

Data Supplement

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








Table e-1. Characteristics of study participants




Reference study, year	Treatment arm	Subjects, no.	Male, (%)	Age, years, mean (SD)	GCS, median (IQR)	Baseline NIHSS mean (SD)/ median (IQR)	ICH volume, ml, mean (SD)/ median (IQR)	Onset to randomization, hours mean (SD)/ median (IQR)
Koch et al., 2008 [9]	Intensive	21	42.9	61.2 (13.0)	13.5 (9-15)	12.0 (7.0)	12.5 (17.2)	3.13 (2.22) [†]
	Conservative	21	66.7	60.0 (11.0)	15 (10-15)	10.9 (6.5)	8.5 (9.8)	3.23 (2.24) [†]
INTERACT-1, 2008 [10]	Intensive	203	60.6	63.0 (12.0)	14 (13-15)	9 (5-14)	14.2 (14.5)	3.70 (2.90-4.80)
	Conservative	201	69.2	62.0 (13.0)	14 (12-15)	9 (5-16)	12.7 (11.6)	3.60 (2.90-4.90)
INTERACT-2, 2013 [11]	Intensive	1399	64.2	63.0 (13.1)	14 (12-15)	10 (6-15)	11 (6-19)	3.70 (2.80-4.80)
	Conservative	1430	61.7	64.1 (12.6)	14 (12-15)	11 (6-16)	11 (6-20)	3.70 (2.90-4.70)
ICH-ADAPT, 2013 [12]	Intensive	39	66.7	70.7 (12.5)	15 (4-15)	10 (6-18)	25.98 (30.84)	7.83 (3.25-16.75)
	Conservative	36	77.8	68.7 (11.1)	15 (6-15)	11 (5.5-15.5)	26.86 (25.24)	8.54 (3.80-15.75)
ATACH-2, 2016 [13]	Intensive	500	60.8	62.0 (13.1)	15 (13-15)	11 (0-40) [‡]	10.3 (2.3-85.2) [‡]	3.04 (0.95)
	Conservative	500	63.2	61.9 (13.1)	15 (13-15)	11 (0-40) [‡]	10.2 (0.98-79.1) [‡]	3.08 (0.95)

[†]Onset to treatment. [‡]Median (range).

Abbreviations: ATACH=Antihypertensive Treatment of Acute Cerebral Hemorrhage; GCS=Glasgow Coma Scale; ICH=intra-cerebral hemorrhage; ICH ADAPT=The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial; INTERACT=Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial; IQR=interquartile range; NIHSS=National Institute of Health Stroke Scale; SD=standard deviation.

Table e-2 Risk of bias summary table

Study \ Bias	Koch et al., 2008	INTERACT- 1, 2008	INTERACT- 2, 2013	ICH- ADAPT, 2013	ATACH-2, 2016
Random sequence generation (Selection Bias)					
Allocation concealment (Selection Bias)					
Blinding of participants and personnel (Performance Bias)					
Blinding of outcome assessment (Detection Bias)					
Incomplete outcome data (Attrition Bias)					
Selective reporting (Reporting Bias)					
Other sources of bias					

Legend:  low,  unclear and  high risk of bias.

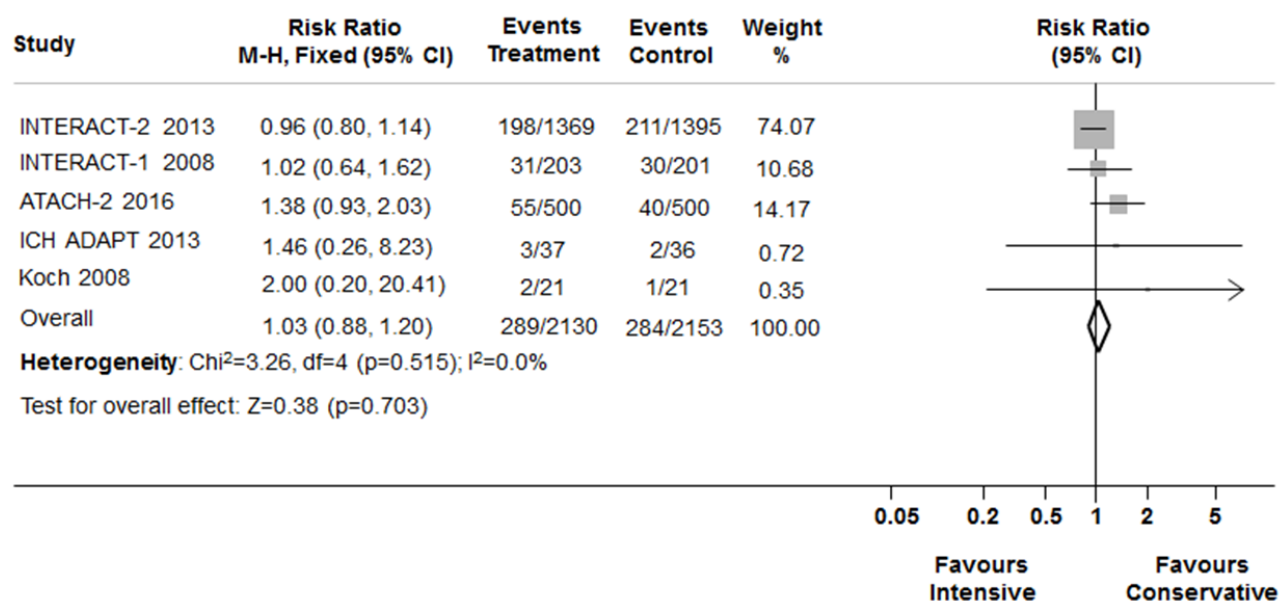
Abbreviations: ATACH=Antihypertensive Treatment of Acute Cerebral Hemorrhage; ICH

ADAPT=The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial;

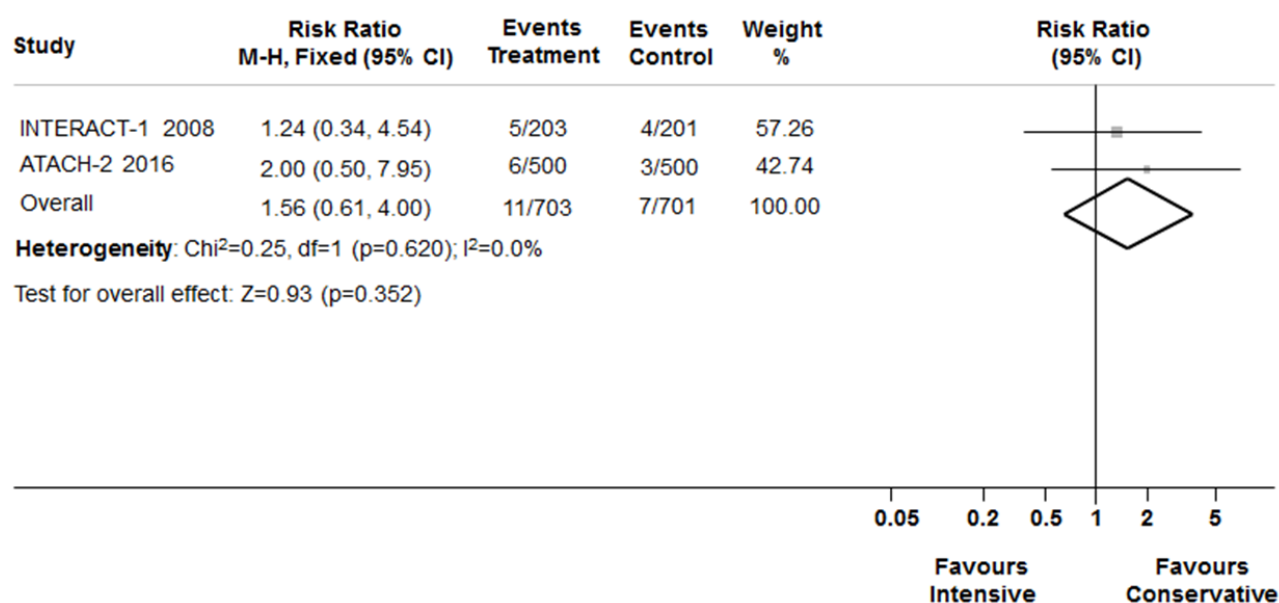
INTERACT=Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial.

Figure e-1: Early neurological deterioration, hypotension, severe hypotension, serious treatment-related adverse events, recurrent stroke, acute coronary event and renal failure in intensive versus conservative blood pressure lowering therapy

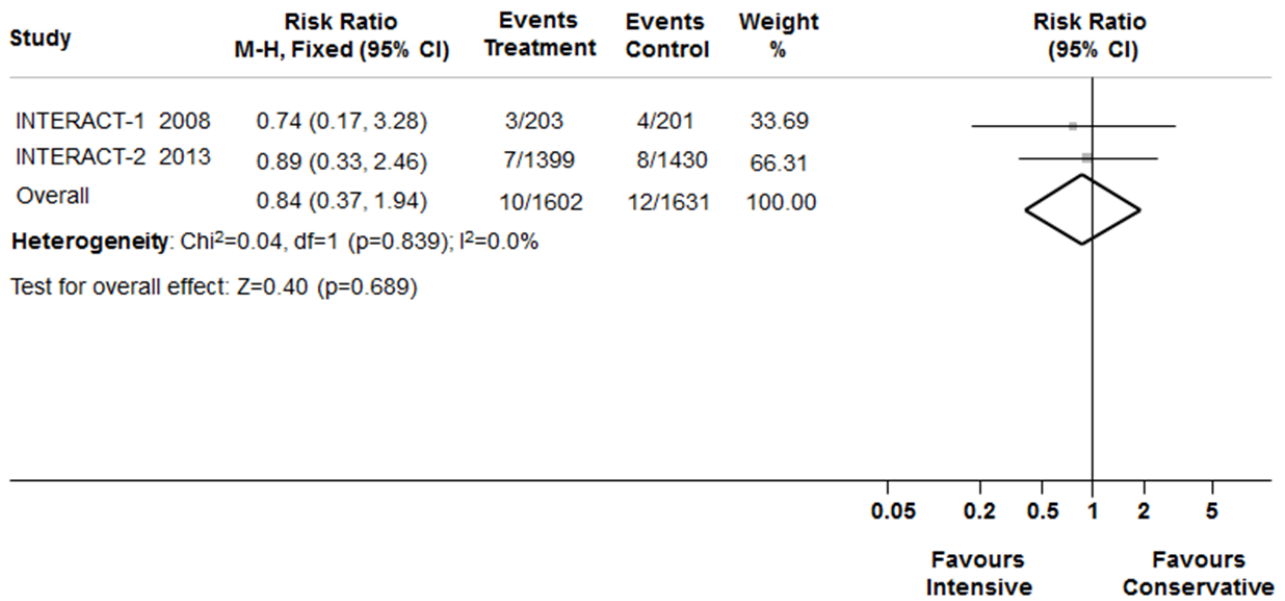
A. Early neurological deterioration



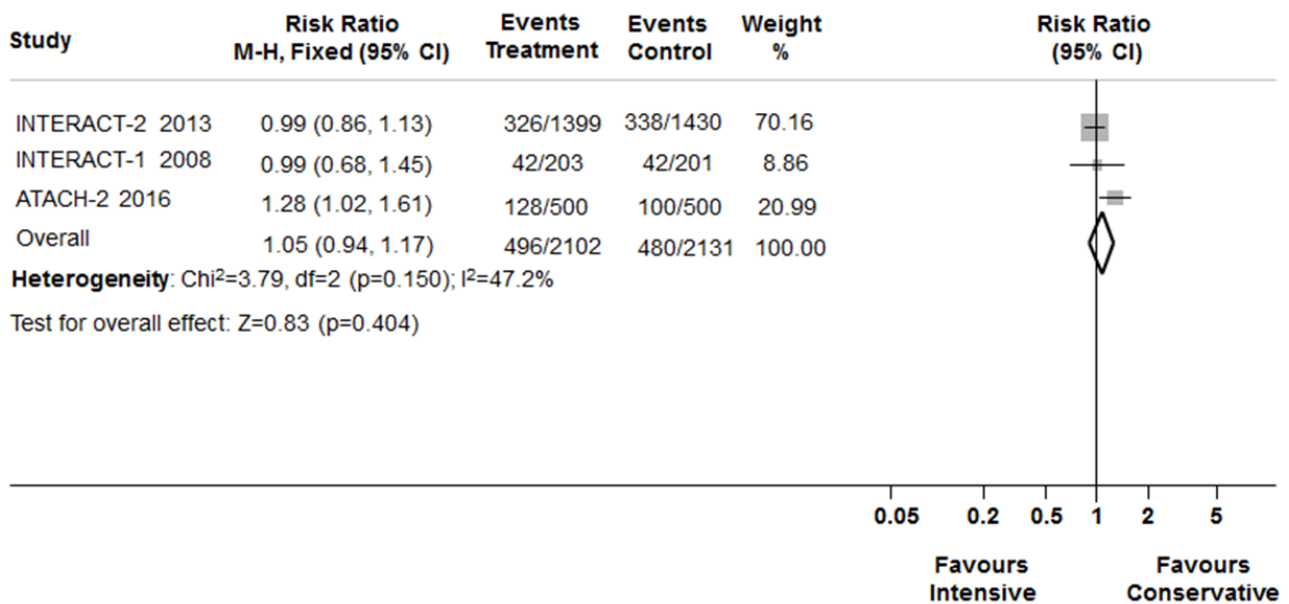
B. Hypotension within 72 hours after randomization



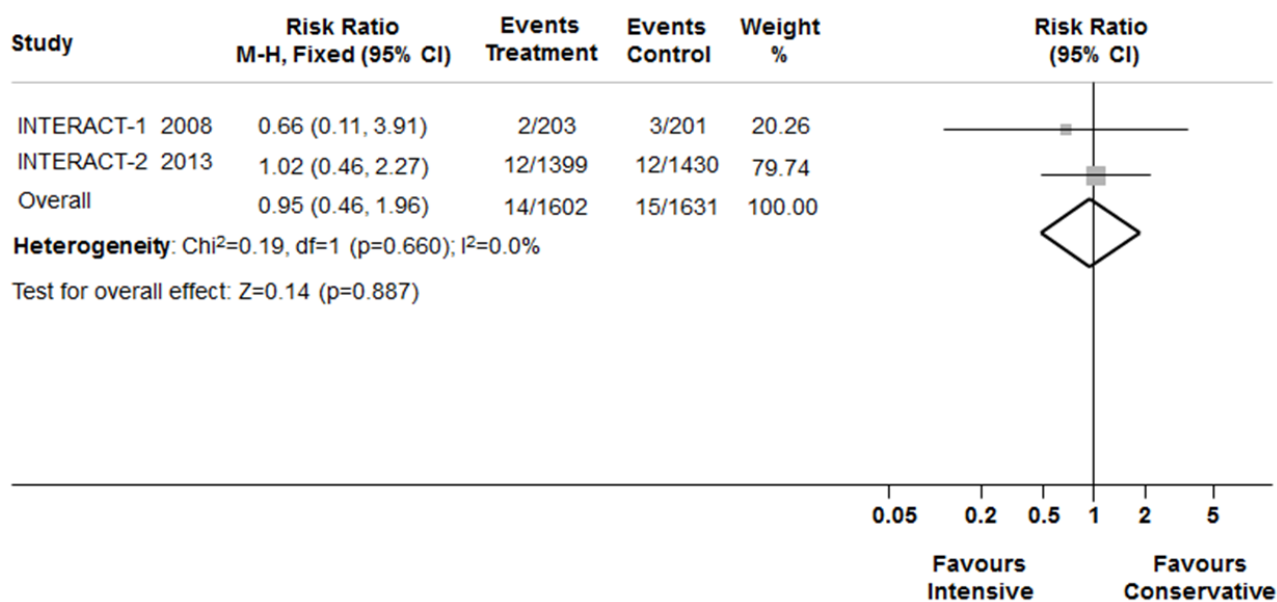
C. Severe hypotension within 72 hours after randomization



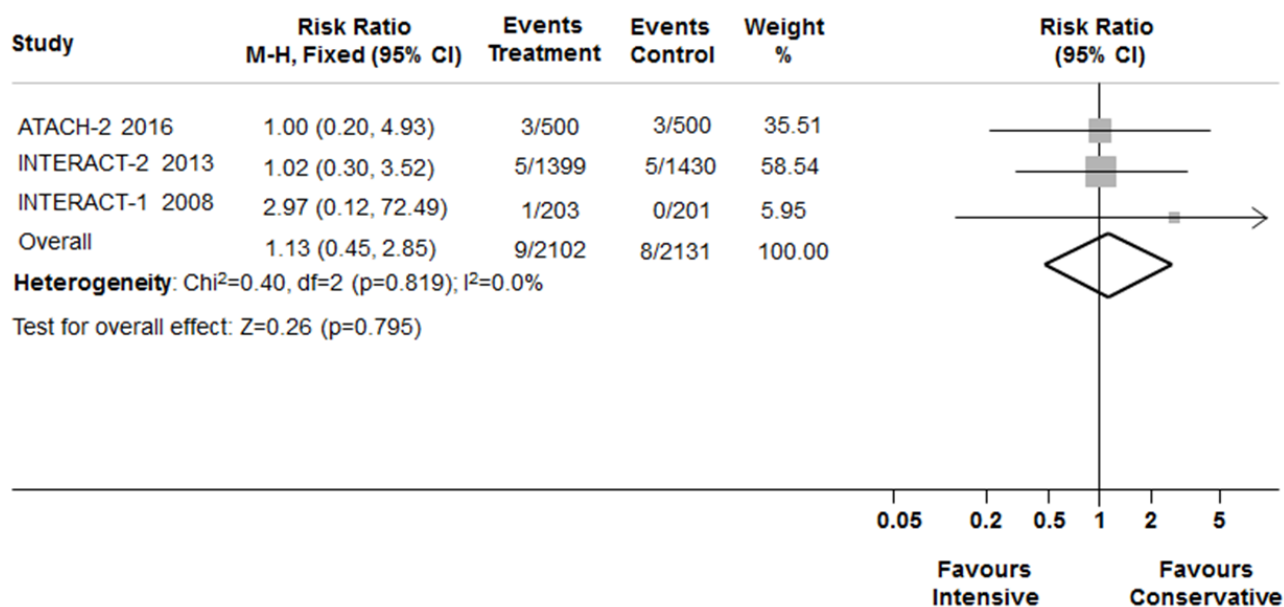
D. Any serious treatment-related adverse event within 3-months after randomization



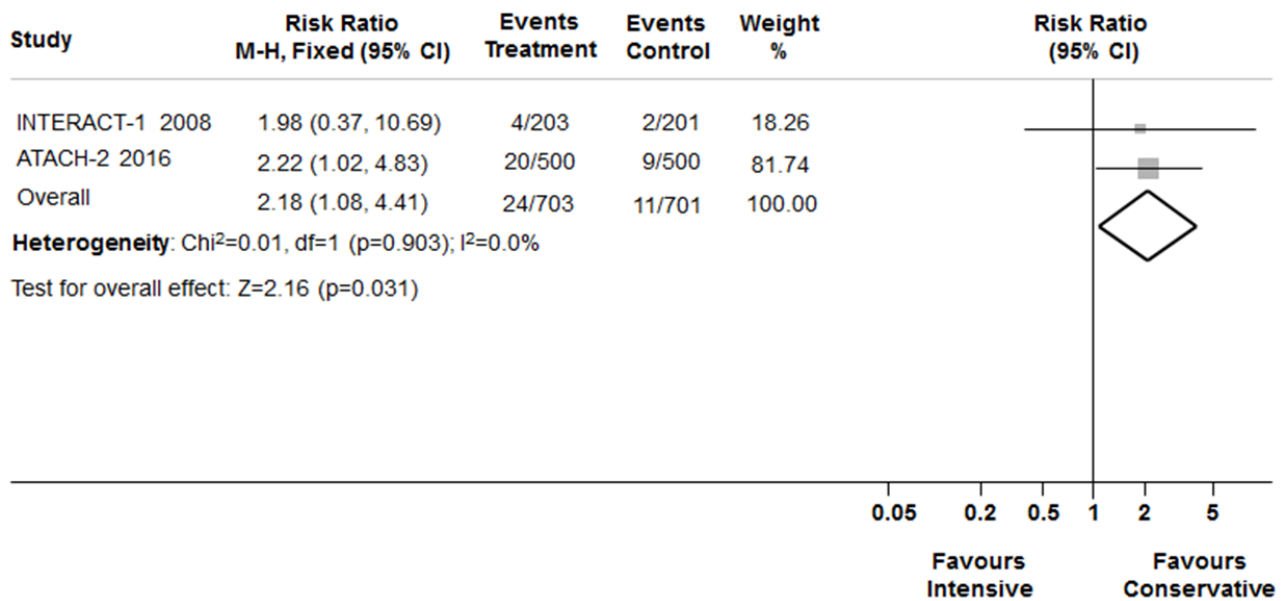
E. Recurrent stroke (ischemic or haemorrhagic)



F. Acute coronary events



G. Renal failure



Effect estimates are based on a fixed-effects model.

Abbreviations: ATACH=Antihypertensive Treatment of Acute Cerebral Hemorrhage;

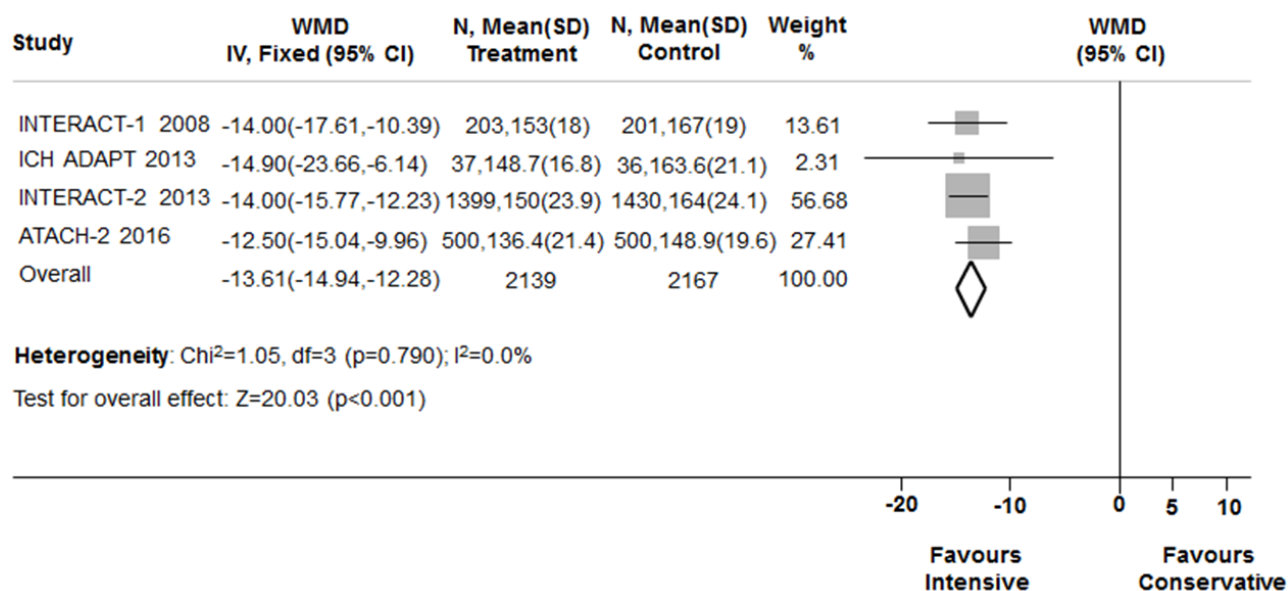
CI=confidence interval; df =degree of freedom; ICH ADAPT=The Intracerebral Hemorrhage

Acutely Decreasing Arterial Pressure Trial; INTERACT=Intensive Blood Pressure Reduction in

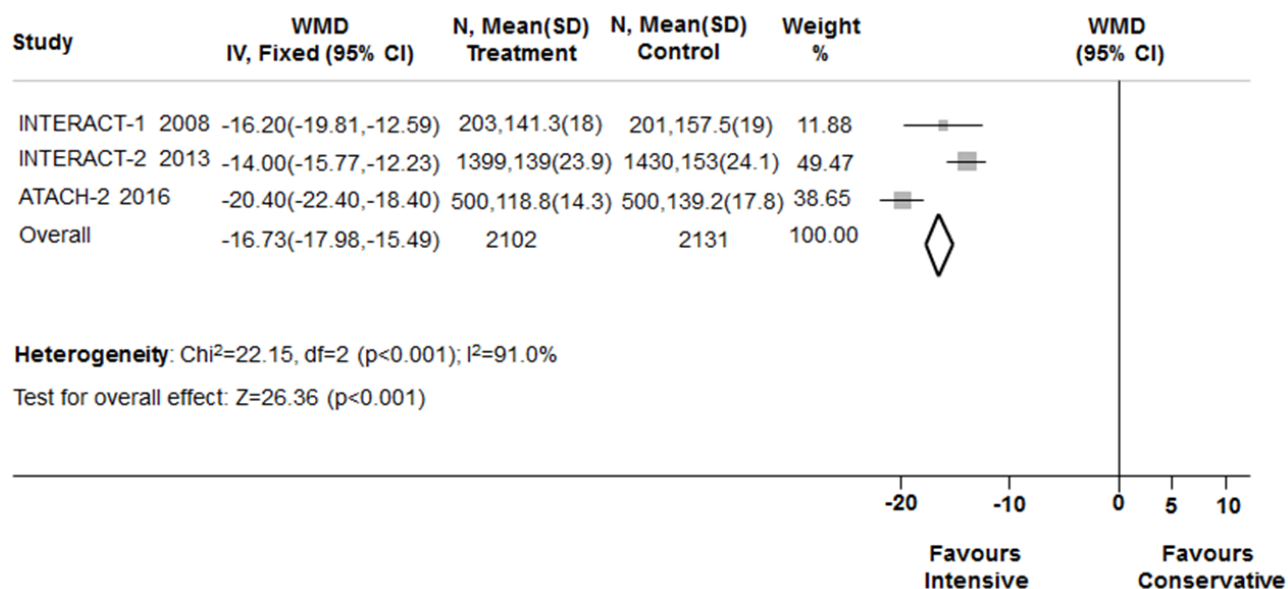
Acute Cerebral Haemorrhage Trial; M-H=Mantel-Haenszel.

Figure e-2: Systolic blood pressure levels at 1, 6 and 24 hours since randomization in intensive versus conservative treatment

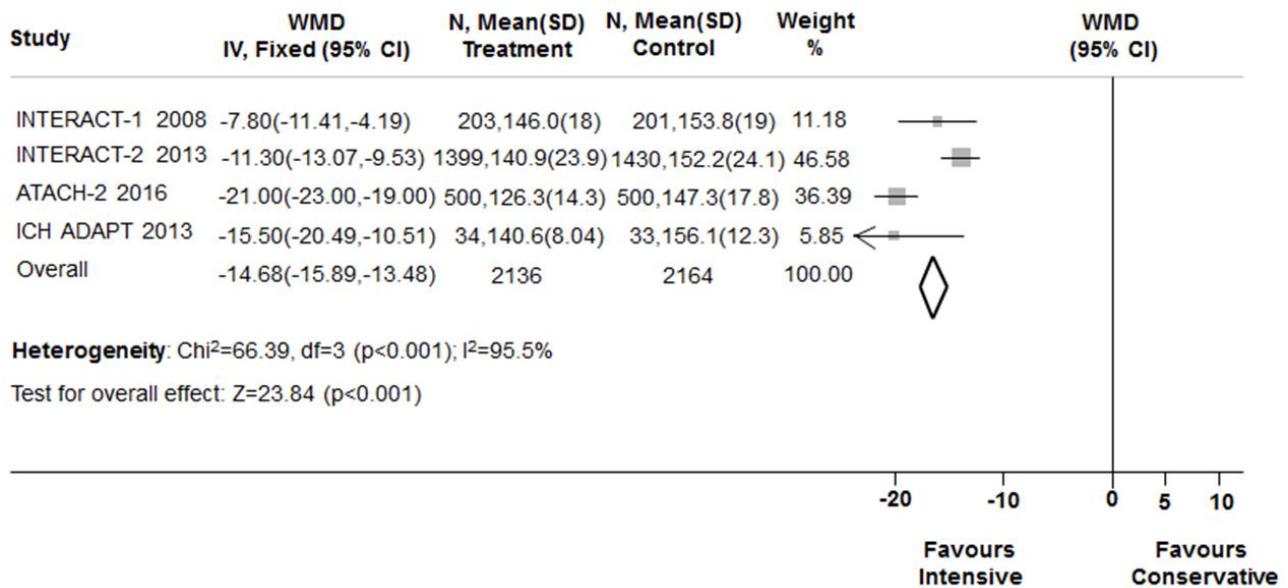
A. Systolic blood pressure at 1 hour since randomization



B. Systolic blood pressure at 6 hours since randomization



C. Systolic blood pressure at 24 hours since randomization



Effect estimates are based on a fixed-effects model. Where SD was not provided or could not be obtained from graph in trial publication, baseline data were used as conservative strategy.

Abbreviations: ATACH=Antihypertensive Treatment of Acute Cerebral Hemorrhage;

CI=confidence interval; df =degree of freedom; ICH ADAPT=The Intracerebral Hemorrhage

Acutely Decreasing Arterial Pressure Trial; INTERACT=Intensive Blood Pressure Reduction in

Acute Cerebral Haemorrhage Trial; IV=inverse variance; SD=standard deviation; WMD=weighted mean difference.

Table e-3 Estimates of outcomes from random-effects analysis

Outcome	No. of studies	Effect size (95% CI)
Three-month mortality	5	RR 0.99 (0.83-1.17)
Three-month death or major disability	4	RR 0.96 (0.91-1.01)
Absolute hematoma growth at 24 hours after randomization	3	WMD -1.53 (-2.94 to -0.13)
Substantial hematoma growth at 24 hours after randomization	5	RR 0.86 (0.74-1.01)
Early neurological deterioration	5	RR 1.03 (0.88-1.19)
Hypotension within 72 hours after randomization	2	RR 1.55 (0.60-4.00)
Severe hypotension within 72 hours after randomization	2	RR 0.84 (0.37-1.95)
Any serious treatment-related adverse event within 3 months after randomization	3	RR 1.07 (0.90-1.29)
Recurrent stroke (ischemic or haemorrhagic) within 3 months after randomization	2	RR 0.95 (0.46-1.97)
Acute coronary events within 3 months after randomization	3	RR 1.11 (0.44-2.83)
Renal failure within 3 months after randomization	2	RR 2.18 (1.08-4.41)
Systolic blood pressure at 1 hour since randomization	4	WMD -13.61 (-14.94 to -12.28)
Systolic blood pressure at 6 hours since randomization	3	WMD -16.88 (-21.32 to -12.44)
Systolic blood pressure at 24 hours since randomization	4	WMD -13.94 (-20.19 to -7.68)

Abbreviations: CI=confidence interval; RR=risk ratio; WMD=weighted mean difference.

e-Appendix I

PubMed search strategy

The strategy was based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials.^{e-1}

- #1 random* OR trial* [Title/Abstract]
- #2 "Randomized Controlled Trial"[Publication Type]
- #3 "Controlled Clinical Trial"[Publication Type]
- #4 #1 OR #2 OR #3
- #5 blood pressure [Title/Abstract] OR blood-pressure [Title/Abstract] OR blood pressure [MeSH Terms]
- #6 intracranial hemorrhage [Title/Abstract] OR cerebral hemorrhage [Title/Abstract] OR intracranial hemorrhage [MeSH Terms] OR cerebral hemorrhage [MeSH Terms]
- #7 #5 AND #6
- #8 #4 AND #7

CENTRAL search strategy (“Cochrane Review Group: Stroke Group” | “Trials”)

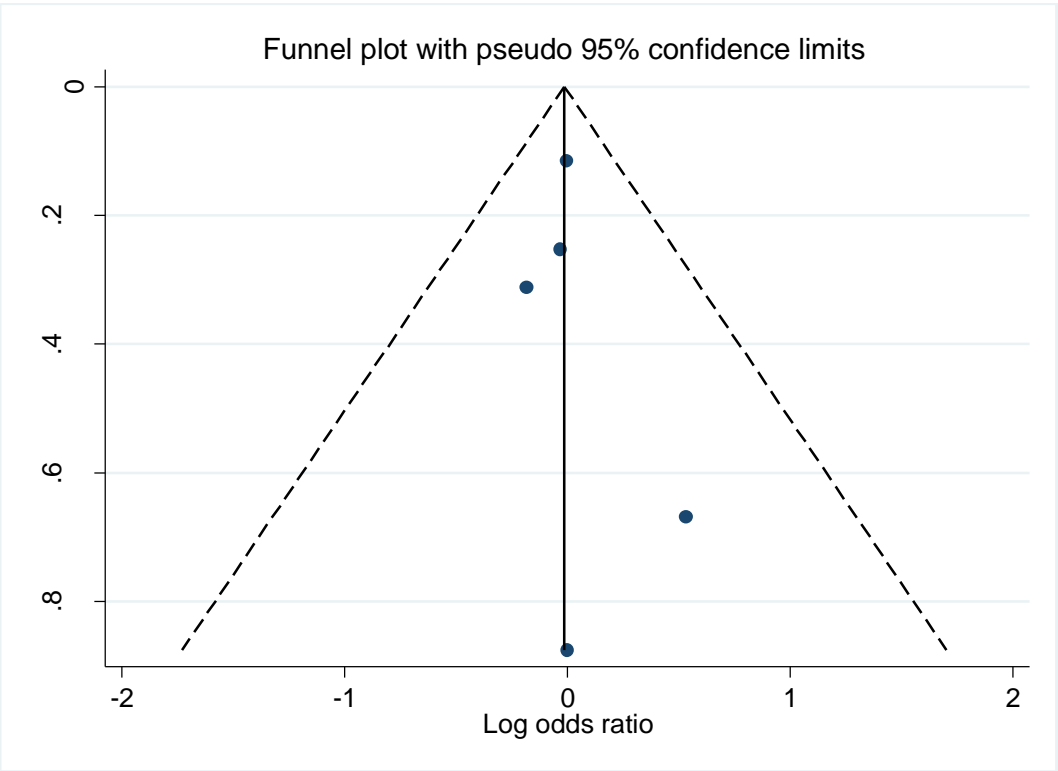
- #1 blood pressure
- #2 intracranial OR cerebral hemorrhage
- #3 (#1 AND #2)

ClinicalTrials.gov search strategy

“blood pressure” AND (intracranial OR cerebral hemorrhage”) | ”Interventional Studies”

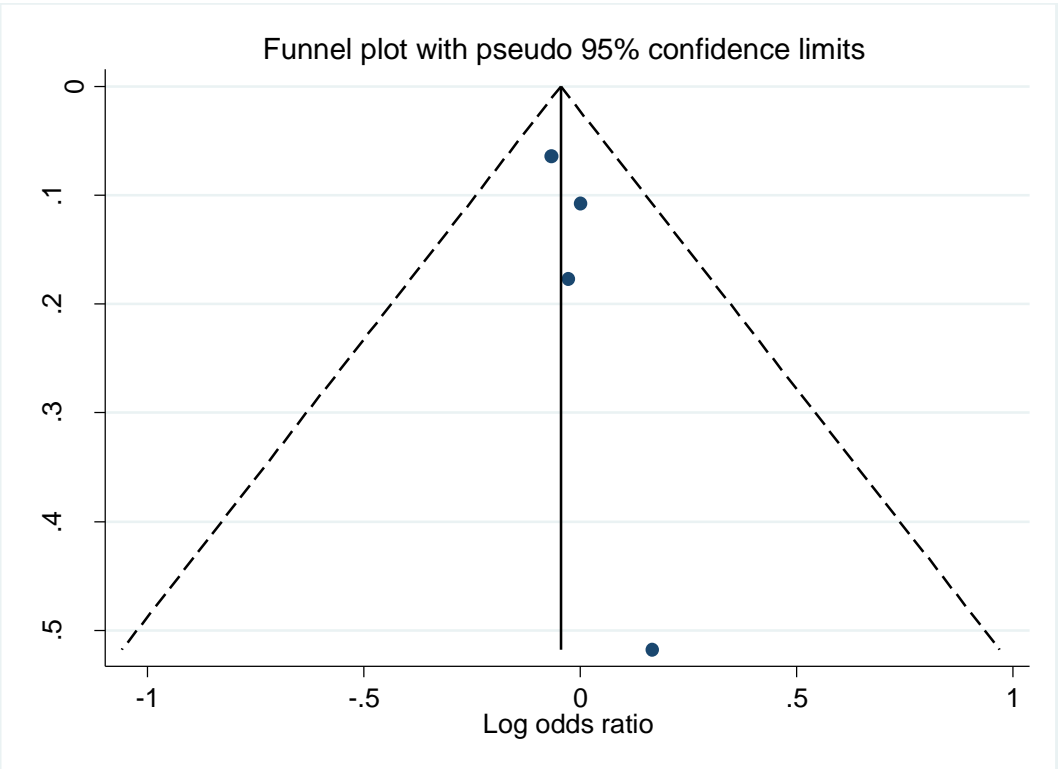
e-Appendix II

Funnel plot of comparison: Intensive versus conservative, outcome: 3-month mortality



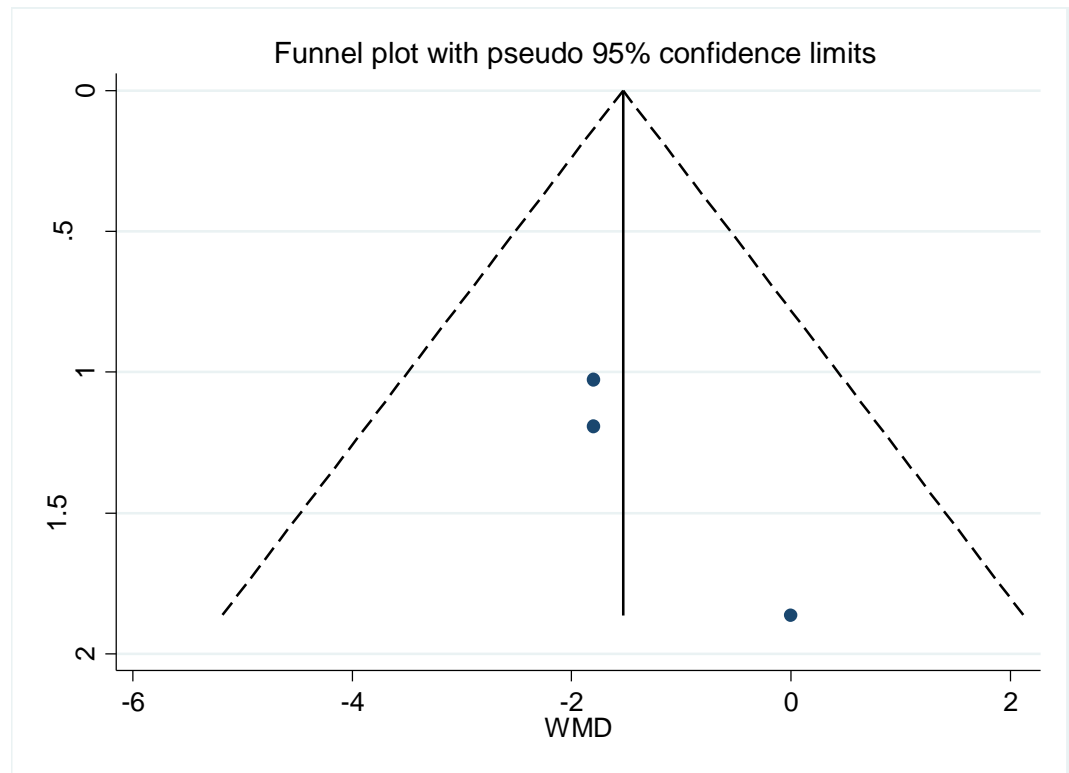
Egger statistical test $p=0.708$

Funnel plot of comparison: Intensive versus conservative, outcome: 3-month death or major disability



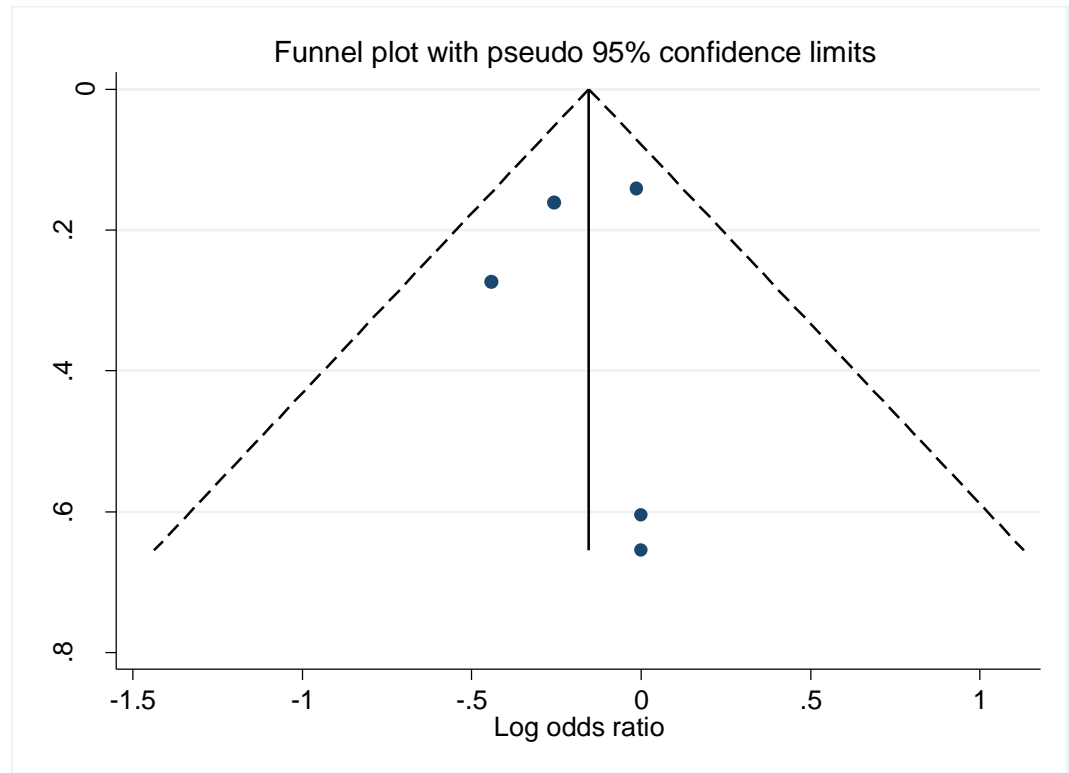
Egger statistical test $p=0.179$

Funnel plot of comparison: Intensive versus conservative, outcome: absolute hematoma growth



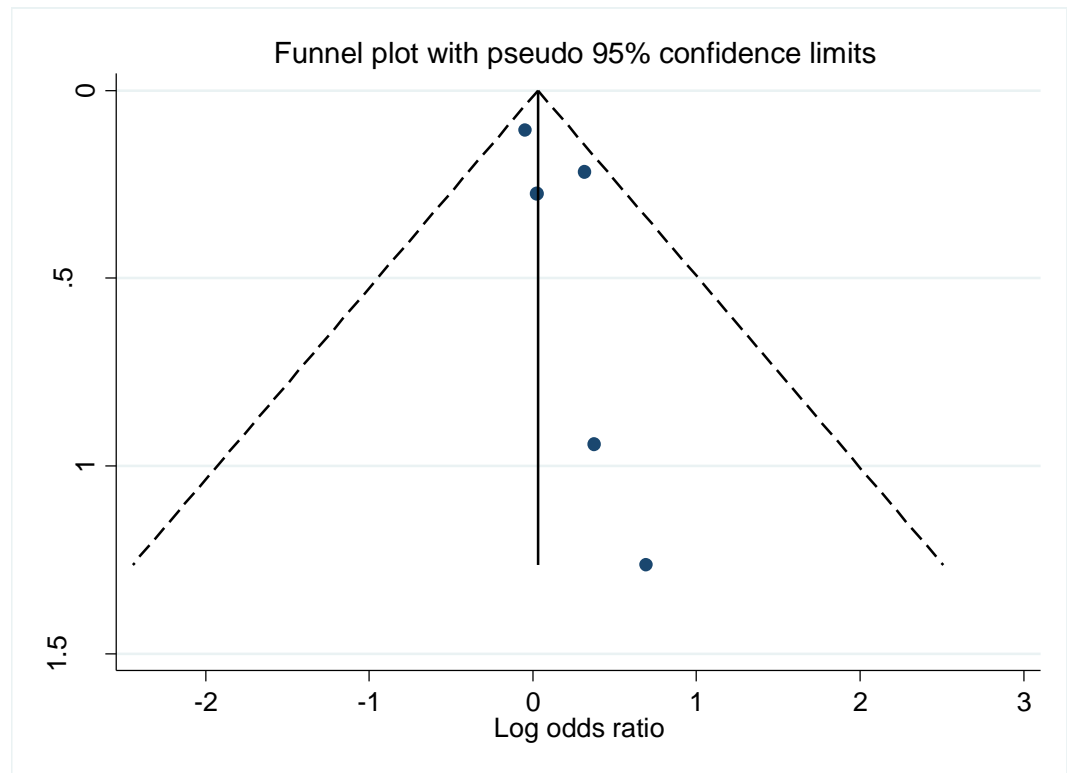
Egger statistical test $p=0.172$

Funnel plot of comparison: Intensive versus conservative, outcome: substantial hematoma enlargement



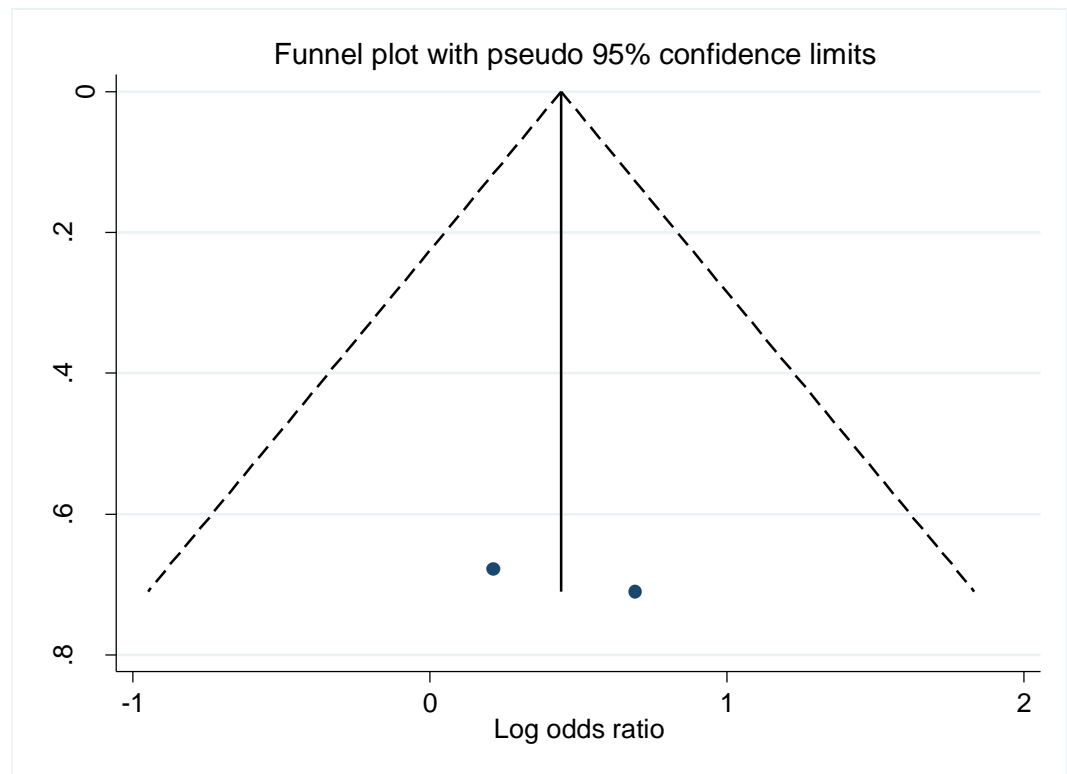
Egger statistical test $p=0.851$

Funnel plot of comparison: Intensive versus conservative, outcome: early neurological deterioration

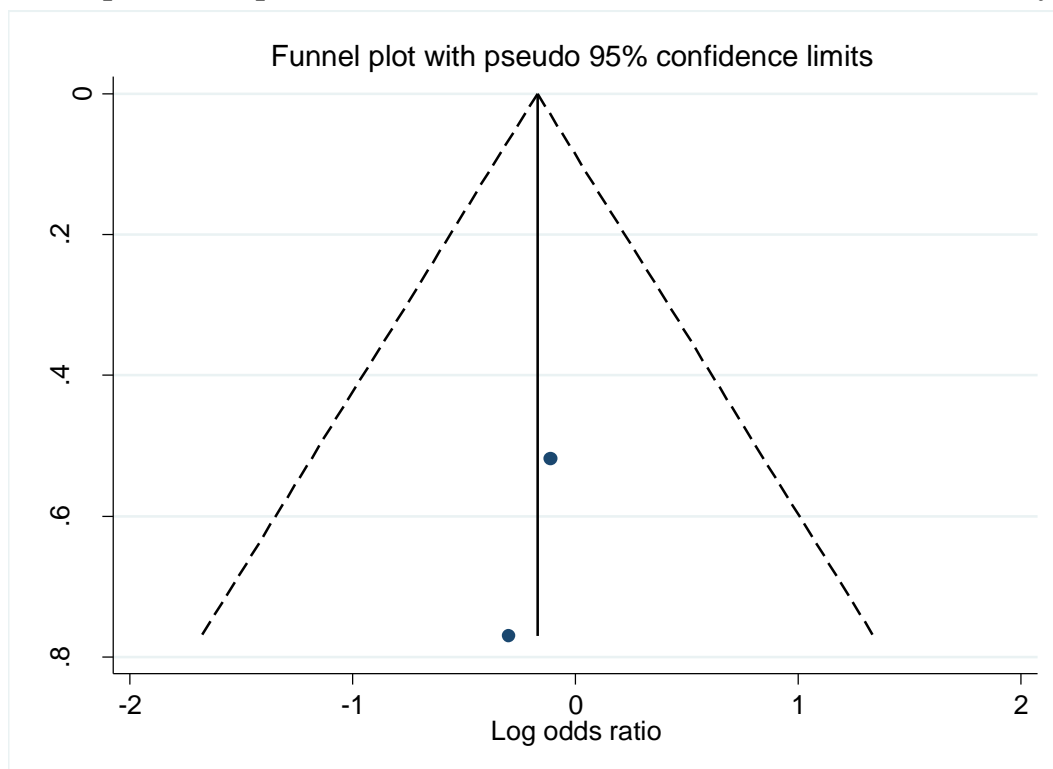


Egger statistical test $p=0.244$

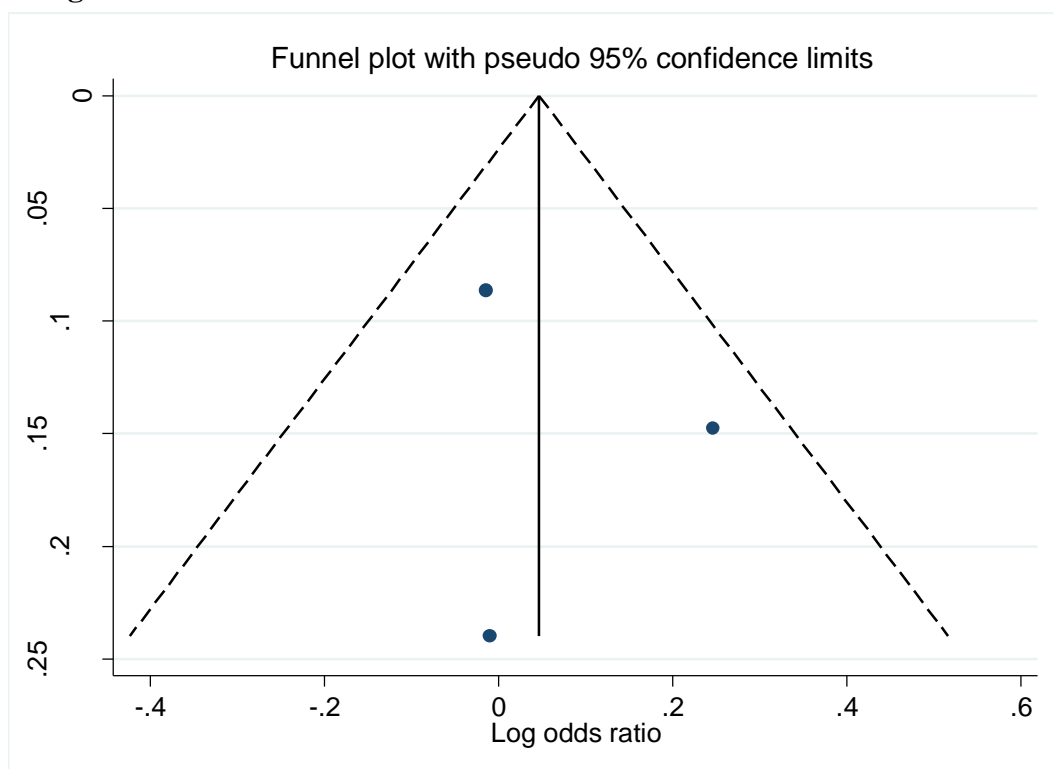
Funnel plot of comparison: Intensive versus conservative, outcome: hypotension



Funnel plot of comparison: Intensive versus conservative, outcome: severe hypotension

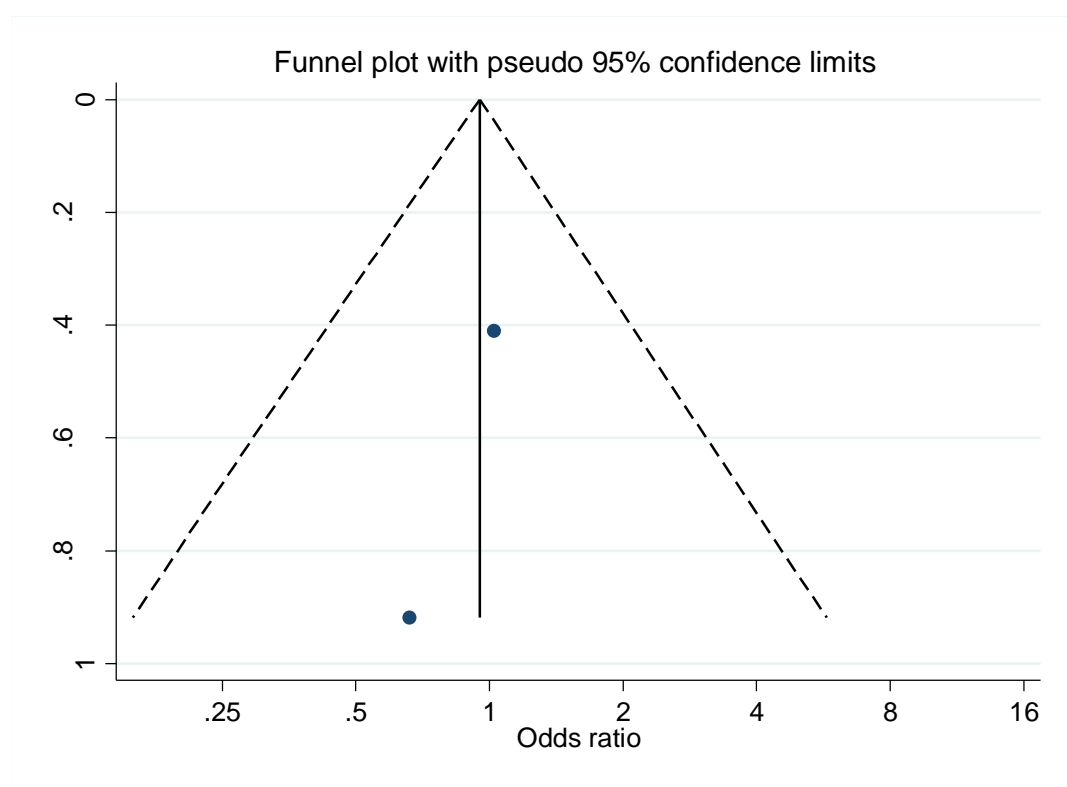


Funnel plot of comparison: Intensive versus conservative, outcome: any serious treatment-emergent adverse event

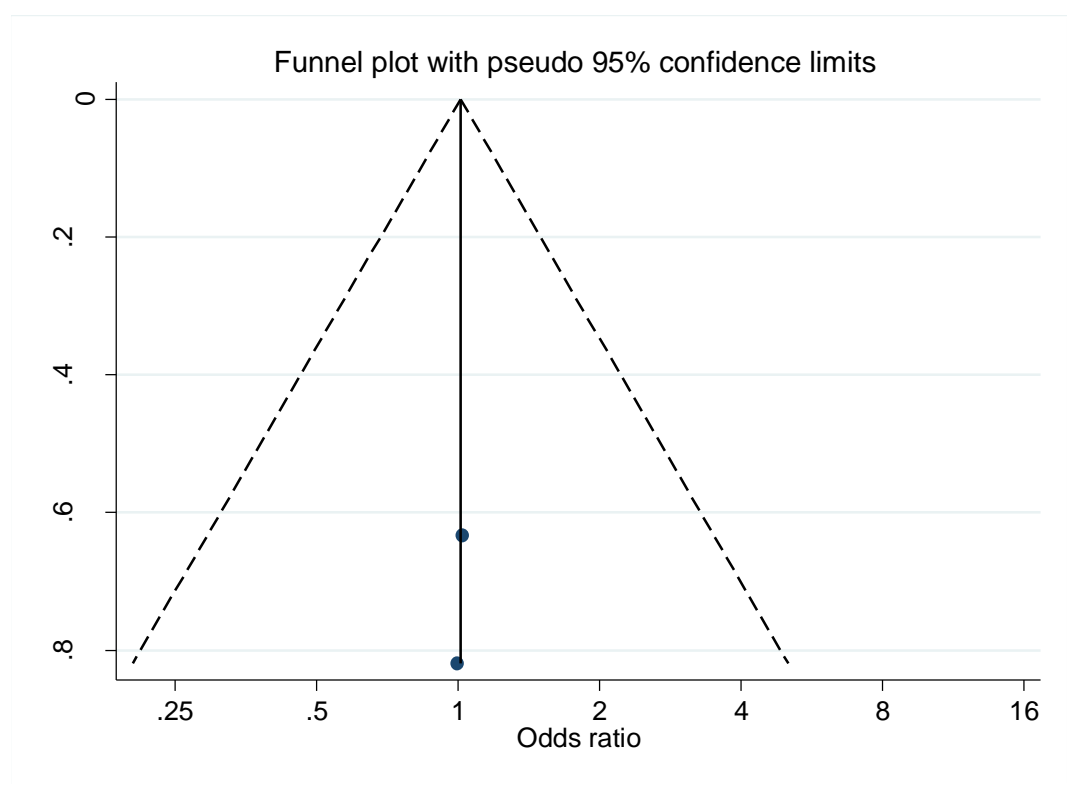


Egger statistical test $p=0.734$

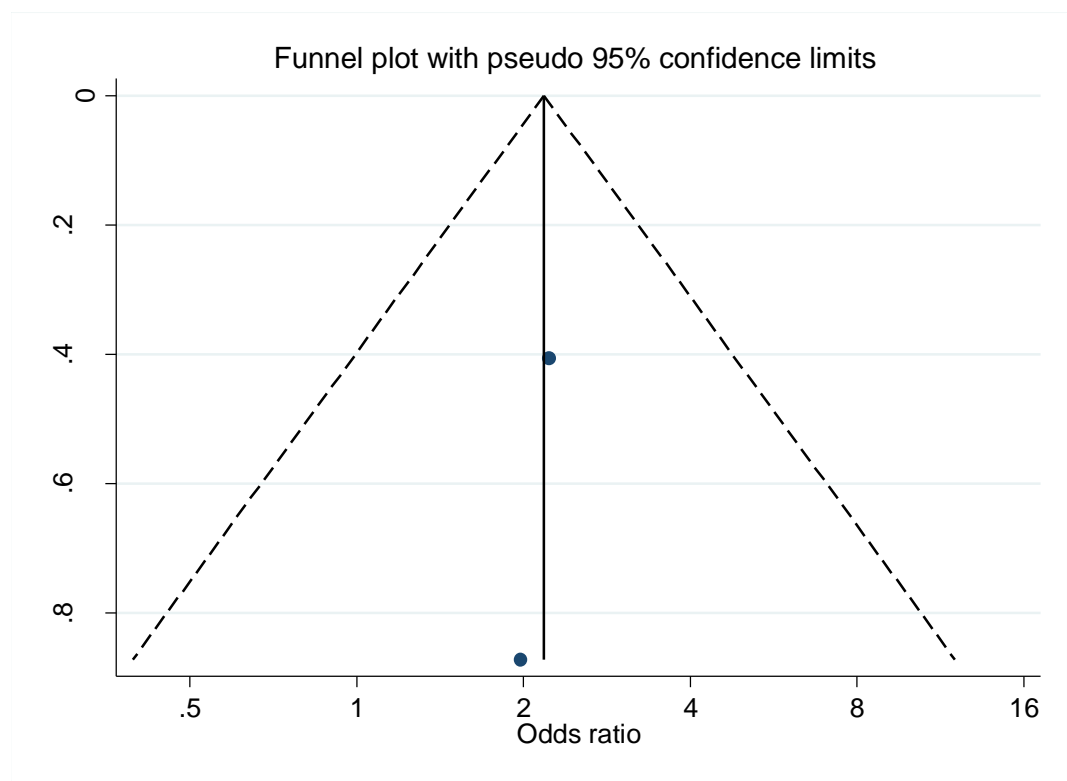
Funnel plot of comparison: Intensive versus conservative, outcome: recurrent stroke



Funnel plot of comparison: Intensive versus conservative, outcome: acute coronary event



Funnel plot of comparison: Intensive versus conservative, outcome: renal failure



e-Reference

e-1 Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from www.cochranehandbook.org.