Comparative safety and efficacy of vasopressors for mortality in septic shock: a network meta-analysis

Supplementary online appendices

Myura Nagendran

Mahiben Maruthappu

Anthony C Gordon

Kurinchi S Gurusamy

APPENDICES

APPENDIX 1 – Search strategies

Medline (OvidSP) 1946 to date of search

1. exp Vasoconstrictor Agents/ or exp Catecholamines/ or exp Metaproterenol/
2. (Epinephrine or epinephrin or Norepinephrine or Catecholoamine or Catecholamines or Orciprenaline or metaproterenol or dobutamine or dopamine or adrenaline or adrenalin or noradrenaline or noradrenalin or vasopressin or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin).af.
3. ((vasoconstrictor* or vasoactive) adj3 (agent or agents or drug or drugs or agonist or agonists)).af.
4. 1 or 2 or 3
5. exp sepsis/ or exp Systemic Inflammatory Response Syndrome/
6. (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood adj6 (poisoning or poisonings)) or (circulatory adj6 (failure or collapse))).af.
7. exp Hypotension/
8. (hypotension or hypotensive).af.
9. 7 or 8
10. exp Critical Care/
11. ((critical or intensive) adj6 (care or therapy)).af.
12. 10 or 11
13. 9 and 12
14. 5 or 6 or 13
15. 4 and 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.
19. placebo.ab.
20. drug therapy.fs.
21. randomly.ab.
22. trial.ab.
23. groups.ab.
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animals/ not humans.sh.
26. 24 not 25
27. 15 and 26

Cochrane library (Wiley) (latest issue)

#1 MeSH descriptor: [Vasoconstrictor Agents] explode all trees
#2 MeSH descriptor: [Catecholamines] explode all trees
#3 MeSH descriptor: [Metaproterenol] explode all trees
#4 (Epinephrine or epinephrin or Norepinephrine or Catecholoamine or Catecholamines or Orciprenaline or metaproterenol or dobutamine or dopamine or adrenaline or adrenalin or noradrenaline or noradrenalin or vasopressin or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin)
#5 ((vasoconstrictor* or vasoactive) near (agent or agents or drug or drugs or agonist or agonists))
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Sepsis] explode all trees
#8 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees

#9 (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood near (poisoning or poisonings)) or (circulatory near (failure or collapse)))
#10 MeSH descriptor: [Hypotension] explode all trees
#11 (hypotension or hypotensive)
#12 #10 or #11
#13 MeSH descriptor: [Critical Care] explode all trees
#14 ((critical or intensive) near (care or therapy)) .
#15 #13 or #14
#16 #12 and #15
#17 #7 or #8 or #9 or #16
#18 #6 and #17

Embase (OvidSP) (1947 to date of search)
1. exp Vasoconstrictor Agent/ or exp Catecholamine/
2. (Epinephrine or epinephrin or Norepinephrine or Catecholoamine or Catecholamines or Orciprenaline or metaproterenol or dobutamine or dopamine or adrenaline or adrenalin or noradrenaline or noradrenalin or vasopressin or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin).af.
3. ((vasoconstrictor* or vasoactive) adj3 (agent or agents or drug or drugs or agonist or agonists)).af.
4. 1 or 2 or 3
5. exp systemic inflammatory response syndrome/
6. (shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood adj6 (poisoning or poisonings)) or (circulatory adj6 (failure or collapse))).af.
7. exp hypotension/
8. (hypotension or hypotensive).af.
9. 7 or 8
10. exp intensive care/
11. ((critical or intensive) adj6 (care or therapy)).af.
12. 10 or 11
13. 9 and 12
14. 5 or 6 or 13
15. 4 and 14
16. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/
17. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af.
18. 16 or 17
19. 15 and 18

Science Citation index (ISI Web of Knowledge) (1900 to present) & Conference Proceedings (ISI Web of Knowledge) (1990 to present)

#1 TS=(Epinephrine or epinephrin or Norepinephrine or Catecholoamine or Catecholamines or Orciprenaline or metaproterenol or dobutamine or dopamine or adrenaline or adrenalin or noradrenaline or noradrenalin or vasopressin or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin)

2 TS=((vasoconstrictor* or vasoactive) and (agent or agents or drug or drugs or agonist or agonists))
#3 #1 OR #2
#4 TS=(shock or Sepsis Syndrome or Sepsis Syndromes or systemic inflammatory response syndrome or SIRS or Septic Shock or toxic shock or endotoxic shock or septicemia or septicemias or septicaemia or septicaemias or bacteremia or bacteremias or bacteraemia or bacteraemias or fungemia or fungemias or fungaemia or fungaemias or pyemia or pyemias or pyaemia or pyaemias or pyohemia or pyohemias or pyohaemia or pyohaemias or (blood AND (poisoning or poisonings)) or (circulatory AND (failure or collapse)))
#5 TS= ((hypotension or hypotensive) AND (critical or intensive) AND (care or therapy))
#6 #4 OR #5
#7 #3 AND #6
#8 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
#9 #7 AND #8

ClinicalTrials.gov (date of search)
random* | Interventional Studies | sepsis or septic shock | Adult, Senior | Phase 2, 3, 4

WHO ICTRP (date of search)
Sepsis or septic shock (condition in advanced search)

APPENDIX 2 – WinBUGS Codes

Explanation
ns= number of studies; ns2 = number of two arm trials; ns3= number of three arm trials; nt=number of treatments; na[] = number of arms; ndata = number of rows; t[,1] indicates control and t[,2] indicates intervention. In a three-arm trial, t[,3] indicates the second intervention.

Binary outcomes:
r indicates the number with events in the particular group; r[,1] indicates the number with events in the control group; n indicates the total number of people in the particular group; n[,1] indicates the total number of people in the control group. r[,2], n[,2], r[,3], and n[,3] indicate the corresponding numbers for intervention and second intervention. In two-arm trials, r[,3] and n[,3] will be entered as 'NA' to indicate empty cells. If no three-arm trials are included under the outcome, the entire columns r[,3] and n[,3] will not be included.

Continuous outcomes (mean differences)
y[,1] indicates the mean in the control group; se[,1] indicates the standard error in the control group. y[,2], se[,2], y[,3], and se[,3] indicate the corresponding numbers for intervention and second intervention. In two-arm trials, y[,3] and se[,3] will be entered as 'NA' to indicate empty cells.

Continuous outcomes (standardised mean differences (SMD))
y[,2] and se[,2] indicate the SMD and its standard error (SE) between treatment 2 and control group. y[,3] and se[,3] indicate the SMD and its standard error between treatment 3 and control group. In two-arm trials, y[,3] and se[,3] will be entered as 'NA' to indicate empty cells. The standardised mean difference and its SE will be calculated by Hedges' adjusted g.

Binary outcome - fixed-effect model
```
# Binomial likelihood, logit link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
```

```
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor
logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Binary outcome - random-effects model

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
```

```
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Binary outcome - inconsistency model (random-effects)

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
delta[i,1]<-0 # treatment effect is zero in control arm
mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var # between-trial precision
} # *** PROGRAM ENDS
```

APPENDIX 3 – Supplementary figures

Figure S2 legend. Forest plot of the odds ratio of 28 day mortality in trials comparing norepinephrine to dopamine.

Figure S3 legend. Forest plot of the odds ratio of 28 day mortality in trials comparing norepinephrine to vasopressins.

Figure S4 legend. Network plot for 28 day mortality analysis. The plot displays the nodes (possible treatment combinations) and the links between them. Node size is proportional to the number of comparisons investigating that node. Line thickness is proportional to the number of studies investigating the 2 connected nodes.

Figure S5 legend. Forest plot of the odds ratio of arrhythmia incidence in trials comparing dopamine to norepinephrine.

Figure S6 legend. Forest plot of the odds ratio of arrhythmia incidence in trials comparing norepinephrine to vasopressins.

Figure S7 legend. Network plot for arrhythmia analysis. The plot displays the nodes (possible treatment combinations) and the links between them. Node size is proportional to the number of comparisons investigating that node. Line thickness is proportional to the number of studies investigating the 2 connected nodes.

Study or Subgroup	Norepinephrine Events	Total	Dopamine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
De Backer 2010	249	502	291	542	79.8%	0.85 [0.67, 1.08]
Patel 2010	51	118	67	134	20.2%	0.76 [0.46, 1.25]
Total (95% CI)		**620**		**676**	**100.0%**	**0.83 [0.67, 1.03]**
Total events	300		358			

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0\%$

Test for overall effect: Z = 1.66 (P = 0.10)

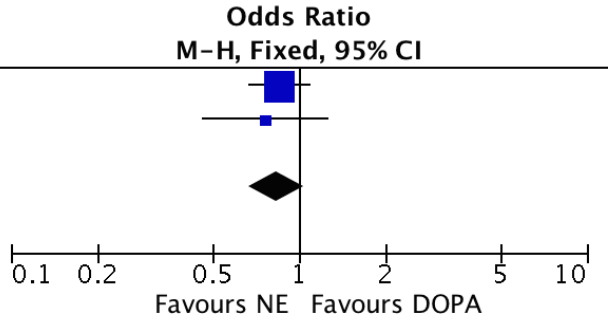


Figure S2.

Study or Subgroup	Norepinephrine Events	Total	Vasopressins Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Russel 2008	150	382	140	397	84.2%	1.19 [0.89, 1.59]
Svoboda 2012	16	17	10	13	0.7%	4.80 [0.44, 52.76]
Zambolim 2014	31	53	36	53	15.1%	0.67 [0.30, 1.47]
Total (95% CI)		**452**		**463**	**100.0%**	**1.13 [0.86, 1.48]**
Total events	197		186			

Heterogeneity: $Chi^2 = 3.22$, df = 2 (P = 0.20); $I^2 = 38\%$

Test for overall effect: Z = 0.90 (P = 0.37)

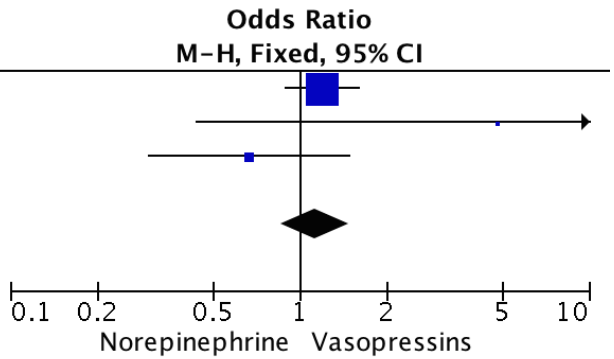
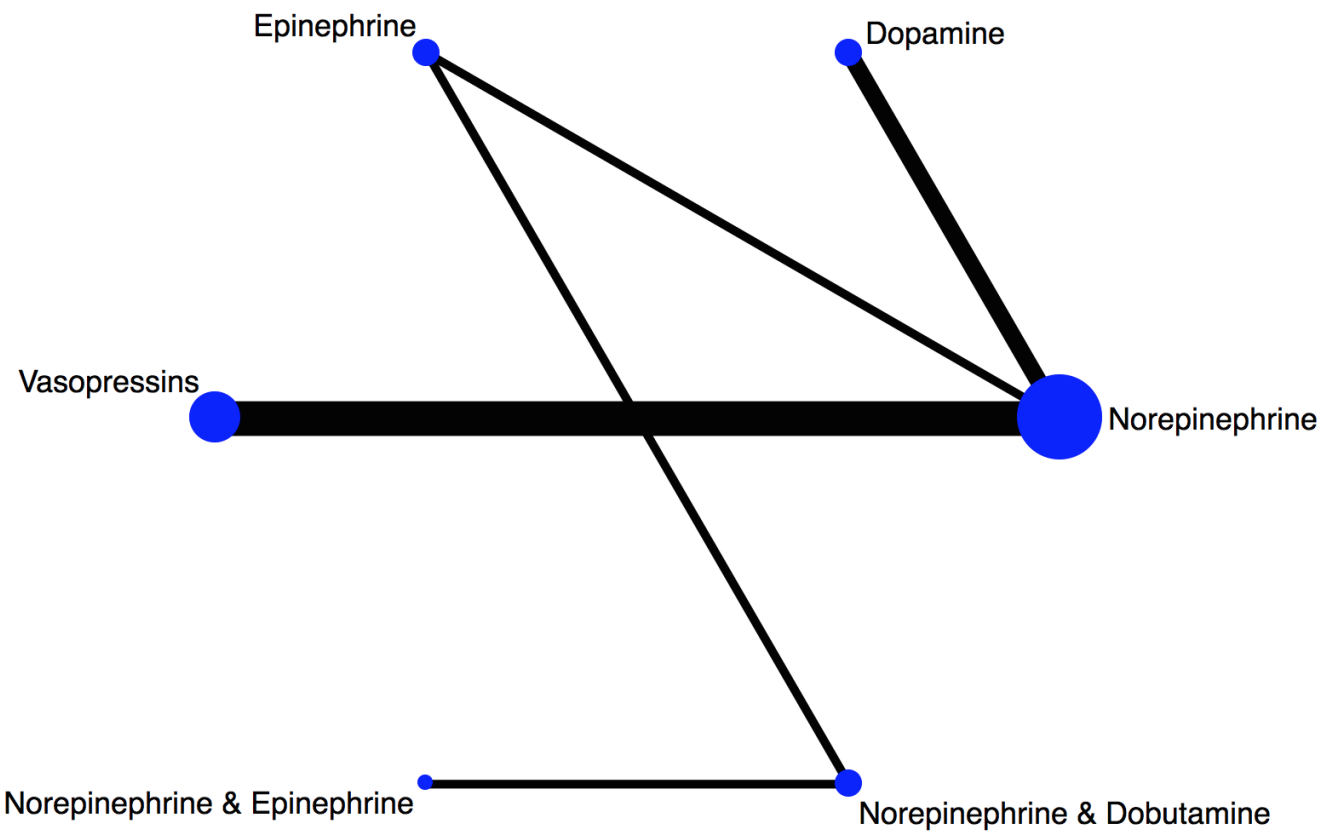


Figure S3.

Figure S4.


Epinephrine
Dopamine
Vasopressins
Norepinephrine
Norepinephrine & Epinephrine
Norepinephrine & Dobutamine

Study or Subgroup	Dopamine Events	Total	Norepinephrine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
De Backer 2010	207	542	102	502	87.7%	2.42 [1.84, 3.20]
Patel 2010	51	134	14	118	12.3%	4.56 [2.36, 8.81]
Total (95% CI)		**676**		**620**	**100.0%**	**2.69 [2.08, 3.47]**
Total events	258		116			

Heterogeneity: $Chi^2 = 3.02$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 7.60 (P < 0.00001)

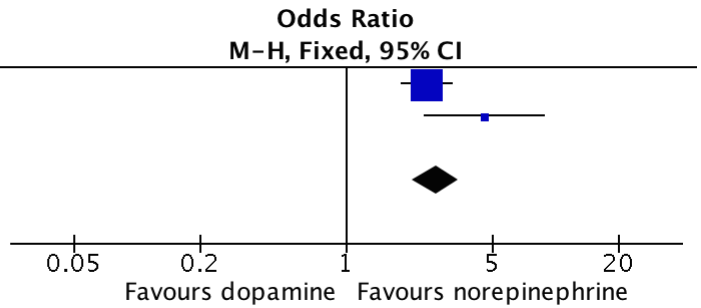


Figure S5.

Study or Subgroup	Norepinephrine Events	Total	Vasopressins Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lauzier 2006	0	9	0	13		Not estimable
Morelli 2009	4	15	1	30	6.0%	10.55 [1.06, 105.03]
Russel 2008	6	382	8	397	94.0%	0.78 [0.27, 2.26]
Total (95% CI)		**406**		**440**	**100.0%**	**1.36 [0.56, 3.31]**
Total events	10		9			

Heterogeneity: $Chi^2 = 4.11$, df = 1 (P = 0.04); $I^2 = 76\%$

Test for overall effect: Z = 0.67 (P = 0.50)

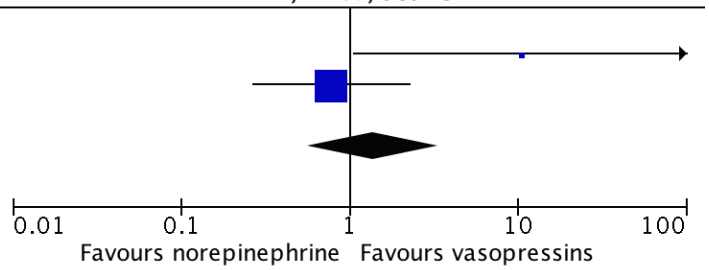


Figure S6.

Figure S7.