# Supplemental Digital Content

# Lower versus higher exposure to vasopressor therapy in vasodilatory hypotension: a systematic review with meta-analysis

Alvin Richards-Belle, Mathieu Hylands, Fiona Muttalib, Shaurya Taran, Bram Rochwerg, Andrew Day, Paul R. Mouncey, Peter Radermacher, Rachel Couban, Pierre Asfar, Neill KJ Adhikari*, Francois Lamontagne*

*contributed equally as joint corresponding authors.

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# 1. Summary of search strategy

### *1.1 Registered trials*

https://www.clinicaltrials.gov/
54 studies found for: shock or hypotension

| | Original search (19 November 2020) | Updated search (15 October 2021) |
|---|---|---|
| MEDLINE | 584 | 37 |
| EMBASE | 2831 | 311 |
| Central | 1007 | 58 |
| PubMed | 132 | 46 |
| Subtotal | 4554 | 452 |
| - duplicates | -1182 | -421 |
| Total | 3372 | 31 |

### *1.2 Original search – 19 November 2020*

*MEDLINE*
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---
1 shock/ or exp systemic inflammatory response syndrome/ (145524)
2 (shock adj3 surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1426)
3 (shock adj3 (surgical or distribut*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1790)
4 (systemic inflammatory adj3 response adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8575)
5 Hypotension/ (22113)
6 hypotensi*.mp. (82445)
7 low blood pressure.mp. (1575)
8 (low adj3 blood* adj3 pressure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3911)
9 or/1-8 (230331)
10 Resuscitation/ (26496)
11 resuscitat*.mp. (81468)
12 exp Critical Care/ (58822)
13 ((critical* or intensive or tertiary) adj3 (care or ill*)).mp. (309979)
14 or/10-13 (378085)
15 9 and 14 (31060)
16 exp Vasoconstrictor Agents/ (259275)
17 exp Vasopressins/ (35981)
18 (vasoconstrict* adj3 (agent or substance or drug)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (531)

19 vasopressin*.mp. (46701)
20 exp Cardiotonic Agents/ (207214)
21 (cardiotonic adj3 (agent or substance or drug)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (403)
22 ((cardiac or myocardial or heart) adj3 stimulant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (200)
23 exp Catecholamines/ or catecholamine*.mp. (279146)
24 exp Epinephrine/ or epinephrine*.mp. (71086)
25 adrenaline*.mp. (19964)
26 exp Norepinephrine/ or norepinephrine*.mp. (110564)
27 noradrenaline*.mp. (38051)
28 Isoproterenol/ or isoprenaline*.mp. (32869)
29 exp Metaproterenol/ or orciprenaline*.mp. (3364)
30 Ephedrine/ or ephedrine*.mp. (6616)
31 exp Phenylephrine/ or phenylephrine*.mp. (22672)
32 exp Dopamine Agents/ or exp Dopamine/ or dopamine*.mp. or exp Dopamine Agonists/ (305562)
33 Dobutamine/ or dobutamine*.mp. (9782)
34 (desmopressin or lyoressub or lypressin* or ornipressin* or terlipressin* or glypressin* or pitressin* or felypressin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6116)
35 Synephrine/ or synephrine*.mp. (580)
36 metaraminol.mp. or Metaraminol/ (1144)
37 Angiotensin II/ (36654)
38 (angiotensin adj (II or two)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (65671)
39 or/16-38 (747443)
40 15 and 39 (2833)
41 random:.tw. or placebo:.mp. or double-blind:.tw. (1280861)
42 ((treatment or control) adj3 group*).ab. (619560)
43 (allocat* adj5 group*).ab. (26328)
44 ((clinical or control*) adj3 trial).ti,ab,kw. (294058)
45 randomized controlled trial.pt. (517352)
46 controlled clinical trial.pt. (93935)
47 clinical trials as topic.sh. (193682)
48 random allocation.sh. (104055)
49 or/41-48 (2085502)
50 exp animals/ not humans.sh. (4757420)
51 49 not 50 (1806203)
52 40 and 51 (549)

*Embase (OVID)*
Database: Embase <1974 to 2020 November 18>
Search Strategy:
---
1 shock/ or exp septic shock/ (82430)
2 exp systemic inflammatory response syndrome/ (278887)

3 (shock adj3 (surgical or distribut*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1087)
4 (systemic inflammatory adj3 response adj3 syndrome).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (15061)
5 hypotension/ (117365)
6 hypotensi*.mp. (180545)
7 low blood pressure.mp. (2421)
8 (low adj3 blood* adj3 pressure).mp. (5531)
9 or/1-8 (474415)
10 resuscitation/ (113030)
11 resuscitat*.mp. (151571)
12 exp intensive care/ (718987)
13 ((critical* or intensive or tertiary) adj3 (care or ill*)).mp. (553396)
14 or/10-13 (1069472)
15 9 and 14 (115458)
16 exp vasoconstrictor agent/ (163105)
17 (vasoconstrict* adj3 agent*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (8937)
18 exp cardiotonic agent/ (191786)
19 (cardiotonic adj3 agent).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (3882)
20 (vasopressor or vasoconstrictor).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (32535)
21 catecholamine*.mp. or exp catecholamine/ (356131)
22 epinephrine.mp. or epinephrine/ (52648)
23 adrenaline.mp. (21437)
24 norepinephrine.mp. (68306)
25 noradrenalin*.mp. or noradrenalin/ (149620)
26 isoprenaline/ or isoprenaline.mp. (59447)
27 isoproterenol.mp. (27805)
28 metaproterenol.mp. or orciprenaline/ (4398)
29 orciprenaline.mp. (4401)
30 ephedrine/ or ephedrine.mp. (14084)
31 phenylephrine.mp. or phenylephrine/ (38745)
32 dopamine/ (115773)
33 exp dopamine receptor stimulating agent/ (211369)
34 dopamine.mp. (226235)
35 dobutamine.mp. or dobutamine/ (26587)
36 vasopressin/ or vasopressin.mp. (60897)
37 argipressin/ or argipressin.mp. (14568)
38 desmopressin.mp. or desmopressin/ (13239)
39 lypressin/ or lypressin.mp. (1759)
40 lyuoressub.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (0)
41 ornipressin.mp. or ornipressin/ (429)
42 terlipressin.mp. or terlipressin/ (3193)
43 glypressin.mp. (257)
44 pitressin.mp. (1292)
45 felypressin.mp. or felypressin/ (402)
46 synephrine.mp. or oxedrine/ (1043)
47 metaraminol.mp. or metaraminol/ (2019)

48 angiotensin II/ (29018)
49 (angiotensin adj (II or two)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (75582)
50 or/16-49 (915459)
51 15 and 50 (19189)
52 random:.tw. or placebo:.mp. or double-blind:.tw. (1865196)
53 ((treatment or control) adj3 group*).ab. (903626)
54 (allocat* adj5 group*).ab. (34943)
55 ((clinical or control*) adj3 trial).ti,ab,kw. (437579)
56 or/52-55 (2611307)
57 51 and 56 (2848)
58 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1092969)
59 Animal experiment/ not (human experiment/ or human/) (2299607)
60 57 not 59 (2631)

*PubMed*
Search: ((vasoconstrictor or vasopressin or cardiotonic or catecholamine or epinephrine or adrenaline or norepinephrine or noradrenaline or Isoproterenol or isoprenaline or Metaproterenol or orciprenaline or ephedrine or phenylephrine or dopamine or dobutamine or desmopressin or lyoressub or lypressin or ornipressin or terlipressin or glypressin or pitressin or felypressin or synephrine or metaraminol or Angiotensin II) AND (Therapy/Broad[filter])) AND (((resuscitation or critical care or intensive care) AND (shock or hypotension or low blood pressure)) AND (("publisher"[Filter] OR "inprocess"[Filter] OR "pubmednotmedline"[Filter] OR "pubstatusaheadofprint"[All Fields]))) Sort by: Publication Date
results 143

*Cochrane Library*
Search Name: BP targets
Date Run: 19/11/2020 22:43:48
Comment:

ID Search Hits
#1 MeSH descriptor: [Shock] this term only 546
#2 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees 4898
#3 ((shock near/3 (surgical or distribut*))):ti,ab,kw (Word variations have been searched)89
#4 (systemic inflammatory near/3 response near/3 syndrome):ti,ab,kw (Word variations have been searched) 1099
#5 MeSH descriptor: [Hypotension] explode all trees 2209
#6 hypotensi* 18439
#7 low blood pressure 19834
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 41968
#9 MeSH descriptor: [Resuscitation] explode all trees 4981
#10 resuscitat* 9239
#11 MeSH descriptor: [Critical Care] explode all trees 2068
#12 ((critical* or intensive or tertiary) near/3 (care or ill*)) 55426
#13 #9 or #10 or #11 or #12 63335
#14 #8 and #13 6285
#15 vasoconstrictor or vasopressin or cardiotonic or catecholamine or epinephrine or adrenaline or norepinephrine or noradrenaline or Isoproterenol or isoprenaline or Metaproterenol or orciprenaline or ephedrine or phenylephrine or dopamine or dobutamine or desmopressin or lyoressub or lypressin or ornipressin or terlipressin or glypressin or pitressin or felypressin or synephrine or metaraminol or Angiotensin II 38889
#16 #14 AND #15 in Trials 942

### *1.3 Updated search – 15 October 2021*

*MEDLINE*
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---
1 shock/ or exp systemic inflammatory response syndrome/ (153663)
2 (shock adj3 surgical).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1440)
3 (shock adj3 (surgical or distribut*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1837)
4 (systemic inflammatory adj3 response adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9640)
5 Hypotension/ (22651)
6 hypotensi*.mp. (85186)
7 low blood pressure.mp. (1659)
8 (low adj3 blood* adj3 pressure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4116)
9 or/1-8 (241389)
10 Resuscitation/ (27292)
11 resuscitat*.mp. (85791)
12 exp Critical Care/ (62145)
13 ((critical* or intensive or tertiary) adj3 (care or ill*)).mp. (340029)
14 or/10-13 (411541)
15 9 and 14 (33645)
16 exp Vasoconstrictor Agents/ (262615)
17 exp Vasopressins/ (36359)
18 (vasoconstrict* adj3 (agent or substance or drug)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (542)
19 vasopressin*.mp. (47321)
20 exp Cardiotonic Agents/ (210291)
21 (cardiotonic adj3 (agent or substance or drug)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (403)
22 ((cardiac or myocardial or heart) adj3 stimulant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (204)
23 exp Catecholamines/ or catecholamine*.mp. (283355)
24 exp Epinephrine/ or epinephrine*.mp. (72029)
25 adrenaline*.mp. (20297)
26 exp Norepinephrine/ or norepinephrine*.mp. (111914)
27 noradrenaline*.mp. (38555)
28 Isoproterenol/ or isoprenaline*.mp. (33136)
29 exp Metaproterenol/ or orciprenaline*.mp. (3367)
30 Ephedrine/ or ephedrine*.mp. (6712)

31 exp Phenylephrine/ or phenylephrine*.mp. (23012)
32 exp Dopamine Agents/ or exp Dopamine/ or dopamine*.mp. or exp Dopamine Agonists/ (313591)
33 Dobutamine/ or dobutamine*.mp. (9996)
34 (desmopressin or lyoressub or lypressin* or ornipressin* or terlipressin* or glypressin* or pitressin* or felypressin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6295)
35 Synephrine/ or synephrine*.mp. (598)
36 metaraminol.mp. or Metaraminol/ (1153)
37 Angiotensin II/ (37305)
38 (angiotensin adj (II or two)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (67385)
39 or/16-38 (762861)
40 15 and 39 (3043)
41 random:.tw. or placebo:.mp. or double-blind:.tw. (1369311)
42 ((treatment or control) adj3 group*).ab. (660788)
43 (allocat* adj5 group*).ab. (28810)
44 ((clinical or control*) adj3 trial).ti,ab,kw. (321172)
45 randomized controlled trial.pt. (546185)
46 controlled clinical trial.pt. (94453)
47 clinical trials as topic.sh. (197738)
48 random allocation.sh. (106012)
49 or/41-48 (2212539)
50 exp animals/ not humans.sh. (4897921)
51 49 not 50 (1918449)
52 40 and 51 (584)
53 limit 52 to ed=20201119-20211015 (37)

*EMBASE (OVID)*
Database: Embase <1974 to 2021 October 14>
Search Strategy:
---
1 shock/ or exp septic shock/ (91601)
2 exp systemic inflammatory response syndrome/ (302125)
3 (shock adj3 (surgical or distribut*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1174)
4 (systemic inflammatory adj3 response adj3 syndrome).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (16355)
5 hypotension/ (123957)
6 hypotensi*.mp. (189379)
7 low blood pressure.mp. (2550)
8 (low adj3 blood* adj3 pressure).mp. (5834)
9 or/1-8 (505905)
10 resuscitation/ (118490)
11 resuscitat*.mp. (159899)
12 exp intensive care/ (737264)
13 ((critical* or intensive or tertiary) adj3 (care or ill*)).mp. (609689)
14 or/10-13 (1130670)
15 9 and 14 (125370)
16 exp vasoconstrictor agent/ (286900)

17 (vasoconstrict* adj3 agent*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (9120)
18 exp cardiotonic agent/ (197267)
19 (cardiotonic adj3 agent).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (4001)
20 (vasopressor or vasoconstrictor).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (33849)
21 catecholamine*.mp. or exp catecholamine/ (366044)
22 epinephrine.mp. or epinephrine/ (56638)
23 adrenaline.mp. (21871)
24 norepinephrine.mp. (69228)
25 noradrenalin*.mp. or noradrenalin/ (152875)
26 isoprenaline/ or isoprenaline.mp. (59712)
27 isoproterenol.mp. (27975)
28 metaproterenol.mp. or orciprenaline/ (4382)
29 orciprenaline.mp. (4386)
30 ephedrine/ or ephedrine.mp. (14425)
31 phenylephrine.mp. or phenylephrine/ (39504)
32 dopamine/ (118678)
33 exp dopamine receptor stimulating agent/ (220246)
34 dopamine.mp. (232009)
35 dobutamine.mp. or dobutamine/ (27559)
36 vasopressin/ or vasopressin.mp. (61980)
37 argipressin/ or argipressin.mp. (14578)
38 desmopressin.mp. or desmopressin/ (13812)
39 lypressin/ or lypressin.mp. (1744)
40 lyuoressub.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (0)
41 ornipressin.mp. or ornipressin/ (427)
42 terlipressin.mp. or terlipressin/ (3327)
43 glypressin.mp. (255)
44 pitressin.mp. (1271)
45 felypressin.mp. or felypressin/ (401)
46 synephrine.mp. or oxedrine/ (1074)
47 metaraminol.mp. or metaraminol/ (2049)
48 angiotensin II/ (30615)
49 (angiotensin adj (II or two)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (77800)
50 or/16-49 (952690)
51 15 and 50 (21057)
52 random:.tw. or placebo:.mp. or double-blind:.tw. (1978882)
53 ((treatment or control) adj3 group*).ab. (959106)
54 (allocat* adj5 group*).ab. (37720)
55 ((clinical or control*) adj3 trial).ti,ab,kw. (455216)
56 or/52-55 (2764945)
57 51 and 56 (3054)
58 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1125080)
59 Animal experiment/ not (human experiment/ or human/) (2360765)
60 57 not 59 (2831)
61 limit 60 to em=202045-202152 (311)

*Cochrane Library*
Date Run: 15/10/2021 16:51:33
Comment:

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Shock] this term only | 590 |
| #2 | MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees | 5113 |
| #3 | ((shock near/3 (surgical or distribut*))):ti,ab,kw (Word variations have been searched) | 102 |
| #4 | (systemic inflammatory near/3 response near/3 syndrome):ti,ab,kw (Word variations have been searched) | 1160 |
| #5 | MeSH descriptor: [Hypotension] explode all trees | 2300 |
| #6 | hypotensi* | 19491 |
| #7 | low blood pressure | 21119 |
| #8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 | 44458 |
| #9 | MeSH descriptor: [Resuscitation] explode all trees | 5336 |
| #10 | resuscitat* | 9952 |
| #11 | MeSH descriptor: [Critical Care] explode all trees | 2157 |
| #12 | ((critical* or intensive or tertiary) near/3 (care or ill*)) | 60306 |
| #13 | #9 or #10 or #11 or #12 | 68791 |
| #14 | #8 and #13 | 6720 |
| #15 | vasoconstrictor or vasopressin or cardiotonic or catecholamine or epinephrine or adrenaline or norepinephrine or noradrenaline or Isoproterenol or isoprenaline or Metaproterenol or orciprenaline or ephedrine or phenylephrine or dopamine or dobutamine or desmopressin or lyoressub or lypressin or ornipressin or terlipressin or glypressin or pitressin or felypressin or synephrine or metaraminol or Angiotensin II | 40453 |
| #16 | #14 AND #15 in Trials | 1007 |
| #17 | #16 with Cochrane Library publication date Between Nov 2020 and Nov 2021 | 58 |

*PubMed*
Search: ((vasoconstrictor or vasopressin or cardiotonic or catecholamine or epinephrine or adrenaline or norepinephrine or noradrenaline or Isoproterenol or isoprenaline or Metaproterenol or orciprenaline or ephedrine or phenylephrine or dopamine or dobutamine or desmopressin or lyoressub or lypressin or ornipressin or terlipressin or glypressin or pitressin or felypressin or synephrine or metaraminol or Angiotensin II) AND (Therapy/Broad[filter])) AND (((resuscitation or critical care or intensive care) AND (shock or hypotension or low blood pressure)) AND (("publisher"[Filter] OR "inprocess"[Filter] OR "pubmednotmedline"[Filter] OR "pubstatusaheadofprint"[All Fields]))) Filters: from 2020 - 2021

## 2. Studies excluded after full-text review

### *2.1 Lower and higher blood pressure targets not compared (35)*

1. Microcirculation Guided Therapy Versus "Standard Treatment" of Severe Sepsis. https://clinicaltrials.gov/show/NCT00484133 2007
2. Effect of recovering vascular hyporeactivity and anti-shock of low-dose terlipressin complexing noradrenaline in severe shock and other severe illness. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-TRC-11001583 2011
3. Midodrine as an Adjunctive VasoprEssor for Refractory Hypotension in Intensive Care (MAVERIC) Study. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12618001158257 2018
4. A Pilot, Randomised, Blinded, Feasibility, Safety and Biochemical and Physiological Efficacy Study of Terlipressin versus Placebo in Hypotensive Sepsis. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12613001191785 2013;(): 2013
5. Midodrine for the prevention of perioperative hypotension http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12620000246987 2020;():2020
6. Norepinephrine / Vasopressin Combination for Resuscitation in Septic Shock https://clinicaltrials.gov/show/NCT04302584 2020;(): 2020
7. A Pilot, Randomised, Blinded, Feasibility, Safety and Biochemical and Physiological Efficacy Study of Terlipressin vs. Placebo in Cardiac Surgery Patients with the Post-operative High Cardiac Output and Hypotension syndrome http://www.who.int/trialsearch/Trial2.aspx? TrialID=ACTRN12613001194752 2013
8. Dua, D.; Jadliwala, R.; Gondalia, D.; Parmar, V.; Jain, A. Comparison of bolus phenylephrine, ephedrine and mephentermine for maintenance of arterial pressure during spinal anaesthesia in caesarean section. International Journal of Pharmaceutical Sciences and Research 2014;5(6):2412-2417.
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### *2.6 Vasopressor not titrated to blood pressure target (3)*


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### *2.7 Blood pressure target combined with non-approved vasopressor (e.g. nitric oxide synthase inhibitor) (1)*


1. A Phase III, Multicenter, Randomized, Placebo-Controlled Study of PHP When Administered by Continuous Infusion in Patients With Catecholamine-Resistant Distributive Shockhttp://www.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00000181 2009;(): 2009


### *2.8 Enrolment ongoing (1)*


1. High Versus Low Target Mean Arterial Pressure in Septic Shock in Critically Ill Cirrhotics. https://clinicaltrials.gov/show/NCT03145168 2017;(): 2017


### *2.9 Wrong outcomes (1)*


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### *2.10 Study not retrieved – unable to be included (1)*


1. Personalized Mean Arterial Pressure Management on Renal Function During Septic Shock (DORESEP). https://clinicaltrials.gov/ct2/show/NCT01473498

## 3. eTable 1. Vasopressor exposure among included studies.

| | Asfar, 2014 | | Lamontagne, 2016 | | Lamontagne, 2020 | |
|---|---|---|---|---|---|---|
| Randomised group | Lower MAP target | Higher MAP target | Lower MAP target | Higher MAP target | Lower MAP target | Higher MAP target |
| N patients | 388 | 388 | 60 | 58 | 1283 | 1300 |
| *Baseline* | | | | | | |
| Dose of vasopressor | | | | | | |
| Median (IQR) norepinephrine dose | 0.35 (0.20, 0.61) | 0.40 (0.20, 0.62) | | | | |
| ≥ 0.1 µg/kg/min, n (%) | | | | | 676 (53.4) | 677 (52.9) |
| MAP | 73 (14) | 74 (15) | *See footnote* | | 69.9 (10.1) | 71.1 (11.5) |
| | | | | | | |
| *Proportion receiving each vasopressor, n/N (%)*[1] | | | | | | |
| Norepinephrine | D1, 367/388 (94.6) | 369/388 (95.1) | 55/59 (93.2) | 54/58 (93.1) | 992/1261 (78.7) | 997/1276 (78.1) |
| Epinephrine | D1, 46/388 (11.9) | 34/388 (8.8) | 11/59 (18.6) | 6/58 (10.3) | 40/1261 (3.2) | 42/1276 (3.3) |
| Metaraminol | | | | | 395/1261 (31.3) | 418/1276 (32.8) |
| Vasopressin | 0/388 (0) | 0/388 (0) | 27/59 (45.8) | 30/58 (51.7) | 123/1261 (9.8) | 126/1276 (9.9) |
| Phenylephrine | | | 5/59 (8.5) | 11/58 (19.0) | 32/1261 (2.5) | 33/1276 (2.6) |
| Terlipressin | 0/388 (0) | 0/388 (0) | | | 10/1261 (0.8) | 14/1276 (1.1) |
| Dopamine | | | 1/59 (1.7) | 4/58 (6.9) | 1/1261 (0.1%) | 2/1276 (0.2) |
| *Dose of vasopressor* | | | | | | |
| Norepinephrine equivalents (µg/kg/min for rate; mg for total dose) | Norepinephrine dose rate D1, 0.50 (0.18, 1.27) D2, 0.24 (0.07, 0.58) | Norepinephrine dose rate D1, 0.61 (0.30, 1.87) D2, 0.40 (0.16, 0.94) | *Daily dose* 10 (2, 19) | *Daily dose* 14 (8, 29) | *Total dose* 17.7 (5.8, 47.2) *Mean dose rate*[2] | *Total dose* 26.4 (8.9, 65.6) *Mean dose rate*[2] |

| | Asfar, 2014 | | Lamontagne, 2016 | | Lamontagne, 2020 | |
|---|---|---|---|---|---|---|
| | D3, 0.13 (0.04, 0.50)<br>D4, 0.12 (0.03, 0.36)<br>D5, 0.16 (0.06, 0.35) | D3, 0.25 (0.09, 0.70)<br>D4, 0.18 (0.06, 0.45)<br>D5, 0.15 (0.05, 0.38) | | | 0.12 (0.06, 0.23) | 0.15 (0.08, 0.26) |
| Metaraminol (mg for total dose; mg/hr for rate) | | | | | *Total dose*<br>22.0 (9.3, 60.0)<br><br>*Mean dose rate*[2]<br>2.35 (1.44, 4.25) | *Total dose*<br>35.0 (12.7, 79.8)<br><br>*Mean dose rate*[2]<br>2.83 (1.95, 4.88) |
| Duration of vasopressor therapy (days) | 3.7 (3.2) | 4.7 (3.7) | 3 (2, 5) | 5 (3, 8) | 1.4 (0.6, 2.3) | 1.6 (0.8, 2.8) |
| *Co-interventions* | | | | | | |
| Steroids, n (%) | 307 (79.1) | 327 (84.3%) | 31 (51.7%) | 30 (51.7%) | 398 (31.6%) [n=1261] | 432 (33.9%) [n=1276] |
| Pure inotropes, n/N (%) | D1, 54/388 (13.9) | 42/388 (10.8) | Dobutamine, 7/60 (11.7)<br>Milrinone, 2/60 (3.3) | 8/58 (13.8)<br>4/58 (6.9) | 268/1261 (21.3) | 256/1276 (20.1) |
| MAP after randomisation | *See footnote* | | 70 (5) | 79 (5) | 66.7 (64.5, 69.8) | 72.6 (69.4, 76.5) |

D, day; MAP, mean arterial pressure.

For details of MAP at baseline in Lamontagne, 2016 please see figure 2 in the main trial publication(1). For details of MAP after randomisation in Asfar, 2014, please see figure 2 in the main trial publication(2).

1 Overall proportion in Lamontagne 2020 refers to the number of patients that received the vasopressor during the first episode of vasopressor therapy. An episode of vasopressor therapy was defined as the completion of a 24-hour period during which the patient received no vasopressors (or ICU discharge or death, if occurring first).

2 Median of the mean hourly dose rate.

## 4. eTable 2. Summary of findings.

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| **90-day all-cause mortality** | | | | | | | | | | | | | |
| 3 | randomised trials | not serious[a] | not serious | not serious | serious[b] | none | 684/1669 (41.0%) | 737/1688 (43.7%) | **RR 0.94** (0.87 to 1.02) | **26 fewer per 1,000** (from 57 fewer to 9 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably lowers 90-day mortality. |
| **In-ICU mortality** | | | | | | | | | | | | | |
| 3 | randomised trials | not serious[a] | not serious | not serious | serious[b] | none | 504/1660 (30.4%) | 532/1683 (31.6%) | **RR 0.96** (0.87 to 1.06) | **13 fewer per 1,000** (from 41 fewer to 19 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably lowers ICU mortality. |
| **In-hospital mortality** | | | | | | | | | | | | | |
| 3 | randomised trials | not serious[a] | not serious | not serious | serious[b] | none | 666/1680 (39.6%) | 707/1696 (41.7%) | **RR 0.95** (0.88 to 1.03) | **21 fewer per 1,000** (from 50 fewer to 13 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably lowers hospital mortality. |
| **28-day all-cause mortality** | | | | | | | | | | | | | |
| 3 | randomised trials | not serious[a] | not serious | not serious | serious[b] | none | 582/1669 (34.9%) | 633/1688 (37.5%) | **RR 0.93** (0.85 to 1.02) | **26 fewer per 1,000** (from 56 fewer to 8 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably lowers 28-day mortality. |
| **60-day all-cause mortality** | | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| 2 | randomised trials | not serious[a] | not serious | not serious | serious[b] | none | 501/1281 (39.1%) | 537/1300 (41.3%) | **RR 0.95** (0.86 to 1.04) | **21 fewer per 1,000** (from 58 fewer to 17 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably lowers 60-day mortality. |
| **180-day all-cause mortality** | | | | | | | | | | | | | |
| 1 | randomised trials | not serious[a] | not serious | not serious | very serious[c] | none | 22/60 (36.7%) | 24/58 (41.4%) | **RR 0.89** (0.56 to 1.39) | **46 fewer per 1,000** (from 182 fewer to 161 more) | ⊕◯◯◯ VERY LOW | CRITICAL | Lower vasopressor exposure has an uncertain effect on 180-day mortality. |
| **New-onset cardiac arrhythmia (supraventricular)** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | serious[e] | none | 33/1730 (1.9%) | 57/1746 (3.3%) | **OR 0.55** (0.36 to 0.86) | **14 fewer per 1,000** (from 21 fewer to 4 fewer) | ⊕⊕◯◯ LOW | IMPORTANT | Lower vasopressor exposure may decrease risk of supra-ventricular arrhythmia. |
| **New-onset cardiac arrhythmia (ventricular)** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 30/1730 (1.7%) | 31/1746 (1.8%) | **OR 0.97** (0.58 to 1.61) | **1 fewer per 1,000** (from 7 fewer to 11 more) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on ventricular arrhythmia. |
| **Mesenteric ischemia** | | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 21/1730 (1.2%) | 23/1746 (1.3%) | **OR 0.91** (0.50 to 1.66) | **1 fewer per 1,000** (from 7 fewer to 9 more) | ⨁⨁⨁◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on mesenteric ischemia. |
| **Digit/limb/skin ischemia** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 16/1730 (0.9%) | 14/1746 (0.8%) | **OR 1.15** (0.56 to 2.36) | **1 more per 1,000** (from 4 fewer to 11 more) | ⨁⨁⨁◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on digit ischemia. |
| **Myocardial ischemia** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 21/1730 (1.2%) | 28/1746 (1.6%) | **OR 0.73** (0.41 to 1.31) | **4 fewer per 1,000** (from 9 fewer to 5 more) | ⨁⨁⨁◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on myocardial ischemia. |
| **Gastrointestinal bleeding** | | | | | | | | | | | | | |
| 1 | randomised trials | serious[d] | not serious | not serious | very serious[f] | none | 42/388 (10.8%) | 31/388 (8.0%) | **OR 1.39** (0.86 to 2.26) | **28 more per 1,000** (from 10 fewer to 84 more) | ⨁◯◯◯ VERY LOW | IMPORTANT | Lower vasopressor exposure has an uncertain effect on gastrointestinal bleeding. |
| **Proportion meeting Stage 3 Acute Kidney Injury defined by KDIGO** | | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| 2 | randomised trials | serious[d] | not serious | serious[h] | serious[g] | none | 202/1670 (12.1%) | 183/1688 (10.8%) | **RR 1.10** (0.93 to 1.29) | **11 more per 1,000** (from 8 fewer to 31 more) | ⊕◯◯◯ VERY LOW | IMPORTANT | Lower vasopressor exposure has an uncertain effect on stage 3 acute kidney injury. |
| **Proportion receiving early RRT** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | serious[h] | serious[g] | none | 462/1666 (27.7%) | 458/1685 (27.2%) | **RR 1.02** (0.91 to 1.14) | **9 more per 1,000** (from 21 fewer to 40 more) | ⊕◯◯◯ VERY LOW | IMPORTANT | Lower vasopressor exposure has an uncertain effect on receiving early RRT. |
| **RRT free days (to 28 days; higher is better)** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | serious[h] | serious[i] | none | 1666 | 1685 | - | MD **1.08 higher** (from 0.19 higher to 1.96 higher) | ⊕◯◯◯ VERY LOW | IMPORTANT | Lower vasopressor exposure has an uncertain effect on RRT free days. |
| **Duration of RRT (days; lower is better)** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | serious[h] | not serious | none | 1666 | 1685 | - | MD **0.03 lower** (from 0.32 lower to 0.25 higher) | ⊕⊕◯◯ LOW | IMPORTANT | Lower vasopressor exposure may have little or no important effect on duration of RRT. |
| **Duration of mechanical ventilation (days; lower is better)** | | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 1655 | 1674 | - | MD **0.09 lower** (from 0.70 lower to 0.53 higher) | ⊕⊕⊕◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on duration of mechanical ventilation. |
| **Ventilator-free days (higher is better)** | | | | | | | | | | | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | serious[j] | none | 1666 | 1685 | - | MD **0.71 higher** (from 0.13 lower to 1.54 higher) | ⊕⊕◯◯ LOW | CRITICAL | Lower vasopressor exposure may have no important effect on ventilator-free days. |
| **Proportion receiving blood products** | | | | | | | | | | | | | |
| 2 | randomised trials | serious[d] | serious[k] | not serious | serious[l] | none | 232/447 (51.9%) | 227/446 (50.9%) | **RR 0.89** (0.57 to 1.38) | **56 fewer per 1,000** (from 219 fewer to 193 more) | ⊕◯◯◯ VERY LOW | IMPORTANT | Lower vasopressor exposure has an uncertain effect on the receipt of blood products. |
| **Blood product requirements (volume; lower is better)** | | | | | | | | | | | | | |
| 2 | randomised trials | serious[d] | not serious | not serious | serious[m] | none | 447 | 446 | - | SMD **0.11 higher** (from 0.02 lower to 0.24 higher) | ⊕⊕◯◯ LOW | IMPORTANT | Lower vasopressor exposure may have no important effect on blood product requirements |
| **Cumulative fluid balance** | | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance | Narrative Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | lower vasopressor exposure | higher vasopressor exposure | Relative (95% CI) | Absolute (95% CI) | | | |
| 3 | randomised trials | serious[d] | not serious | not serious | not serious | none | 1694 | 1714 | - | SMD **0.01 lower** (from 0.16 lower to 0.13 higher) | ⨁⨁⨁◯ MODERATE | IMPORTANT | Lower vasopressor exposure probably has no important effect on cumulative fluid balance |
| **Quality of life at longest reported follow-up (measured using EuroQoL 5-dimension 5-level [EQ-5D-5L] questionnaire; higher better)** | | | | | | | | | | | | | |
| 1 | randomised trials | serious[d] | not serious | not serious | not serious[n] | none | 253 | 241 | - | MD **0.01 lower** (from 0.05 lower to 0.03 higher) | ⨁⨁⨁◯ MODERATE | CRITICAL | Lower vasopressor exposure probably has no important effect on quality of life. |
| **Cognitive outcome at longest reported follow-up (measured using IQCODE and alphaFIM cognitive subscale; higher better)** | | | | | | | | | | | | | |
| 2 | randomised trials | serious[d] | not serious | not serious | Serious[o] | none | 287 | 272 | - | SMD **0.15 lower** (from 0.32 lower to 0.02 higher) | ⨁⨁◯◯ LOW | CRITICAL | Lower vasopressor exposure may have no important effect on long-term cognitive function. |

**CI:** Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference; **SMD:** Standardized mean difference

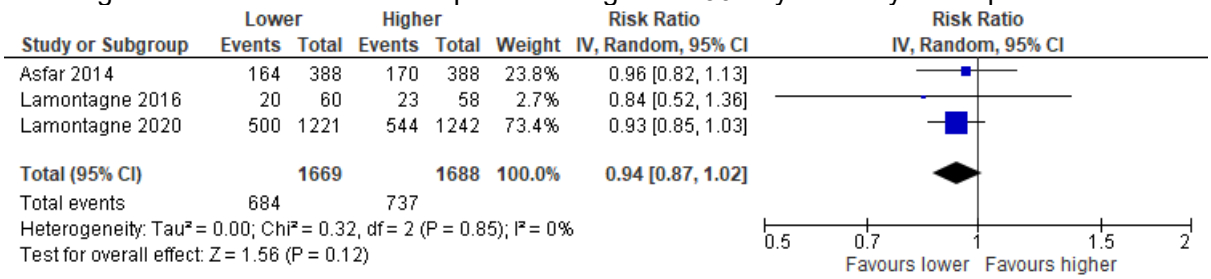
More patients were included for many non-mortality outcomes than for mortality due to assessment at an earlier time point, with fewer losses to follow-up. Vasopressor extravasation is not included because data came only from one trial,[ovation] and there were no events.

[a] Risk of bias not rated down for objectively defined outcomes (e.g. mortality), despite lack of clinician blinding.
[b] The point estimate suggests lower mortality, but confidence interval does not exclude the possibility of harm.
[c] Confidence interval is very wide and include both large benefit and large harm (10% absolute decrease and 10% absolute increase) and therefore we rated down by 3 levels.
[d] Healthcare providers were not blinded to the intervention and the outcome is not as objectively determined as mortality.
[e] Despite the point estimate and confidence interval both favouring lower vasopressor exposure, the number of events is below the optimal information size, leading to imprecision.
[f] Although the point estimate suggests harm with lower vasopressor exposure, the lower end of the confidence interval does not exclude benefit, the number of events was small and derived from a single study and therefore we rated down by 2.
[g] Despite a point estimate that suggests increased AKI and RRT with lower vasopressor exposure, the lower end of the confidence interval does not exclude benefit.
[h] Follow-up for RRT was highly variable across studies and may not adequately reflect outcomes important to patients.
[i] The point estimate suggests an important increase (≥1 day) in RRT-free days, but the confidence interval does not exclude a trivial (<1 day) increase in RRT-free days.
[j] The point estimate suggests a trivial increase in ventilator-free days, but the confidence interval does not exclude an important (≥1 day) increase in ventilator-free days.
[k] Despite the fact that the proportion of patients receiving blood products is higher overall with lower vasopressor exposure, inconsistencies in effect estimates lead to an overall risk that suggests a lower risk of receiving blood products with lower vasopressor exposure.
[l] Despite a point estimate that suggests increased risk of receiving blood products with lower vasopressor exposure, the lower end of the confidence interval does not exclude benefit.
[m] The point estimate suggests a trivial reduction in blood product requirements (SMD <0.2)., but the confidence interval does not exclude important increase (SMD >0.2).
[n] The minimum important difference in the EQ-5D-5L has not been established.

[o] The point estimate suggests trivial harm (SMD <0.2) with lower vasopressor exposure, but the confidence interval does not exclude important harm (SMD >0.2)

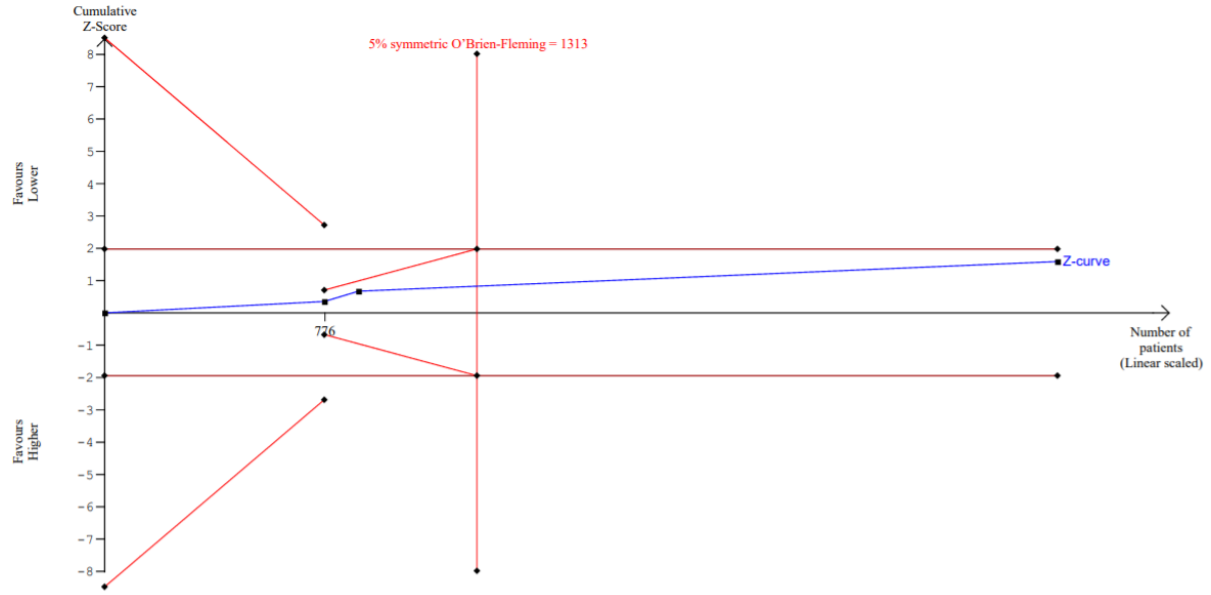
## 4. Primary outcome – 90-day mortality.

4.1. eFigure 1. Effect of lower blood pressure targets on 90-day mortality forest plot.

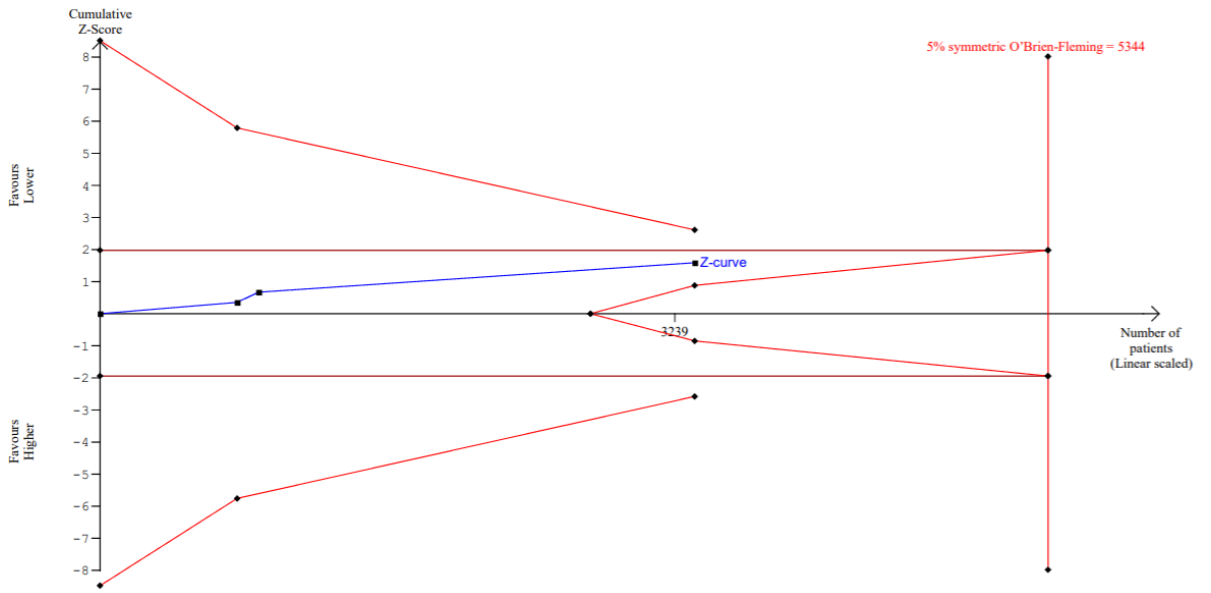



*IV, inverse-variance; CI, confidence intervals; df, degrees of freedom.*

4.2. eFigure 2. Trial sequential analysis – applying sequential monitoring boundaries according to an information size suggested by the trial results and an a priori 20% relative risk reduction.




4.3. eFigure 3. Trial sequential analysis – applying sequential monitoring boundaries according to an information size suggested by the trial results and a post-hoc 10% relative risk reduction.

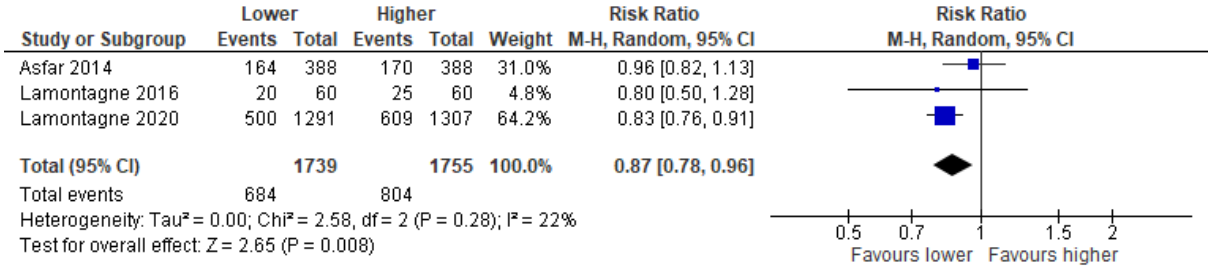


## 5. Sensitivity analyses evaluating the impact of loss to follow-up for 30 and 90-day mortality across studies

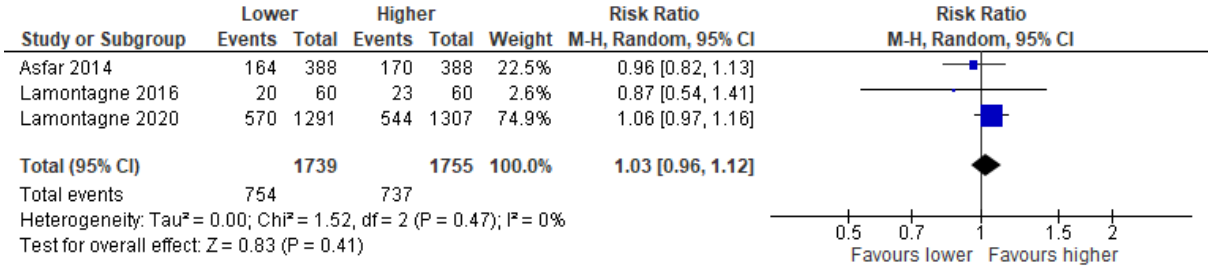
In the 65 Trial, 135 randomised patients (70 lower MAP target, 65 usual care) were excluded from the primary analyses. Apart from one, all were related to consent refusal/withdrawal (one patient in the usual care group was truly lost to follow-up). In the OVATION pilot trial, two randomised patients (higher MAP target) refused/withdrew consent and were excluded from the primary analyses. In the SEPSISPAM trial, no patients were reported as lost to follow-up.

### *5.1 90-day mortality – sensitivity analyses*

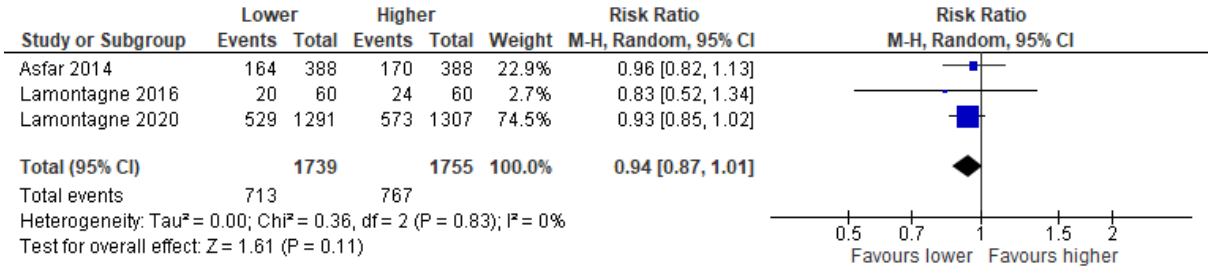
eFigure 4. Best-case scenario (all missing lower blood pressure target patients assumed alive, all missing higher blood pressure target patients assumed dead).




eFigure 5. Worse-case scenario (all missing lower blood pressure target patients assumed dead, all missing higher blood pressure target patients assumed alive).

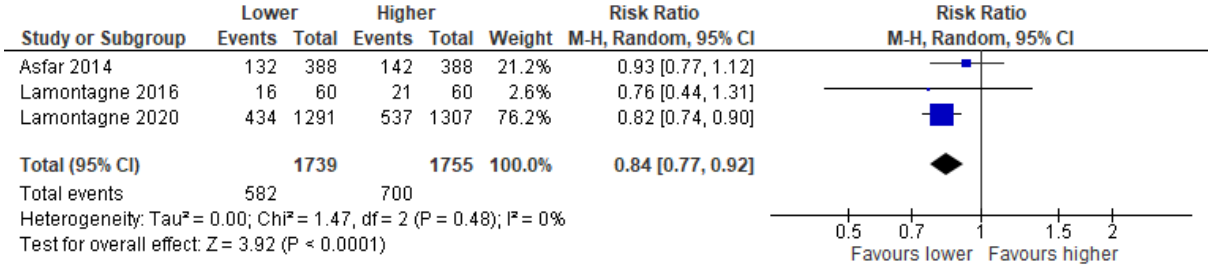



eFigure 6. Patients with missing data assumed to have the same mortality rate as the patients with available data in their randomised group.

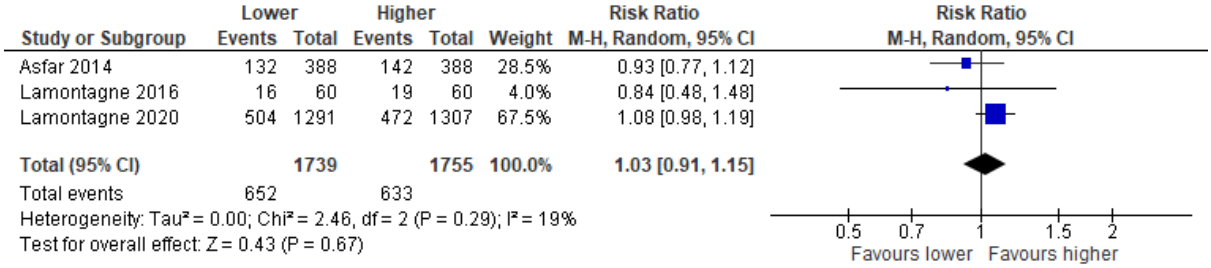


### *5.2. 28-day mortality – sensitivity analyses*

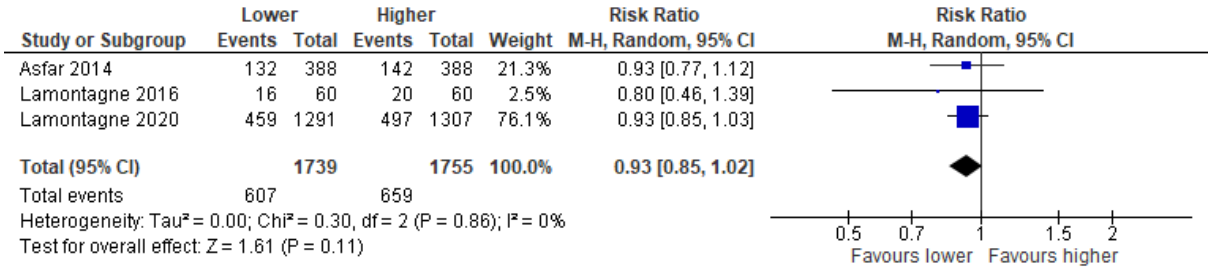
eFigure 7. Best-case scenario (all missing lower blood pressure target patients assumed alive, all missing higher blood pressure target patients assumed dead)




eFigure 8. Worse-case scenario (all missing lower blood pressure target patients assumed dead, all missing higher blood pressure target patients assumed alive)

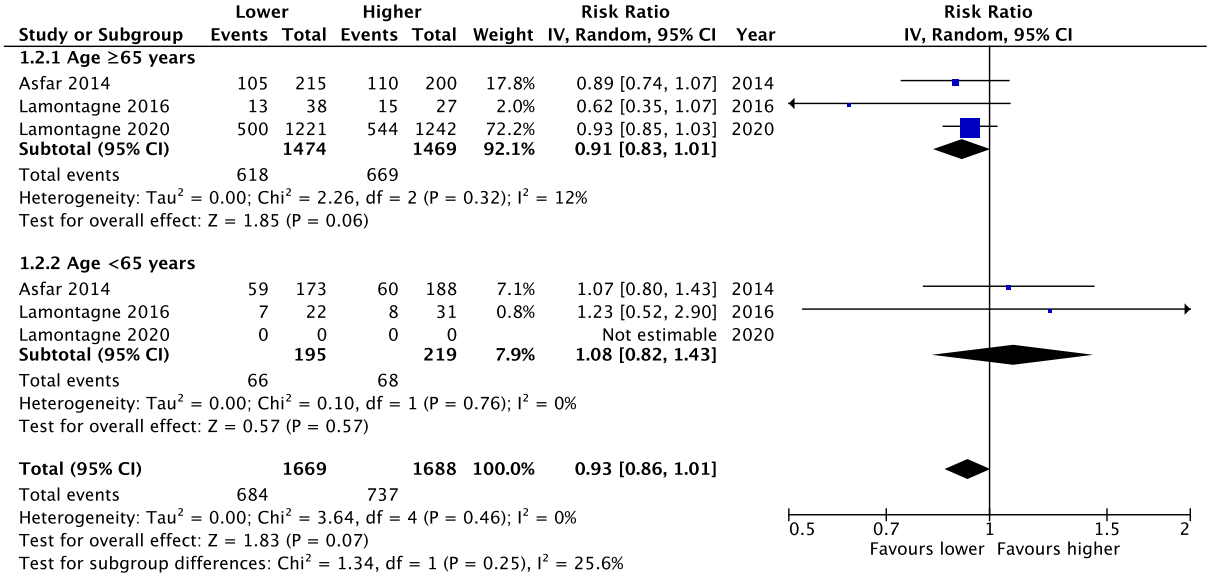



eFigure 9. Patients with missing data assumed to have the same mortality rate as the patients with available data in their randomised group

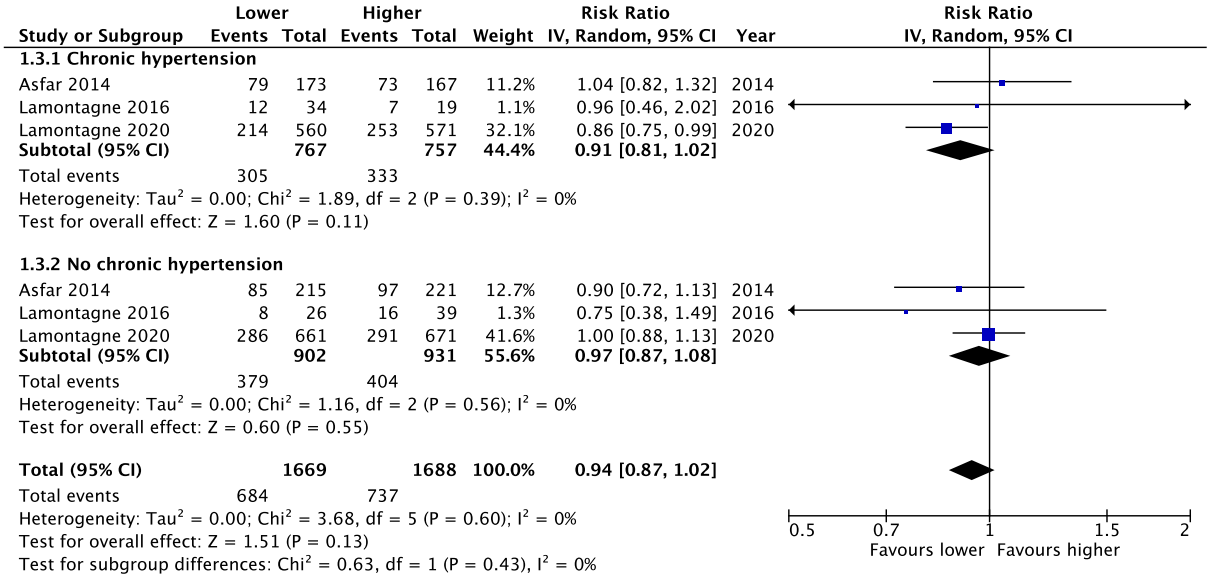


## 6. Forest plots for subgroup analyses of the primary outcome and all secondary outcomes.

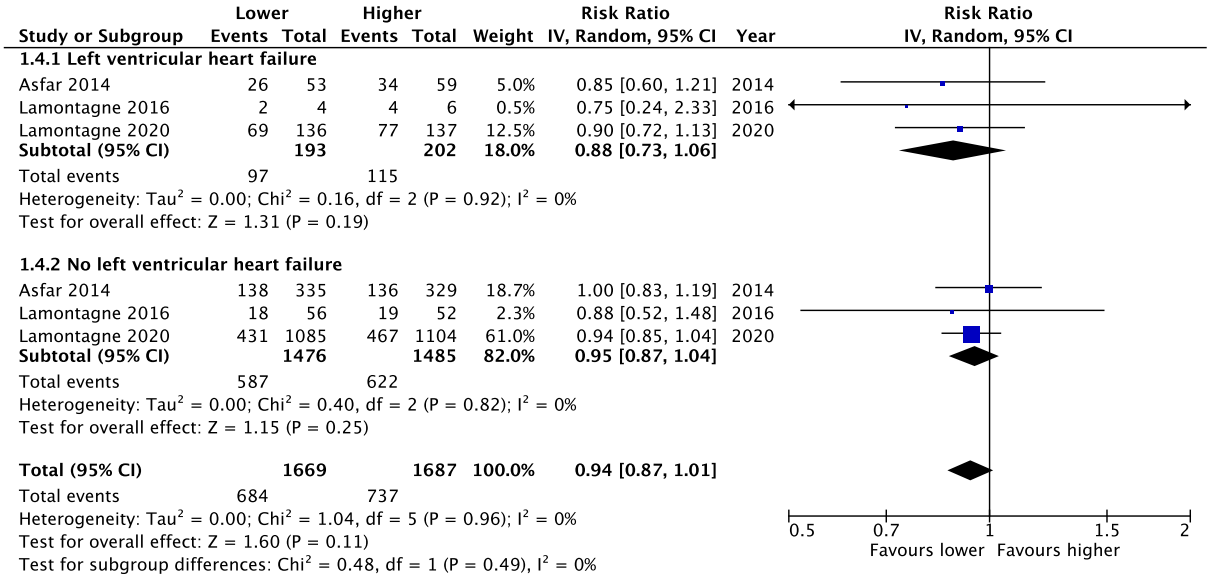
eFigure 10. 90-day mortality – by age.



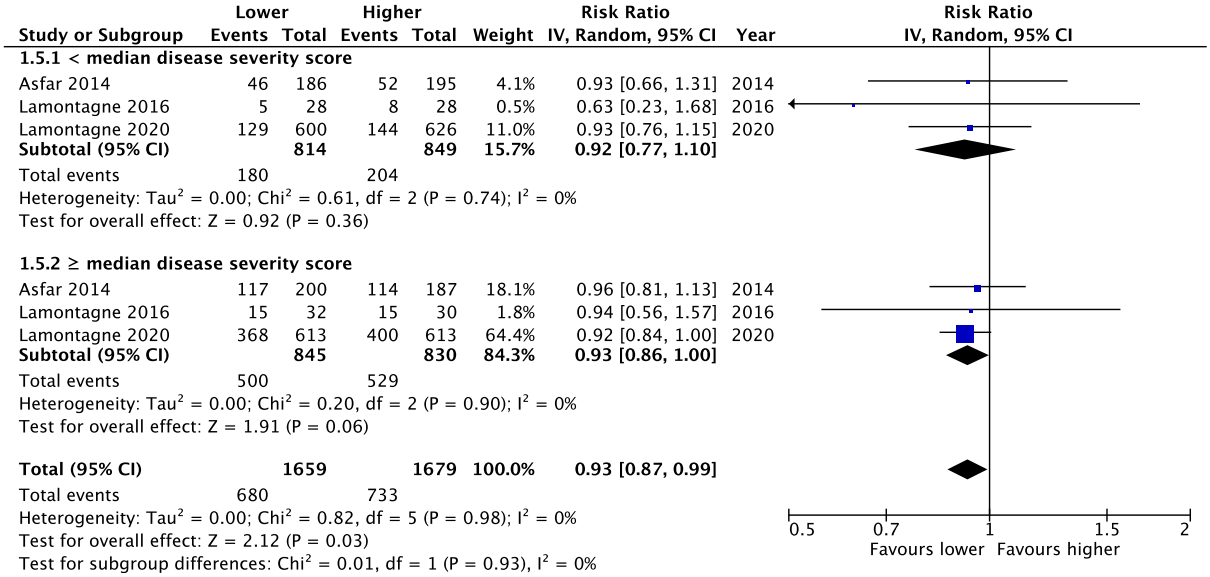

eFigure 11. 90-day mortality – by chronic hypertension status.



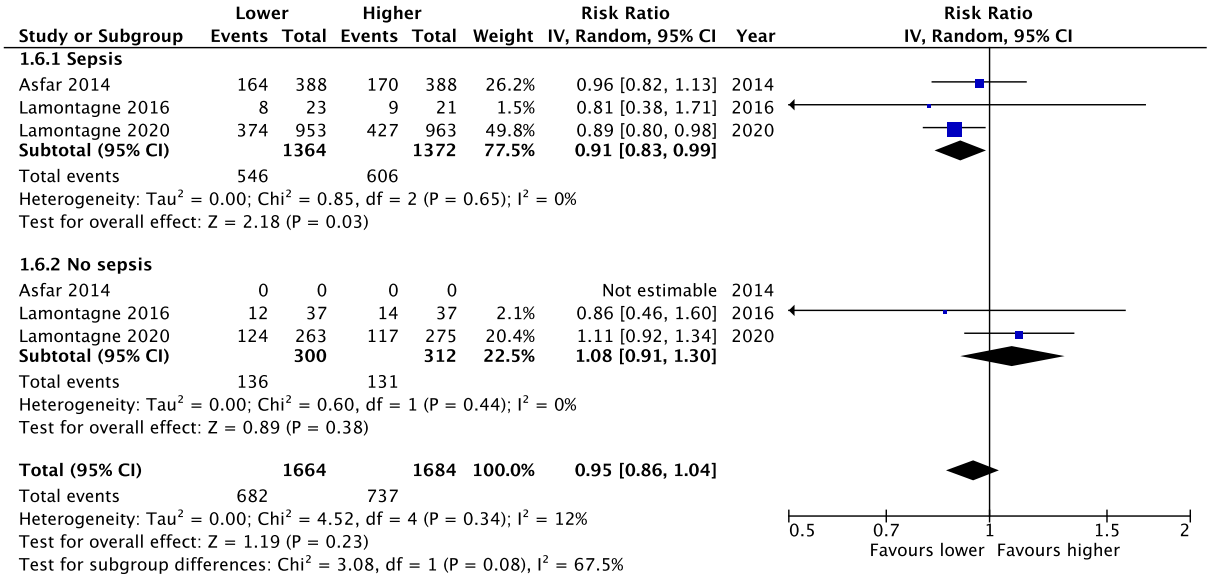
eFigure 12. 90-day mortality – by left ventricular heart failure status.



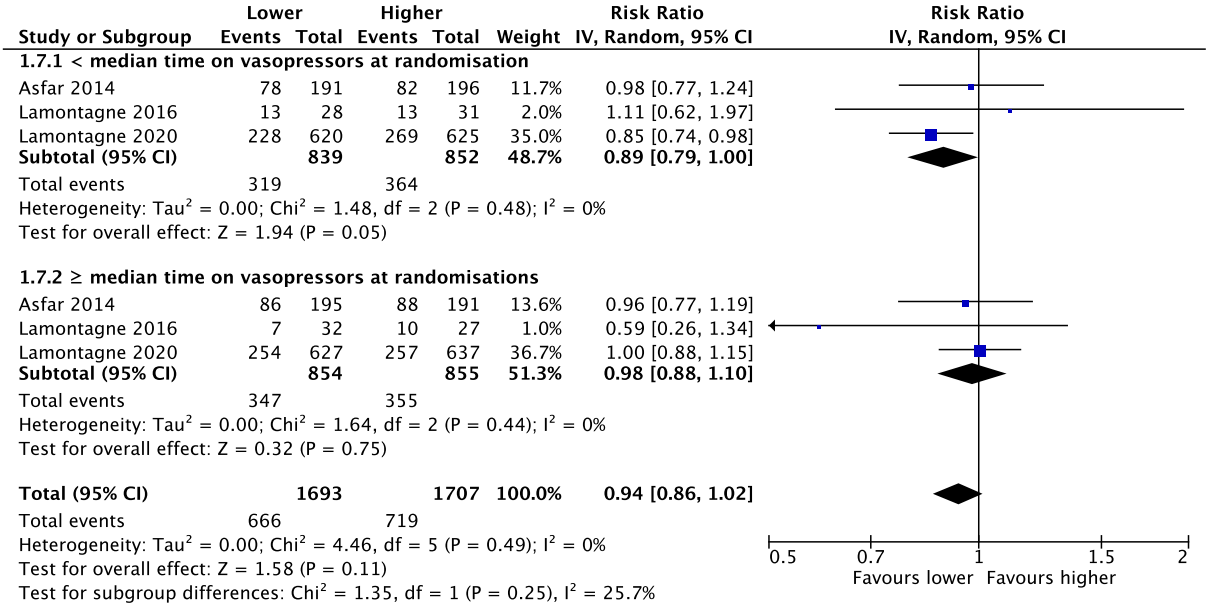

eFigure 13. 90-day mortality – by disease severity at randomisation.



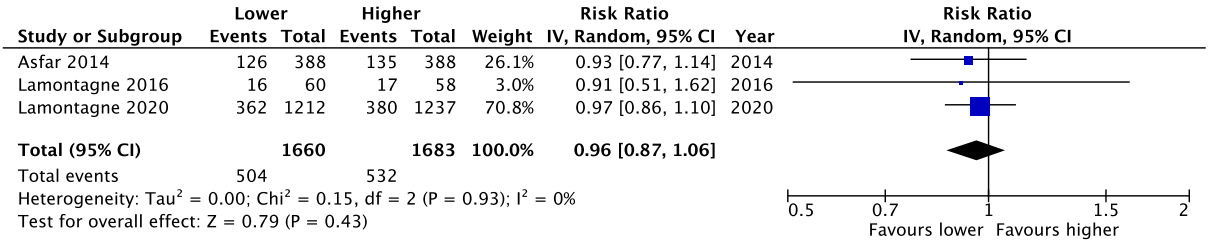
eFigure 14. 90-day mortality – by sepsis status.



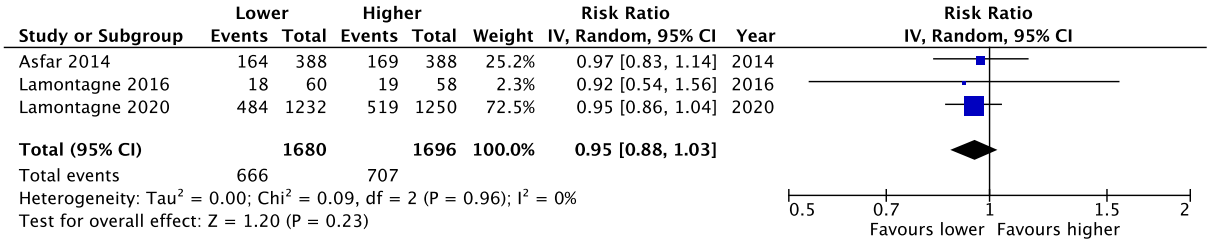

eFigure 15. 90-day mortality – by time on vasopressors at randomisation.



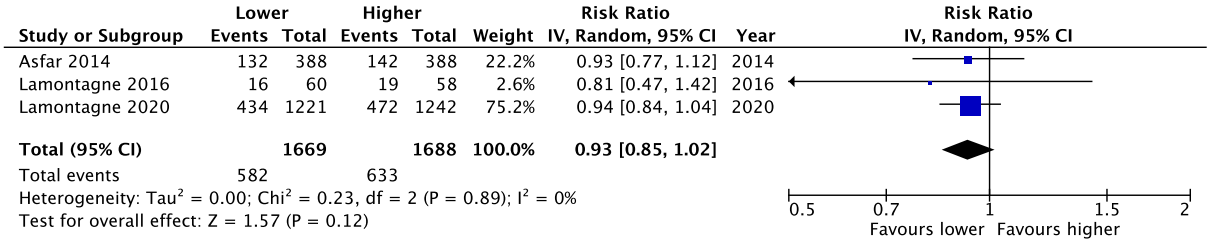

eFigure 16. In-ICU mortality.



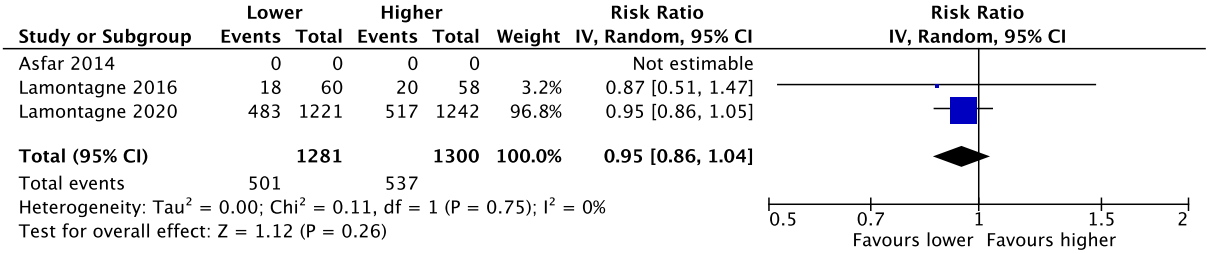
eFigure 17. In-hospital mortality.



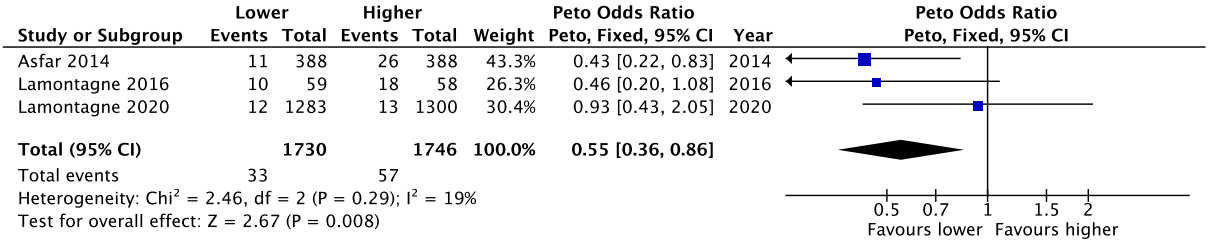

eFigure 18. 28-day mortality.



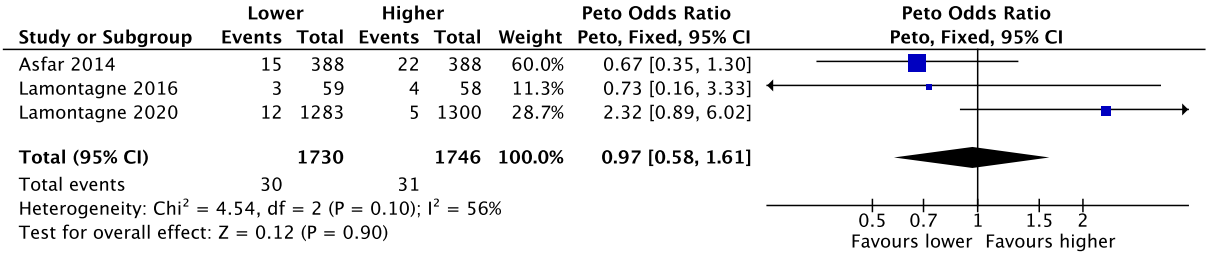

eFigure 19. 60-day mortality.



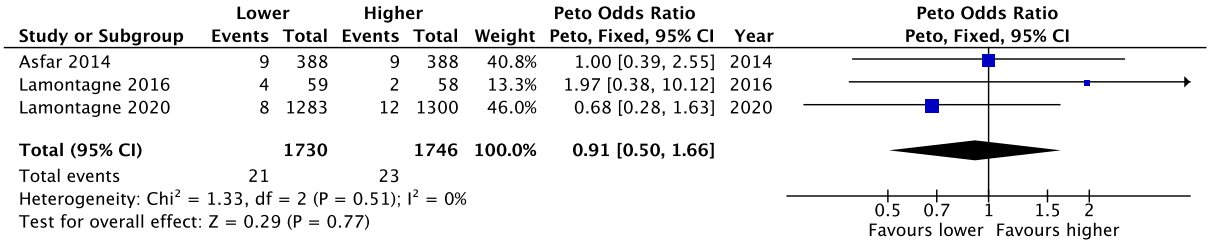

eFigure 20. New-onset supraventricular arrhythmia.



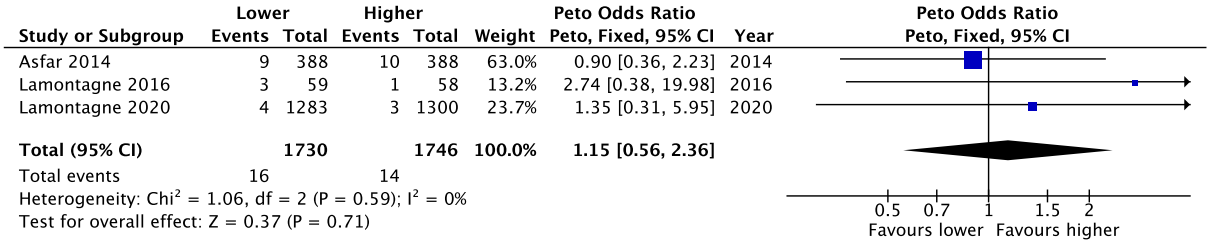

eFigure 21. New-onset ventricular arryhthmia.



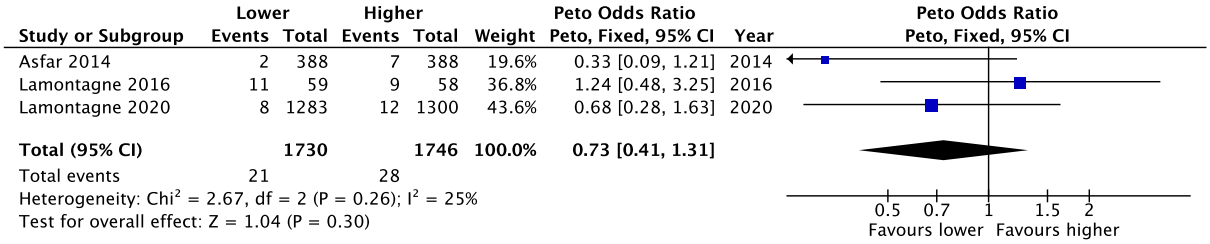
eFigure 22. Mesenteric ischaemia.



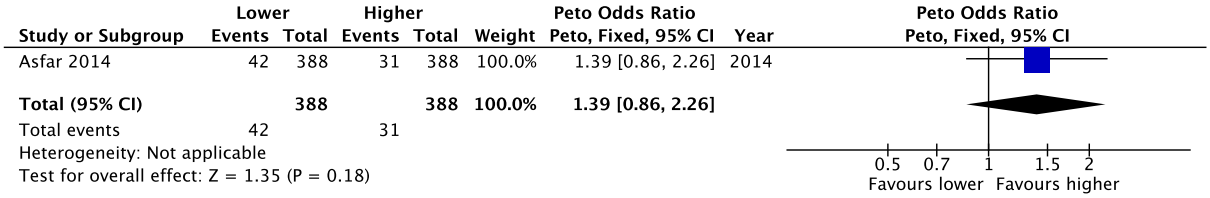

eFigure 23. Digit/limb/skin ischaemia.



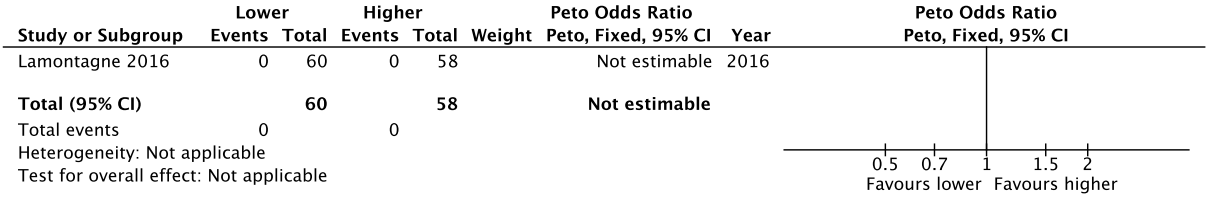

eFigure 24. Myocardial ischaemia.



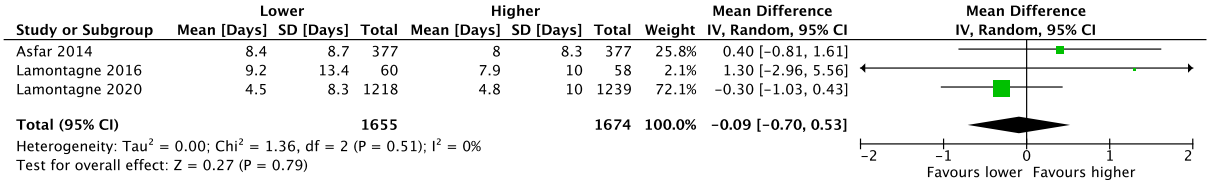

eFigure 25. Gastrointestinal bleeding.



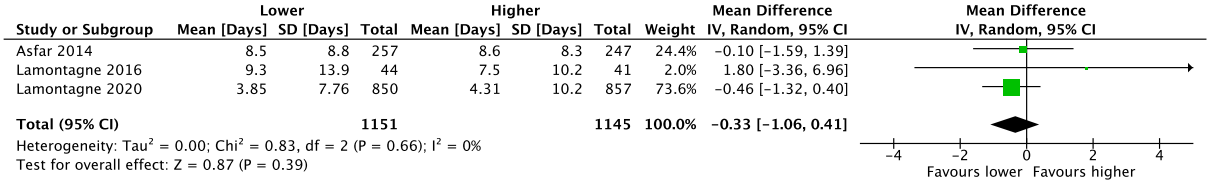

eFigure 26. Vasopressor extravasation.



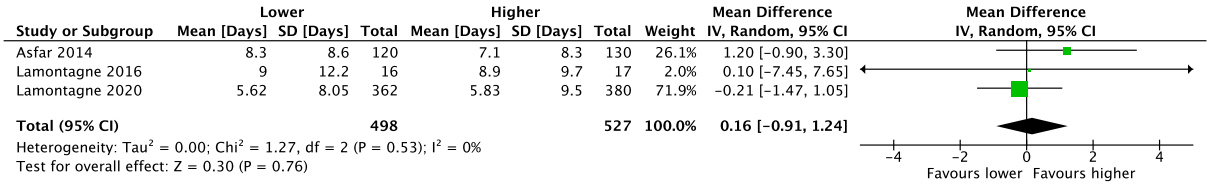
eFigure 27. Duration of mechanical ventilation.



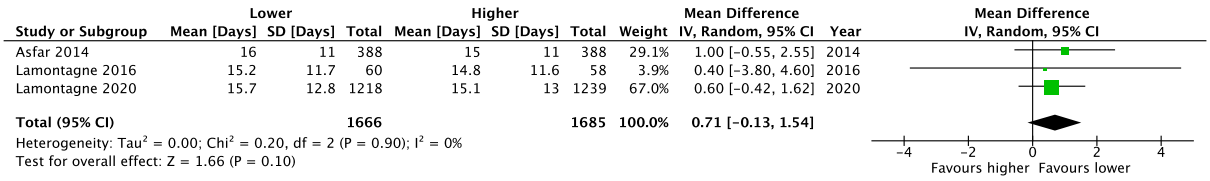

eFigure 28. Duration of mechanical ventilation (in ICU survivors).



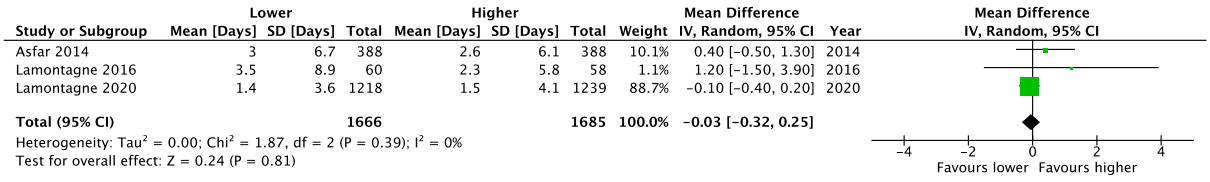

eFigure 29. Duration of mechanical ventilation (in ICU non-survivors).



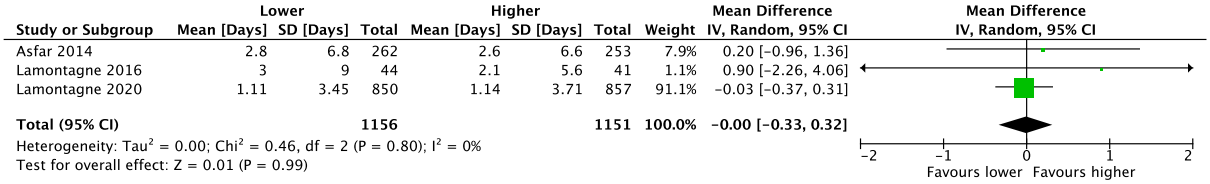

eFigure 30. Ventilator-free days (to day 28).



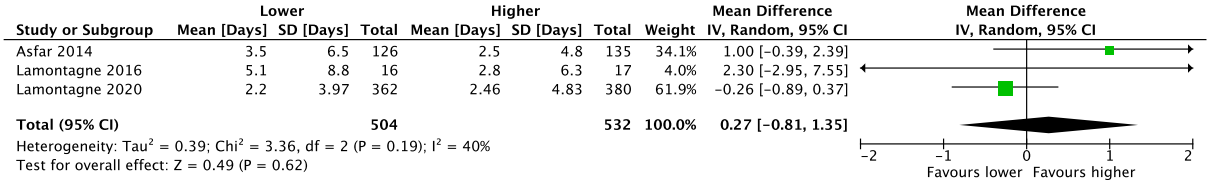

eFigure 31. Duration of renal replacement therapy.



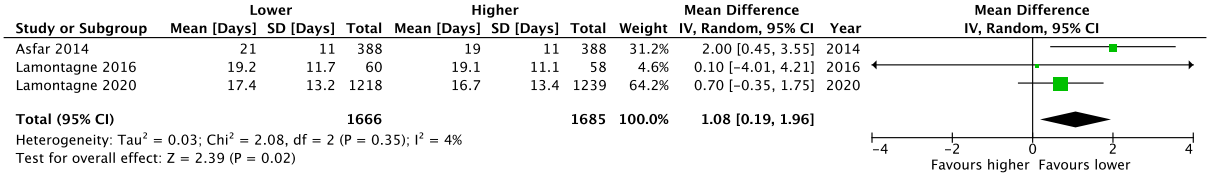

eFigure 32. Duration of renal replacement therapy (in ICU survivors).



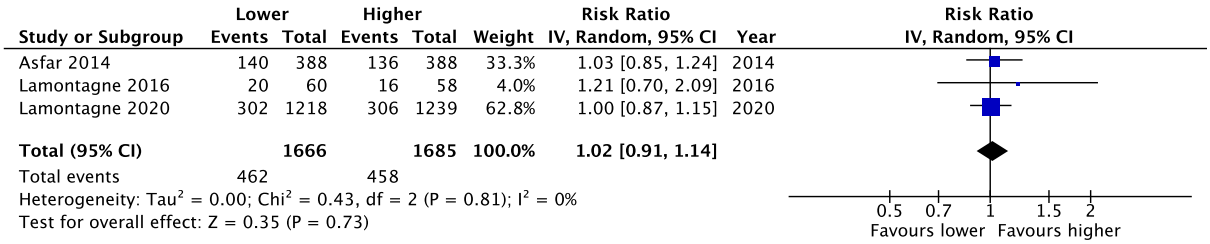
eFigure 33. Duration of renal replacement therapy (in ICU non-survivors).



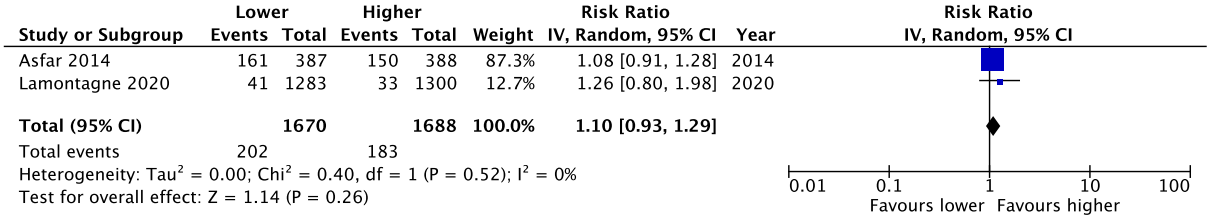

eFigure 34. Renal replacement therapy-free days (to day 28).



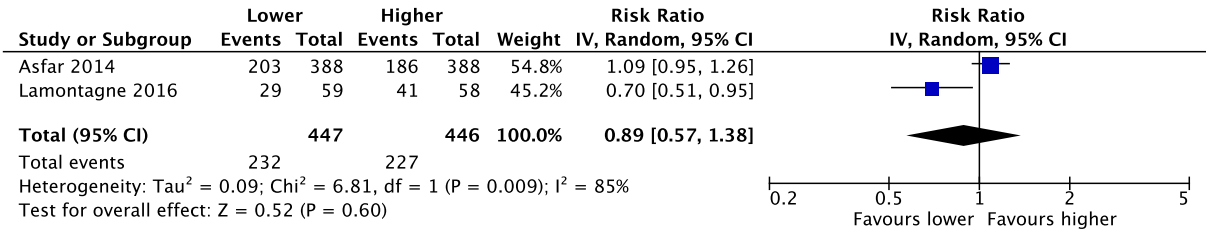

eFigure 35. Proportion receiving early renal replacement therapy.



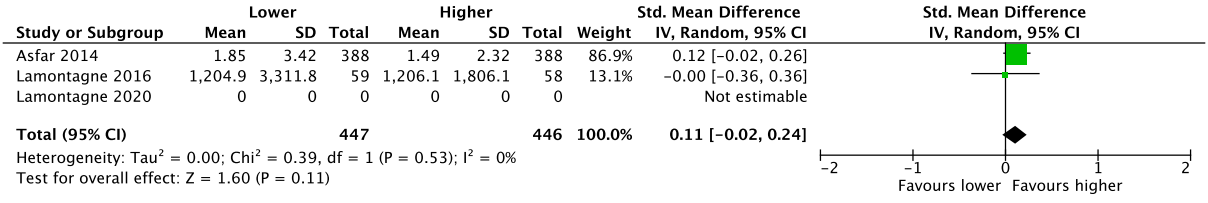

eFigure 36. Proportion meeting stage 3 acute kidney injury defined by KDIGO.



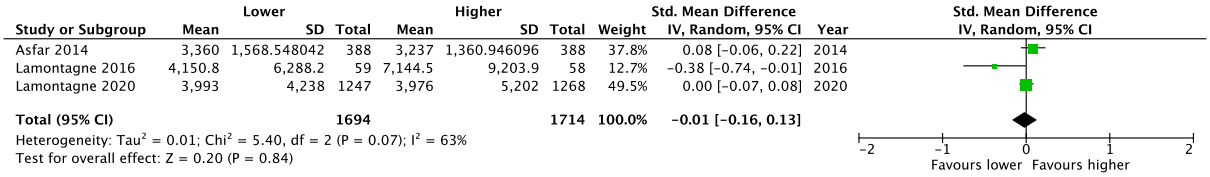

eFigure 37. Proportion receiving blood products.



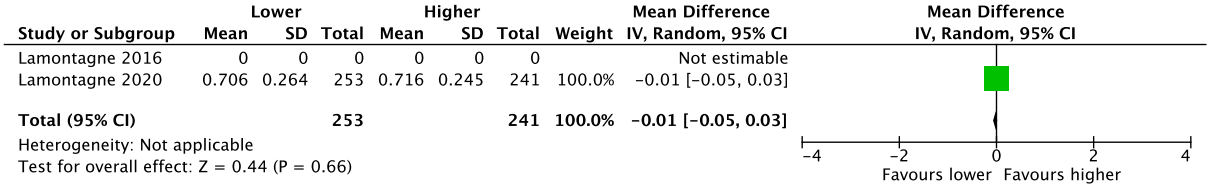

eFigure 38. Blood product requirement (quantity/volume).



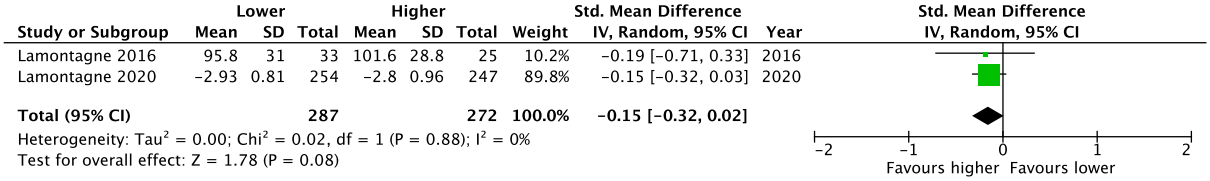
eFigure 39. Fluid requirement (cumulative volume).




eFigure 40. Quality of life at longest reported follow-up.




eFigure 41. Neurological outcome at longest reported follow-up.



## 7. Supplementary References.

1. Lamontagne F, Meade MO, Hebert PC, Asfar P, et al: Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016; 42(4):542-550

2. Asfar P, Meziani F, Hamel JF, Grelon F, et al: High versus low blood-pressure target in patients with septic shock. *The New England journal of medicine* 2014; 370(17):1583-1593