Supplementary Online Content

McIntyre WF, Um KJ, et al. Vasopressin in addition to catecholaminergic vasopressors in the treatment of vasodilatory shock: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2018.4528

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

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eAppendix 1 – MEDLINE Search Strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Feb 25 2018
Search Strategy:
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1 exp shock/ or exp Sepsis Syndrome/ or exp Shock, Septic/ or exp Shock, Surgical/ or exp Shock, Traumatic/ or exp hypotension/ or exp Intensive Care/ (226606)
2 (shock or sepsi* or septi* or vasoplegic shock or distributive shock or surgical shock or traumatic shock or anaphylactic shock or allergic shock or burn shock or vasodilatory shock).mp. (329552)
3 ((circulatory adj6 failure) or (hypotension and (care adj5 (critical or intensive)))).mp. (5838)
4 1 or 2 or 3 (442735)
5 exp Vasopressins/ or exp Argipressin/ or exp Deamino Arginine Vasopressin/ or exp Lypressin/ or exp Felypressin/ or exp Ornipressin/ or exp Terlipressin/ (34972)
6 (Vasopressin* or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin or Pituitrin).mp. (46770)
7 5 or 6 (46770)
8 exp Epinephrine/ or exp Norepinephrine/ or exp Catecholamines/ or exp Orciprenaline/ or exp dobutamine/ or exp dopamine/ (248859)
9 (Epinephrin* or Norepinephrin* or Catecholamin* or Orciprenalin* or dobutamin* or dopamin* or adrenalin* or noradrenalin*).mp. (345736)
10 8 or 9 (385350)
11 4 and 7 and 10 (872)
12 (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or random allocation.sh. or double-blind method.sh. or single-blind method.sh. or clinical trial.pt. or explode clinical trials as topic.mp. or (clinic: adj25 trial:).ti,ab. or ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).ti,ab. or placebos.sh. or placebo:.ti,ab. or random:.ti,ab. or research design.sh. or comparative study.sh. or explode evaluation studies.mp. or follow-up studies.sh. or prospective studies.sh. or (control: or prospectiv: or volunteer:).ti,ab. or cross-over studies.sh. or latin square:.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6554473)
13 (animals not humans).sh. (4396188)
14 12 not 13 (5375354)
15 11 and 14 (314)

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eAppendix 2 – EMBASE search strategy

Database(s): EMBASE 1980 to 2018 Week 09
Search Strategy:

#	Searches	Results
1	exp Septic Shock/ or exp Shock/ or exp Sepsis/ or exp Traumatic Shock/ or exp Hypotension/ or exp Intensive Care/	930538
2	(shock or sepsi* or septi* or vasoplegic shock or distributive shock or surgical shock or traumatic shock or anaphylactic shock or allergic shock or burn shock or vasodilatory shock or ((circulatory adj6 failure) or (hypotension and (care adj5 (critical or intensive))))).ti,ab.	342788
3	1 or 2	1090977
4	Vasopressin Derivative/ or Argipressin/ or Lypressin/ or Felypressin/ or Ornipressin/ or Terlipressin/	22557
5	(Vasopressin* or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin or Pituitrin).ti,ab.	38774
6	4 or 5	47953
7	exp Adrenalin/ or exp Noradrenalin/ or exp Norepinephrine/ or exp Epinephrine/ or exp Catecholamine/ or exp Orciprenaline/ or exp Dobutamine/ or exp Dopamine/	288424
8	(Epinephrin* or Norepinephrin* or Catecholamin* or Orciprenalin* or dobutamin* or dopamin* or adrenalin* or noradrenalin*).ti,ab.	320276
9	7 or 8	440462
10	3 and 6 and 9	2181
11	(controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) and human*.ec,hw,fs.	1565407
12	random:.tw. or clinical trial:.mp. or exp health care quality/	4439121
13	11 or 12	4614283
14	10 and 13	1006

eAppendix 3 – Cochrane CENTRAL search strategy

Date Run: 25/02/18 19:48:43.175
Description:

ID	Search	Hits
#1	MeSH descriptor: [Shock] explode all trees	1638
#2	MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees	3970
#3	MeSH descriptor: [Shock, Septic] explode all trees	565
#4	MeSH descriptor: [Shock, Surgical] explode all trees	8
#5	MeSH descriptor: [Shock, Traumatic] explode all trees	51
#6	MeSH descriptor: [Hypotension] explode all trees	1705
#7	MeSH descriptor: [Vasoplegia] explode all trees	3
#8	MeSH descriptor: [Critical Care] explode all trees	2219
#9	circulatory near failure:ti,ab,kw (Word variations have been searched)	95
#10	shock or sepsi* or septi* or vasoplegic shock or distributive shock or surgical shock or traumatic shock or anaphylactic shock or allergic shock or burn shock or vasodilatory shock	16646
#11	hypotension and ((critical near care) or (intensive near care))	1623
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	22957
#13	MeSH descriptor: [Vasopressins] explode all trees	1178
#14	MeSH descriptor: [Arginine Vasopressin] explode all trees	622
#15	MeSH descriptor: [Deamino Arginine Vasopressin] explode all trees	343
#16	MeSH descriptor: [Lypressin] explode all trees	170
#17	MeSH descriptor: [Felypressin] explode all trees	24
#18	MeSH descriptor: [Ornipressin] explode all trees	13
#19	Vasopressin* or argipressin or desmopressin or lypressin or felypressin or ornipressin or terlipressin or glypressin or pituitrin	2716
#20	#13 or #14 or #15 or #16 or #17 or #18 or #19	2716
#21	MeSH descriptor: [Epinephrine] explode all trees	4147
#22	MeSH descriptor: [Norepinephrine] explode all trees	2543
#23	MeSH descriptor: [Catecholamines] explode all trees	9170
#24	MeSH descriptor: [Dobutamine] explode all trees	497
#25	MeSH descriptor: [Dopamine] explode all trees	1119
#26	epinephrin* or norepinephrin* or catecholamin* or dobutamin* or dopamin* or adrenalin* or noradrenalin*	21551
#27	#21 or #22 or #23 or #24 or #25 or #26	23700
#28	#12 and #20 and #27	185

eAppendix 4 – Basis for Outcome Selection

A number of different outcomes are important for patients with vasodilatory shock. The Core Outcome Measures in Effectiveness Trials Initiative database contains a single article reporting on core outcome sets in patients with shock.[1] This publication from the International Sepsis Forum acknowledges the heterogeneous clinical populations and recommends that studies choose outcome measures that reflect the underlying physiology. Thus, in addition to mortality, length of stay and general quality of life, this review includes specific indicators of organ injury, all of which can result in significant functional impairment and disability and are generally considered to be patient-important.[2] Outcome importance scores were derived from a convenience sample of 5 physicians, 2 physicians' assistants, 5 nurses and 4 patients. Mortality, stroke, myocardial injury, requirement for renal replacement therapy, limb ischemia and ICU length of stay were rated as "critically important". Ventricular arrhythmia, length of hospital stay and atrial fibrillation were rated as "important".

Outcome importance Scores

We evaluated the importance of each outcome as per GRADE with scores 1-3 meaning not important, 4-6 meaning important and 7-9 meaning critically important. Importance scores were obtained by polling a convenience sample of patients and healthcare providers in three intensive care units (2 medical-surgical and one post-cardiac surgery) at a large, academic tertiary hospital.

eAppendix 5 – Outcome Importance for Choice of Vasopressor in Patients with Vasodilatory Shock

	Mean	Standard Deviation
Mortality (28 days)	**9**	**1**
Stroke	**8**	**2**
Myocardial Injury	**7**	**2**
Requirement for Renal Replacement Therapy	**7**	**1**
Limb Ischemia	**7**	**2**
ICU LOS	**7**	**2**
Ventricular Arrhythmia	**6**	**2**
Atrial Fibrillation	**6**	**2**
Hospital LOS	**6**	**2**

9 = Critically Important, 1 = Not Important
Respondents: ICU Physicians (3), Non-ICU Physicians (2), ICU Physicians Assistants (2), ICU Nurses (5), Patients (4)

ICU = Intensive Care Unit; LOS = Length of Stay

Assessed with an in-person survey at Hamilton General Hospital in March 2017

Respondents:

ICU Physicians (3)

ICU Physicians' Assistants (2)

ICU Nurses (5)

Patients (4)

eAppendix 6 – Characteristics of Included Studies

Abdullah 2012[3]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Egypt	
Participants	Adult patients with paracentesis-induced vasodilatory shock and end-stage liver disease Mean age = 59 years, 74% male, Childs C score = 62% (N=34)	
Interventions	Terlipressin 1 mg over 30 minutes then continuous infusion of 2mcg/kg/h, titrated up, weaned within 24 h Versus Norepinephrine starting at 0.1 mcg/kg/min, titrated up, weaned within 24 h	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, myocardial injury (e.g. altered ST segments), ventricular arrhythmia, acute kidney injury (numbers provided for only one group).	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	No funding source. Declarations of interest: not stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Described as randomized but method not mentioned
Allocation concealment (selection bias)	Likely low risk of bias	Randomized through closed envelopes, no specification of opacity
Blinding of participants and personnel (performance bias)	High risk of bias	Not blinded
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Not blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Not blinded, but objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	No loss of data after randomization
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	All primary outcomes reported, protocol mentioned
Other bias	Low risk of bias	None detected

Acevedo 2009[4]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Spain	
Participants	Adult participants with cirrhosis and septic shock (N=24)	
Interventions	Terlipressin 1-2mg/4h versus Adrenergic drugs as needed	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Abstract	Mortality (ICU, in-hospital), acute kidney injury, and other non-specified adverse events	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	No funding source stated. Declarations of interest: not stated.	
Notes	Abstract only.	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Described as randomized but method not mentioned
Allocation concealment (selection bias)	Likely high risk of bias	No description of concealment, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour
Blinding of participants and personnel (performance bias)	High risk of bias	Open-label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Not blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Not blinded, but objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk of bias	Not specified whether or not exclusion happened after randomization, but very short follow-up
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol, but expected outcomes
Other bias	High risk of bias	Published only as abstract

Albanese 2005[5]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in France	
Participants	Adult participants with septic shock and two or more organ dysfunctions Mean age = 66 years, 65% male, 70% lung infection, APACHE II score = 28.5 (N = 20)	
Interventions	Terlipressin 1 mg bolus, followed by second bolus 1 mg if MAP <65 mm Hg versus Norepinephrine started with 0.3 mcg/kg and increased by 0.3 mcg/kg every 4 minutes until MAP 65 to 75 mm Hg	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	In-hospital mortality, renal function (urine flow, creatinine clearance up to 8 hours [presented on a graph only, no numbers provided], hemodynamic parameters, blood gas, lactate at 6 hours. For the mortality analysis, we used data on in-hospital mortality	
Outcomes Clarified by Contacting Authors	Authors indicated that no further data was available.	
Potential Conflicts	No funding source. Declarations of interest: none.	
Notes	Unpublished information made available from authors.	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk	Computer generated randomization schedule
Allocation concealment (selection bias)	Likely low risk	No description of concealment, but balanced groups and experienced research centre
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High Risk	Not blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk	Not blinded, but objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk	Not specified whether exclusion happened after randomization, but very short follow-up
Selective reporting (reporting bias) *All outcomes*	Likely low risk	All outcomes reported as specified
Other bias	Low risk	None detected

Barzegar 2014[6]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Iran	
Participants	Adult participants with septic shock within 12 hours of ICU admission. Mean age = 64 years, 63% male, 43% lung infection, SOFA score = 12 (N= 30)	
Interventions	Vasopressin 0.03 u/min versus Norepinephrine adjusted to MAP > 65 mm Hg	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Mortality (e.g. ICU, 28 days), requirement for renal replacement therapy, limb ischemia (i.e. digital ischemia), and ICU length of stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	No funding source stated. Declarations of interest: none stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Data-processor generated random number list
Allocation concealment (selection bias)	Likely high risk of bias	No description of concealment, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Neither clinicians nor researchers were blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	High risk of bias	Open-label
Blinding of outcome assessment (detection bias) *Other outcomes*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	Randomization after exclusion. Reasons mentioned. Complete follow up
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	All primary outcomes pre-specified and reported. Protocol is explained.
Other bias	Low risk of bias	None detected

Capoletto 2017[7]

Methods	Double-blind randomized controlled study at a hospital in Brazil	
Participants	Adult participants with cancer and septic shock (N=107)	
Interventions	Vasopressin (not described) versus Norepinephrine (not described)	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Abstract	28-day mortality, other unspecified serious adverse events	
Outcomes Clarified by Contacting Authors	Atrial Fibrillation, Ventricular Arrhythmia, Myocardial Injury, Stroke, Acute Kidney Injury, Renal Replacement Therapy, Limb Ischemia, Length of ICU Stay, Length of Hospital Stay, 30 and 90 day mortality	
Potential Conflicts	Funding source: not stated. Declarations of interest: none stated.	
Notes	NCT01718613	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Not stated, but authors have no issues previously
Allocation concealment (selection bias)	Likely low risk of bias	Not stated, but authors have no issues previously
Blinding of participants and personnel (performance bias)	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk of bias	No issues previously with authors
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	Outcomes consistent with NCT registered protocol
Other bias	High risk of bias	Abstract only

Chen 2017[8]

Methods	Single-blind randomized controlled study at a hospital in China	
Participants	Adult participants with ARDS and septic shock (N=57)	
Interventions	Terlipressin (0.01-0.04U/min) and norepinephrine as needed to maintain MAP between 65 and 75 mm Hg versus Norepinephrine (>1mcg/min)	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	28-day mortality, Length of ICU Stay, Length of Hospital Stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No response from authors	
Potential Conflicts	Funding source: Social Development Fund of Jiangxi Province (20151BBG70120). Declarations of interest: none stated.	
Notes		
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Randomization by randomised number table derived by computer.
Allocation concealment (selection bias)	Likely high risk of bias	Not described
Blinding of participants and personnel (performance bias)	High risk of bias	Single blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Single blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely high risk of bias	Large numbers of post-randomization exclusions in both arms
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol to review, but standard outcomes are reported
Other bias	Low risk of bias	None detected

Choudhury 2016[9]

Methods	Single-centre open-label randomized controlled study at an institutional hospital in India	
Participants	Adult participants with cirrhosis and septic shock Mean age = 48 years, 82% male, 35% lung infection, SOFA score = 14.3 (N=84)	
Interventions	Terlipressin 1.3-5.2mcg/min over 24 h versus Norepinephrine 7.5-60mcg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, 28-day mortality, ventricular arrhythmia (e.g. ventricular tachycardia), limb ischemia (i.e. peripheral cyanosis), hospital and ICU lengths of stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	Funding source not stated. Declarations of interest: none stated.	
Notes	NCT01836224	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Describes block randomization, but does not describe how blocks were generated
Allocation concealment (selection bias)	Low risk of bias	Used SNOSE technique
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All patients accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	All primary outcomes pre-specified and reported. Protocol is explained.
Other bias	Low risk of bias	None detected

Clem 2016[10]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in the United States	
Participants	Adult participants with septic shock APACHE II score = 26 (N=82)	
Interventions	Vasopressin and norepinephrine: norepinephrine (0.05 to 0.5 mcg/kg/min) and vasopressin (0.04 units/min) given by continuous infusion to achieve and maintain a target mean arterial pressure (65-75 mm Hg) versus Norepinephrine (0.05 to 0.5 mcg/kg/min) will be given by continuous infusion to achieve and maintain a target mean arterial pressure (65-75 mm Hg)	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Abstract	Mortality	
Outcomes Clarified by Contacting Authors	Atrial fibrillation, Ventricular Arrhythmia	
Potential Conflicts	Funding source not stated. Declarations of interest: not stated.	
Notes	Unpublished information made available from authors. NCT02454348, NOVEL Trial	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	No description, but described as randomized
Allocation concealment (selection bias)	Likely low risk of bias	No description but registered protocol, experienced research team and no obvious differences between groups.
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk of bias	Complete follow up
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	All primary outcomes pre-specified and reported. Protocol is registered and explained.
Other bias	High risk of bias	Currently published only as abstract

Dünser 2003[11]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Austria	
Participants	Adult participants (some post cardiotomy) with vasodilatory shock. Systemic Inflammatory Response Syndrome (29%), Septic Shock (31%), Post-cardiotomy shock (40%) Mean age = 68 years, MODS score = 12 (N=48)	
Interventions	Vasopressin at a constant rate of 4 U/h versus Norepinephrine: in NE patients, MAP 70 mm Hg was achieved by adjusting NE infusion as necessary. For those patients in whom NE requirements exceeded 2.26 mcg/ kg/min, AVP was added	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, ICU mortality, myocardial injury (e.g. myocardial infarction or ischemia), requirement for renal replacement therapy, ICU length of stay	
Outcomes Clarified by Contacting Authors	Atrial Fibrillation, Mortality, Myocardial Infarction, Acute Kidney Injury	
Potential Conflicts	Funding source: Lorenz Böhler Fund. Declarations of interest: none stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Using a random number-generating scheme
Allocation concealment (selection bias)	Low risk of bias	No description, but experienced research team and no obvious differences between groups.
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All outcomes reported
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	No protocol, standard outcomes
Other bias	Low risk of bias	None detected

Fonseca Ruiz 2013[12]

Methods	Single-centre open-label randomized controlled study at a hospital in Colombia	
Participants	Adult participants with septic shock Mean age = 58 years, 59% male, 34% lung infection, APACHE II score = 19 (N=30)	
Interventions	Vasopressin: noradrenaline plus vasopressin at titrated doses of 0.01 U / min and increasing every 10 minutes 0.01 U / min to achieve a mean arterial pressure (MAP) of 65 mm Hg or until reaching maximum doses of 0.04 U / min. versus Norepinephrine	
Open-label Catecholamines Permitted	Yes	
Outcomes	28-day mortality, limb ischemia (e.g. digital ischemia), hospital length of stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	Funding source: not stated. Declarations of interest: none stated.	
Notes	Identified by contacting the authors of an abstract that met inclusion criteria. Full-text in Spanish	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Patient randomization was done with statistical software
Allocation concealment (selection bias)	Low risk of bias	Assignment to the treatments was carried out using sealed envelopes
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All subjects accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	No protocol, but standard outcomes
Other bias	Low risk of bias	None detected

Gordon 2016[13]

Methods	Multicentre 2x2 factorial double blind with hydrocortisone randomized controlled study at 18 adult ICUs in the UK	
Participants	adult patients who had septic shock requiring vasopressors despite fluid resuscitation within a maximum of 6 hours after the onset of shock. Mean age = 66, 58% male, 40% lung infection, APACHE II score = 24 (N=421)	
Interventions	Vasopressin up to 0.06 U/min with target MAP 65-75 mm Hg or physician discretion Versus Norepinephrine up to 12 mcg/min with target MAP 65-75 mm Hg or physician discretion	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Mortality (e.g. ICU and 28 days), myocardial injury (e.g. acute coronary syndrome), requirement for renal replacement therapy, acute kidney injury, limb ischemia (e.g. digital ischemia), hospital and ICU lengths of stay	
Outcomes Clarified by Contacting Authors	Atrial fibrillation, Myocardial Ischemia	
Potential Conflicts	Funding source: UKNIHR. Declarations of interest: All authors submitted the ICMJE Form for Disclosure.	
Notes	ISRCTN20769191, VANISH Trial	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Variable block size randomization (4 and 8) using computer-generated random numbers, stratified by center.
Allocation concealment (selection bias)	Low risk of bias	Allocation sequence was prepared by an independent statistician in the Clinical Trials Unit and concealed from all investigators and clinicians.
Blinding of participants and personnel (performance bias)	Low risk of bias	Matching placebo and drug ampules.
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Blinded
Incomplete outcome data (attrition bias) *All outcomes*	Likely high risk of bias	Modified intention to treat analysis, 9 patients randomized in vasopressin arm but not analyzed exceed fragility threshold
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Consistent with published protocol
Other bias	Low risk of bias	None detected

Hajjar 2017[14]

Methods	Single-centre double-blind randomized controlled study at a tertiary care university hospital in Brazil	
Participants	Adult participants with post cardiac surgery vasoplegia Mean age = 55 years, 54% male (N=330)	
Interventions	Vasopressin 0.01 to 0.06 U/min with MAP >65 mm Hg Versus Norepinephrine 10-60 mcg/min with MAP >65 mm Hg	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, 30-day mortality, myocardial injury (e.g. postoperative acute myocardial infarction), ventricular arrhythmias, acute kidney injury, stroke, limb ischemia (not specified),hospital and ICU lengths of stay The initial primary outcomes were days alive and free of organ dysfunction at 28 days. However, after the trial had already started, because of the lack of outcome data in cardiac surgery, the study management committee decided that a more appropriate endpoint for cardiac surgery patients would be a composite endpoint of mortality or severe postoperative complications within 30 days	
Outcomes Clarified by Contacting Authors	None	
Potential Conflicts	Funding source: University of Brazil, Sanus Pharmaceutical. Declarations of interest: not stated.	
Notes	NCT01505231, VANCS Study	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Patients were assigned according to a computer-generated random list
Allocation concealment (selection bias)	Low risk of bias	Allocation was concealed using opaque envelopes.
Blinding of participants and personnel (performance bias)	Low risk of bias	Both study solutions were identical in appearance
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Blinded
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	High risk of bias	Described modified ITT, did per-protocol, exclusions were not specified in protocol
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Protocol change does not affect reported outcomes
Other bias	Low risk of bias	None detected

Han 2012[15]

Methods	Single-centre open-label randomized controlled study at a hospital in China	
Participants	Adult participants with septic shock Mean age = 72, 71% male, 56% lung infection, APACHE II score = 27.4 (N=139)	
Interventions	Pituitrin 1.0-2.5 U/h versus Norepinephrine 2-20 mcg/kg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	28-day mortality, ICU length of stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	Funding source: not stated. Declarations of interest: not stated.	
Notes	Full-text article in Chinese	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely high risk of bias	Process not described, large difference between arms
Allocation concealment (selection bias)	Likely high risk of bias	No description of concealment, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour, imbalance between groups
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely high risk of bias	Unclear why patients were excluded
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol, but standard outcomes
Other bias	N/A	N/A

Hua 2013[16]

Methods	Single-centre open-label randomized controlled study at a hospital in China	
Participants	Adult participants with acute respiratory distress syndrome (ARDS) and septic shock Mean age = 54 years, 56% male, 53% lung infection, APACHE II score = 18.5 (N=32)	
Interventions	Terlipressin continuous infusion of 1.3 mg/kg/h versus Dopamine infusion up to 20 mg/kg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	28-day mortality, hospital and ICU lengths of stay	
Outcomes Clarified by Contacting Authors	Authors contacted. No reply received.	
Potential Conflicts	Funding source: not stated. Declarations of interest: not stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-generated random number table
Allocation concealment (selection bias)	Likely high risk of bias	No description of concealment, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour, imbalance between groups
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Other outcomes*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All patients accounted for
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol, but standard outcomes
Other bias	Low risk of bias	None detected

Lauzier 2006[17]

Methods	Two-centre open-label randomized controlled study at tertiary care university hospitals in Canada	
Participants	Adult participants with septic shock Mean age = 55 years, 63% male, 47% lung infection, APACHE II score = 23.2 (N=23)	
Interventions	Vasopressin 0.04–0.20 U/min versus Norepinephrine 0.1–2.8 mcg/kg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, ICU mortality, myocardial injury (e.g. acute coronary syndrome), ventricular arrhythmias, requirement for renal replacement therapy	
Outcomes Clarified by Contacting Authors	None.	
Potential Conflicts	Funding source: Cardiovascular Critical Care Research Network FRSQ and departmental funding. Declarations of interest: not stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-generated block randomization list
Allocation concealment (selection bias)	Low risk of bias	Randomization was concealed using numbered, opaque sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All subjects accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	No protocol, but standard outcomes
Other bias	Low risk of bias	None detected

Malay 1999[18]

Methods	Single-centre double-blind randomized controlled study at a university hospital in the United States	
Participants	Adult participants with septic shock Mean age = 55 years, 80% male, 40% lung infection, APACHE II score = 27 (N=10)	
Interventions	Vasopressin 0.04 U/min versus Placebo	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, 24-hr mortality, myocardial injury (not specified), ventricular arrhythmias	
Outcomes Received by Contacting Authors	Atrial fibrillation	
Potential Conflicts	Funding source: Allegheny-Singer Research Institute. Declarations of interest: not stated.	
Notes	Unpublished information made available from authors.	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-generated list
Allocation concealment (selection bias)	Likely low risk of bias	Described as handled by pharmacist
Blinding of participants and personnel (performance bias)	Low risk of bias	Double-blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double-blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Blinded, objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All subjects accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	No protocol, but standard outcomes
Other bias	Low risk of bias	None detected

Morelli 2009[19]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Italy	
Participants	Adult participants with septic shock Mean age = 66 years, 73% male, 38% lung infection, SAP score = 60 (N=45)	
Interventions	Vasopressin continuous infusion 0.03 U/min over a period of 48 hrs versus Norepinephrine titrated as needed versus Terlipressin continuous infusion 1.3 mcg/kg over a period of 48 hrs	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, ICU mortality, requirement for renal replacement therapy, ICU length of stay	
Outcomes Clarified by Contacting Authors	Atrial Fibrillation	
Potential Conflicts	Funding source: Department of Anesthesiology and Intensive Care of the University of Rome 'La Sapienza'. Declarations of interest: None stated.	
Notes	Unpublished information made available from authors. NCT00481572	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-based procedure
Allocation concealment (selection bias)	Likely low risk of bias	No description, but experienced research team and no obvious differences between groups
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All subjects accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Reported outcomes consistent with registered protocol
Other bias	Low risk of bias	None detected

Oliveira 2014[20]

Methods	Single-centre double-blind randomized controlled study at a hospital in Brazil	
Participants	Adult participants with septic shock (N=387)	
Interventions	Vasopressin 0.01-0.03 U/min versus Norepinephrine 0.05-2.0 mcg/kg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Abstract	Mortality (e.g. 14 days, 28 days)	
Outcomes Clarified by Contacting Authors	Unable to locate author contact information	
Potential Conflicts	Funding source: not stated. Declarations of interest: none stated.	
Notes	EVAS Study	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely high risk of bias	No description of randomization, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour
Allocation concealment (selection bias)	Likely high risk of bias	No description of concealment, no registered protocol, no previous publications by research team upon which to judge prior methodological rigour
Blinding of participants and personnel (performance bias)	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely high risk of bias	Large trial, cannot confirm follow up or intention to treat
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol, but appears to report standard outcomes
Other bias	High risk of bias	Abstract only without published protocol

Patel 2002[21]

Methods	Multicentre double-blinded randomized controlled study at two tertiary care university hospitals in Canada	
Participants	Adult participants with septic shock Mean age = 68 years, 75% male gender, 55% lung infection, APACHE II score = 23 (N=24)	
Interventions	Vasopressin 0.01- 0.08 units/min versus Norepinephrine 2 -16 mcg/min	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Myocardial injury (e.g. no change in ST segments), ventricular arrhythmias	
Outcomes Clarified by Contacting Authors	Authors contacted. Reported that data was not available.	
Potential Conflicts	Funding source: British Columbia Lung Association/St. Paul's Hospital Foundation, Vancouver, British Columbia, Canada. Declarations of interest: none stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-based procedure
Allocation concealment (selection bias)	Likely low risk of bias	No description, but no issue in authors' previous work
Blinding of participants and personnel (performance bias)	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Double blind, objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Low risk of bias	All subjects accounted for
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	No protocol but standard outcomes
Other bias	Low risk of bias	None detected

Prakash 2017[22]

Methods	Open-label randomized controlled study in India	
Participants	Adult participants with cirrhosis and sepsis (N=184)	
Interventions	Terlipressin (fixed dose infusion at 2mg/24hrs) and noradrenaline (3.75 to 30 mcg/min), target MAP > 65 mm Hg versus Noradrenaline (7.5 to 60 mcg/min)	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Abstract	30-day mortality	
Outcomes Clarified by Contacting Authors	No response yet	
Potential Conflicts	Funding source: not stated. Declarations of interest: none stated.	
Notes	NCT02468063	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Likely low risk of bias	Not described but described as having comparable baseline demographic, clinical and laboratory parameters
Allocation concealment (selection bias)	Likely low risk of bias	Not described but described as having comparable baseline demographic, clinical and laboratory parameters
Blinding of participants and personnel (performance bias)	High risk of bias	Open-label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open-label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk of bias	No evidence of missing data
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Outcomes consistent with NCT registered protocol
Other bias	High risk of bias	Abstract only

Russell 2008[23]

Methods	Multicentre double-blind randomized controlled study at hospitals in Canada, Australia, and the United States	
Participants	Adult participants with septic shock Mean age = 61 years, 61% male, 42% lung infection, APACHE II score = 27.1 (N=802)	
Interventions	Vasopressin started at 0.01 U/min, titrated up to 0.03 U/min with target MAP 65-75 mm Hg or physician discretion Versus Norepinephrine 5 mcg/min up to 15 mcg/min with target MAP 65-75 mm Hg or physician discretion	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, mortality (e.g. 28 days, 90 days), myocardial injury (e.g. acute myocardial infarction or ischemia), stroke (e.g. cerebrovascular accident), limb ischemia (e.g. digital), hospital and ICU lengths of stay	
Outcomes Clarified by Contacting Authors	None	
Potential Conflicts	Funding source: Canadian Institutes of Health Research. Declarations of interest: Stake in related companies.	
Notes	SRCTN94845869, VASST Trial, Atrial Fibrillation data from Day 1 values from sub-study: Mehta, S et al..*Critical Care (London, England)*2013; 17(3):R117.	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Central telephone randomization system
Allocation concealment (selection bias)	Low risk of bias	Central telephone randomization system
Blinding of participants and personnel (performance bias)	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Double blind, objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely low risk of bias	All subjects accounted for, intention to treat analysis for mortality outcome, modified intention to treat for others
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Consistent with protocol
Other bias	Low risk of bias	None stated

Russell 2017[24]

Methods	Multicentre double-blind randomized controlled study of patients from Belgium, Denmark and the United States	
Participants	Adult participants with septic shock Median age = 63.2 years, 45 and 71% mal, APACHE II score = 12 (N=53)	
Interventions	Selepressin infused at 1.25, 2.5 or 3.75 ng/kg/min until shock resolution or a maximum of 7 days Placebo Open label norepinephrine to achieve MAP > 65	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Atrial fibrillation, mortality (e.g. 28 days), myocardial injury, limb ischemia	
Outcomes Clarified by Contacting Authors	None	
Potential Conflicts	Funding source: Ferring pharmaceuticals, patents related to the use of vasopressin in septic shock	
Notes	NCT01000649	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Central computer randomization
Allocation concealment (selection bias)	Low risk of bias	Central computer randomization
Blinding of participants and personnel (performance bias)	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	Low risk of bias	Double blind
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Double blind, objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	High Risk of bias	2/19 lost to follow up in group 1
Selective reporting (reporting bias) *All outcomes*	Low risk of bias	Consistent with protocol
Other bias	Low risk of bias	None stated

Svoboda 2012[25]

Methods	Single-centre open-label randomized controlled study at a hospital in the Czech Republic	
Participants	Adult participants with septic shock Mean age = 73 years, 61% male, 24% lung infection, SOFA score = 18 (N=32)	
Interventions	Terlipressin 4 mg/24 h for 72 h versus Norepinephrine as needed	
Open-label Catecholamines Permitted	Yes	
Outcomes Reported in Manuscript	Mortality (e.g. 4 days, 28 days), other serious adverse events (not specified)	
Outcomes Clarified by Contacting Authors	Atrial Fibrillation, Ventricular Arrhythmias, Myocardial Injury, Stroke, Limb Ischemia	
Potential Conflicts	Funding source: grant of IGA MZ CR NR 9284-3. Declarations of interest: None stated.	
Notes	N/A	
Risk of bias		
Bias domain	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk of bias	Computer-generated random treatment list
Allocation concealment (selection bias)	Low risk of bias	Sequentially numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias)	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *AF, RRT, digital ischemia, myocardial injury and VT*	High risk of bias	Open label
Blinding of outcome assessment (detection bias) *Mortality, Stroke, LOS*	Low risk of bias	Objective outcomes
Incomplete outcome data (attrition bias) *All outcomes*	Likely high risk of bias	Two patients who died were excluded post randomization
Selective reporting (reporting bias) *All outcomes*	Likely low risk of bias	No protocol but expected outcomes
Other bias	Low risk of bias	None detected

eAppendix 7 – Characteristics of Important Excluded Studies

Argenziano 1997[26]

Methods	Single-centre blinded randomized controlled study at a hospital in the United States
Participants	Adult participants with congestive heart failure and vasodilatory shock Mean age = 52 years (N=20)
Interventions	Vasopressin at 0.1 U/min versus Placebo (normal saline)
Outcomes	None of interest
Potential Conflicts	Funding source: grant from the Saydman Trust to Dr. Landry. Declarations of interest: not stated. No relevant outcomes
Notes	N/A

Elmenesy 2008[27]

Methods	Single-centre open-label randomized controlled study at a hospital in Egypt
Participants	Adult participants with septic shock (N=40)
Interventions	Vasopressin versus Norepinephrine
Outcomes	None of interest
Potential Conflicts	Funding source: not stated. Declarations of interest: not stated.
Notes	Assessed abstract only – still attempting to obtain full text

Lückner 2006[28]

Methods	Single-centre open-label randomized controlled study at a tertiary care university hospital in Austria
Participants	Adult participants with vasodilatory shock following cardiac or major surgery Mean age = 69 years, 61% male, MODS score = 12.3 (N=18)
Interventions	Pitressin (in addition to norepinephrine) at continuous rate of 4 IU/hour versus Norepinephrine to maintain MAP above 65 mm Hg
Outcomes	None of interest
Protocol registration	Funding source: Grant from Aguettant Laboratories, Lyon, France, for one of the authors. Declarations of interest: None stated.
Notes	N/A

Morelli 2011[29]

Methods	Single-centre blinded randomized controlled study at a tertiary care university hospital in Italy
Participants	Adult participants with septic shock Mean age = 67 years, 62% male, 55% lung infection, SAPS II score = 52 (N=60)
Interventions	Vasopressin 0.04 U/min versus Placebo versus Terlipressin 1mcg/kg/hr
Outcomes	None of interest
Potential Conflicts	Funding source: not reported. Declarations of interest: none reported.
Notes	N/A

eAppendix 8 – Characteristics of Ongoing Studies

Small Doses of Pituitrin Versus Norepinephrine for the Management of Vasoplegic Syndrome in Patients After Cardiac Surgery

Methods	Allocation: Randomized Intervention Model: Parallel Assignment
Participants	Patients diagnosed as vasoplegic syndrome (defined as mean arterial pressure less than 65 mmHg resistant to fluid challenge and cardiac index greater than 2.2 L/min · m2) within 24 hours after cardiac surgery.
Interventions	**Experimental:** Pituitrin arm To begin with 0.02 U/min to maintain mean arterial pressure(MAP) higher than 65 mmHg. **Experimental:** Norepinephrine arm To begin with 0.04 μg/kg.min to maintain mean arterial pressure(MAP) higher than 65 mmHg.
Outcomes	**Primary Outcome Measures:** Rate of in-hospital acute renal injury [Time Frame: 30 days] **Secondary Outcome Measures:** In-hospital mortality [Time Frame: 30 days] All-cause mortality Rate of new arrhythmias [Time Frame: 30 days] Rate of new arrhythmias after cardiac surgery Hormone levels [Time Frame: 30 days] Serum hormone levels after cardiac surgery, including vasopressin, catecholamine, corticosteroid and corticotropin-releasing hormone Rate of ECMO or LVAD support [Time Frame: 30 days] Receiving extracorporeal membrane oxygenation (ECMO) or left ventricle assist device (LVAD) support Duration on ventilator support [Time Frame: 30 days] Duration on ventilator support after cardiac surgery ICU length of stay [Time Frame: 30 days] ICU length of stay Hospital length of stay after cardiac surgery [Time Frame: 30 days]
Notes	NCT03106831

Vasoactive Drugs in Intensive Care Unit A Randomized Double Blind Trial of Vasoactive Drugs for the Management of Shock in the ICU

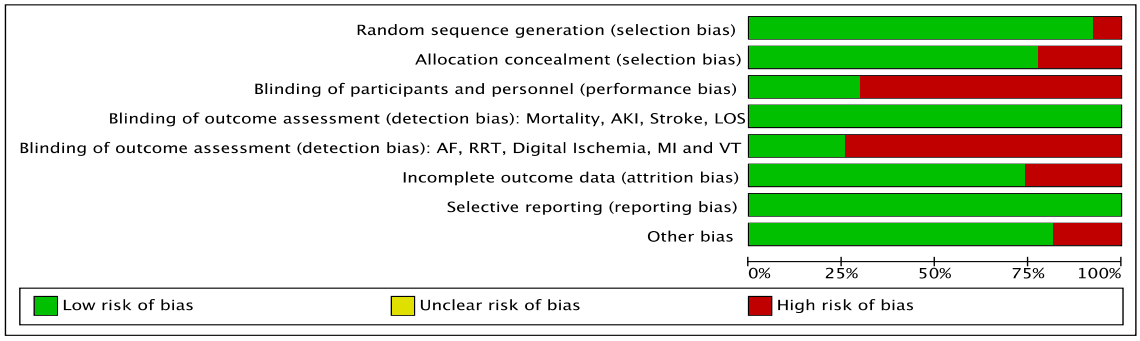
Methods	Randomized, Double Blind
Participants	Patients diagnosed as vasoplegic syndrome (defined as mean arterial Requirement for vasoactive drugs via a central venous catheter for the treatment of shock. Shock will be defined as mean arterial pressure less than 70 mmHg or systolic blood pressure less than 100 mmHg despite administration of at least 1000 mL of crystalloid or 500 mL of colloid, unless there is an elevation in the central venous pressure to > 12 mmHg or in the pulmonary artery occlusion pressure to > 14 mmHg coupled with signs of tissue hypoperfusion (e.g. altered mental state, mottled skin, urine output < 0.5 mL/kg body weight for one hour, or a serum lactate level of > 2 mmol per liter).
Interventions	Drug: Epinephrine Drug: Norepinephrine Drug: Phenylephrine Drug: Vasopressin
Outcomes	**Primary Outcome** Hospital mortality [Time Frame: Six months] **Secondary Outcome(s)** Heart rate [Time Frame: Six months] Incidence of tachydysrhythmia [Time Frame: Six months]
Notes	NCT02118467

Infusion of low dose of vasopressin versus phenylephrine for prevention of cardiopulmonary bypass induced vasoplegic syndrome in patients undergoing coronary artery bypass grafting surgery

Methods	Randomized, Double Blind
Participants	Patients 18 up to 70 years olds who are candidate for elective cardiac surgery using cardiopulmonary bypass
Interventions	**Intervention 1:** Starting infusion of vasopressin (Exir pharmaceutical co. Iran) 0.1 IU/min with starting of cardiopulmonary bypass and continuing it up to 4 hours after weaning from cardiopulmonary bypass. **Intervention 2:** Starting infusion of phenylephrine (West-ward Pharmaceutical Corp. USA) 0.1 µg/kg/min (prepared as 5 mg in 50 ml normal saline) with starting of cardiopulmonary bypass and continuing it up to 4 hours after weaning from cardiopulmonary bypass.. **Intervention 3:** Placebo group: Starting NaCl 0.9% Infusion (2 ml/h) with starting of cardiopulmonary bypass and continuing it up to 4 hours after weaning from cardiopulmonary bypass.
Outcomes	**Primary Outcome(s)** severity of post operative vasoplegic shock. Timepoint: post cardiopulmonary bypass and post operative period. Method of measurement: Needs to vasoactive drugs **Secondary Outcome(s)** Post operative complications. Timepoint: Post operatively in intensive care unit. Method of measurement: Clinical evaluation
Notes	ICRT201408201127N2

AF = Atrial Fibrillation; ICU = Intensive Care Unit; LOS = Length of Stay; RRT = Renal Replacement Therapy; VT = Ventricular Arrhythmia

eAppendix 9 – Risk of Bias Graphs: Review Authors' Judgments About Each Risk of Bias Item Presented as Percentages Across All 23 Randomized Trials

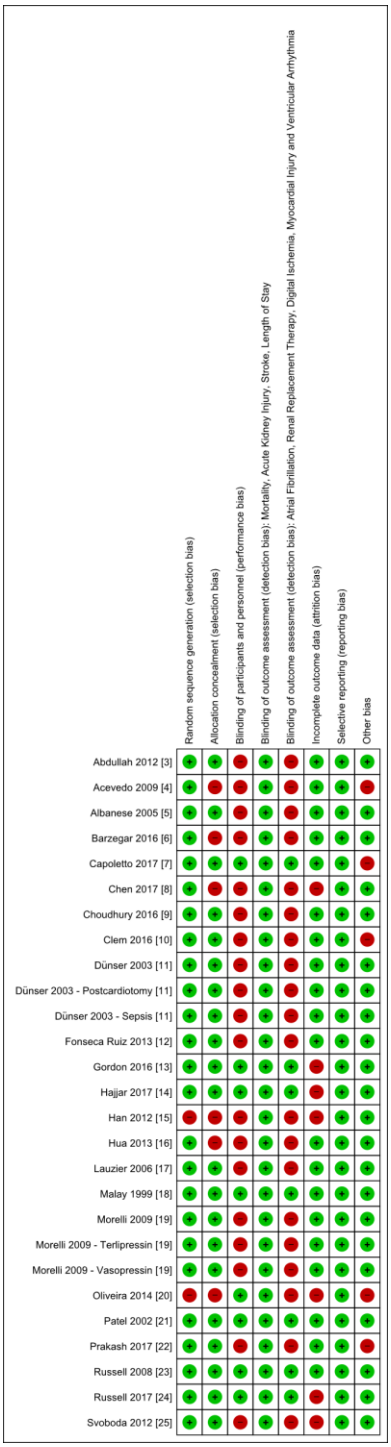


Footnote

The X axis denotes the % of studies deemed to be at high or low risk of bias in this domain.

AF = Atrial Fibrillation; AKI = Acute Kidney Injury; LOS = Length of Stay; MI = Myocardial Injury; RRT = Requirement for Renal Replacement Therapy; VT = Ventricular Arrhythmia

eAppendix 10 – Risk of Bias Summary: Review Authors' Judgments About Each Risk of Bias Item for Each Included Study

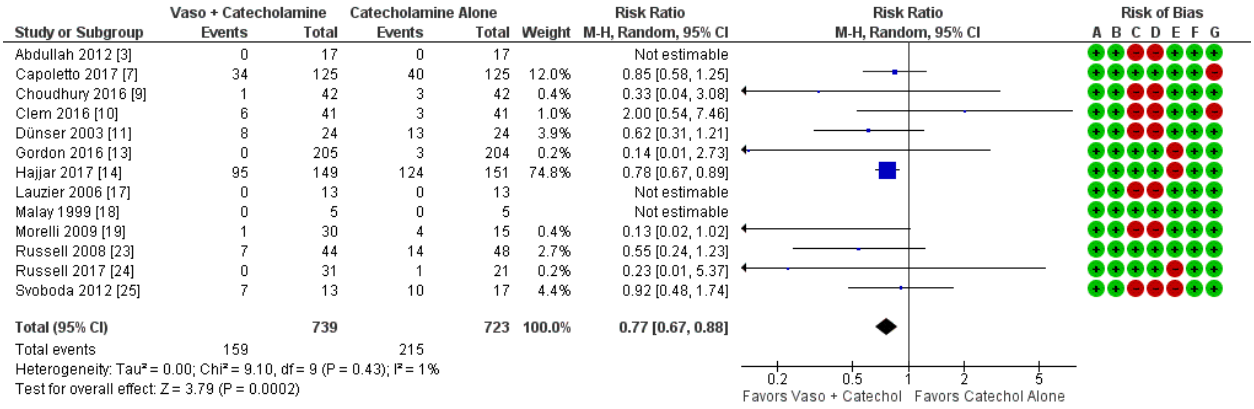


Footnote

Green circle with "+" denotes low risk of bias in this domain;
Red circle with "-" denotes high risk of bias in this domain

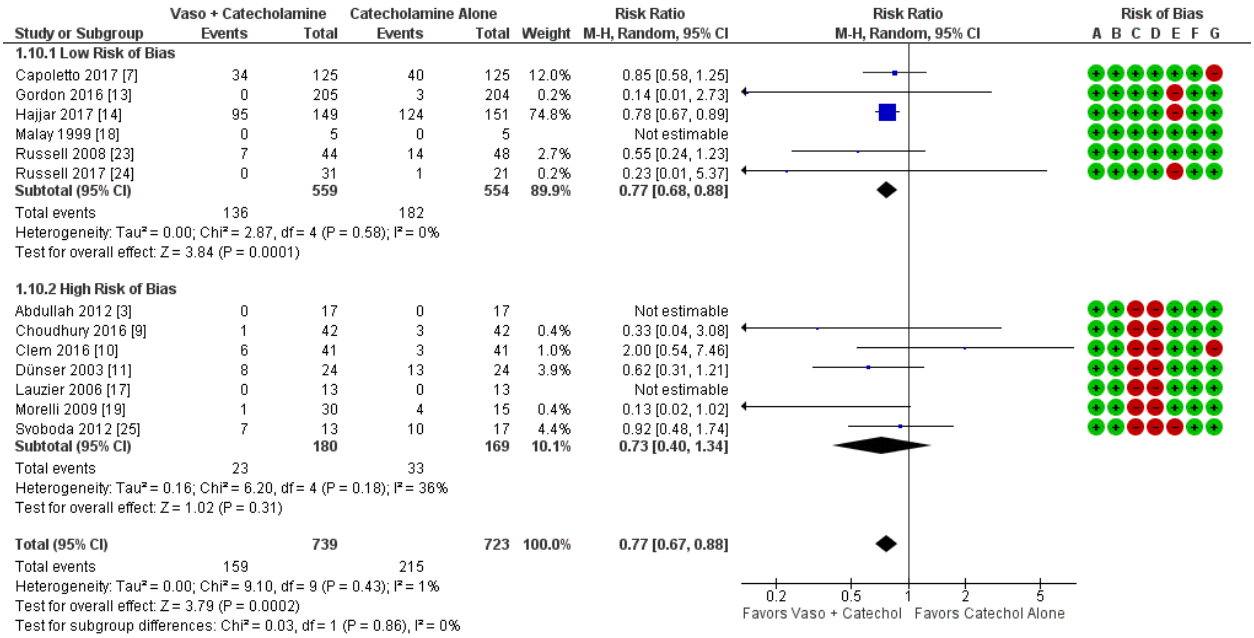
eAppendix 11 – Forest Plots for All Outcomes, Including Sensitivity Analyses

Atrial Fibrillation – All Studies[a,b]



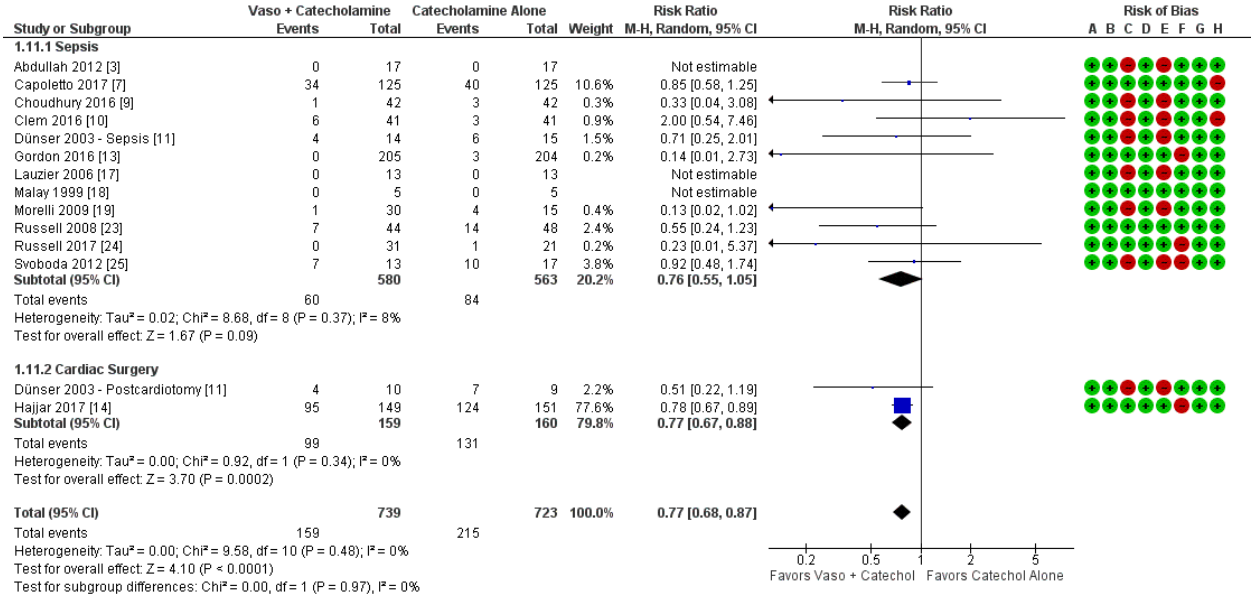
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Atrial Fibrillation, Renal Replacement Therapy, Digital Ischemia, Myocardial Injury and Ventricular Arrhythmia
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Atrial Fibrillation – Risk of Bias[a,b]



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Atrial Fibrillation, Renal Replacement Therapy, Digital Ischemia, Myocardial Injury and Ventricular Arrhythmia
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Atrial Fibrillation – Shock Etiology[a,b,c]



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay

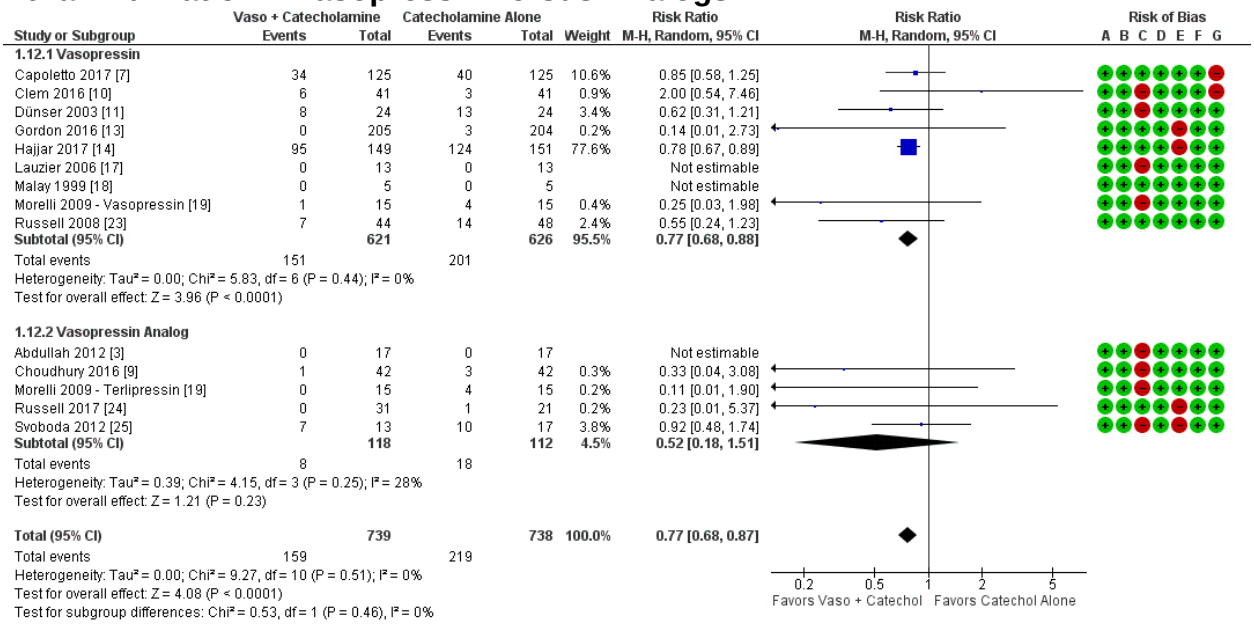
(**E**) Blinding of outcome assessment (detection bias): Atrial Fibrillation, Renal Replacement Therapy, Digital Ischemia, Myocardial Injury and Ventricular Arrhythmia

(**F**) Incomplete outcome data (attrition bias)

(**G**) Selective reporting (reporting bias)

(**H**) Other bias

Atrial Fibrillation – Vasopressin versus Analogs[a,b,d]



Risk of bias legend

(**A**) Random sequence generation (selection bias)

(**B**) Allocation concealment (selection bias)

(**C**) Blinding of participants and personnel (performance bias)

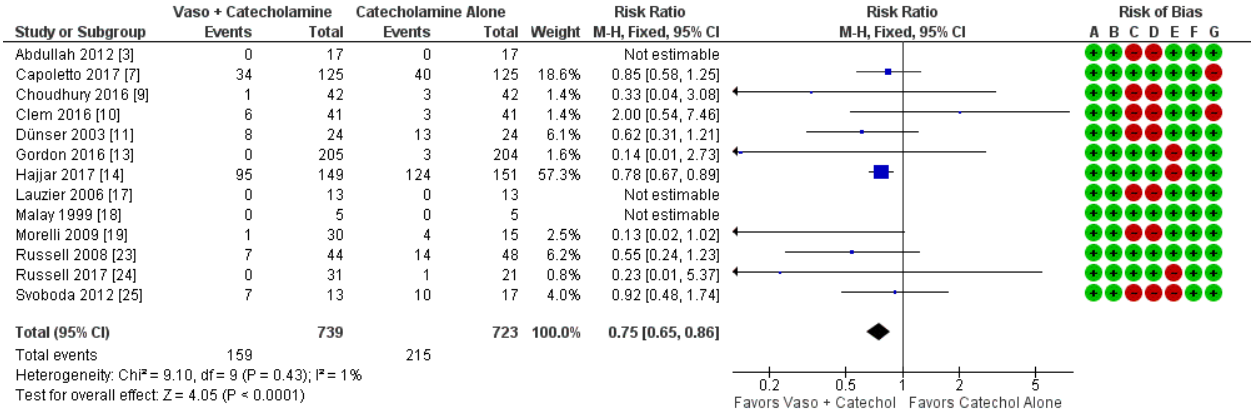
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay

(**E**) Incomplete outcome data (attrition bias)

(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Atrial Fibrillation – Analysis Using Fixed Effect Model[a,b]

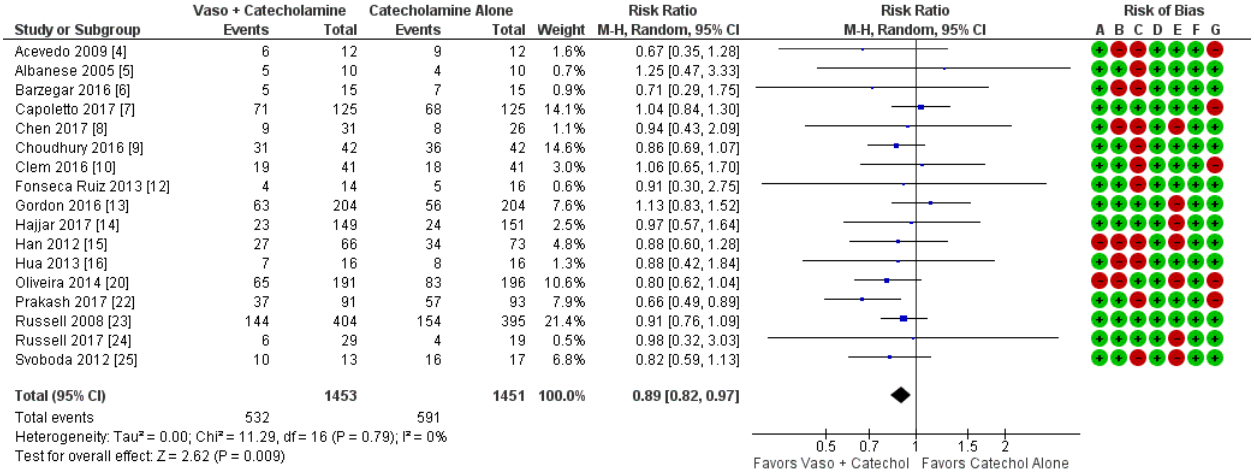


Study or Subgroup	Vaso + Catecholamine Events	Total	Catecholamine Alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdullah 2012 [3]	0	17	0	17		Not estimable
Capoletto 2017 [7]	34	125	40	125	18.6%	0.85 [0.58, 1.25]
Choudhury 2016 [9]	1	42	3	42	1.4%	0.33 [0.04, 3.08]
Clem 2016 [10]	6	41	3	41	1.4%	2.00 [0.54, 7.46]
Dünser 2003 [11]	8	24	13	24	6.1%	0.62 [0.31, 1.21]
Gordon 2016 [13]	0	205	3	204	1.6%	0.14 [0.01, 2.73]
Hajjar 2017 [14]	95	149	124	151	57.3%	0.78 [0.67, 0.89]
Lauzier 2006 [17]	0	13	0	13		Not estimable
Malay 1999 [18]	0	5	0	5		Not estimable
Morelli 2009 [19]	1	30	4	15	2.5%	0.13 [0.02, 1.02]
Russell 2008 [23]	7	44	14	48	6.2%	0.55 [0.24, 1.23]
Russell 2017 [24]	0	31	1	21	0.8%	0.23 [0.01, 5.37]
Svoboda 2012 [25]	7	13	10	17	4.0%	0.92 [0.48, 1.74]
Total (95% CI)		**739**		**723**	**100.0%**	**0.75 [0.65, 0.86]**
Total events	159		215			

Heterogeneity: Chi² = 9.10, df = 9 (P = 0.43); I² = 1%
Test for overall effect: Z = 4.05 (P < 0.0001)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Atrial Fibrillation, Renal Replacement Therapy, Digital Ischemia, Myocardial Injury and Ventricular Arrhythmia
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

28 or 30 Day Mortality – All Studies[a,b]

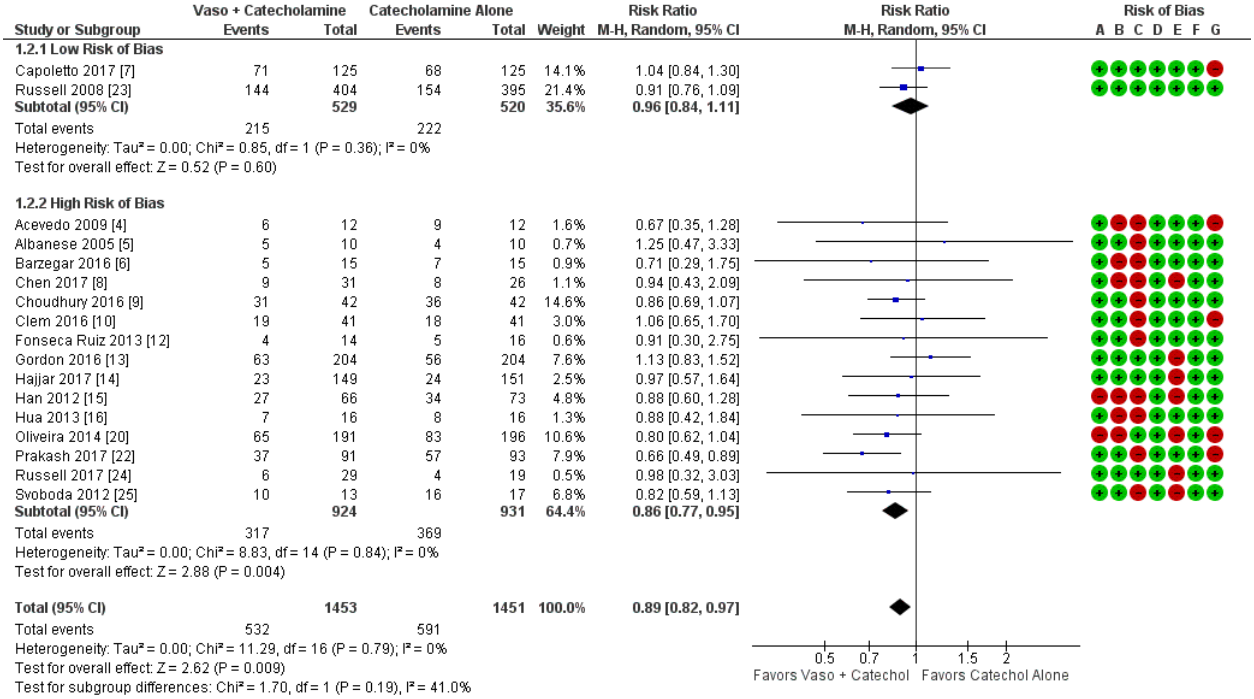


Study or Subgroup	Vaso + Catecholamine Events	Total	Catecholamine Alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Acevedo 2009 [4]	6	12	9	12	1.6%	0.67 [0.35, 1.28]
Albanese 2005 [5]	5	10	4	10	0.7%	1.25 [0.47, 3.33]
Barzegar 2016 [6]	5	15	7	15	0.9%	0.71 [0.29, 1.75]
Capoletto 2017 [7]	71	125	68	125	14.1%	1.04 [0.84, 1.30]
Chen 2017 [8]	9	31	8	26	1.1%	0.94 [0.43, 2.09]
Choudhury 2016 [9]	31	42	36	42	14.6%	0.86 [0.69, 1.07]
Clem 2016 [10]	19	41	18	41	3.0%	1.06 [0.65, 1.70]
Fonseca Ruiz 2013 [12]	4	14	5	16	0.6%	0.91 [0.30, 2.75]
Gordon 2016 [13]	63	204	56	204	7.6%	1.13 [0.83, 1.52]
Hajjar 2017 [14]	23	149	24	151	2.5%	0.97 [0.57, 1.64]
Han 2012 [15]	27	66	34	73	4.8%	0.88 [0.60, 1.28]
Hua 2013 [16]	7	16	8	16	1.3%	0.88 [0.42, 1.84]
Oliveira 2014 [20]	65	191	83	196	10.6%	0.80 [0.62, 1.04]
Prakash 2017 [22]	37	91	57	93	7.9%	0.66 [0.49, 0.89]
Russell 2008 [23]	144	404	154	395	21.4%	0.91 [0.76, 1.09]
Russell 2017 [24]	6	29	4	19	0.5%	0.98 [0.32, 3.03]
Svoboda 2012 [25]	10	13	16	17	6.8%	0.82 [0.59, 1.13]
Total (95% CI)		**1453**		**1451**	**100.0%**	**0.89 [0.82, 0.97]**
Total events	532		591			

Heterogeneity: Tau² = 0.00; Chi² = 11.29, df = 16 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

28 or 30 Day Mortality – Risk of Bias[a,b]



Risk of bias legend
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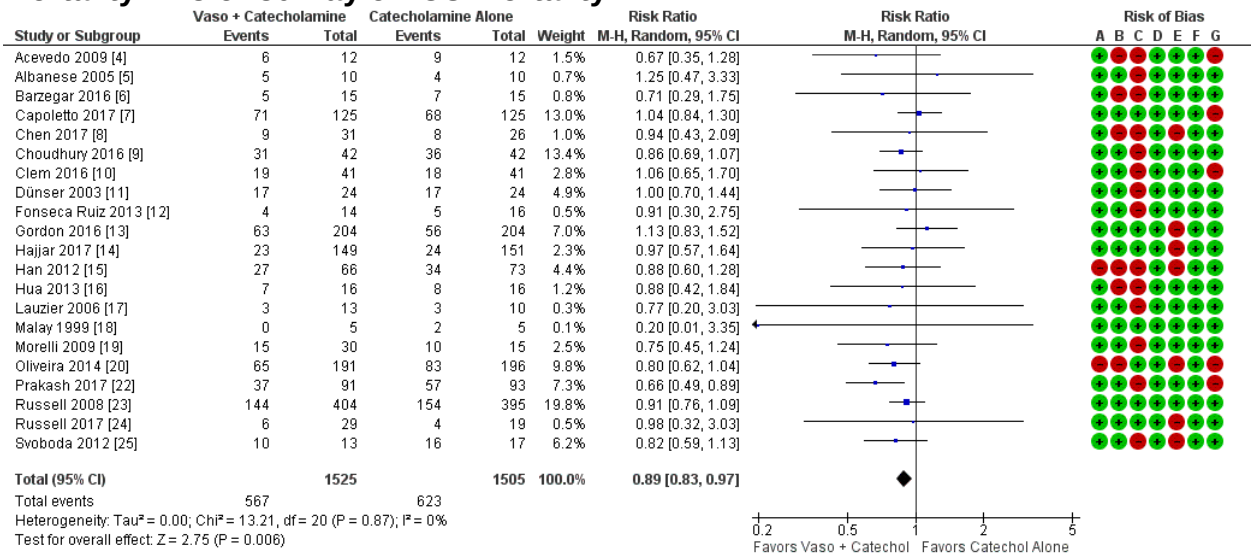
Mortality – 28 or 30 Day or ICU Mortality[a,b,e]



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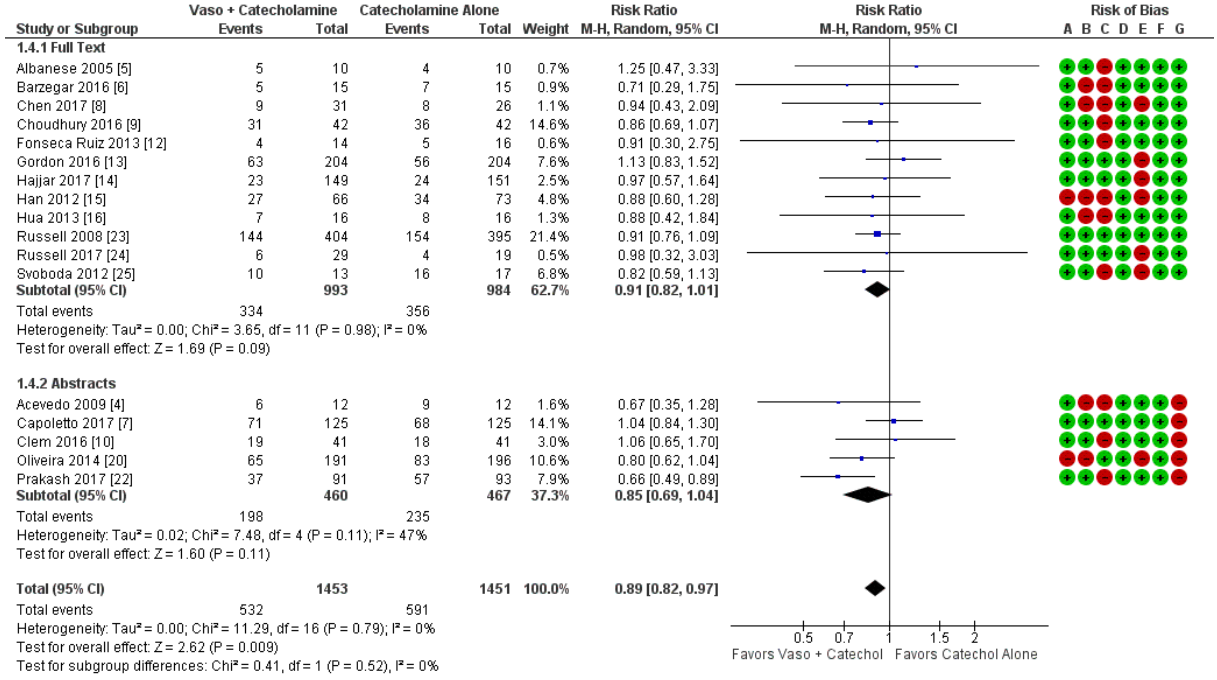
(**G**) Other bias

28 or 30 Day Mortality – Full Text versus Abstract-only Publication[a,b,f]



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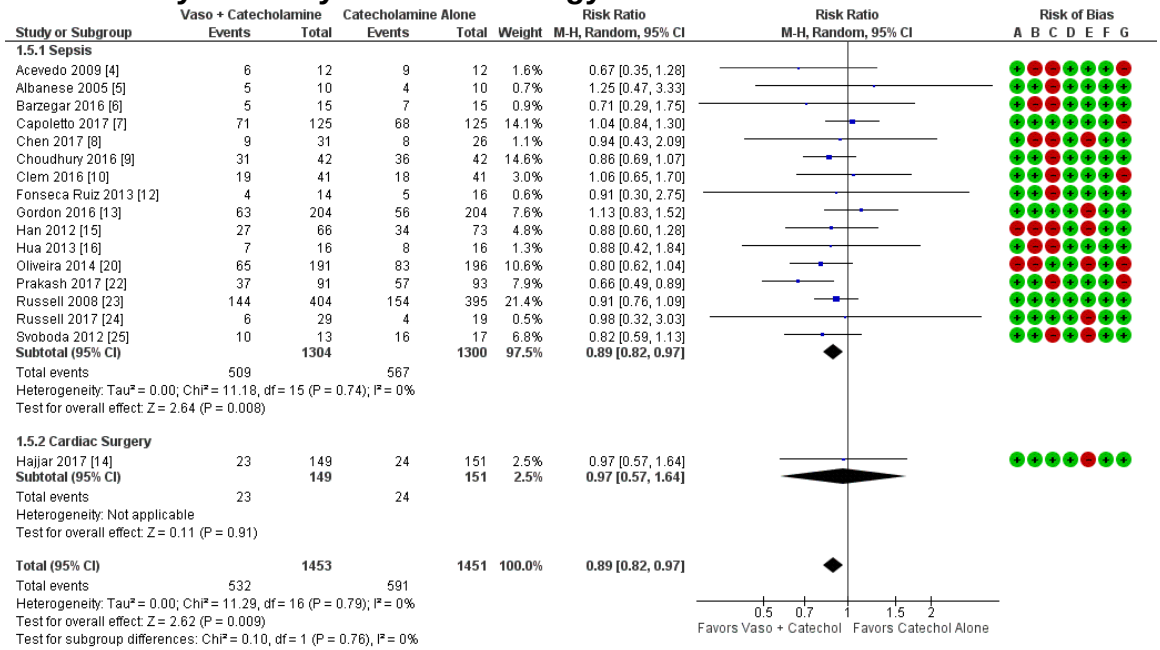
(**G**) Other bias

28 or 30 Day Mortality – Shock Etiology[a,b,c]



Risk of bias legend
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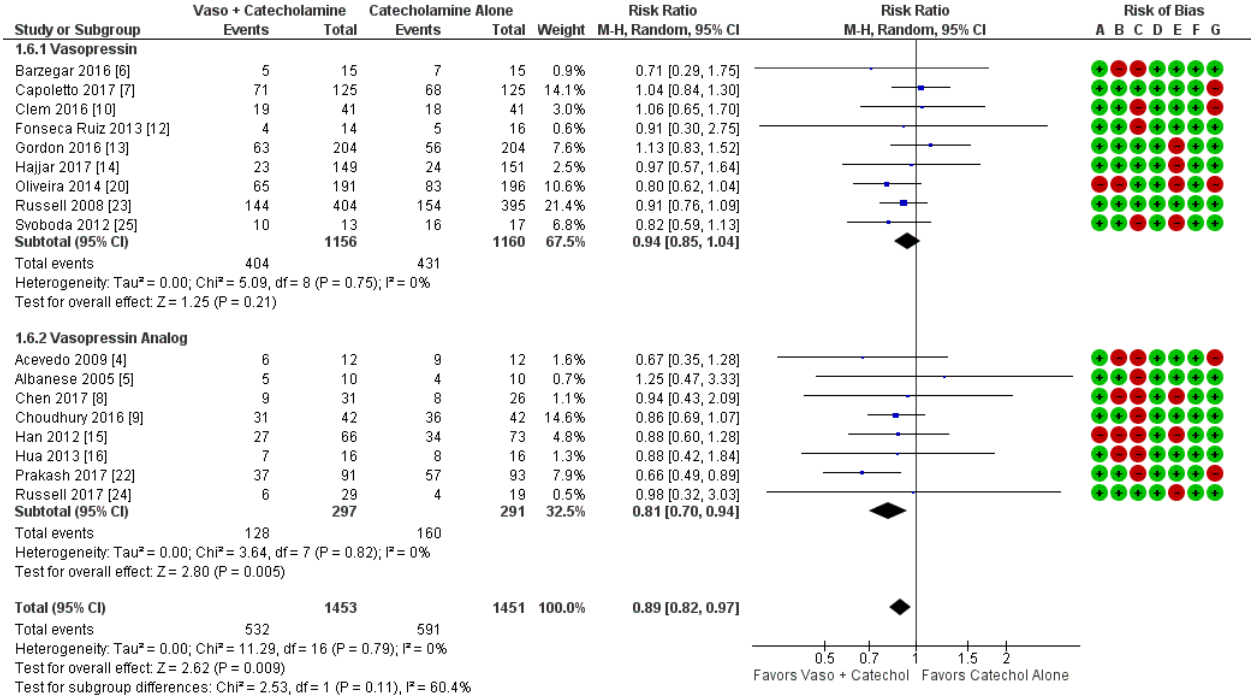
28 or 30 Day Mortality – Vasopressin versus Analogs[a,b,d]



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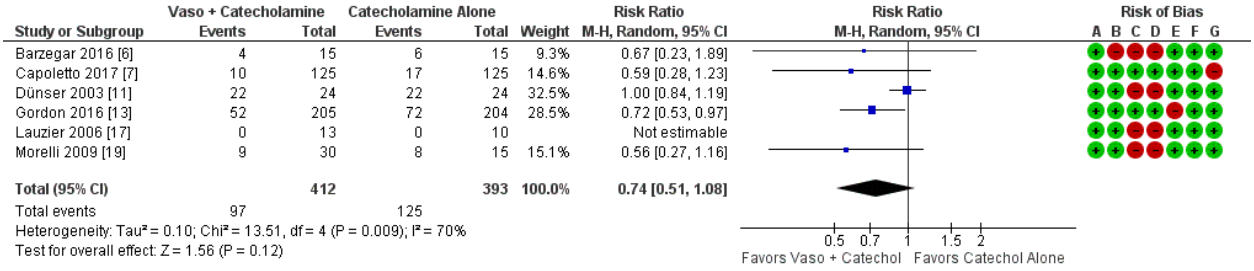
Requirement for Renal Replacement Therapy – All Studies[a,b]



Risk of bias legend
(**A**) Random sequence generation (selection bias)
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(**E**) Incomplete outcome data (attrition bias)
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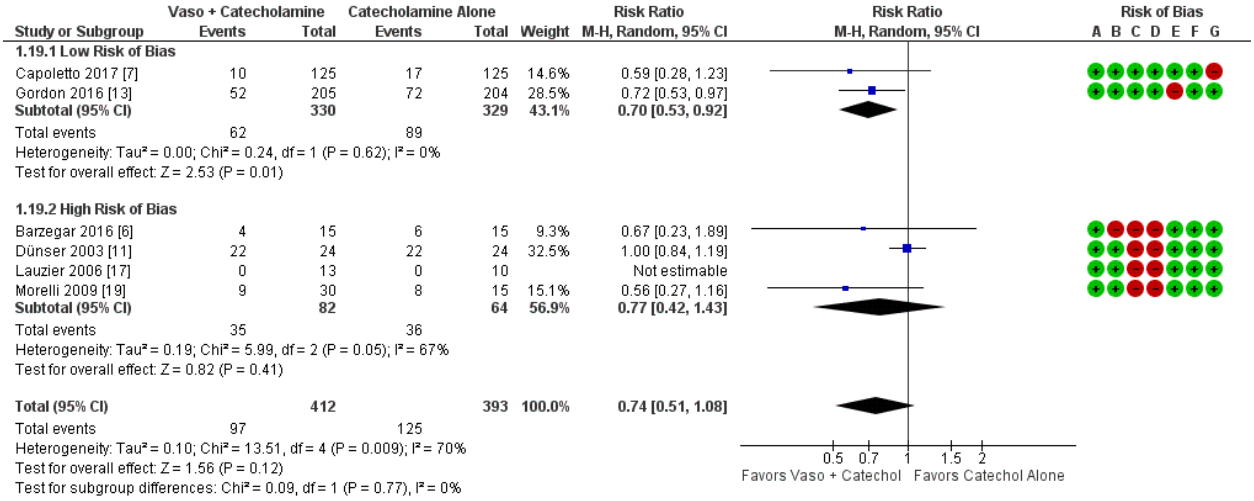
(**G**) Other bias

Requirement for Renal Replacement Therapy – Risk of Bias[a,b]



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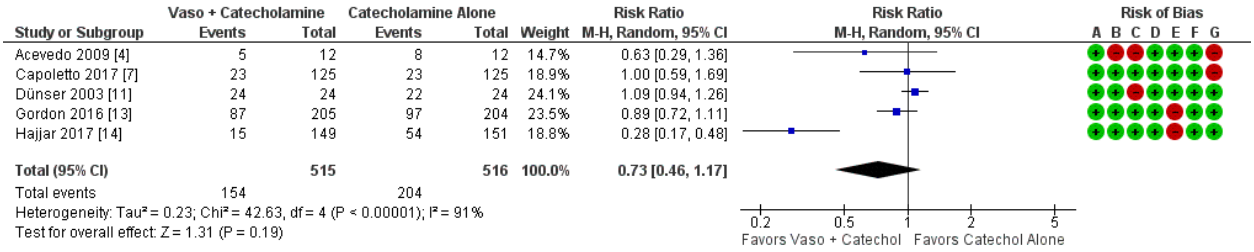
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Requirement for Renal Replacement Therapy – Acute Kidney Injury as Outcome[a,b]



Risk of bias legend
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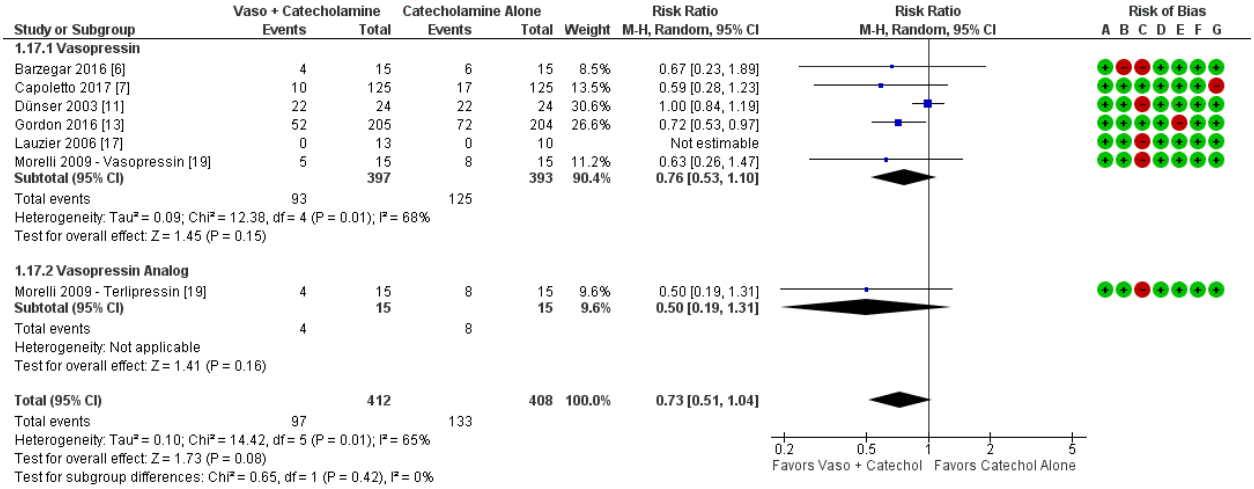
(**G**) Other bias

Requirement for Renal Replacement Therapy – Vasopressin versus Analogs[a,b,d]



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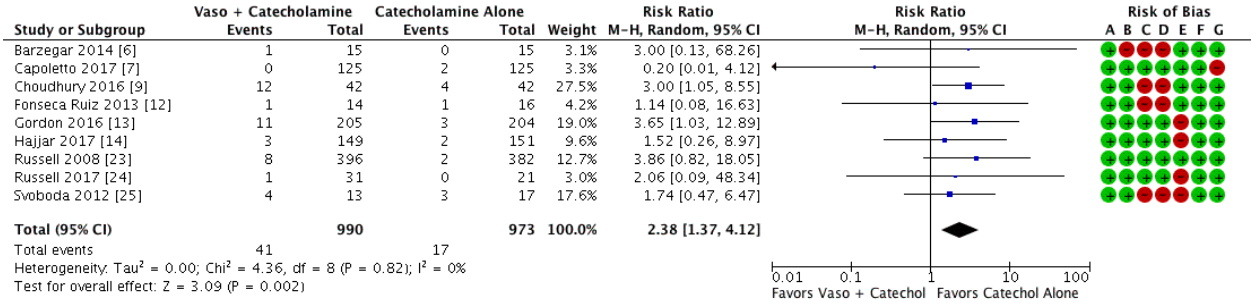
(**G**) Other bias

Digital Ischemia – All Studies[a,b]



Risk of bias legend
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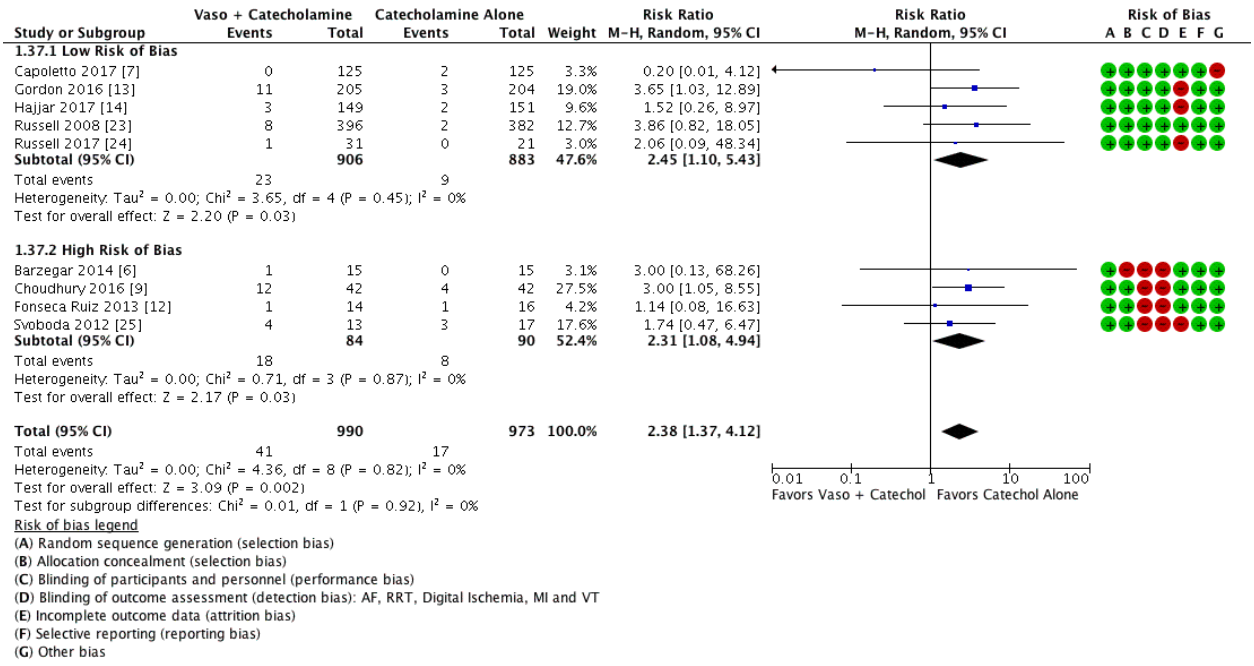
Digital Ischemia – Risk of Bias[a,b]



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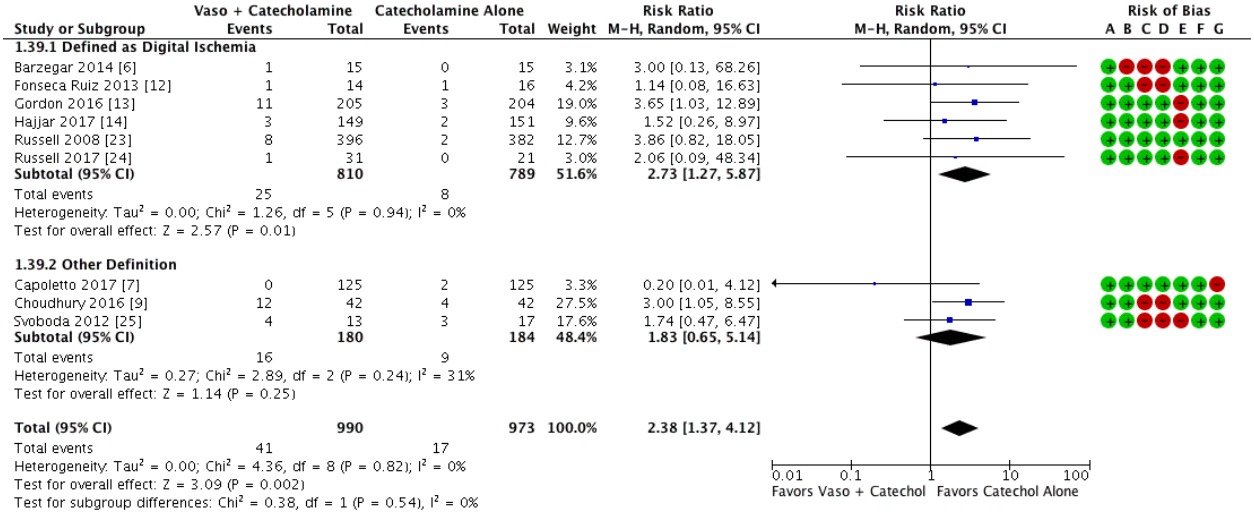
(**G**) Other bias

Digital Ischemia – Defined as Digital Ischemia[a,b,g]



Risk of bias legend
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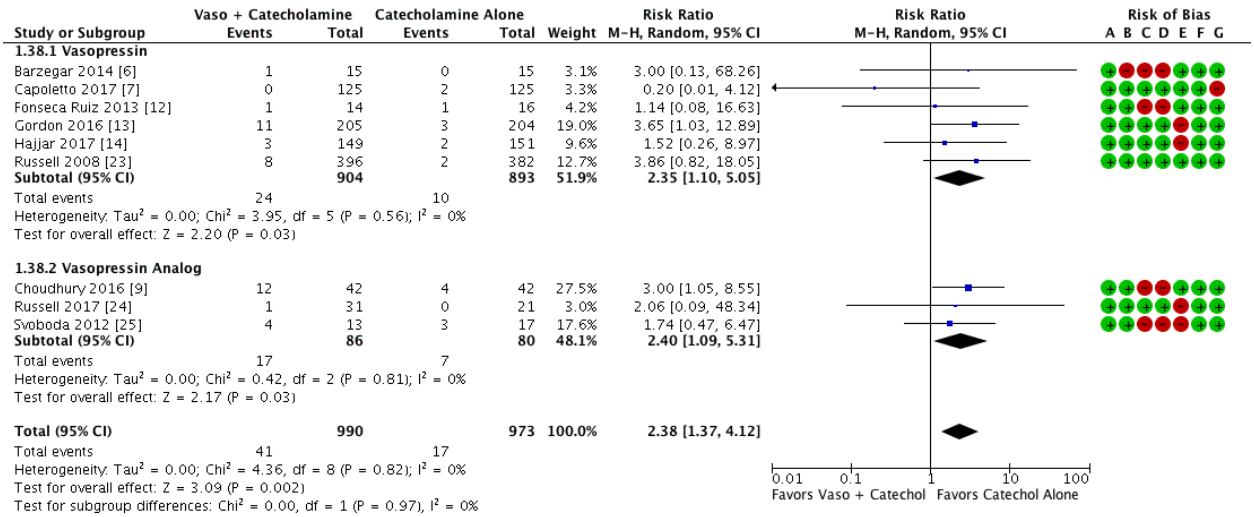
(**G**) Other bias

Digital Ischemia – Vasopressin versus Analogs[a,b]



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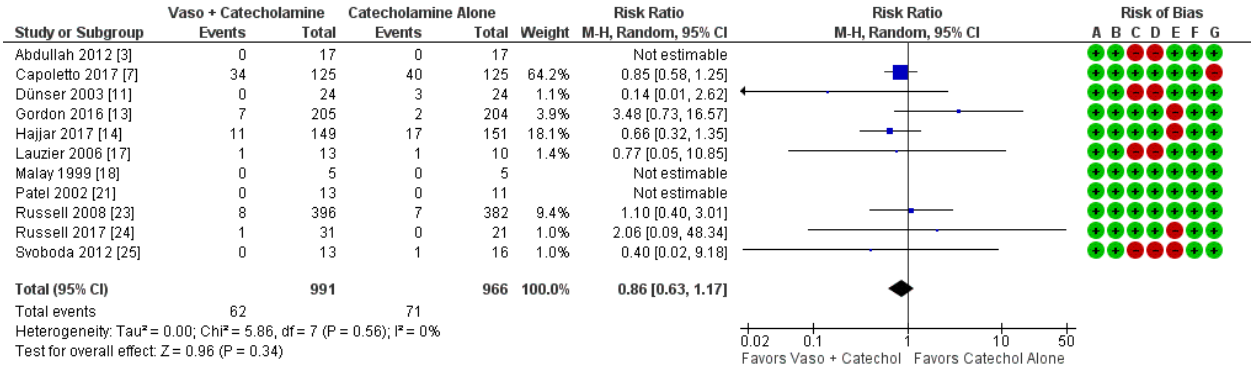
(**G**) Other bias

Myocardial Injury – All Studies[a,b]



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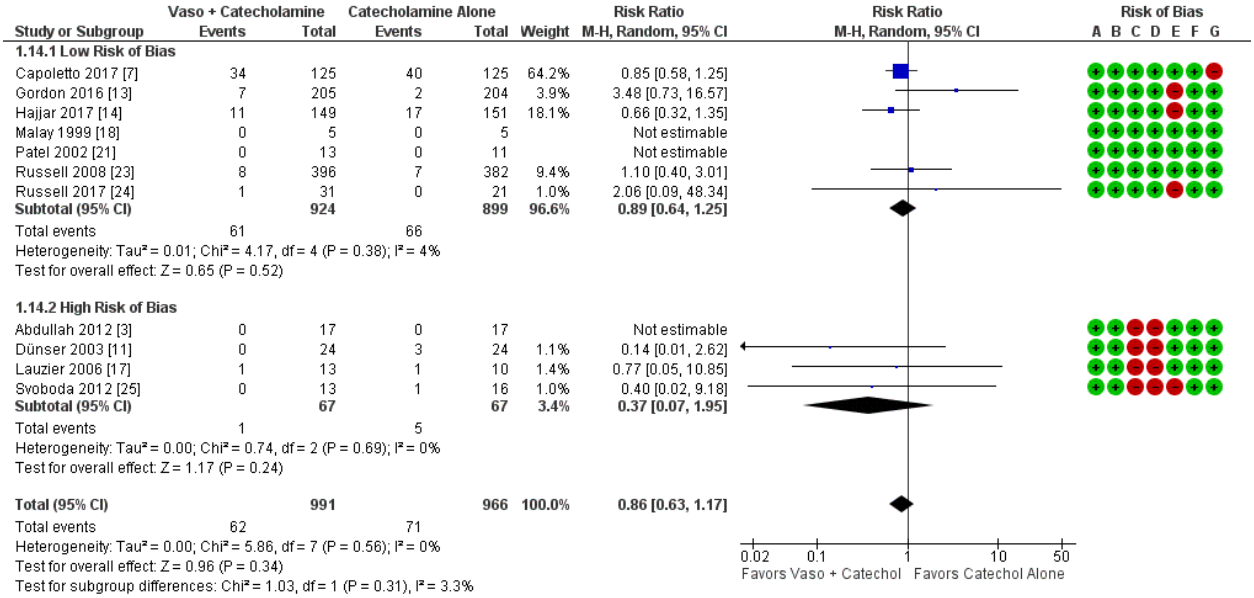
(**G**) Other bias

Myocardial Injury – Risk of Bias[a,b]



Risk of bias legend

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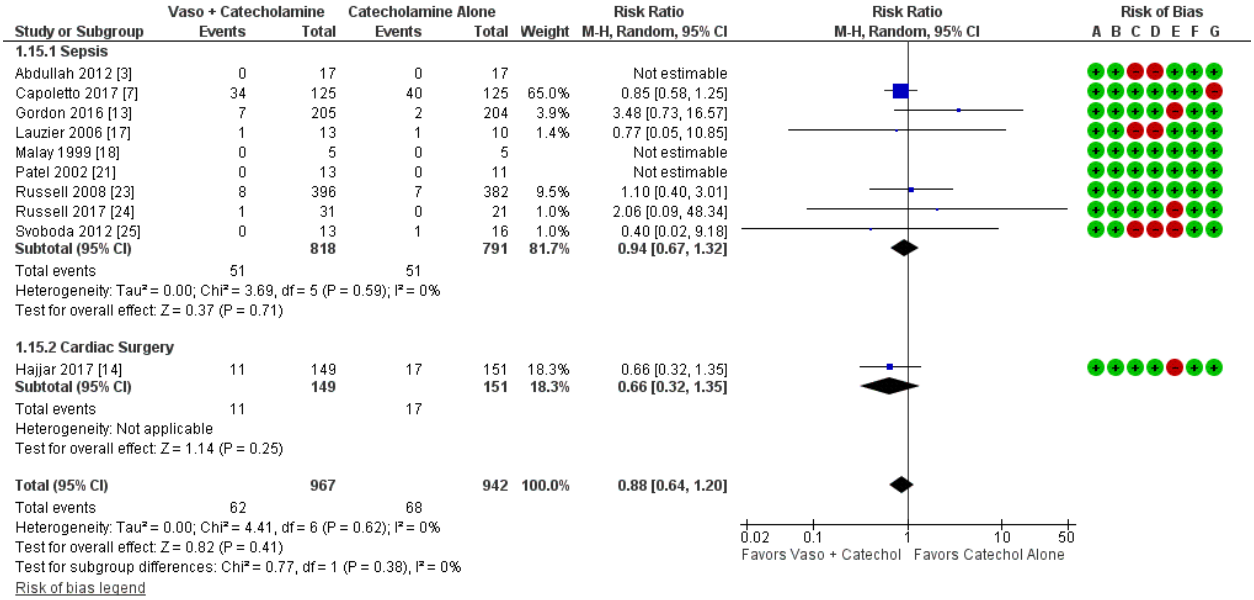
(**F**) Selective reporting (reporting bias)

(**G**) Other bias

Myocardial Injury – Shock Etiology[a,b,c]



Risk of bias legend

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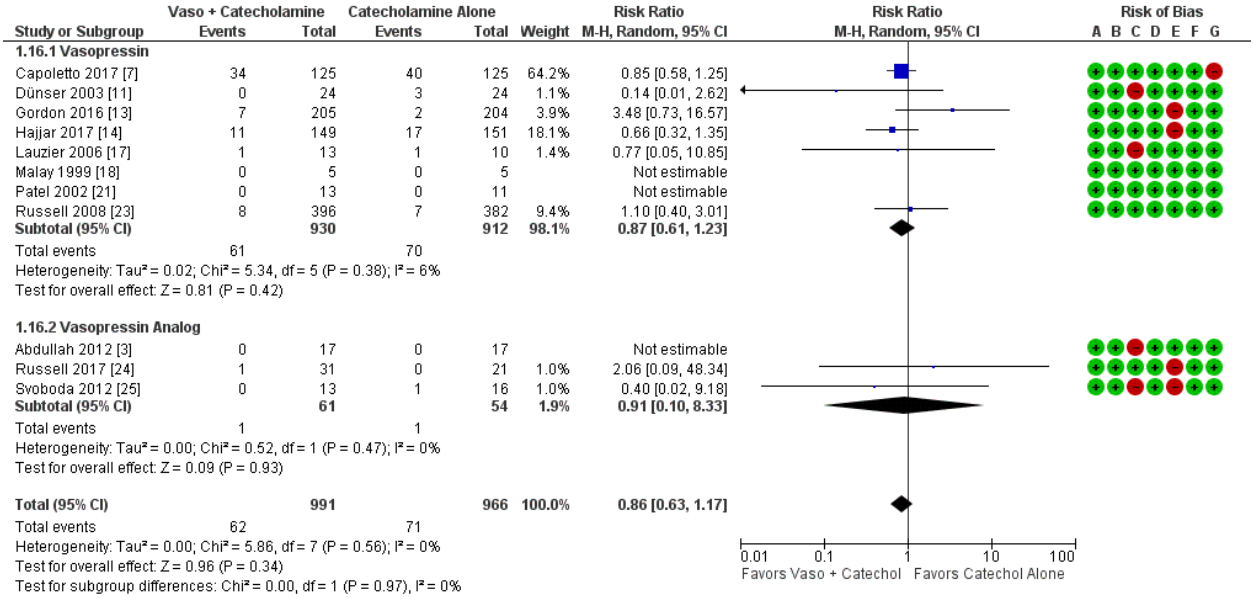
(**G**) Other bias

Myocardial Injury – Vasopressin versus Analogs[a,b,d]



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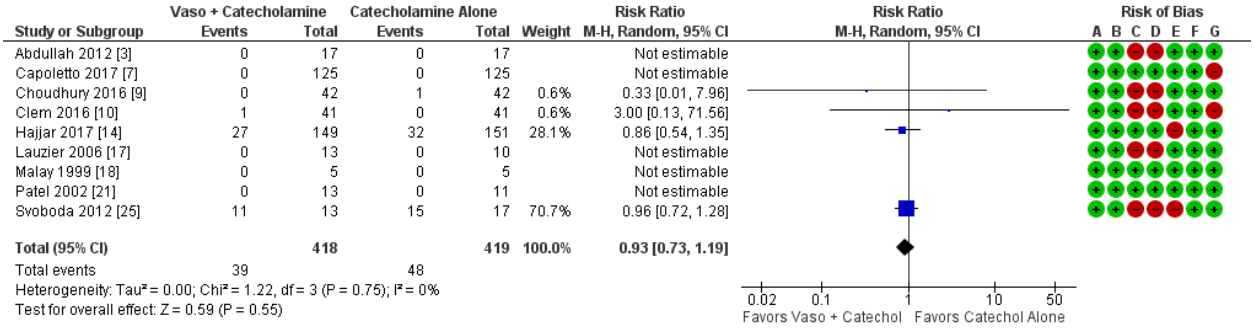
Ventricular Arrhythmia – All Studies[a,b]



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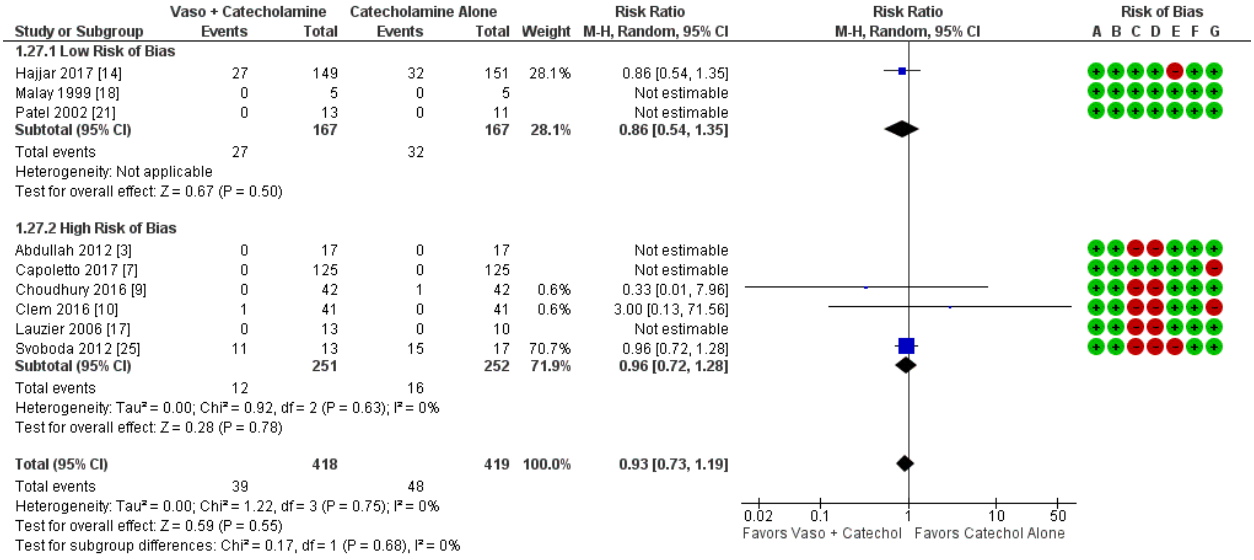
Ventricular Arrhythmia – Risk of Bias[a,b]



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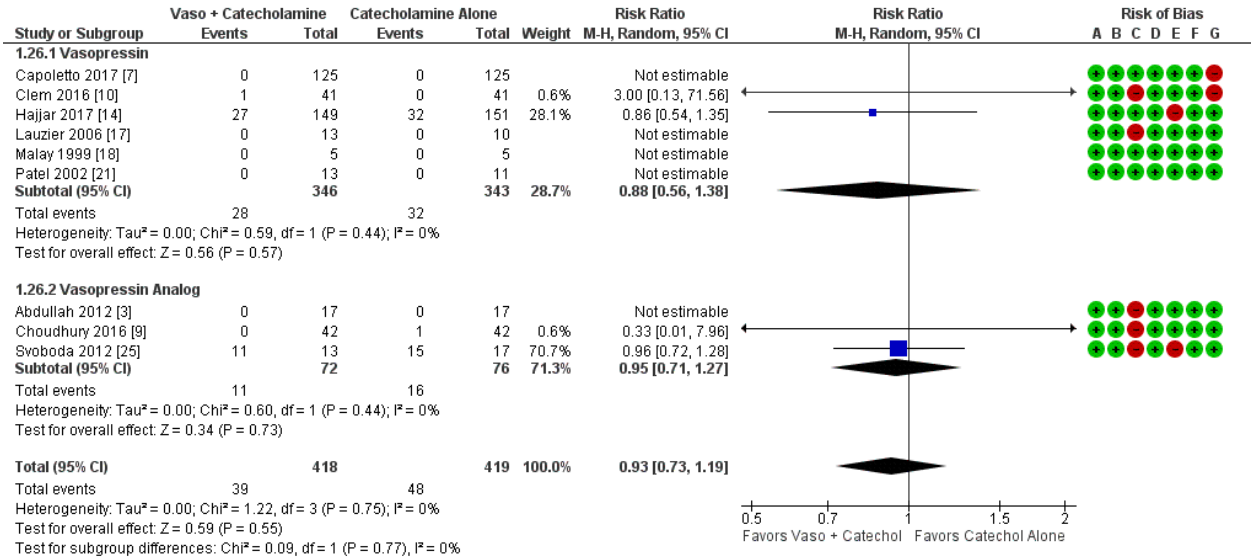
Ventricular Arrhythmia – Vasopressin versus Analogs[a,b,d]



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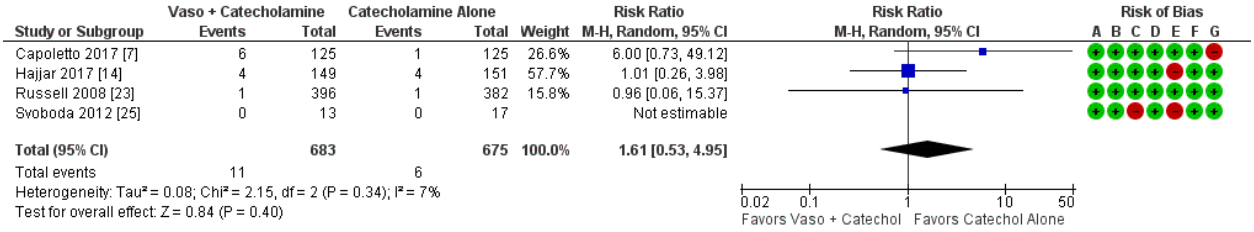
Stroke – All Studies[a,b]



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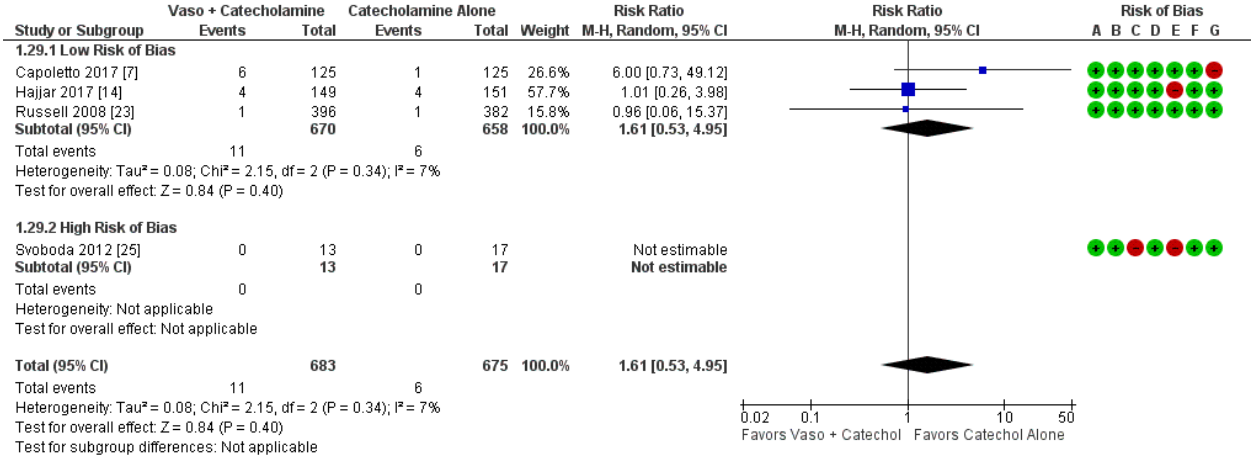
Stroke – Risk of Bias[a,b]



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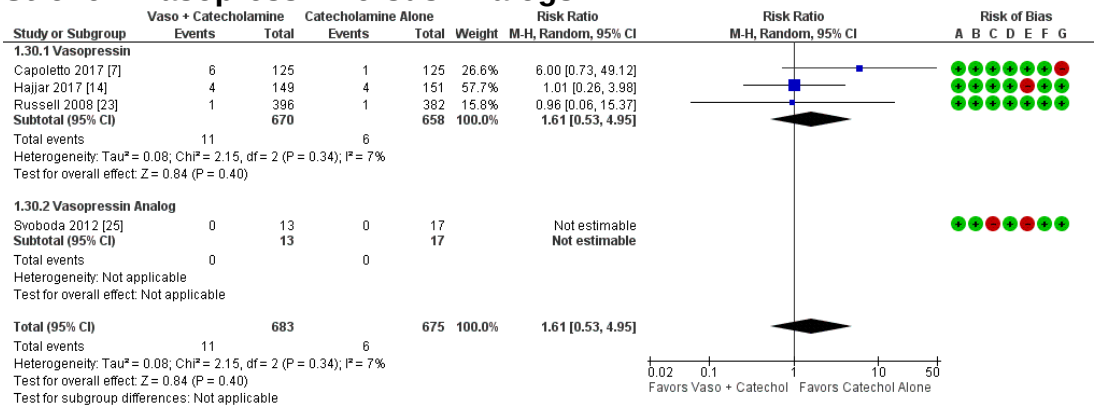
Stroke – Vasopressin versus Analogs[a,b,d]



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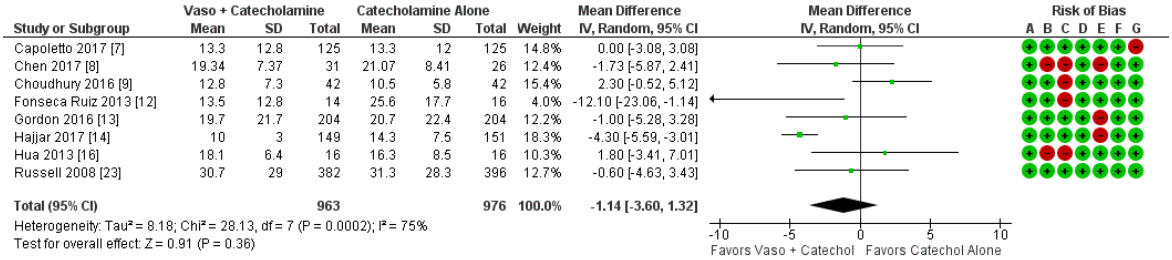
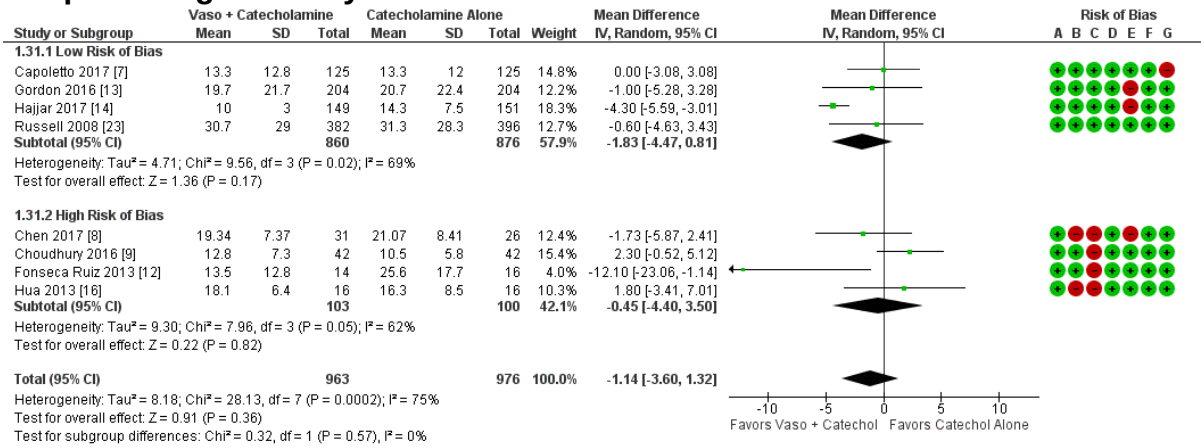
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Hospital Length of Stay – All Studies[a,b]



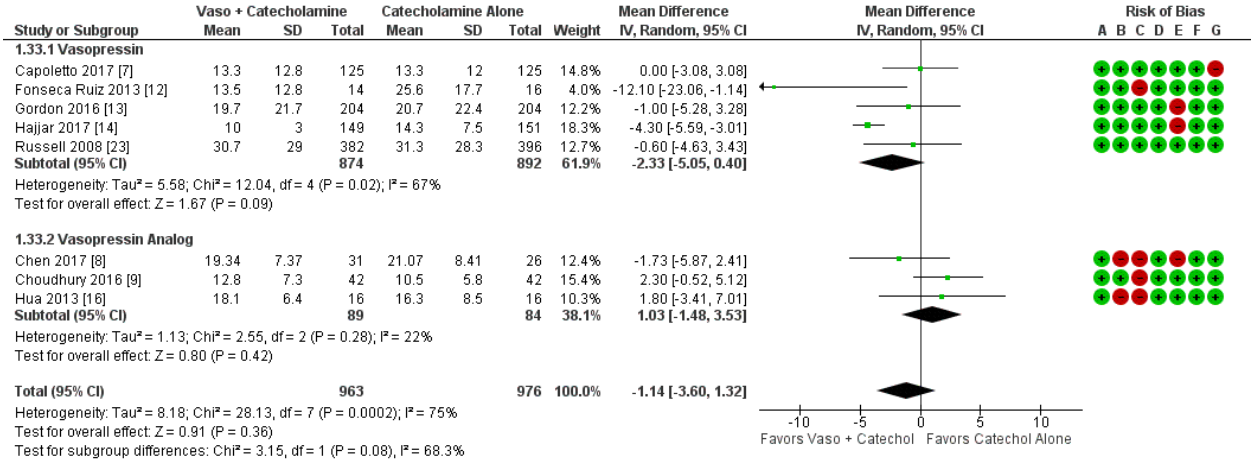
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Hospital Length of Stay – Risk of Bias[a,b]



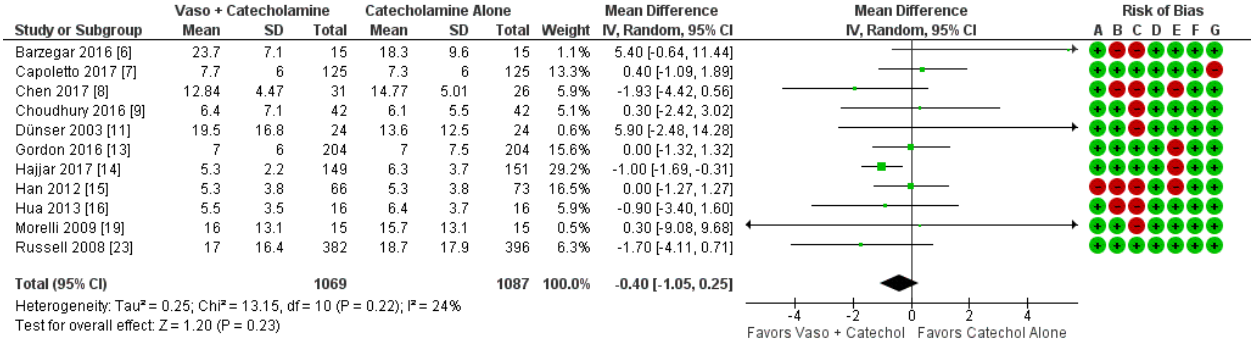
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Hospital Length of Stay – Vasopressin versus Analogs[a,b,d]



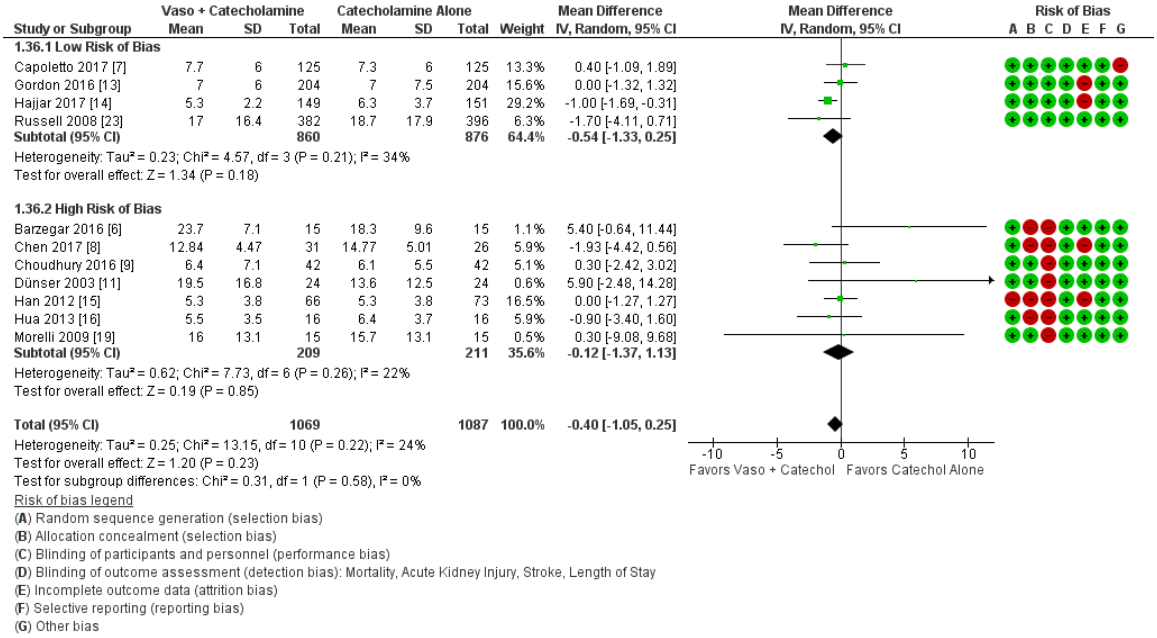
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

ICU Length of Stay – All Studies[a,b]



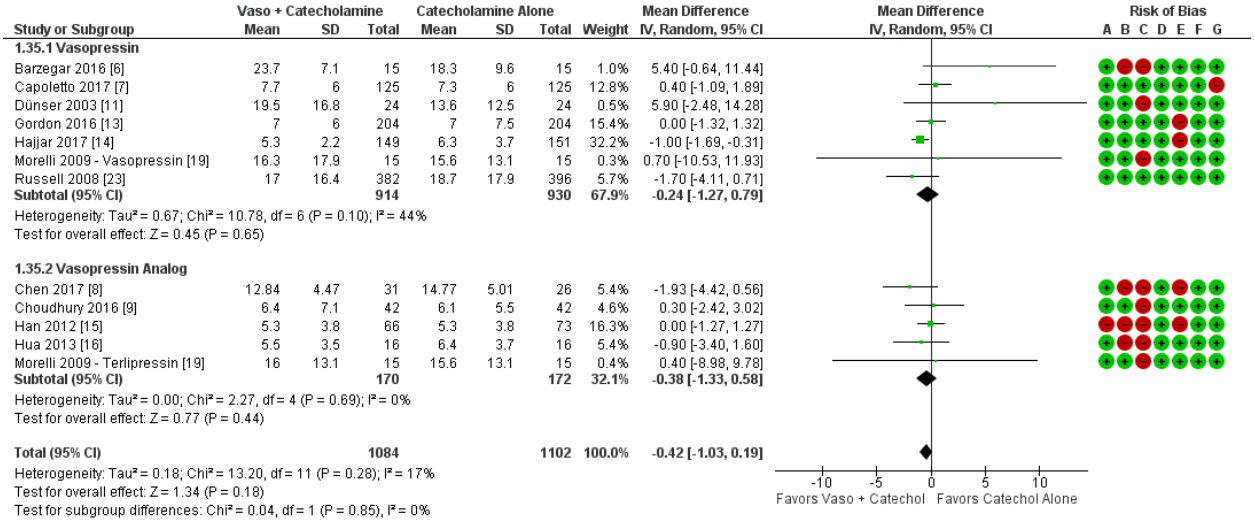
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

ICU Length of Stay – Risk of Bias[a,b]



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

ICU Length of Stay – Vasopressin versus Analogs[a,b,d]



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias): Mortality, Acute Kidney Injury, Stroke, Length of Stay
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Footnotes

[a] Vaso + Catecholamine/Vaso + Catechol = Vasopressin (or analog, *i.e.* terlipressin, selepressin or pituitrin) plus Catecholamine Vasopressors
"Events" refers to numbers of patients with events.

[b] The sizes of data markers of the point estimates are proportional to study weight. Green circle with "+" denotes low risk of bias in this domain; red circle with "-" denotes high risk of bias in this domain.

[c] The study "Dünser 2003" included patients with both sepsis and post-cardiac surgery vasoplegia, but subgroup data were obtained for atrial fibrillation only.[11] This paper is excluded from other outcomes when sepsis and post-cardiac surgery vasoplegia are compared.

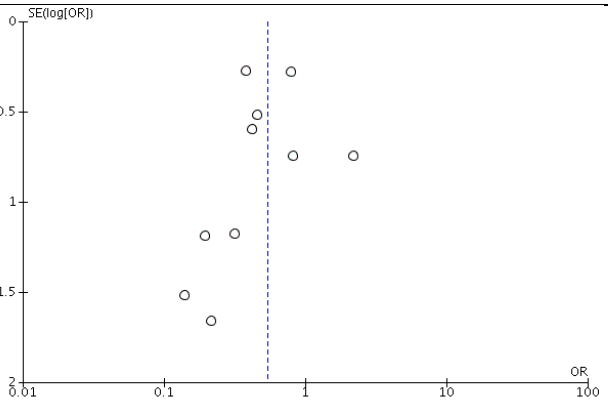
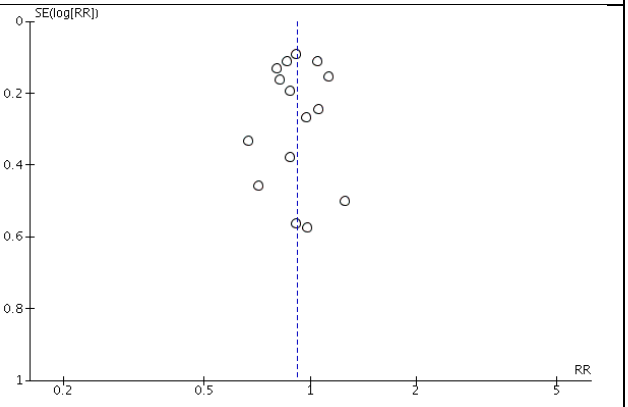
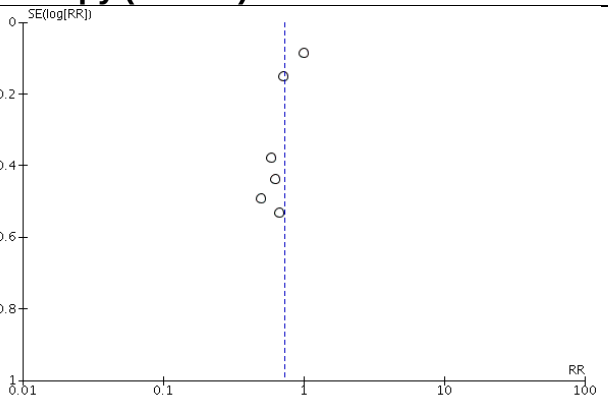
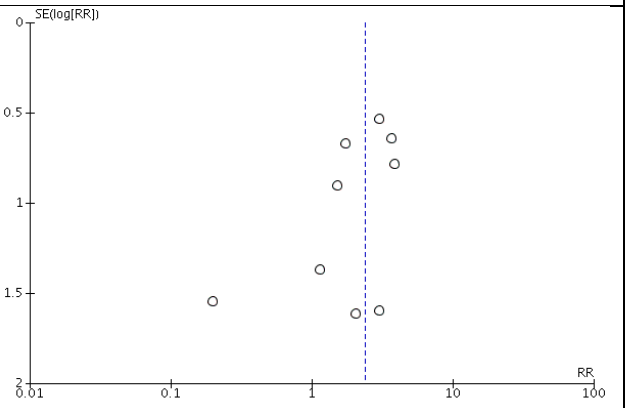
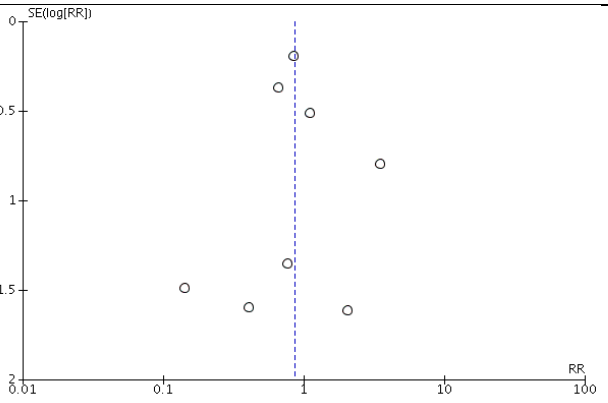
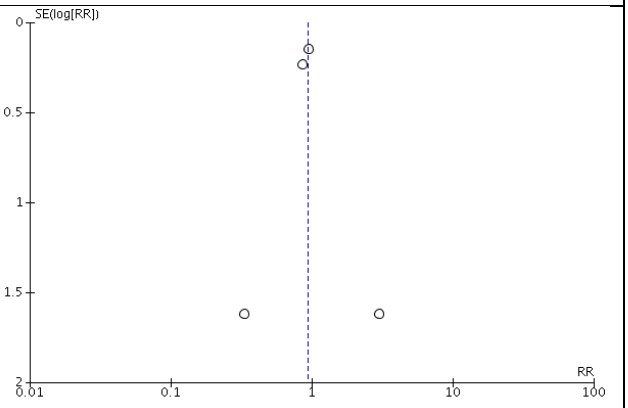
[d] The study "Morelli 2009" comprised three groups (vasopressin versus terlipressin versus norepinephrine).[19] It was considered as two separate trials (vasopressin versus norepinephrine and terlipressin versus norepinephrine) in the comparison between vasopressin and vasopressin analogs. It was considered as a single trial (vasopressin or terlipressin versus norepinephrine) in all other comparisons.

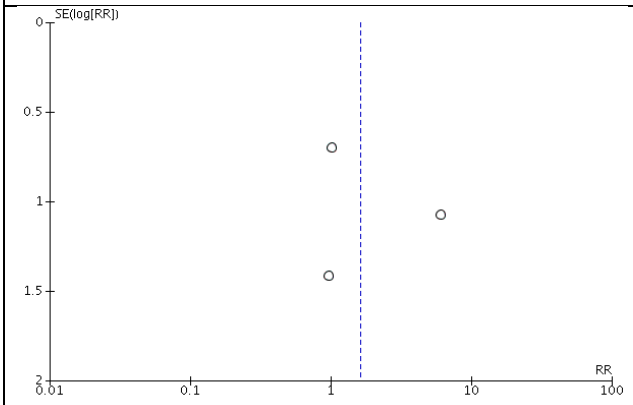
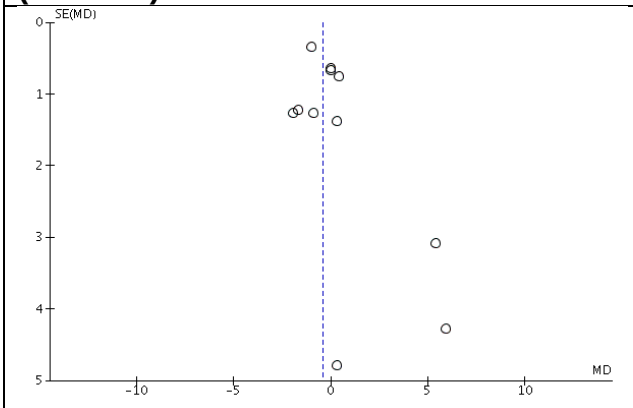
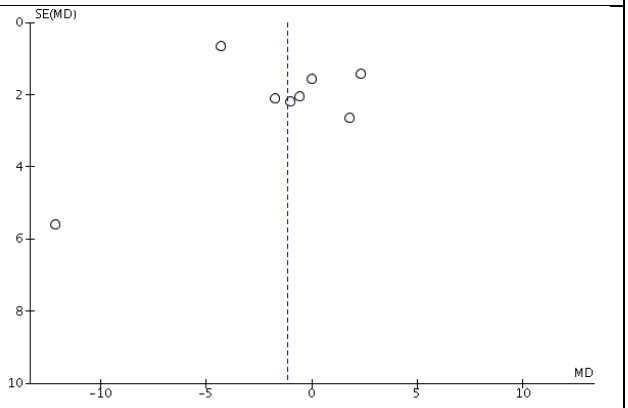
[e] Added 4 studies that reported on ICU mortality

[f] Full text only refers to studies not published only as abstracts

[g] "Defined as Digital Ischemia" Includes only studies where the authors described the outcome as Digital Ischemia. Peripheral cyanosis and limb ischemia were excluded.

eAppendix 12 – Funnel Plots for Main Outcome Comparisons

Atrial Fibrillation (13 trials)[a]	Mortality (17 trials)
	
Requirement for Renal Replacement Therapy (7 trials)	**Digital Ischemia (9 trials)**
	
Myocardial Injury (11 trials)	**Ventricular Arrhythmia (9 trials)**
	

Stroke (4 trials)	
	
Intensive Care Unit Length of Stay (11 trials)	**Hospital Length of Stay (8 trials)**
	

[a]Test for publication bias:
Outcome: Atrial Fibrillation (all studies with at least one outcome event (n=10)
Egger's test: bias = -0.44713 (95% CI = -1.25924 to 0.36498) P = 0.2399
Interpretation: no evidence of publication bias

SE = Standard Error; RR = Risk Ratio; MD = Mean Difference

eAppendix 13 – Reported lengths of stay in primary studies and transformation of median and interquartile range to mean and standard deviation

Hospital Length of Stay

Study and Group	Vasopressin Plus Catecholamines					Catecholamines Alone				
	N	Median	IQR	Mean[a]	SD	N	Median	IQR	Mean[a]	SD
Capoletto[7]	125	12	6-22	13.3	12.0	125	12	6-22	13.3	12.0
Chen[8]	31			19.3	7.4	26			21.1	8.4
Choudhury[9]	42	13	8-17.5	12.8	7.3	42	10	7-14.5	10.5	5.8
Fonseca Ruiz[12]	14	13	6-21.5	13.5	12.8	16	27.5	13.7-35.5	25.6	17.7
Gordon[13]	204	16	7-36	19.7	21.7	204	16	8-38	20.7	22.4
Hajjar[14]	149	10	8-12	10	3.0	151	13	10-20	14.3	7.5
Russell[23]	382	27	13-52	30.7	29.0	396	26	15-53	31.3	28.3

Intensive Care Unit Length of Stay

Study and Group	Vasopressin Plus Catecholamines					Catecholamines Alone				
	N	Median	IQR	Mean[a]	SD	N	Median	IQR	Mean[a]	SD
Barzegar[6]	15			23.7	7.1	15			18.3	9.6
Capoletto[7]	125	7	4-12	7.7	6.0	125	6	4-12	7.3	6.0
Chen[8]	31			12.8	4.5	26			14.8	5.0
Choudhury[9]	42	6	2-11.2	6.4	7.1	42	5	3-10.2	6.1	5.5
Dunser[11]	24			19.5	16.8	24			13.6	12.5
Gordon[13]	204	7	3-11	7	6.0	204	5	3-13	7	7.5
Hajjar[14]	149	5	4-7	5.3	2.2	151	6	4-9	6.3	3.7
Han[15]	66	5	3-8	5.3	3.8	73	5	3-8	5.3	3.8
Hua[16]	16			5.5	3.5	16			6.4	3.7

Morelli[19]	15	17	5-27	16.3	18.0	15	17	7-23	15.7	13.1
Morelli[19]	15	14	9-25	16	13.1					
Russell[23]	382	15	7-29	17	16.4	396	16	8-32	18.7	17.9

IQR = Interquartile Range; N = Total number of patients randomized to treatment group; SD = Standard Deviation

[a]Where studies reporting on length of stay provided only a median and a measure of dispersion, this was converted to mean and standard deviation assuming a normal distribution.[30]

[b] For the three-arm study by Morelli et al, the first row lists the data for participants assigned to vasopressin and the second row lists the data for participants assigned to terlipressin

eAppendix 14 – Summary of Findings Tables

Certainty assessment							Number of patients[a]		Effect		Certainty	Importance[b]
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vasopressin	Catecholamines	Relative (95% CI)	Absolute (95% CI)		
Atrial Fibrillation												
13	randomised trials	not serious	not serious	not serious	not serious	none	159/739 (21.5%)	215/723 (29.7%)	**RR 0.77** (0.67 to 0.88)	**68 fewer per 1,000** (from 36 fewer to 98 fewer)	HIGH	IMPORTANT
28 or 30 Day Mortality												
17	randomised trials	very serious	not serious	not serious	not serious	none	532/1453 (36.6%)	591/1451 (40.7%)	**RR 0.89** (0.82 to 0.97)	**45 fewer per 1,000** (from 12 fewer to 73 fewer)	LOW	CRITICAL
Requirement for Renal Replacement Therapy												
6	randomised trials	not serious	not serious	not serious	serious	none	97/412 (23.5%)	133/393 (33.8%)	**RR 0.74** (0.51 to 1.08)	**88 fewer per 1,000** (from 27 more to 166 fewer)	MODERATE	CRITICAL
Digital Ischemia												
9	randomised trials	not serious	not serious	not serious	not serious	Post hoc outcome	41/990 (4.1%)	17/973 (1.7%)	**RR 2.38** (1.37 to 4.12)	**24 more per 1,000** (from 6 more to 55 more)	MODERATE	CRITICAL

Summary of Findings – Continued

Certainty assessment							Number of patients[a]		Effect		Certainty	Importance[b]
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vasopressin	Catecholamines	Relative (95% CI)	Absolute (95% CI)		
Myocardial Injury												
10	randomised trials	not serious	not serious	serious	serious	none	62/991 (6.3%)	71/966 (7.3%)	**RR 0.86** (0.63 to 1.17)	**10 fewer per 1,000** (from 12 more to 27 fewer)	LOW	CRITICAL
Ventricular Arrhythmia												
9	randomised trials	not serious	not serious	serious	serious	none	39/418 (9.3%)	48/419 (11.5%)	**RR 0.93** (0.73 to 1.19)	**8 fewer per 1,000** (from 22 more to 31 fewer)	LOW	IMPORTANT
Stroke												
4	randomised trials	not serious	not serious	not serious	serious	none	11/683 (1.6%)	6/675 (0.9%)	**RR 1.61** (0.53 to 4.95)	**5 more per 1,000** (from 4 fewer to 35 more)	MODERATE	CRITICAL
Hospital Length of Stay												
7	randomised trials	not serious	**serious**	not serious	**serious**	none	963	976	-	MD **1.1 lower** (3.9 lower to 1.7 higher)	LOW	IMPORTANT
ICU Length of Stay												
11	randomised trials	not serious	not serious	not serious	**serious**	none	1069	1087	-	MD **0.4 lower** (1.05 lower to 0.25 higher)	MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

[a] For binary outcomes, the numerator refers to the number of patients with the event across all studies and the denominator refers to the number of patients at risk of the event across all studies. For continuous outcomes (i.e. length of stay), the number provided is the number of patients with available data for that outcome.
[b]Outcome importance is based upon the GRADE framework and is based on the polling in Appendix 5

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