Appendix

Search Criteria

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 16, 2017>
Search Strategy:
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1 exp femoral artery/ (855)
2 exp iliac artery/ (148)
3 exp popliteal artery/ (291)
4 exp renal artery/ (126)
5 exp tibial arteries/ (35)
6 exp pulmonary artery/ (426)
7 exp iliac vein/ (42)
8 exp popliteal vein/ (62)
9 exp pulmonary veins/ (358)
10 exp femoral vein/ (209)
11 exp Saphenous vein/ (631)
12 (infrainguinal adj inguin*).mp. (1)
13 *femor*/ or *popliteal/ (0)
14 saphenous.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (1366)
15 *renal/ (0)
16 (iliac or tibial).mp. or *inguinal/ [mp=ti, ot, ab, sh, hw, kw, tx, ct] (4068)
17 ("vascular surgery" adj3 (low* or leg or periph* or extremit*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (114)
18 exp Vascular Surgical Procedures/ (13351)
19 exp Vascular Patency/ (822)
20 Blood Vessel Prosthesis/ (428)
21 (bypass or surgery or construct* or reconstruct* or re-construct* or re-vasculari* or revasculari* or graft* or endovascular).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (138629)
22 (occlu* or reocclu* or re-occlu).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (14259)
23 exp Graft Occlusion, Vascular/ (579)
24 or/1-16 (7141)
25 or/18-23 (152137)
26 24 and 25 (4059)
27 exp aortic aneurysm/ (603)
28 exp aneurysm false/ (21)
29 (aneurysm adj4 (abdom* or thoracoabdom* or thoraco-abdom* or aort*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (1249)
30 (aort* adj3 (ballon* or dilat* or bulg*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (131)
31 AAA*.mp. (887)
32 exp aorta, abdominal/ (305)
33 (EVAR or EVRAR or RAAA or TEVAR).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (248)
34 or/27-33 (2106)
35 17 or 26 or 34 (6046)
36 exp cardiac surgical procedures/ (11802)

37 cardiopulmonary bypass/ (2560)
38 exp Coronary Artery Bypass/ (5074)
39 (heart adj5 bypass).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (1394)
40 (heart adj surgery).mp. (2852)
41 (cardiac adj5 surgery).mp. (5733)
42 CABG.mp. (3387)
43 (coronary adj5 surger:).mp. (5490)
44 (coronary adj5 bypass*).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (9011)
45 (coronary adj5 surgical).mp. (428)
46 (cardiac adj surgical).mp. (2287)
47 (valv3 adj5 surgery).mp. (0)
48 (valv* adj5 surgical).mp. (414)
49 (valv* adj5 replac*).mp. (1712)
50 or/36-49 (20880)
51 exp blood transfusion/ (3213)
52 (transfus* adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (1178)
53 (((Red blood cell* or RBC) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)) and (therap* or transfus*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (287)
54 ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (1025)
55 (transfus* adj5 (restrict* or liberal*)).mp. (260)
56 (blood transfus* adj3 (management or program*)).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct] (39)
57 or/51-56 (4836)
58 35 or 50 (26062)
59 57 and 58 (892)
60 limit 59 to up=20130301-20171117 (21)

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Database: All Ovid Medline <1946 - present>
Search Strategy:

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1 Cardiopulmonary Bypass/ (24390)
2 (heart adj4 bypass*).tw. (3065)
3 (heart adj4 (surgery or surgical)).tw. (23640)
4 (cardiac adj4 (surgery or surgical)).tw. (45442)
5 exp Coronary Artery Bypass/ (53606)
6 CABG.tw. (16845)
7 (coronary adj4 (surgery or surgical)).tw. (26700)
8 (coronary adj4 bypass*).tw. (48064)
9 exp Cardiac Surgical Procedures/ (211107)
10 (valv* adj4 replac*).tw. (33494)
11 (valv* adj4 (surgery or surgical)).tw. (15727)

12 or/1-11 (283643)
13 exp Vascular Surgical Procedures/ or Peripheral Vascular Diseases/su, th (245225)
14 exp Aortic Aneurysm, Abdominal/su, th (12807)
15 exp Aortic Aneurysm, Thoracic/su, th (8619)
16 exp Endarterectomy, Carotid/ or Amputation/su, th (8469)
17 (Aorta, Abdominal/ or Aorta, Thoracic/) and surgery.ti,ab. (6628)
18 exp Carotid Stenosis/su, th (8433)
19 exp Atherosclerosis/su, th (4416)
20 exp Intermittent Claudication/su, th (3186)
21 ((vascular or aort* or aneurysm or carotid) adj3 (repair or procedur* or surg* or operat*)).mp. (86626)
22 ((abdominal or thoracic or thoracoabdominal or endovascular) adj3 aneurysm*).mp. (38662)
23 (femoropopliteal adj3 (bypass or graft)).mp. (965)
24 carotid endarterectomy.mp. (10111)
25 peripheral revascularisation.mp. (16)
26 infrainguinal bypass.mp. (658)
27 amputation.ti,ab. (30517)
28 or/13-27 (334368)
29 *Blood Transfusion/ (34989)
30 ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp. (7364)
31 29 or 30 (41294)
32 exp Reference Standards/ (42889)
33 standards.fs. (676252)
34 methods.fs. (3549323)
35 32 or 33 or 34 (4048101)
36 31 and 35 (8607)
37 (transfus* adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (6605)
38 ((Red blood cell* or RBC) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (1457)
39 ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (4287)
40 (transfus* adj5 (restrict* or liberal*)).mp. (902)
41 ((blood or transfus*) adj3 (management or program*)).mp. (6888)
42 36 or 37 or 38 or 39 or 40 or ((blood or transfus*) adj3 (management or program*)).mp. (24314)
43 randomized controlled trial.pt. (505454)
44 controlled clinical trial.pt. (100423)
45 placebo.ab. (205367)
46 clinical trials as topic.sh. (197043)
47 randomly.ab. (304955)
48 trial.ti. (199259)
49 43 or 44 or 45 or 46 or 47 or 48 (1076343)
50 (animals not (humans and animals)).sh. (4708391)
51 49 not 50 (996765)

52 (12 or 28) and 42 and 51 (300)
53 12 and 42 and 51 (260)
54 limit 53 to ed=20130301-20171117 (68)

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Database: Embase Classic+Embase <1947 to 2017 November 16>
Search Strategy:
---
1 *Blood Transfusion/ (40905)
2 ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp. (12543)
3 1 or 2 (51895)
4 exp standard/ (395376)
5 3 and 4 (1038)
6 (transfus* adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (11100)
7 ((Red blood cell* or RBC) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (2348)
8 ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp. (6359)
9 (transfus* adj5 (restrict* or liberal*)).mp. (1504)
10 ((blood or transfus*) adj3 (management or program*)).mp. (10641)
11 5 or 6 or 7 or 8 or 9 or 10 (28425)
12 exp heart surgery/ (338038)
13 (cardiopulmonary adj4 bypass$).tw. (37432)
14 (heart adj4 (surgery or surgical)).tw. (29820)
15 (cardiac adj4 (surgery or surgical)).tw. (60931)
16 (coronary adj4 bypass$).tw. (57891)
17 (heart adj4 bypass$).tw. (3950)
18 (coronary adj4 (surgery or surgical)).tw. (32325)
19 (valv* adj4 (surgery or surgical or replac*)).tw. (56744)
20 CABG.tw. (27337)
21 or/12-20 (394610)
22 exp Randomized Controlled Trial/ (482745)
23 exp controlled clinical trial/ (656712)
24 randomi?ed.ab,ti. (722793)
25 placebo.ab. (260209)
26 *Clinical Trial/ (19193)
27 randomly.ab. (372250)
28 trial.ti. (244043)
29 22 or 23 or 24 or 25 or 26 or 27 or 28 (1446051)
30 exp animal/ not (exp human/ and exp animal/) (5129638)
31 29 not 30 (1321041)
32 11 and 21 and 31 (348)
33 claudica$.ti,ab. (13993)

34 (peripher$ adj3 (occlu$ or arteri$ or vascular)).ti,ab. (54215)
35 (arteri$ adj3 (obstruct$ or occlusi$ or stenos$ or lesion?)).ti,ab. (42987)
36 ((leg or limb) adj3 (isch?emia or occlusi$ or obstruct$ or lesion or stenos$)).ti,ab. (15086)
37 (arteriosclerosis or atherosclerosis).ti,ab. (160338)
38 INTERMITTENT CLAUDICATION/ (10550)
39 PERIPHERAL VASCULAR DISEASE/ (21532)
40 CLAUDICATION/ (6621)
41 BLOOD VESSEL OCCLUSION.mp. or exp blood vessel occlusion/ (150642)
42 LEG ISCHEMIA/ (5729)
43 ILIAC ARTERY/ (15357)
44 SUPERFICIAL FEMORAL ARTERY/ (3150)
45 INTERNAL ILIAC ARTERY/ (3484)
46 ((femoral or renal or iliac or popliteal) adj3 artery).ti,ab. (66339)
47 (occlu$ or obstruct$ or stenos$ or lesion).ti,ab. (1205898)
48 ((femoral or renal or iliac or popliteal) adj3 artery).ti,ab. (66339)
49 (occlu$ or obstruct$ or stenos$ or lesion).ti,ab. (1205898)
50 ARTERY OCCLUSION/ (24533)
51 or/44-49 (1248961)
52 (occlu$ or obstruct$ or stenos$ or lesion).ti,ab. (1205898)
53 52 and (50 or 51) (1205898)
54 or/33-43 (412713)
55 ABDOMINAL AORTA ANEURYSM/ (24126)
56 AORTA RUPTURE/ (7195)
57 ANEURYSM RUPTURE/ (13370)
58 THORACIC AORTA ANEURYSM/ (6694)
59 (aort$ adj5 aneurysm$).ti,ab. (46243)
60 ((abdominal or thoracic) adj5 aneurysm$).ti,ab. (29718)
61 (thoracoabdominal adj5 aneurysm$).ti,ab. (2456)
62 FALSE ANEURYSM/ and ABDOMINAL AORTA/ (246)
63 FALSE ANEURYSM/ and THORACIC AORTA/ (446)
64 ANEURYSM SURGERY/ and ABDOMINAL AORTA/ (240)
65 ANEURYSM SURGERY/ and THORACIC AORTA/ (160)
66 or/55-65 (68413)
67 VASCULAR SURGERY/ (34793)
68 ((vascular or endovascular) adj3 surg$).ti,ab. (34780)
69 ENDOVASCULAR SURGERY/ (20838)
70 ANGIOPLASTY/ (22442)
71 FEMOROFEMORAL BYPASS/ (815)
72 FEMOROPOPLITEAL BYPASS/ (1936)
73 SAPHENOUS VEIN GRAFT/ (6485)
74 SAPHENOUS VEIN/ (14575)
75 (Femoro$ or popliteal or infra$).ti,ab. (217792)
76 (graft$ or anastomos$).ti,ab. (488821)
77 (bypass or surg$).ti,ab. (2394705)
78 (52 or 74 or 75) and (76 or 77) (352272)
79 Lower limb amput$.ti,ab. (2408)

80 exp LEG AMPUTATION/ (11076)
81 67 or 68 or 69 or 70 or 71 or 72 or 73 or 78 or 79 or 80 (440811)
82 (peripheral adj5 aneurysm$).ti,ab. (1470)
83 (femoral adj5 aneurysm$).ti,ab. (1245)
84 (popliteal adj5 aneurysm$).ti,ab. (1572)
85 (il?ac adj5 aneurysm$).ti,ab. (2684)
86 or/82-85 (6444)
87 53 or 54 or 66 or 81 or 86 (1600336)
88 (21 or 87) and 11 and 31 (493)
89 limit 88 to dd=20130301-20171117 (156)

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Approximate Bayesian computation (ABC)

Studies reporting only median, interquartile range, min-max and/or range cannot be directly used in the traditional meta-analysis. To overcome this issue, we imputed means and standard deviations based on the abovementioned summary statistics using a flexible ABC model described previously [1]. Briefly, outcomes are considered random variables that follow a specific family distribution (e.g normal, beta, gamma, Poisson etc). Once the family distribution is chosen either based on clinical grounds or empirical evidence, a large number of similar statistical distributions is generated, but each with a slightly different set of parameters. For each study arm without a reported mean and standard deviation, we generated 100,000 distributions. For each generated distribution, we calculated the Euclidean distance between the real (reported) summary statistics and the corresponding statistics from the pseudo-data sampled from the distribution thought to be the distribution of unavailable data. The top 0.1% distributions (i.e. 100 distributions) were kept and served as the basis for estimation of means and standard deviations. This approach has been demonstrated to furnish a reasonable approximation of the posterior distribution via the available summary statistics – given that a tight tolerance level is used (e.g. the 0.1% top distributions with the smallest Euclidean distances). Estimates for the mean and the standard deviation were computed by the "simulation method", that is, the mean and the standard deviation are the averages of means and standard deviations from the randomly generated data, respectively. We also tested the "plug-in method" as discussed by Kwon and Reis [1], and results were virtually identical. For outcomes that were thought to follow approximately a Poisson distribution, the ABC model employed medians and minimum values only to compute the Euclidean distance. When the underlying distribution is assumed to be approximately Poisson, our simulations show that the ABC model is substantially less biased when the

maximum values are not considered (data not shown). The assumed family distribution was as follows: RBC units (gamma), ICU length of stay (Poisson) and hospital length of stay (Poisson). Prior parameters for the gamma distributions were assumed to follow a uniform distribution: $\alpha \sim$ Unif(0,50) and $\beta \sim$ Unif(0,50). Similarly, for the Poisson distributions, we assumed that $\lambda \sim$ Unif(0, 50).

References

1. Kwon D, Reis IM. Simulation-based estimation of mean and standard deviation for meta-analysis via Approximate Bayesian Computation (ABC). BMC Med Res Methodol. 2015 Aug 12;15:61.

Trial sequential analysis

We conducted two different trial sequential analyses, one to investigate inferiority of the restrictive as compared with the liberal strategy, and one to investigate non-inferiority. Both of these investigations were considered one-sided. We first estimated that a critical information size of 12904 patients would be needed to have 80% power to detect a 30% relative risk increase in mortality in the restrictive as compared to the liberal transfusion group in a fixed-effect meta-analysis at a one-sided alpha of 2.5%, assuming a mortality rate in the liberal transfusion group of 3%. The same critical information size would be required to detect non-inferiority with 80% power at a one-sided alpha of 2.5%, using the 30% relative risk increase above as non-inferiority margin. We then built trial sequential monitoring boundaries, based on the Lan-DeMets alpha spending function, which relies on the selected alpha level, as well as on the information fraction (i.e. the accumulated number of patients recruited by the trials included in the analysis divided by 12904) [1]. To determine whether there is conclusive evidence about the inferiority or non-inferiority of restrictive versus liberal blood transfusion, we built a one-sided monitoring boundary based on a spending function of a one-sided alpha of 2.5%, and to determine whether there is conclusive evidence about the futility of inferiority or non-inferiority of restrictive versus liberal blood transfusion, we built a one-sided monitoring boundary based on a spending function of a beta of 20%. We then conducted a fixed-effect meta-analysis to calculate the cumulative Z-statistic, which is the sequential and cumulative pooling of Z-statistics across trials, every time a trial is published. If the cumulative Z-statistic crosses the inferiority monitoring boundary, then it can be concluded without the need of further trials to reach the overall number of 12904 patients, that restrictive is inferior to liberal blood transfusion. Likewise, if it crosses the non-inferiority monitoring boundary, it can be concluded without the need of further trials that restrictive is non-

inferior to liberal blood transfusion. We conducted sensitivity analyses using random-effects meta-analyses. To calculate the sample size needed in the presence of between-trial variance of the treatment effect to conduct the random-effect trial sequential analysis, we applied a heterogeneity correction factor to the sample size calculated under a fixed-effect assumption. The heterogeneity correction factor was based on an assumption of a I-squared of 30%, and was calculated as following: 1/(1 - I-squared) [2]. The sample size needed assuming an I-squared of 30% was 18434. All trial sequential analyses were performed in Stata (Release 14, College Station, TX).

References

1. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1938; 70(3): 659-663

2. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). Copenhagen Trial Unit. 2017 Available at: http://www.ctu.dk/tsa/files/tsa_manual.pdf.

Table S1. Assessment of the risk of bias of each study

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective Reporting (reporting bias)
Bracey 1999	High risk *Patients randomized by medical record number*	High Risk *Allocation concealment was not specified*	High Risk *No blinding of medical personnel or participants*	High Risk *Study does not indicate outcome assessment was blinded*	Low Risk *Complete outcome data available for all patients*	Low Risk *All outcomes in methods were reported in results*
Chkhaidze 2013	Unclear Risk *Abstract does not indicate randomization sequence*	Unclear Risk *Abstract does not indicate if allocation was concealed*	High Risk *No blinding of medical personnel or participants*	Unclear Risk *Abstract does not indicate outcome assessment was blinded*	Unclear Risk *Abstract does not indicate whether complete outcome data were available for all patients*	Low Risk *All outcomes in methods were reported in results*
Chkhaidze 2014	Unclear Risk *Abstract does not indicate randomization sequence*	Unclear Risk *Abstract does not indicate if allocation was concealed*	High Risk *No blinding of medical personnel or participants*	Unclear Risk *Abstract does not indicate outcome assessment was blinded*	Unclear Risk *Abstract does not indicate whether complete outcome data were available for all patients*	Low Risk *All outcomes in methods were reported in results*
Cholette 2011	High Risk *Random sequence generation not specified*	High Risk *Allocation concealment was not specified*	Unclear risk *Cardiac surgeon, anesthetist, perfusionists were blinded but not patients or clinical staff*	Unclear risk Independent data safety monitor was blinded	Low Risk *Complete outcome data available for 97% of patients*	High Risk *All clinical outcomes were not indicated a priori*
Cholette 2017	High Risk *Random sequence generation not specified*	High Risk *Allocation concealment was not specified*	High Risk *No blinding of medical personnel or participants*	High Risk *Study does not indicate outcome assessment was blinded*	Low Risk *Complete outcome data available for all patients*	High Risk *All clinical outcomes were not pre-specified*
de Gast-Bakker 2013	High Risk *Random sequence generation not specified*	High Risk *Allocation was by sealed envelope that was not specified to be sequentially numbered or opaque*	High Risk *No blinding of medical personnel or participants Attending physician knew the transfusion thresholds*	High Risk *Study does not indicate outcome assessment was blinded*	Low Risk *Complete outcome data available for all patients*	High Risk *Severe adverse events measured not defined a priori*

Hajjar 2010	High Risk *Random sequence generation not specified*	Low Risk *Allocation concealed via sealed opaque envelopes*	Unclear risk *The patient and outcome assessors were blinded.*	Low Risk *Outcome assessment was blinded*	Low Risk *Complete outcome data available for ~98% of patients*	Low Risk *All outcomes in methods were reported in results*
Koch 2017	High Risk *Study does not provide detail on how randomization sequence was generated*	High Risk *Study does not indicate if allocation was concealed*	Unclear Risk *The surgeon, personnel assessing outcomes and patients were blinded*	High Risk *Study does indicate outcomes were adjudicated but does not indicate outcome assessment was blinded*	High Risk *The first 200 patients within one site were not assessed for select outcomes*	High Risk *Vascular morbidity was excluded from composite outcome due to low frequency*
Laine 2017	High Risk *Study does not provide detail on how randomization sequence was generated*	High Risk *Study does not indicate if allocation was concealed*	High Risk *No blinding of medical personnel or participants*	High Risk *Study does not indicate all outcome assessment was blinded*	Low Risk *Complete outcome data available for all patients*	High Risk *Myocardial infarction was not indicated a priori*
Mazer 2017	Low Risk *Computer generated randomization sequence utilized*	Low Risk *Allocation concealed via randomization through computerized system*	High Risk *No blinding of medical personnel or participants*	Low Risk *Outcome assessment was blinded*	Low Risk *Complete outcome data available for ~97% of patients*	Low Risk *All outcomes in methods were reported in results*
Murphy 2015	Low Risk *Computer generated randomization sequence utilized*	Low Risk *Allocation concealed via randomization through computerized system*	High Risk *No blinding of medical personnel* *Participants were blinded*	Low Risk *Outcome assessment was blinded*	Low Risk *Complete outcome data available for ~99% of patients*	Low Risk *All outcomes in methods were reported in results*
Shehata 2012	Low Risk *Randomization sequence generated by off-site independent statistician*	Low Risk *Allocation concealed via sealed opaque envelopes*	High Risk *No blinding of medical personnel or participants*	High Risk *Study does not indicate outcome assessment was blinded*	Low Risk *Complete outcome data available for all patients*	Low Risk *All outcomes in methods were reported in results*
Willems 2010	Low Risk *Computer generated randomization sequence utilized*	Low Risk *Allocation concealed via randomization through computerized system*	High Risk *Clinical staff and parents were not blinded*	High Risk *Study does not indicate outcome assessment was blinded* *Statistician was blinded*	Low Risk *Complete outcome data available for ~98% of patients*	Low Risk *All outcomes in methods were reported in results*

Table S2: Risk ratios and mean differences as estimated by the inverse variance approach using a random-effects model

	Adult transfusion threshold trials: Effect size (95% CI)	Pediatric transfusion threshold trials: Effect size (95% CI)	Adult + pediatriac transfusion threshold trials: Effect size (95% CI)
Risk ratio			
Mortality[a]	0.99 (0.72, 1.36)	1.01 (0.39, 2.57)	0.96 (0.76, 1.21)
Myocardial infarction[a]	1.01 (0.81, 1.26)	--	1.01 (0.81, 1.26)
Stroke[a]	0.92 (0.67, 1.26)	2.93 (0.12, 70.82)	0.93 (0.68, 1.27)
Renal failure[a]	0.96 (0.76, 1.20)	Not estimable	0.96 (0.76, 1.20)
Infection[a]	1.12 (0.97, 1.29)	1.18 (0.73, 1.91)	1.12 (0.98, 1.29)
Arrhythmia[a]	0.99 (0.86, 1.14)	0.34 (0.01, 8.15)	0.99 (0.87, 1.12)
Patients transfused[a]	0.69 (0.65, 0.73)	0.35 (0.18, 0.70)	0.63 (0.57, 0.70)
Mean difference			
Number of units transfused (units)[b]	-0.93 (-1.17, -0.69)	-1.00 (-2.37, 0.37)	-0.94 (-1.17, -0.71)
Estimated blood loss (mL)[b]	3.86 (-27.15, 34.87)	8.11 (-28.97, 45.19)	5.61 (-18.18, 29.40)
ICU length of stay (days)[b]	0.06 (-0.11, 0.23)	-0.20 (-0.62, 0.22)	0.03 (-0.12, 0.18)
Hospital length of stay (days)[b]	0.35 (-0.15, 0.86)	-0.11 (-1.12, 0.89)	0.23 (-0.21, 0.66)

[a]These values are risk ratios; [b]These values are mean differences; CI indicates confidence interval, ICU indicates intensive care unit

Figure S1: Funnel Plot for Mortality

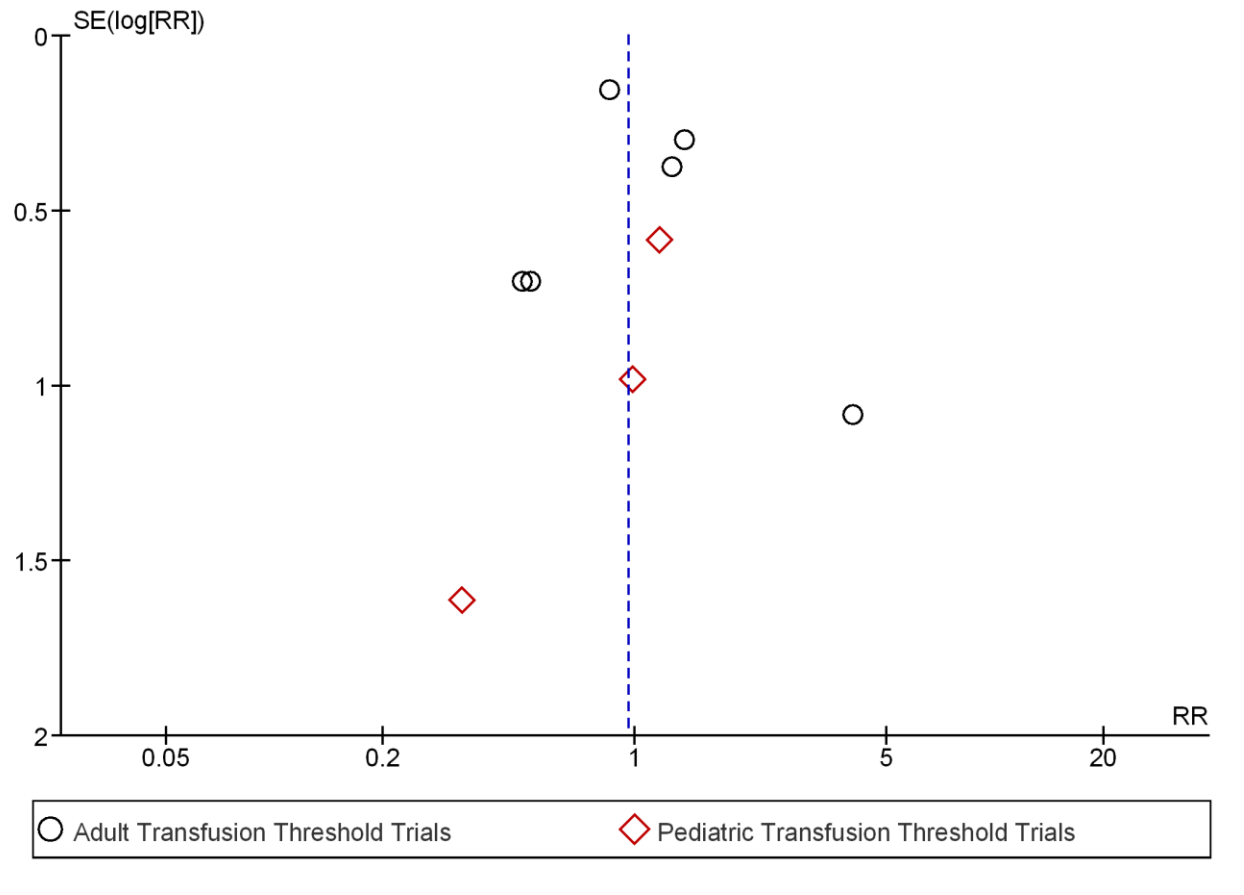


Figure S2: Myocardial infarction in randomized controlled trials of adult cardiac surgery patients. Fixed-effects meta-analysis.

	Restrictive			Liberal				Risk Ratio
Study or Subgroup	**Events**	**Total**	**Percent**	**Events**	**Total**	**Percent**	**Weight**	**IV, Fixed, 95% CI**
1.2.1 Adult Transfusion Trials								
Bracey 1999	1	212	0.5%	0	216	0.0%	0.5%	3.06 [0.13, 74.61]
Shehata 2012	1	25	4.0%	0	25	0.0%	0.5%	3.00 [0.13, 70.30]
Murphy 2015	1	1000	0.1%	3	1003	0.3%	1.0%	0.33 [0.03, 3.21]
Laine 2017	1	40	2.5%	0	40	0.0%	0.5%	3.00 [0.13, 71.51]
Mazer 2017	144	2428	5.9%	144	2429	5.9%	97.6%	1.00 [0.80, 1.25]
Subtotal (95% CI)	**148**	**3705**	**4.0%**	**147**	**3713**	**4.0%**	**100.0%**	**1.01 [0.81, 1.26]**
Heterogeneity: Chi² = 2.30, df = 4 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Total (95% CI)	**148**	**3705**	**4.0%**	**147**	**3713**	**4.0%**	**100.0%**	**1.01 [0.81, 1.26]**
Heterogeneity: Chi² = 2.30, df = 4 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.05 (P = 0.96)								
Test for subgroup differences: Not applicable								

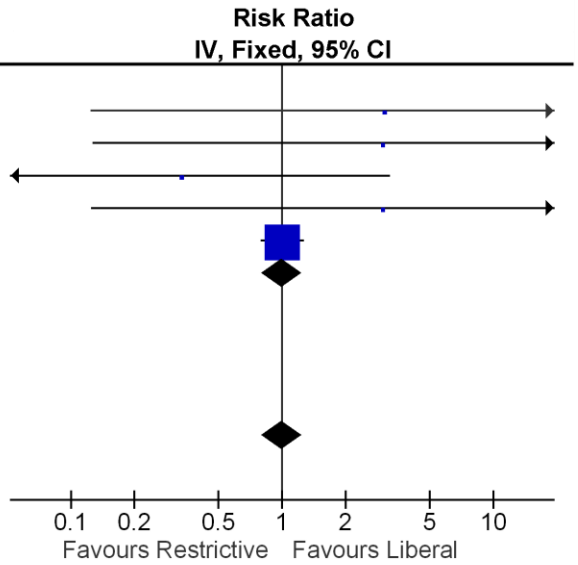


Figure S3: Stroke in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

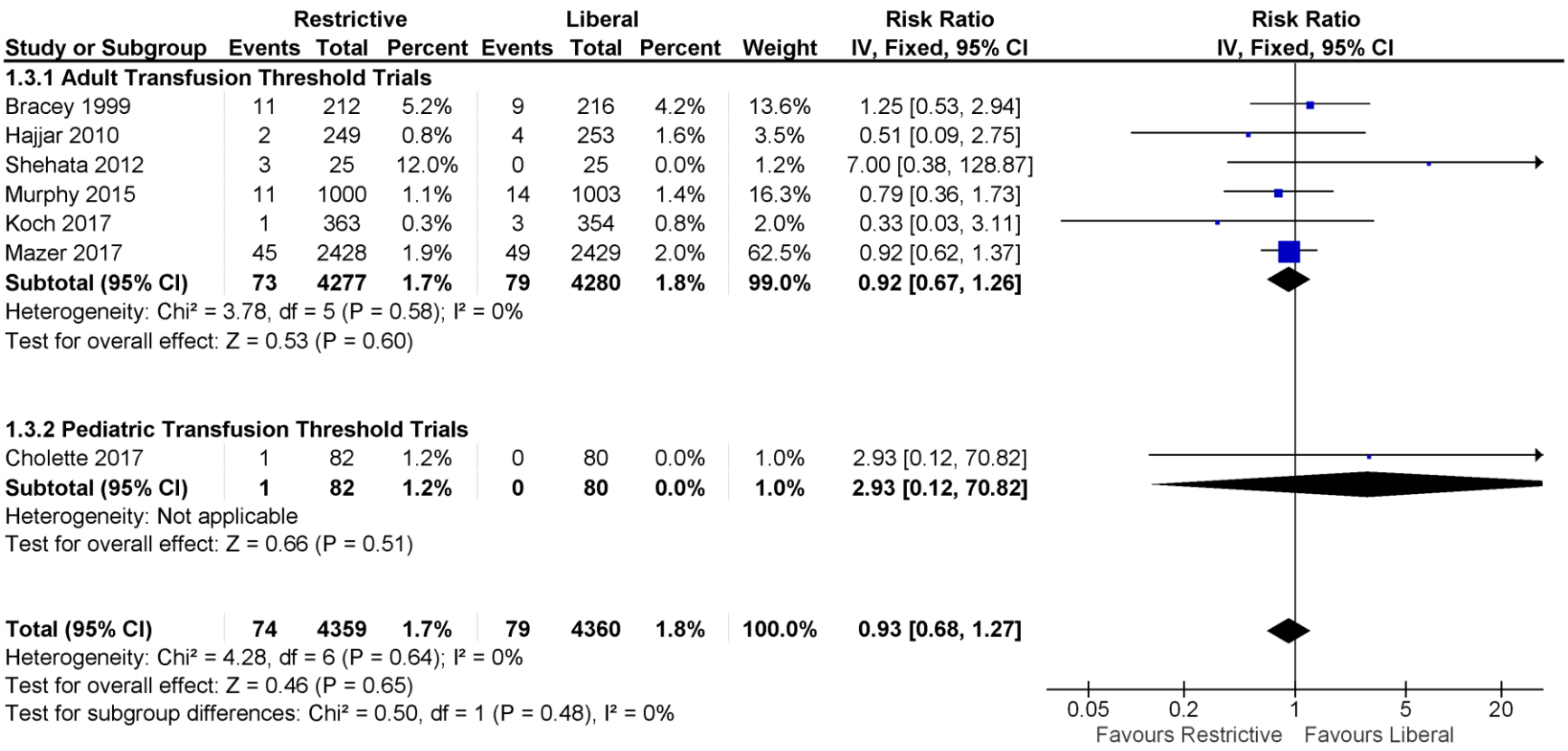
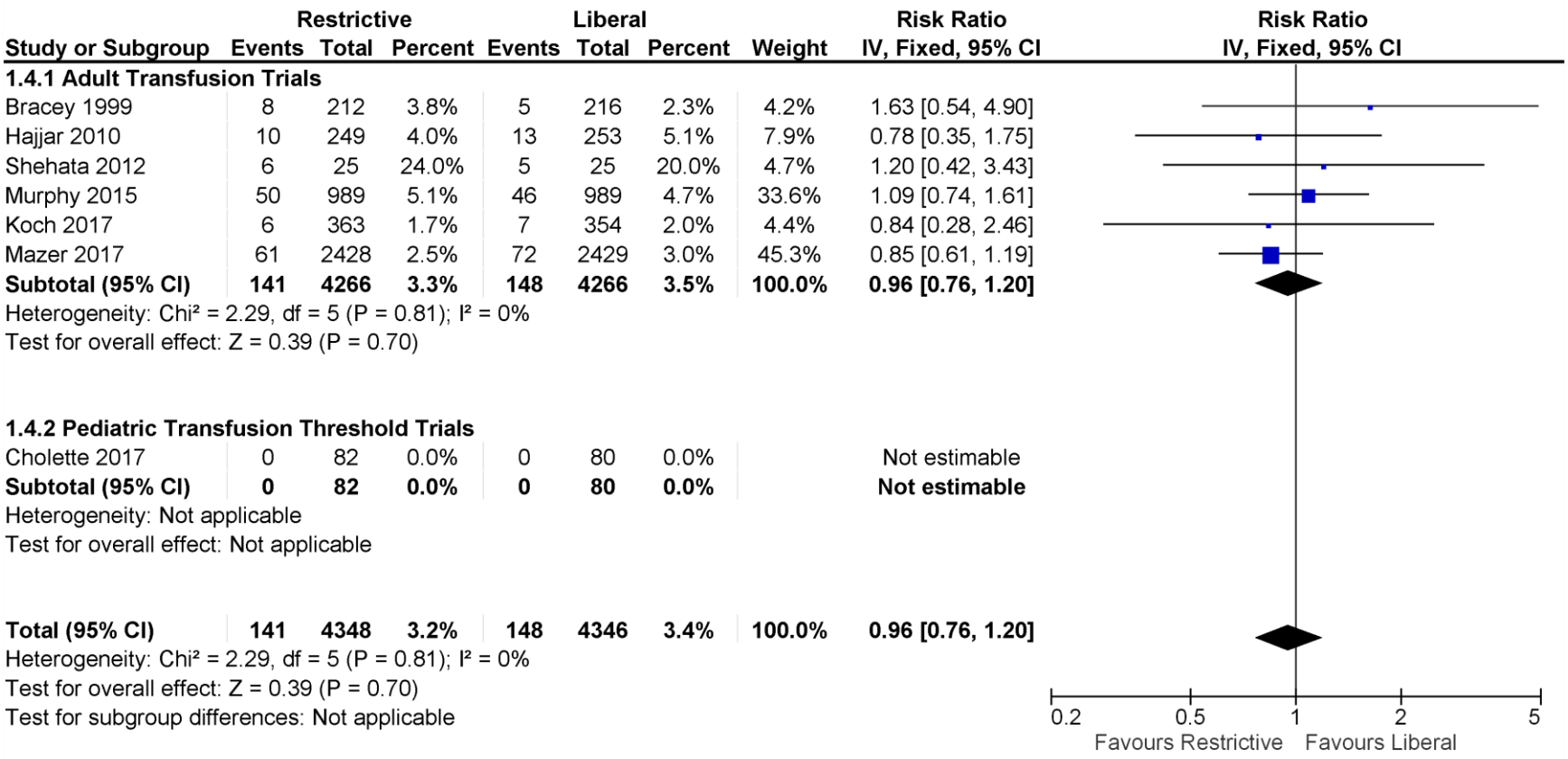


Figure S4: Renal failure in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.



Renal failure was not clearly defined in the study by Koch et al. In the study by Murphy et al, renal failure was defined more than 3-fold increase or ≥4.0 mg/dl (≥354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l), or urine output 0.3 ml/kg per hour for 24 hours or anuria for 12 hours, or need for renal replacement therapy three months following randomization.

Figure S5: Infection in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

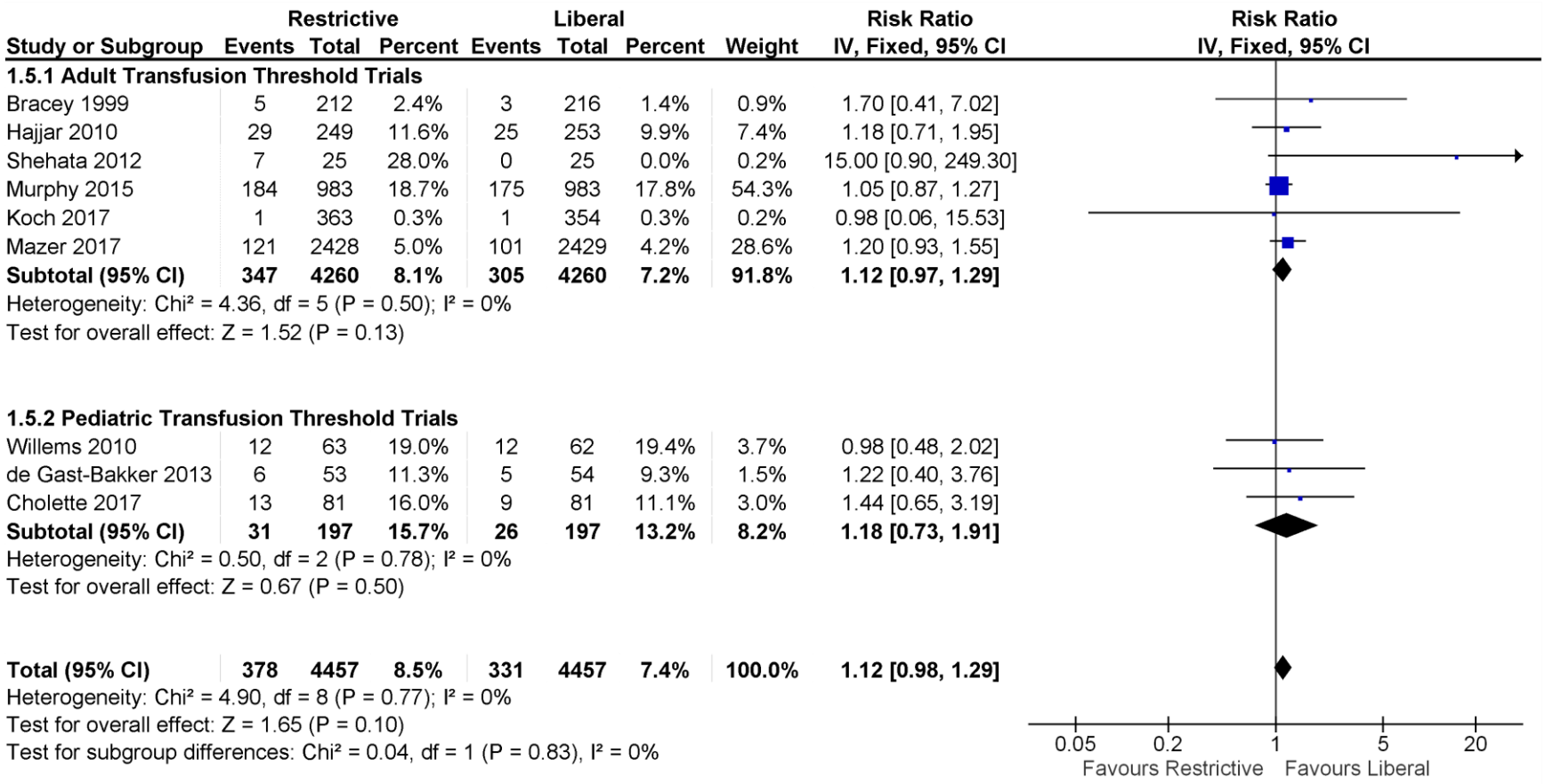
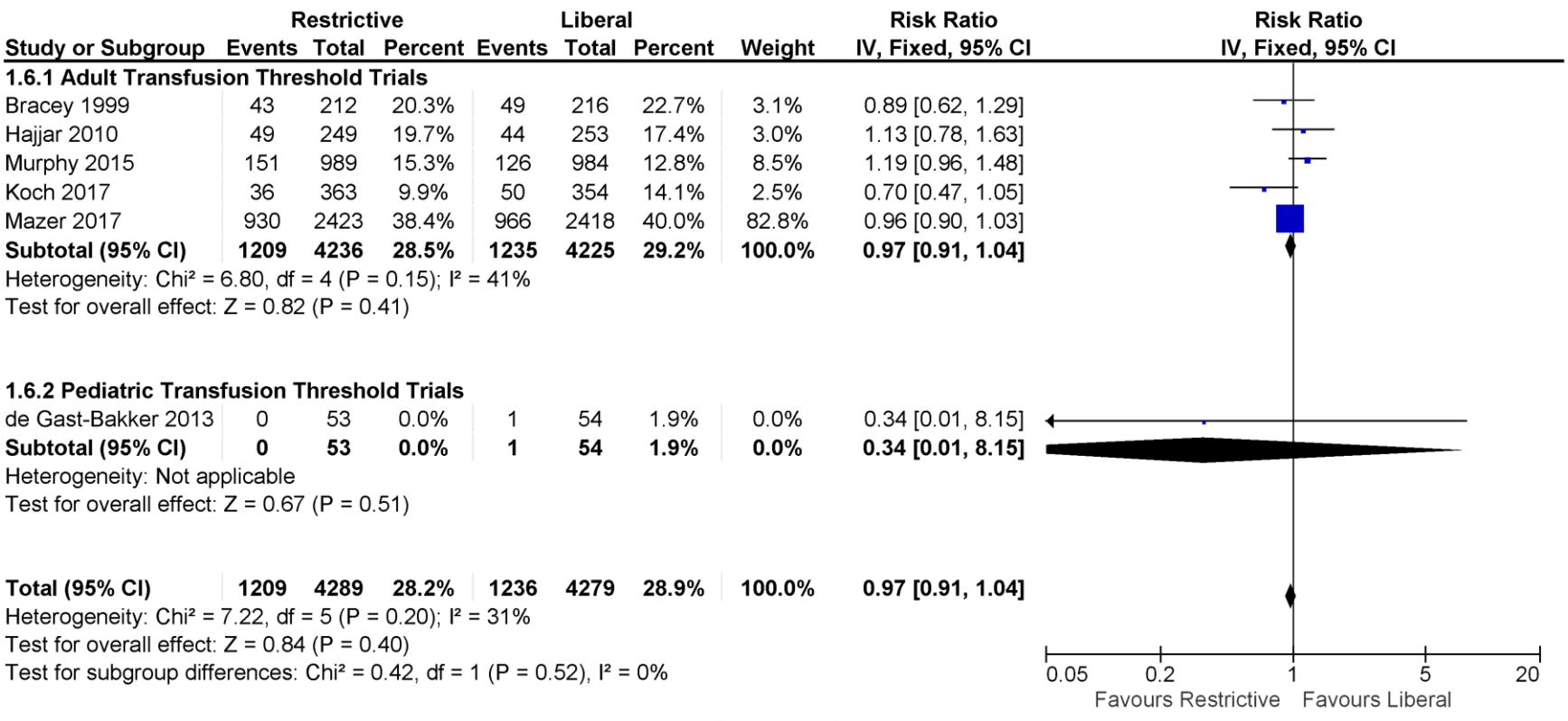


Figure S6: Arrhythmia in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.



Arrhythmia was determined for 90 days for the trial by Murphy and colleagues but in hospital incidence by the remainder of the trials.

Figure S7: Mean units transfused in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

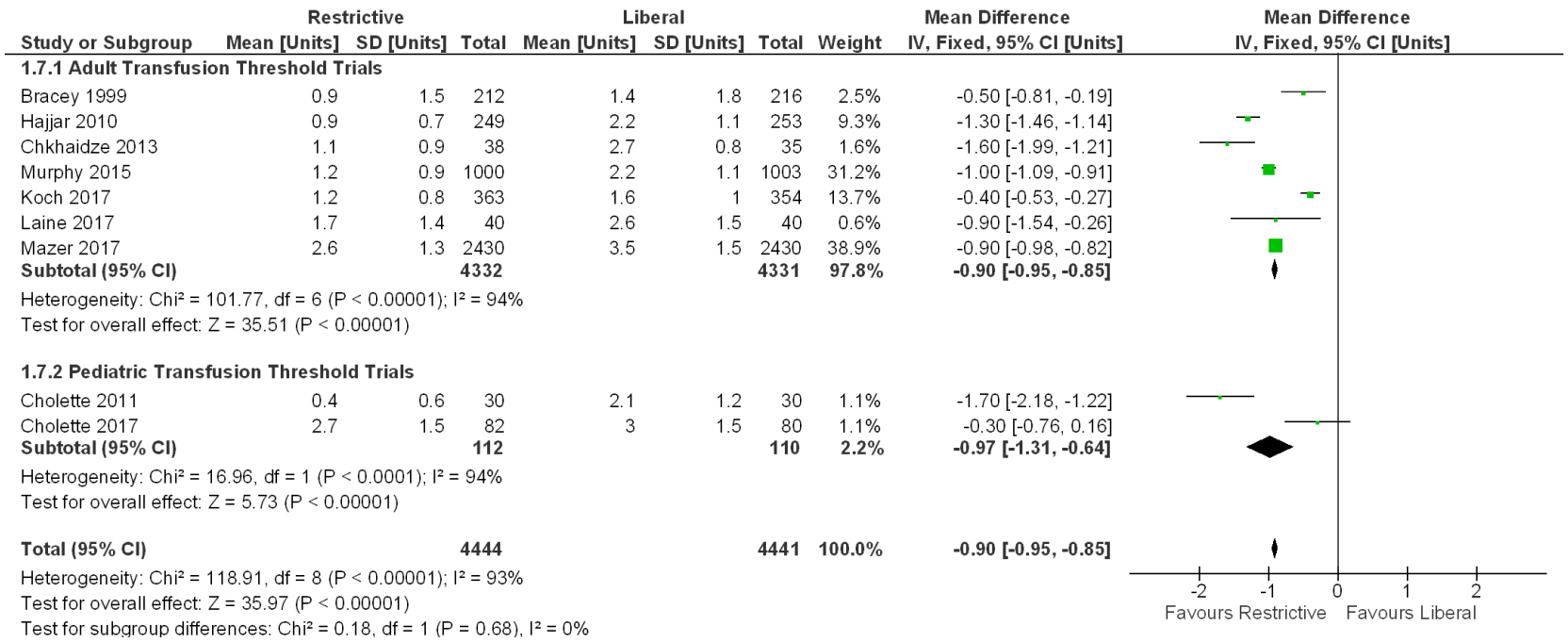
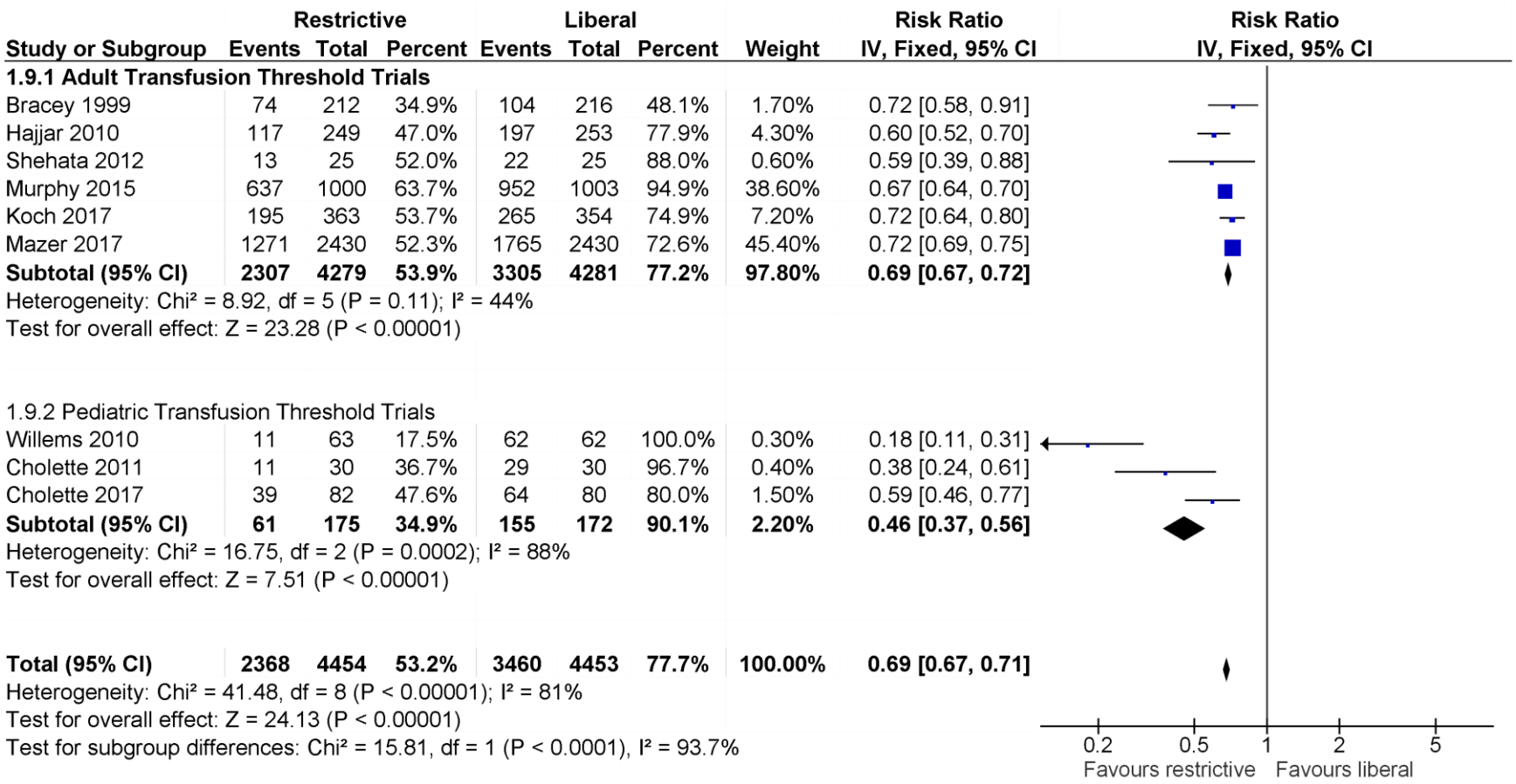


Figure S8: The proportion of patients transfused red blood cells in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.



In the trial by Murphy and colleagues, the proportion of patients transfused included those patients transfused before and after randomization whereas the remainder of the trials the proportion transfused was determined following randomization.

Figure S9: Blood loss in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

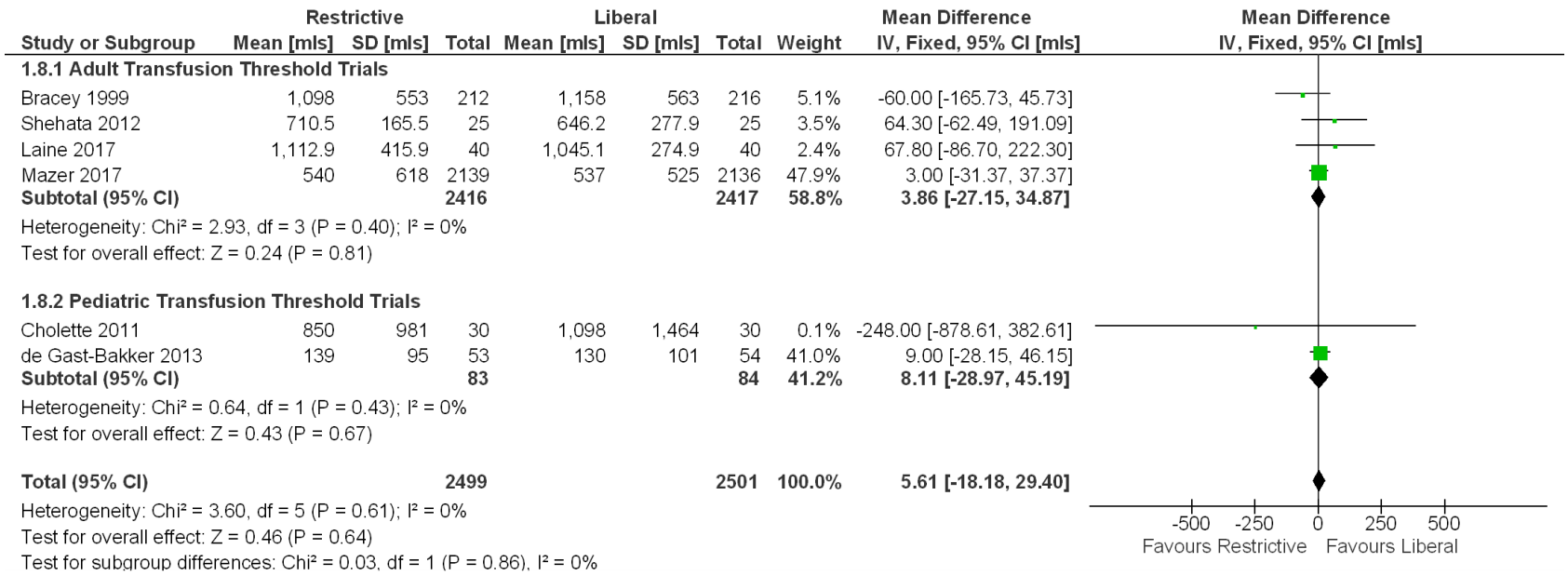


Figure S10: The duration of hospitalization in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

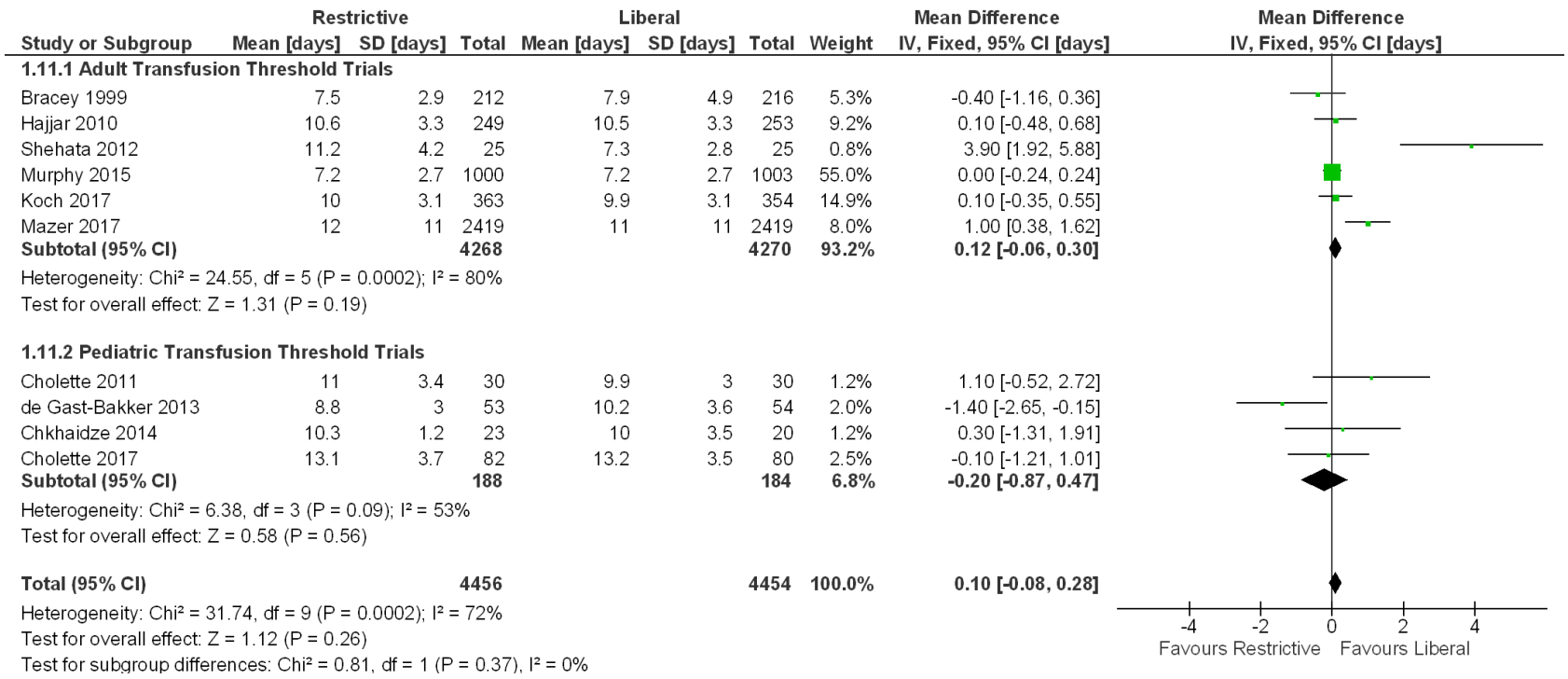


Figure S11: The length of stay of stay in an intensive care unit in randomized controlled trials of adult and pediatric cardiac surgery patients. Fixed-effects meta-analysis.

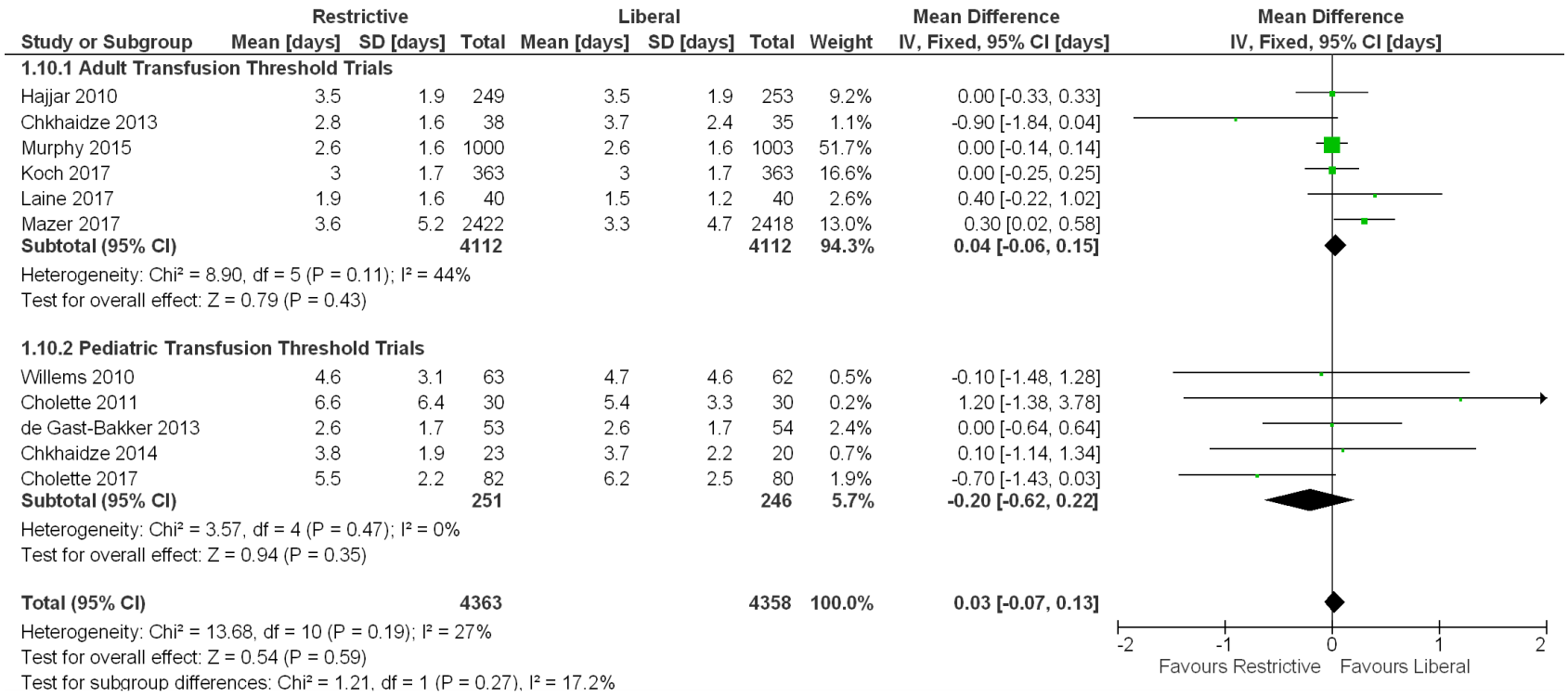
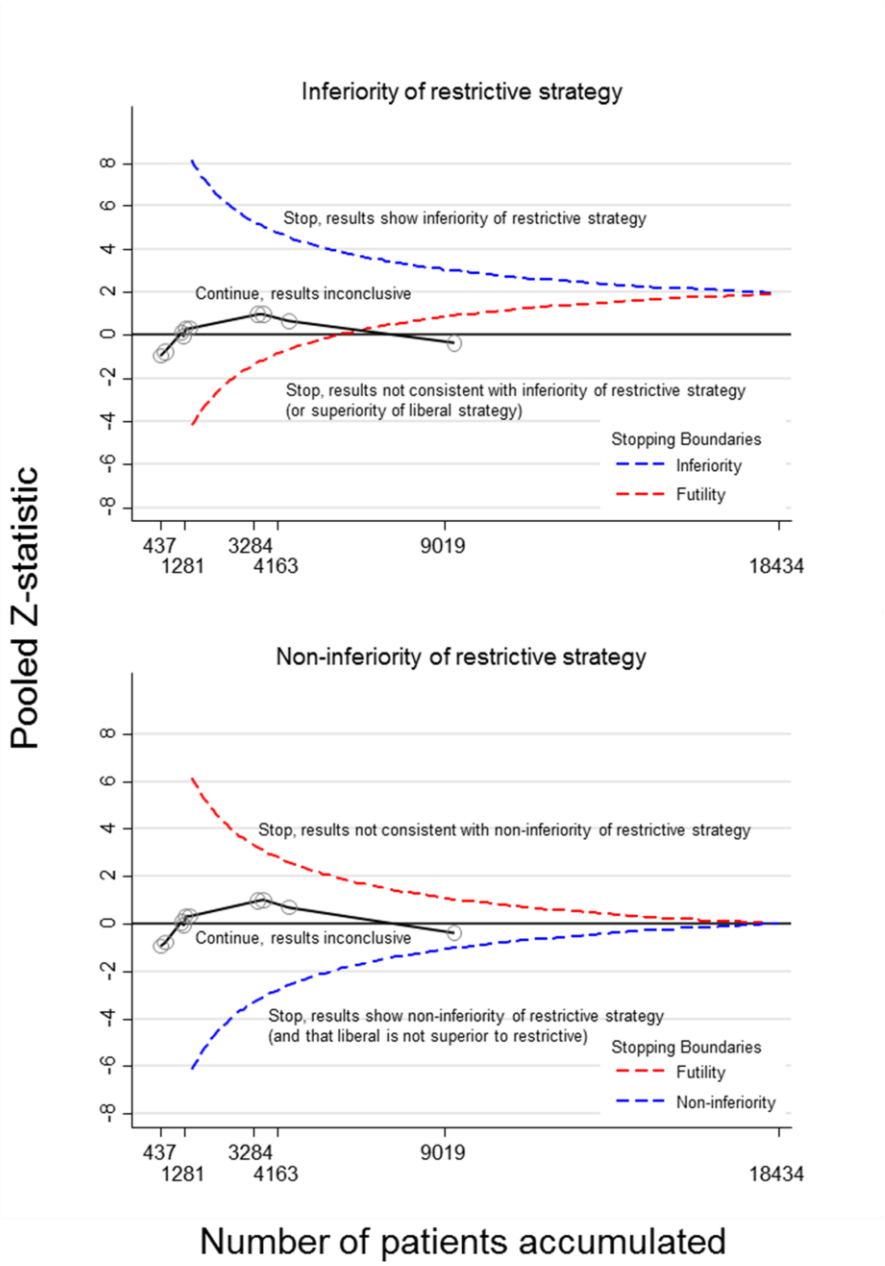
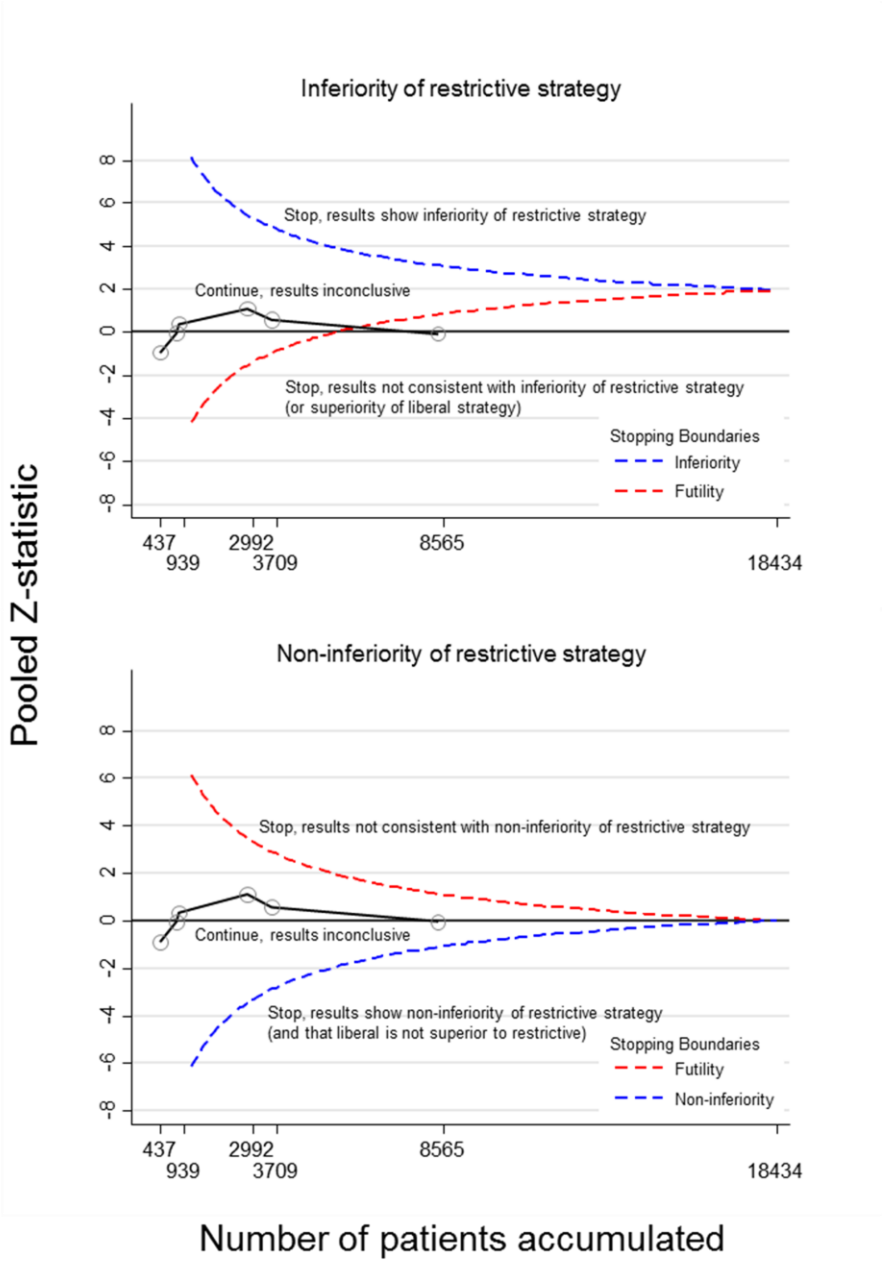


Figure S12: Trial sequential analysis for mortality within 30 days of surgery for adult and pediatric patients undergoing cardiac surgery using a random-effects model.



Trials are added in chronological order and the most recent studies were the largest studies published. The information size (9019 patients) was adequate to demonstrate that the restrictive strategy was not inferior to the liberal strategy (and that the liberal strategy was not superior to restrictive) as the futility boundary was crossed (upper panel).

Figure S13: Trial sequential analysis for mortality within 30 days of surgery for adult patients undergoing cardiac surgery using a random-effects model.



Trials are added in chronological order and the most recent studies were the largest studies published. The information size (8565 patients) was adequate to demonstrate that the restrictive strategy was not inferior to the liberal strategy (and that the liberal strategy was not superior to restrictive) as the futility boundary was crossed (upper panel).