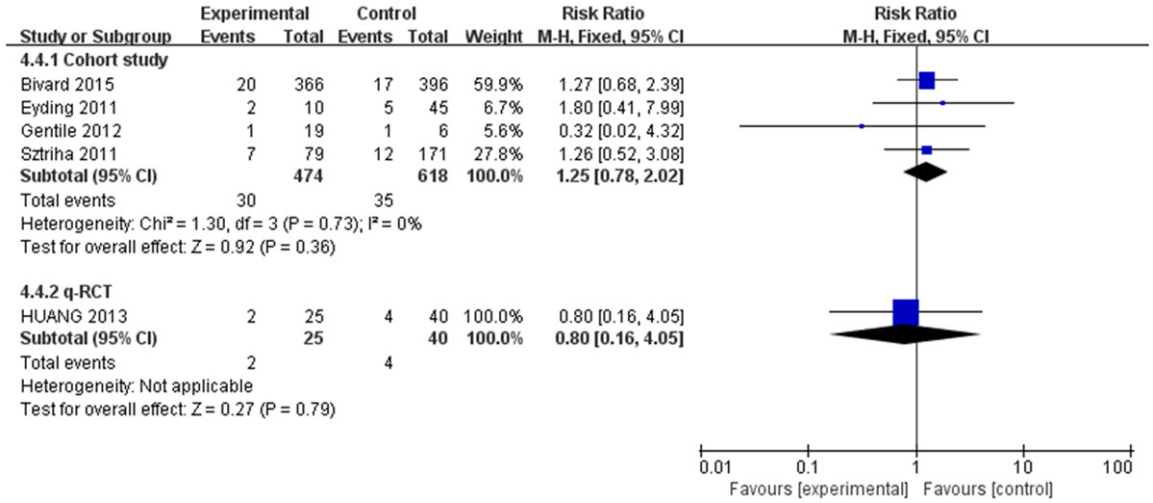
Supplemental Figure 6. Sensitivity analysis of mortality by using alternative effect measure risk ratio based on raw data.



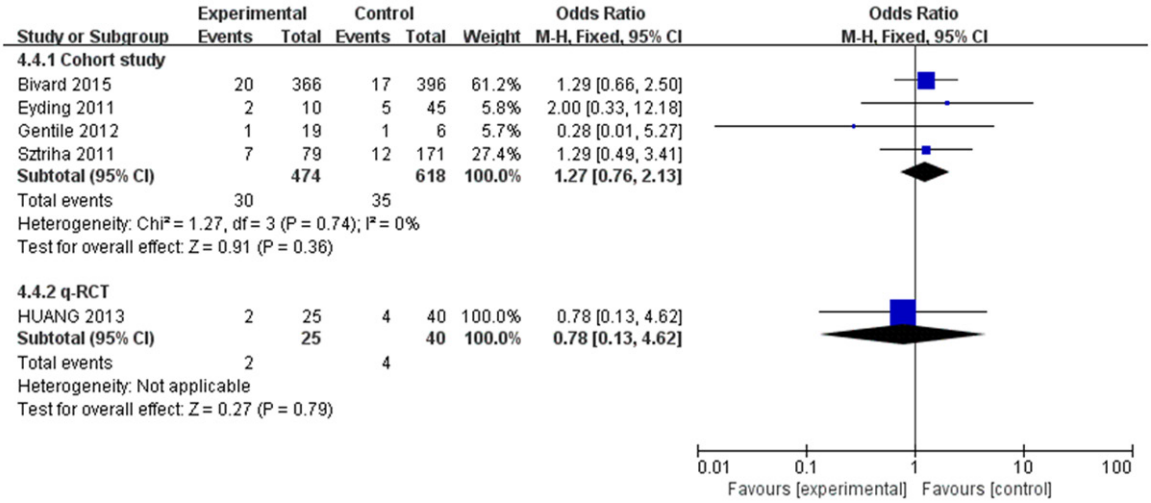
Supplemental Figure 7. Sensitivity analysis of mortality by using fixed Mantel-Hanszel statistical model based on raw data.



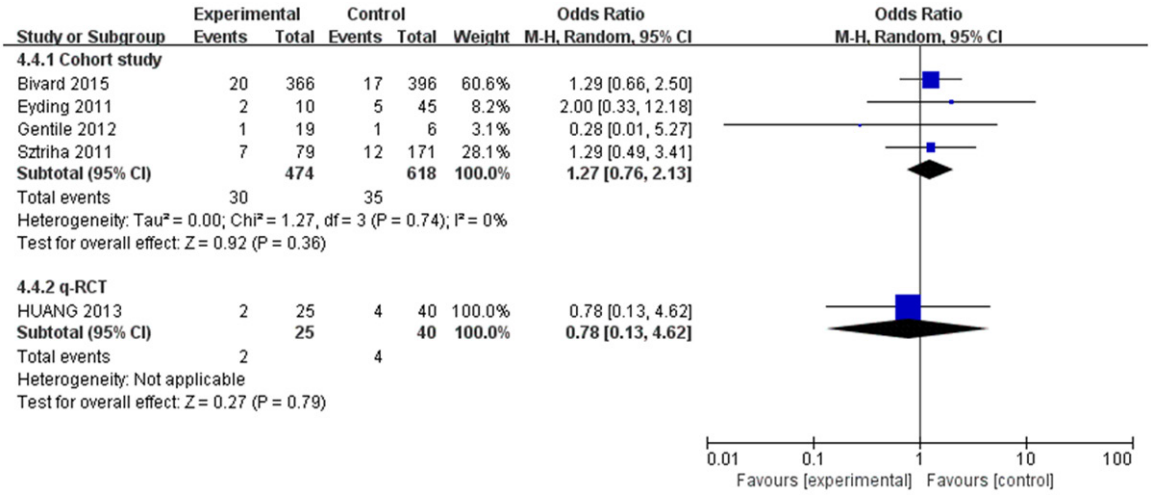
Supplemental Figure 8. Sensitivity analysis of mortality by using random effects model based on raw data.



Supplemental Figure 9. Sensitivity analysis of ICH by using alternative effect measure risk ratio based on raw data.



Supplemental Figure 10. Sensitivity analysis of ICH by using fixed Mantel-Hanszel statistical model based on raw data.



Supplemental Figure 11. Sensitivity analysis of ICH by using random effects model based on raw data.