SUPPLEMENTS 2: FULL DATA OF THE META-ANALYSES (SECTION 1) AND POST-HOC META-ANALYSES (SECTION 2)

Dopamine in critically ill patients with cardiac dysfunction: a systematic review with meta-analysis and trial sequential analysis

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1.1. E-Table 1: In- and exclusion criteria and outcome of the included trials

Trial	Year	Inclusion criteria	Exclusion criteria	Outcomes
Acute heart failure				
Kamiya [1]	2015	▪ NYHA class III–IV	▪ Age <20 years or >85 years ▪ Systolic blood pressure <90 mmHg ▪ Severe liver injury (ASAT/ALAT >100 IU/L) ▪ Severe renal failure (creatinine >2.0 mg/dL) ▪ Acute myocardial infarction within 3 months	Mortality (in-hospital) Serious adverse events Arrhythmias
Chen [4]	2013	▪ Age ≥18 years ▪ Prior clinical diagnosis of HF ▪ Enrolled <24 hours of hospital admission ▪ Anticipated hospitalization of ≥72 hours ▪ At least one symptom (dyspnoea, orthopnoea, or oedema) and one sign (rales on auscultation, peripheral oedema, ascites, pulmonary vascular congestion on chest radiography ▪ Estimated GFR >15 but <60 mL/min/1.73 m^2 ▪ Ability to have a PICC or central line placed <12 hours of randomization and study drug infusion started	▪ Received or anticipated need for IV vasoactive treatment or ultrafiltration therapy for HF ▪ Systolic blood pressure <90 mmHg ▪ Haemoglobin <9 g/dL (<5.6 mmol/L) ▪ Renal replacement therapy ▪ History of renal artery stenosis >50% ▪ Haemodynamically significant arrhythmias <4 weeks ▪ Acute coronary syndrome <4 weeks ▪ HF secondary to: active myocarditis, hypertrophic obstructive cardiomyopathy, greater than moderate stenotic valvular disease, restrictive or constrictive cardiomyopathy, complex congenital heart disease, constrictive pericarditis ▪ Non-cardiac pulmonary oedema ▪ Clinical evidence of digoxin toxicity ▪ Need for mechanical hemodynamic support ▪ Sepsis ▪ Terminal illness with expected survival of <1 year ▪ Pregnancy or nursing mothers ▪ Anticipated need for IV contrast use	Mortality (60 days) Serious adverse events Arrhythmias
Varriale [10]	1997	▪ Severe chronic CHF (NYHA class III or IV) ▪ *Depressed left ventricular function* ▪ Etiologically related to coronary artery disease or idiopathic dilated cardiomyopathy ▪ Signs of advanced pulmonary and systemic oedema	▪ Systolic blood pressure <100 mmHg ▪ Oliguria ▪ Serum creatinine >2.9 mg/dL ▪ Serum potassium <3.0 mmol/dL ▪ Haematocrit <30%	Mortality (in-hospital) Arrhythmias

		▪ Chemical markers of renal impairment: urea nitrogen ≥25 mg/dL and creatinine ≥1.5 mg/dL.		
Shah [2]	2014	▪ Age ≥18 years ▪ HF and on daily use of oral loop diuretic > 1 month ▪ Enrolled <24h of hospital admission ▪ At least one symptom (dyspnoea, orthopnoea, or oedema) and one sign (rales on auscultation, peripheral oedema, ascites) or pulmonary vascular congestion on chest radiography ▪ Anticipated need for IV loop diuretics for ≥48 h	▪ Systolic blood pressure <90 mmHg ▪ Serum creatinine >3.0 mg/dL or renal replacement therapy ▪ Anticipated need for IV contrast use	Mortality (30 days) Serious adverse events
Arutiunov [6]	2010	▪ Age >18 years ▪ Decompensated congestive HF with an ischemic origin ▪ Sinus rhythm or persistent tachycardia at rest ▪ Pulmonary artery wedge pressure >20 mmHg ▪ Cardiac index <2.6 L/min/m^2 ▪ *LVEF <35%* ▪ Systolic blood pressure >85 mmHg ▪ Serum creatinine <200 µmol/L	▪ Systolic blood pressure <85 mmHg) ▪ Creatinine >200 µmol/L, GFR <30 ml/min ▪ Acute coronary syndrome <2 months ▪ Rheumatic valvular heart disease ▪ Chronic obstructive pulmonary disease ▪ Obstructive or restrictive cardiomyopathy ▪ Mobitz II or III atrioventricular blockade without pacemaker ▪ Arrhythmia or atrial flutter ▪ Heart rate <40 beats/minute ▪ Pregnancy or period of breastfeeding ▪ Acute cerebrovascular accident <6 months ▪ Regular intake of β-blockers	Mortality (30 days) Myocardial infarction
Hsueh [7]	1998	▪ HF of NYHA class III or IV; ▪ Previously untreated HF or had stopped medications by personal decision for >2 weeks ▪ *LVEF ≤45%*	▪ Active myocarditis ▪ Thyroid disease ▪ Severe hypertension ▪ Atrial flutter-fibrillation ▪ High-degree atrioventricular block ▪ Pacemaker therapy ▪ Chronic obstructive lung disease ▪ Severe hepatic or renal disease ▪ Diabetes mellitus	Mortality (72 hours) Arrhythmias
Cotter [9]	1997	▪ Hospitalised because of congestive HF	▪ Severe renal failure (serum creatinine >200 µmol/L or creatinine clearance <30 ml/min) ▪ Systolic blood pressure ≤110 mm Hg ▪ Severe valvular disease ▪ LVEF >40%	Mortality (in-hospital) Arrhythmias

Giamouzis [5]	2010	▪ Age >18 years ▪ History of HF ▪ Oxygen saturation <90% on admission ▪ Deterioration of HF symptoms <6 hours: dyspnoea at rest, orthopnoea, and paroxysmal nocturnal dyspnoea, accompanied by signs of congestion (3rd heart sound, jugular venous distension, pulmonary rales) ▪ B-type natriuretic peptide >400 pg/mL or NT-proBNP >1500 pg/mL	▪ Acute de novo HF ▪ Systolic blood pressure <90 mmHg ▪ Severe renal failure (admission creatinine >215 mmol/L or estimated GFR >30 mL/min/1.73 m^2 ▪ Severe valvular disease ▪ HF secondary to congenital heart disease ▪ Scheduled cardiac surgery <2 months ▪ Anticipated need for IV contrast use	Mortality (60 days) Serious adverse events
Triposkiadis [3]	2014	▪ Age >18 years ▪ History of HF ▪ Dyspnoea on minimal exertion or rest dyspnoea and oxygen saturation <90% on admission ▪ At least one or more: signs of congestion (3rd heart sound or pulmonary rales >⅓ or lower extremity/ sacral oedema >1+), interstitial congestion or pleural effusion on chest radiography, and B-type natriuretic peptide >400 pg/mL or NT-proBNP >1500 pg/mL	▪ Creatinine >200 µmol/L or GFR >30 mL/min/1.73 m^2 ▪ Systolic blood pressure <90 mmHg ▪ Severe valvular disease ▪ HF secondary to complex congenital heart disease ▪ Suspected or confirmed acute coronary syndrome ▪ Scheduled cardiac surgery <6 months ▪ Anticipated need for IV contrast use	Mortality (1 year) Serious adverse events Arrhythmias Renal replacement therapy
Sindone [8]	1998	▪ HF of NYHA class IV	▪ Not described (abstract only)	Mortality (1 year)
Cardiac surgery				
Sirivella [14]	2000	▪ Manifested with either acute oliguric or anuric renal failure in the postoperative period ▪ Adequate cardiac output and tissue perfusion	▪ Acute renal failure associated with inadequate cardiac output and tissue perfusion ▪ Preoperative renal replacement therapy	Renal replacement therapy
Costa [12]	1990	▪ Cardiac surgery requiring cardiopulmonary bypass ▪ Preoperative renal dysfunction: creatinine clearance ≤50 mL/min	▪ Usage of enflurane ▪ Usage of diuretics	Renal replacement therapy
Bove [13]	2005	▪ Age >18 years ▪ Continuous Improvement in Cardiac Surgery Program (CICSP) score >10	▪ Emergent procedure ▪ Pre-operative renal replacement therapy ▪ Glaucoma	Mortality (in-hospital) Renal replacement therapy
Rosseel [15]	1997	▪ Elective CABG ▪ *Low cardiac output syndrome*, defined as a CI <2.2 L/min/m^2 in the absence of hypovolaemia (central venous pressure ≥8 mmHg and/or pulmonary capillary wedge pressure ≥12 mmHg and/or diastolic pulmonary artery pressure ≥12 mm Hg)	▪ Age >75 years ▪ Preoperative renal dysfunction (serum creatinine > 200 mmol/L) ▪ Liver dysfunction (g-GT >20% above normal) ▪ Pheochromocytoma ▪ With monoamine oxidase inhibitors	Mortality (in-hospital) Serious adverse events

			▪ Pregnancy	
Hausen [17]	1992	▪ Age >18 years ▪ Mitral valve operation ▪ Mitral valve disease ▪ CI <2.5 L/min/m^2 pre-operatively at rest	▪ Revascularization procedures ▪ Aortic valve operations	Mortality (6 ± 3 months) Myocardial infarction Arrhythmias
Oppizzi [11]	1997	▪ Severe left ventricular dysfunction (*LVEF <35%*) ▪ Requiring CABG	▪ The need for an associated intervention during cardiac surgery	Mortality (in-hospital) Serious adverse events Myocardial infarction Arrhythmias
Tarr [16]	1993	▪ Mitral valve surgery from the time of weaning from cardiopulmonary bypass	▪ Failure of drug measured by hemodynamic parameters and the patient's clinical condition	Mortality (in-hospital)

Trials are sorted by setting and dose administered. * The timing of starting the experimental administration differed between these two treatment arms. Abbreviations: AHF, acute heart failure; LVEF, left-ventricular ejection fraction; CABG, coronary artery bypass grafting; CI, cardiac index; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York health association.

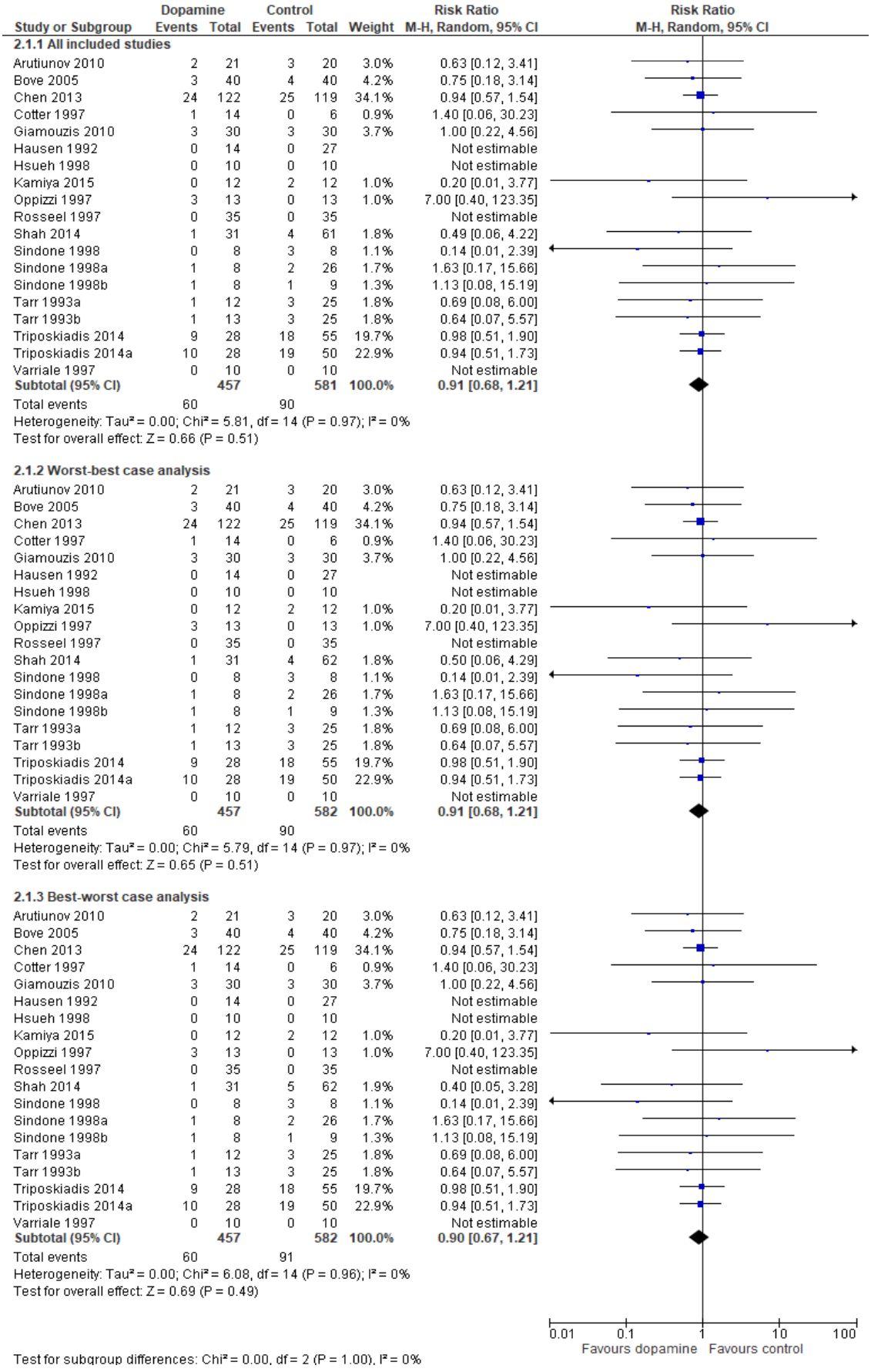
1.2. E-Table 2: Risk and odds ratios of all outcomes with subgroups analyses

	Trials*	Patients	Events	RR or OR	95% CI	Test for Interaction
Mortality	**15**	**1038**	**150**	**0.92**	**0.68 to 1.23**	**P = 1.00**
(1) Placebo or control	5	452	84	0.93	0.63 to 1.38	
(1) Potentially active control	12	586	66	0.90	0.14 to 5.84	
(2) Low dose dopamine	7	568	68	0.84	0.54 to 1.30	
(2) Moderate dose dopamine	7	403	74	0.98	0.65 to 1.47	
(3) Acute heart failure	10	746	132	0.90	0.67 to 1.23	
(3) Cardiac surgery	5	292	18	0.93	0.35 to 2.48	
Serious adverse events	**6**	**582**	**113**	**1.18**	**0.91 to 1.53**	**P = 0.92**
(1) Placebo or control	2	324	41	1.48	0.82 to 2.67	
(1) Potentially active control	5	258	72	1.12	0.84 to 1.50	
(2) Low dose dopamine	3	335	80	1.16	0.78 to 1.71	
(2) Moderate dose dopamine	3	267	33	1.70	0.86 to 3.39	
(3) Acute heart failure	4	486	59	1.54	0.94 to 2.53	
(3) Cardiac surgery	2	96	54	1.45	0.43 to 4.90	
Myocardial infarction	**5**	**339**	**16**	**1.32**	**0.42 to 4.09**	**P = 1.00**
(1) Placebo or control	1	83	2	2.00	0.06 to 62.2	
(1) Potentially active control	5	256	14	1.21	0.35 to 4.20	
(2) Low dose dopamine	2	111	8	1.68	0.15 to 18.8	
(2) Moderate dose dopamine	3	228	8	1.99	0.47 to 8.36	
(3) Acute heart failure	2	202	7	2.91	0.55 to 15.3	
(3) Cardiac surgery	3	137	9	1.09	0.27 to 4.33	
Ventricular tachyarrhythmias	**8**	**538**	**24**	**2.59**	**0.85 to 7.91**	**P = 0.99**
(1) Placebo or control	3	329	12	3.49	0.71 to 17.1	
(1) Potentially active control	6	209	12	1.94	0.40 to 9.32	
(2) Low dose dopamine	3	270	10	2.12	0.08 to 55.3	
(2) Moderate dose dopamine	5	268	14	1.09	0.35 to 3.43	
(3) Acute heart failure	6	471	21	1.29	0.38 to 4.39	
(3) Cardiac surgery	2	67	3	2.18	0.17 to 27.6	
Renal replacement therapy	**4**	**371**	**51**	**0.40**	**0.06 to 2.85**	**P = 0.93**
(1) Placebo or control	2	113	1	1.00	0.03 to 29.0	
(1) Potentially active control	3	258	50	0.42	0.05 to 3.58	
(2) Low dose dopamine	3	210	48	0.26	0.02 to 3.43	
(2) Moderate dose dopamine	1	161	3	1.16	0.15 to 9.15	
(3) Acute heart failure	1	161	3	1.16	0.15 to 9.15	
(3) Cardiac surgery	3	210	48	0.26	0.02 to 3.43	
Atrial tachyarrhythmias	**2**	**181**	**3**	**1.68**	**0.10 to 27.2**	**P = 1.00**
(1) Placebo or control	2	103	1	1.00	0.03 to 29.0	
(1) Potentially active control	1	78	2	1.81	0.06 to 50.8	
(2) Low dose dopamine	1	20	0	-	-	
(2) Moderate dose dopamine	1	161	3	1.16	0.14 to 9.65	
(3) Acute heart failure	2	181	3	1.16	0.14 to 9.65	
(3) Cardiac surgery	0	0	0	-	-	

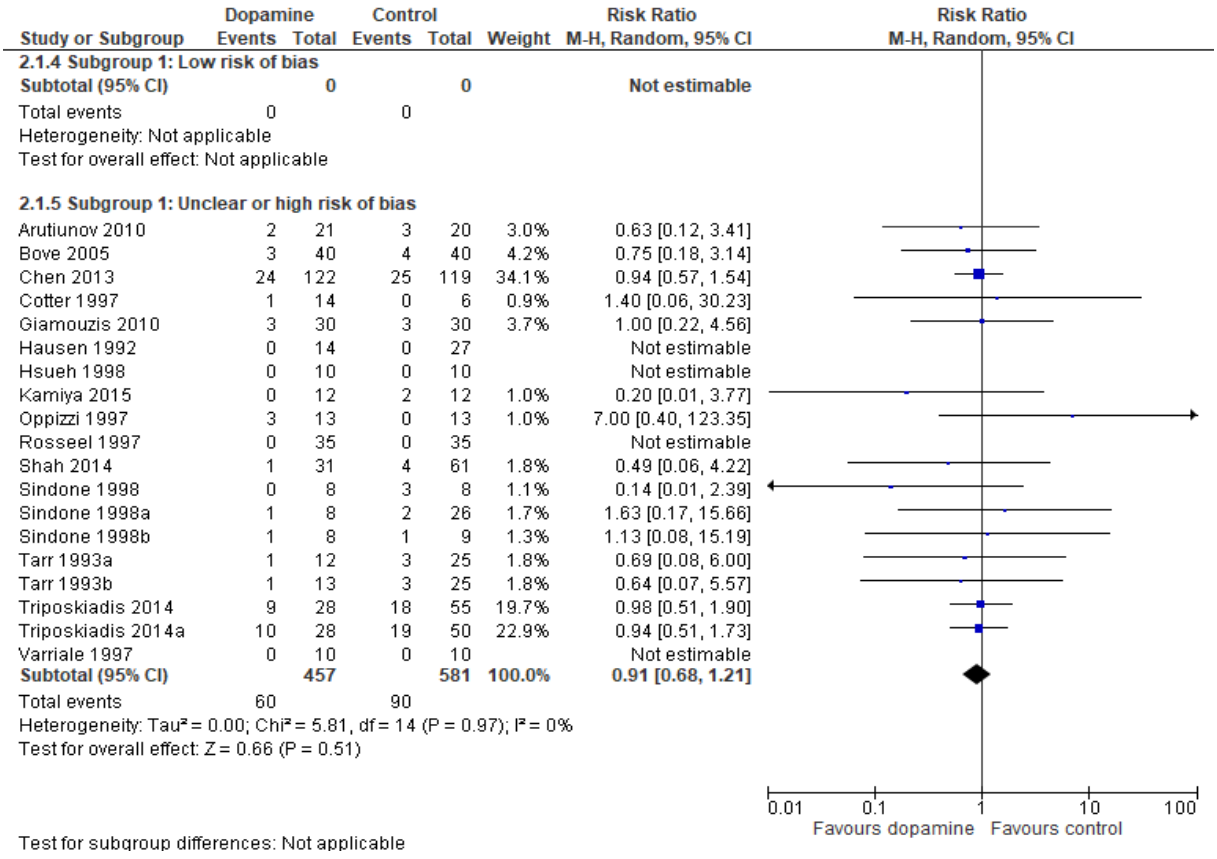
*Some trials compared dopamine with both a control intervention and a potentially active control (i.e. three-arm design), which is why the combined number of trials in subgroup analysis 1 differ from the total amount.
Abbreviations: RR, relative risk; OR, odds ratio; CI, confidence interval.

1.3. Forest plots of mortality

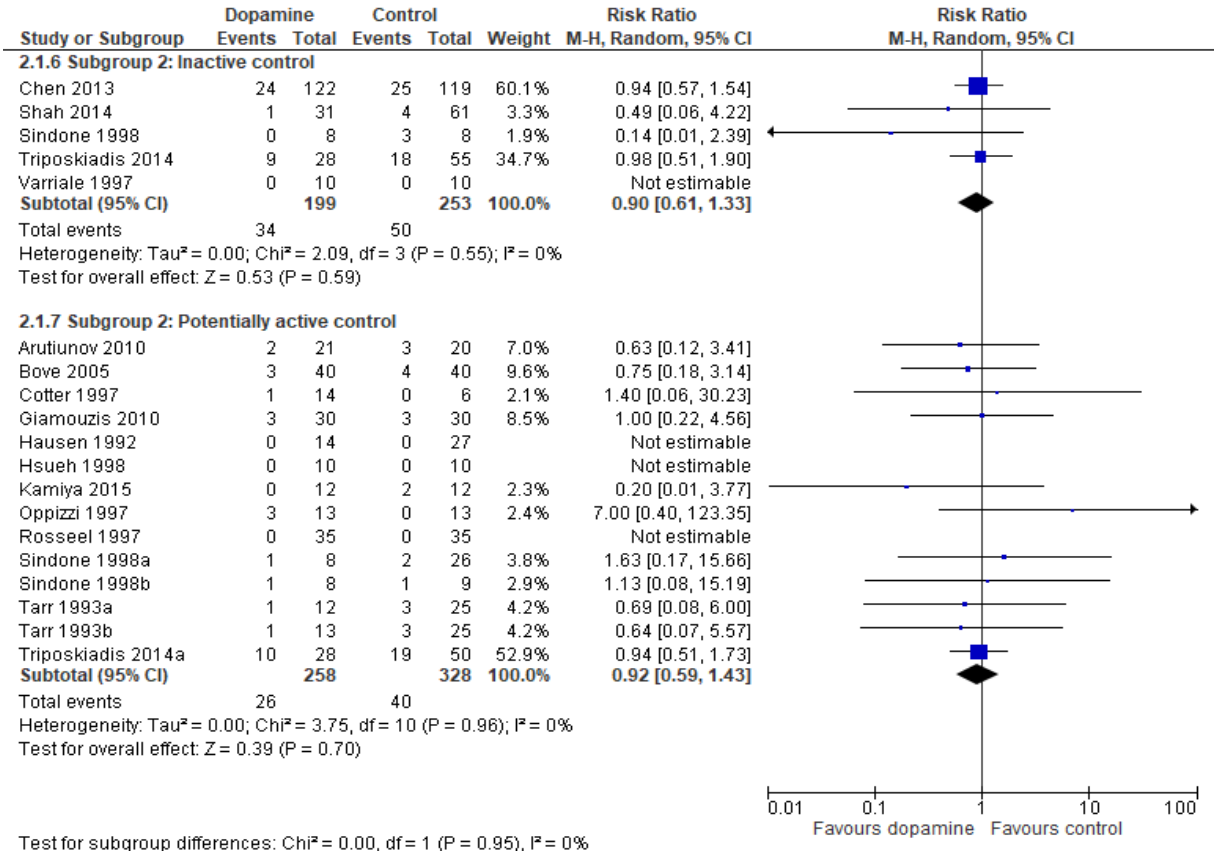
E-Figures 1.1.1-1.1.3: all trials with worst-best and best-worst case analyses



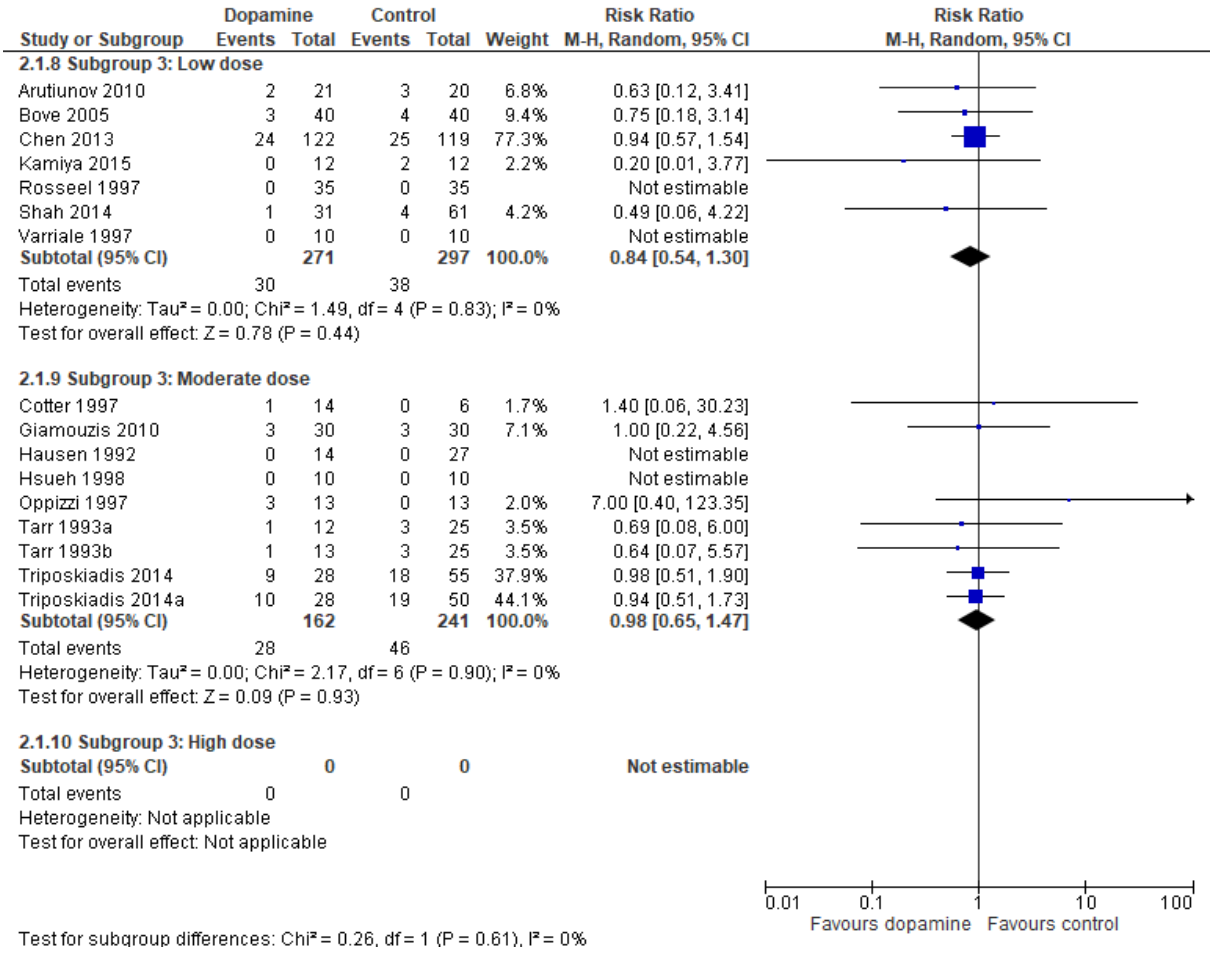
E-Figures 1.1.4-1.1.5: subgroup analysis 1 - trials subdivided by risk of bias



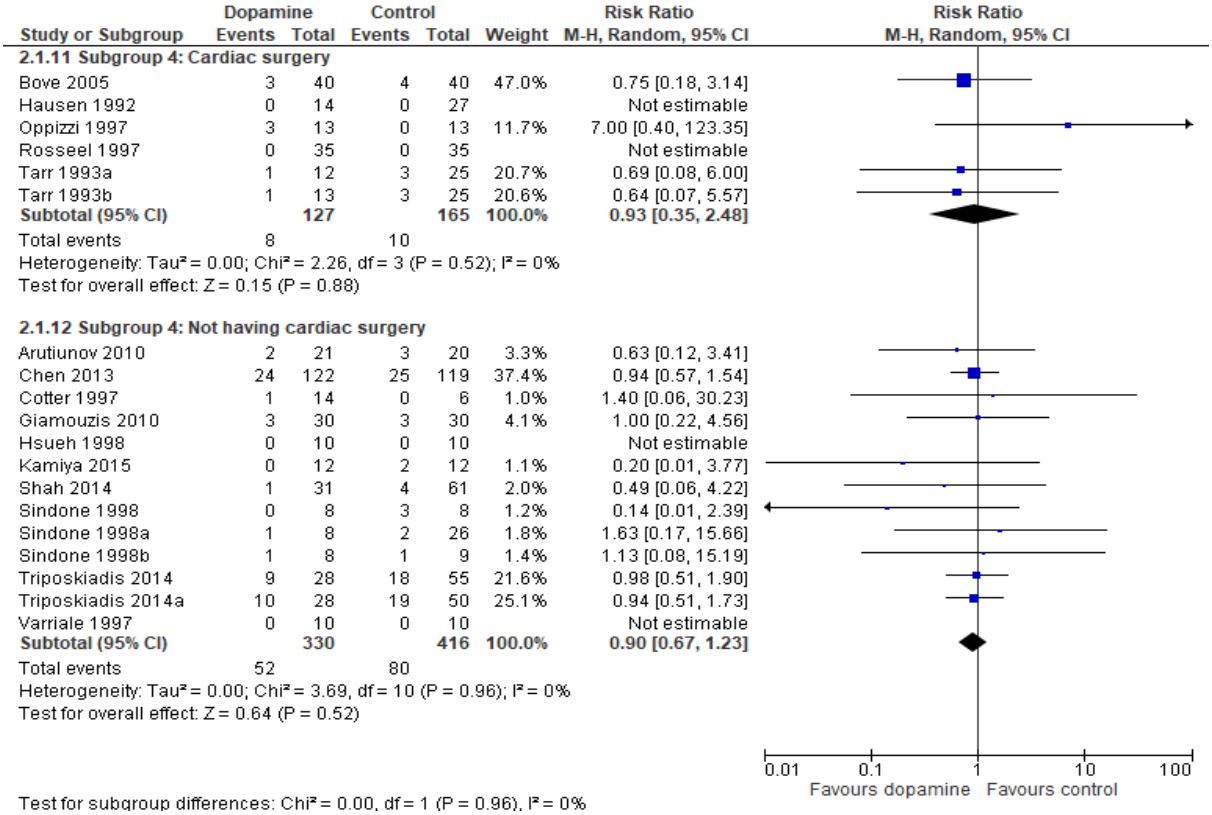
E-Figures 1.1.6-1.1.7: subgroup analysis 2 – trials subdivided by comparator intervention



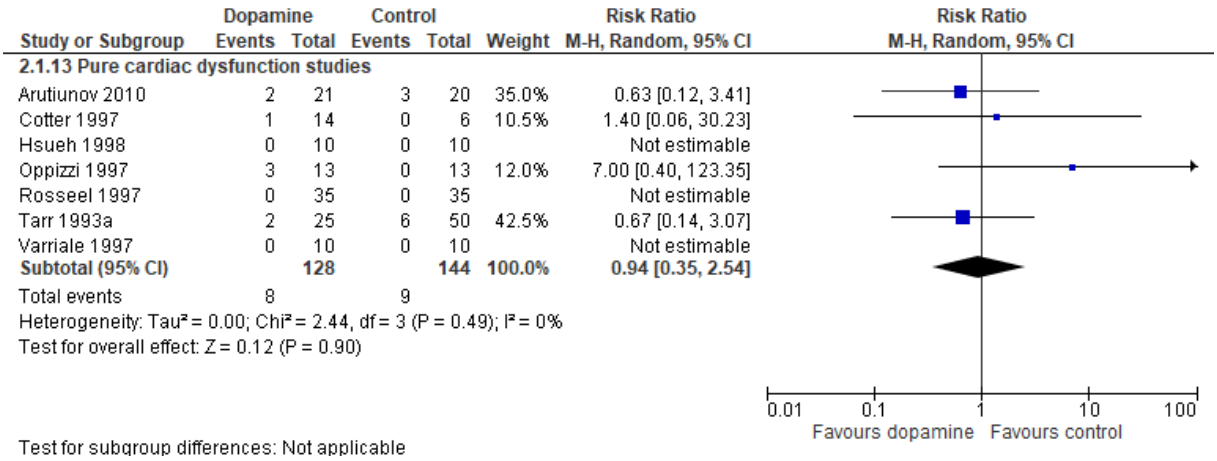
E-Figures 1.1.8-1.1.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 1.1.11-1.1.12: subgroup analysis 4 – trials subdivided by clinical setting

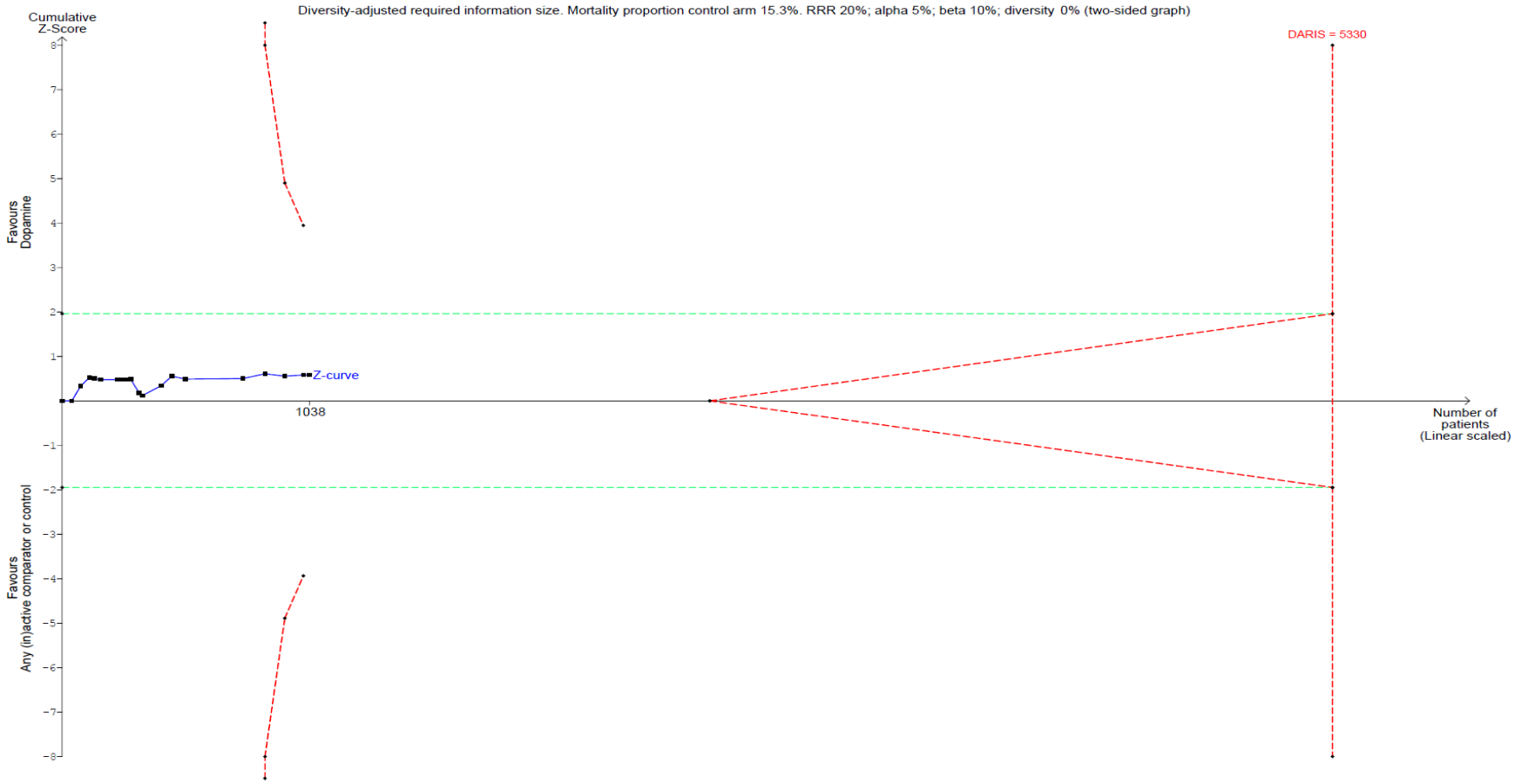


E-Figure 1.1.13: sensitivity analysis – trials including only patients with cardiac dysfunction



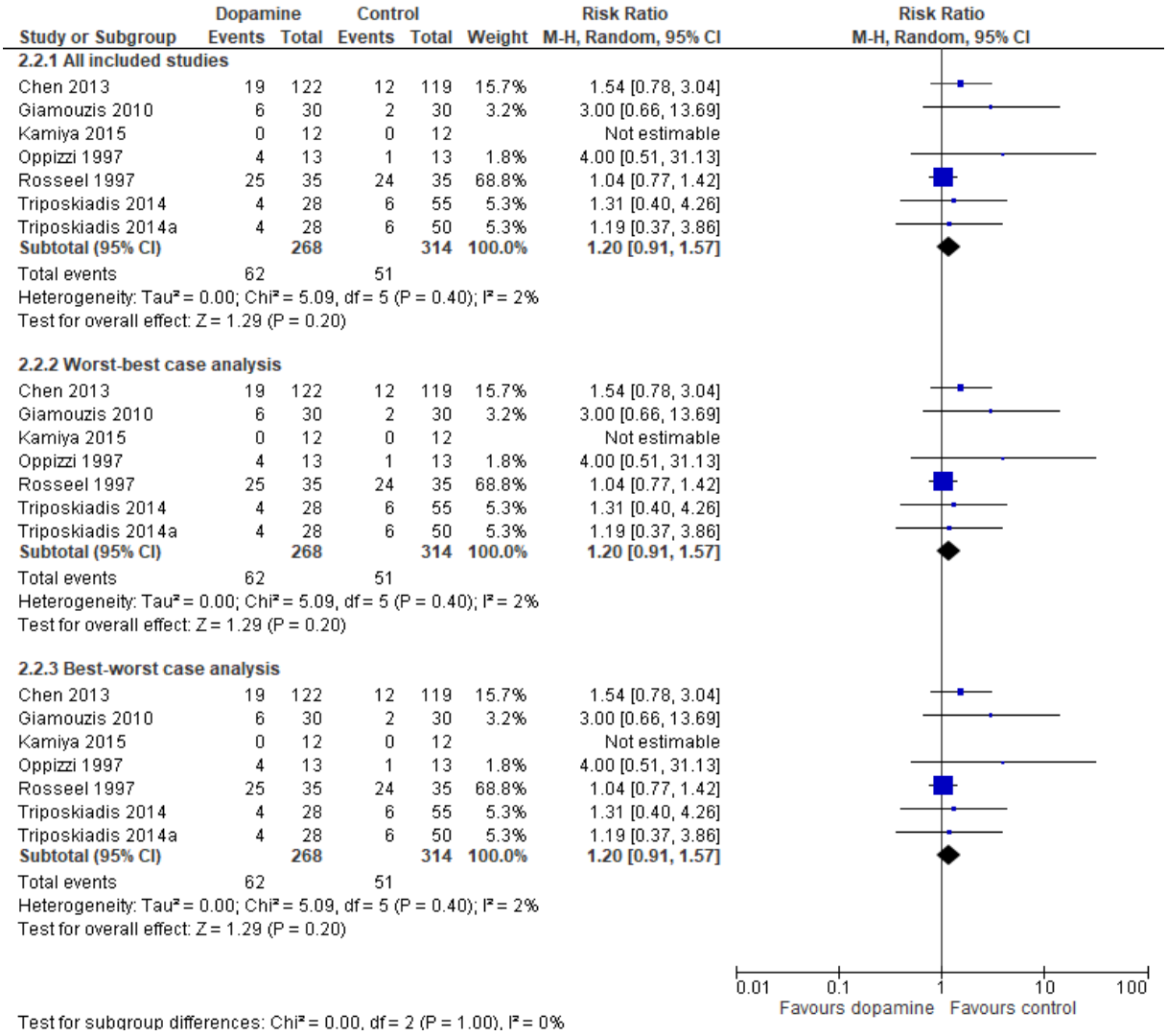
1.4. Trial sequential analysis of mortality (same as in manuscript)

E-Figure 1.2: the TSA is based on 15 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

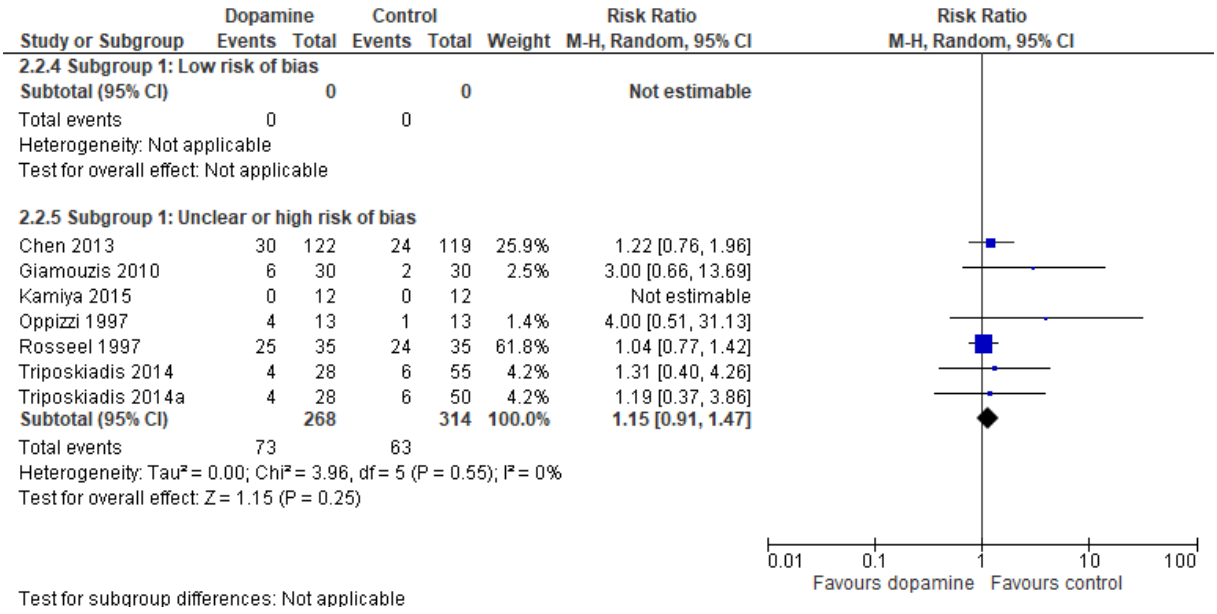


1.5. Forest plots of serious adverse events

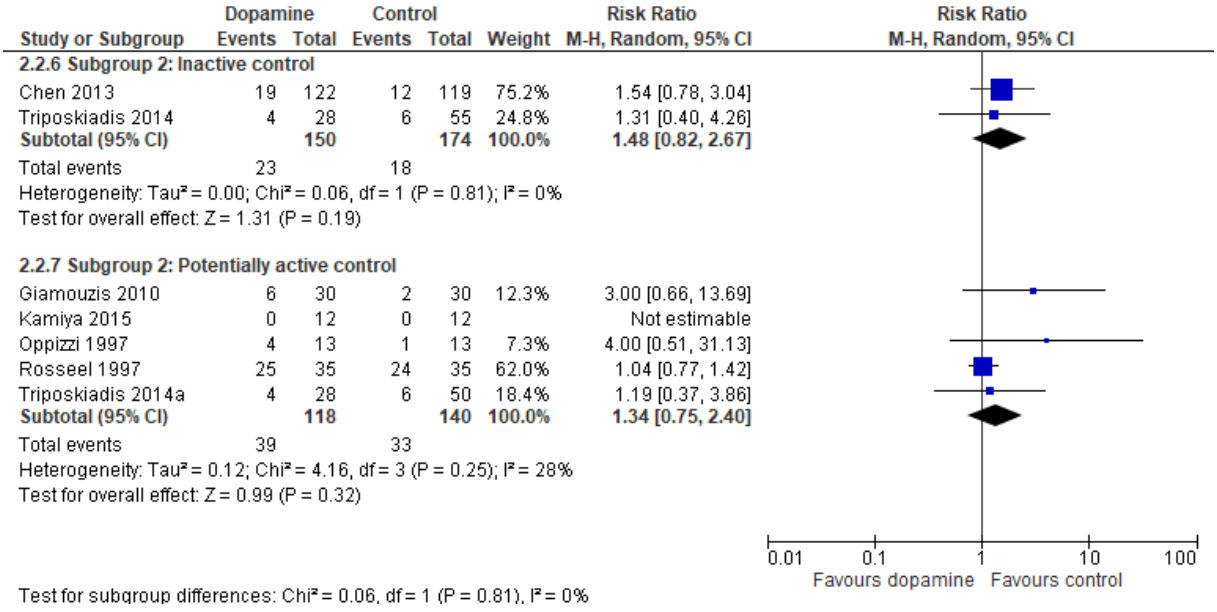
E-Figures 1.3.1-1.3.3: all trials with worst-best and best-worst case analyses



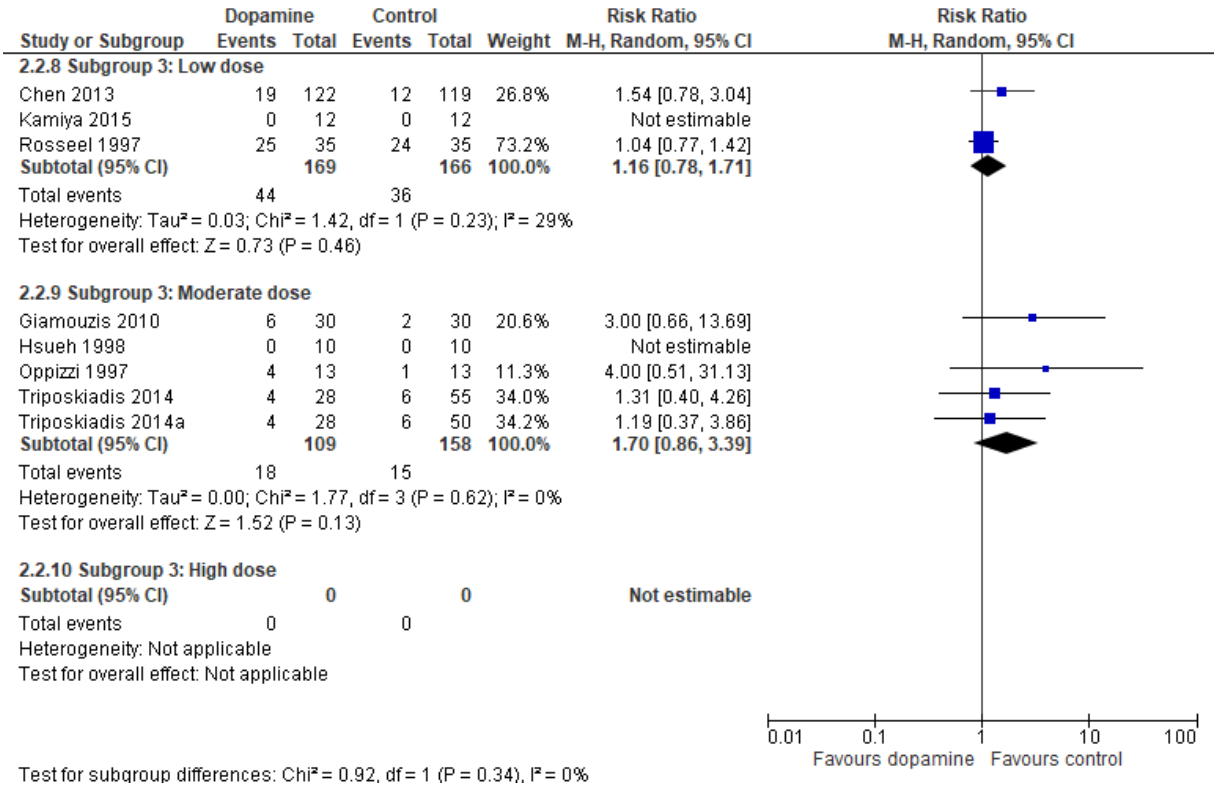
E-Figures 1.3.4-1.3.5: subgroup analysis 1 - trials subdivided by risk of bias



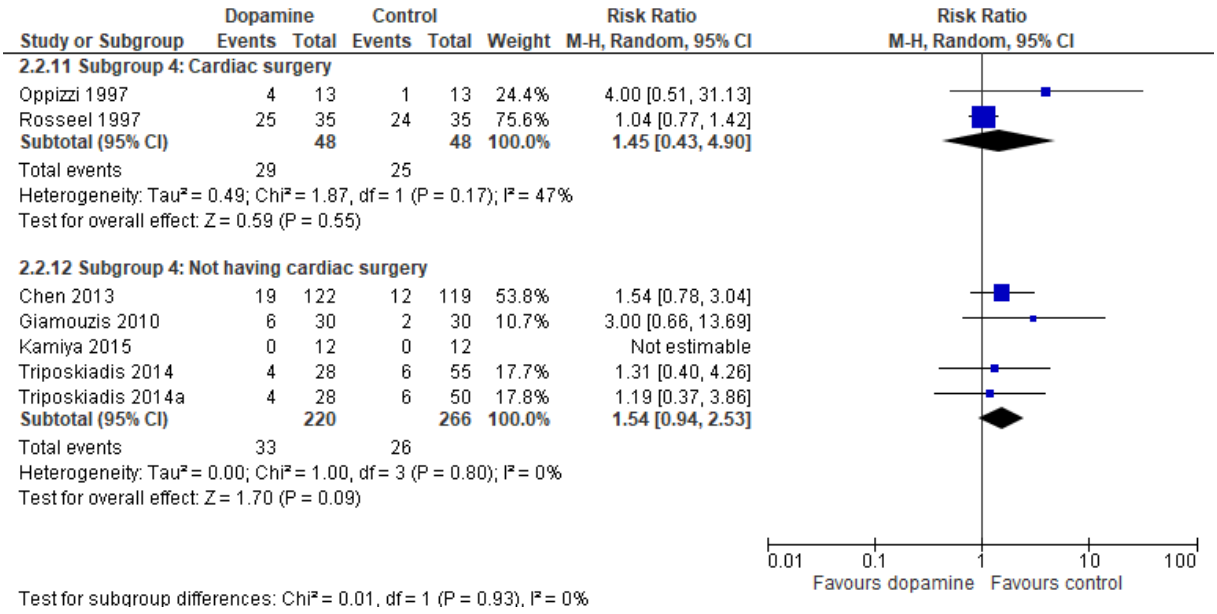
E-Figures 1.3.6-1.3.7: subgroup analysis 2 – trials subdivided by comparator intervention



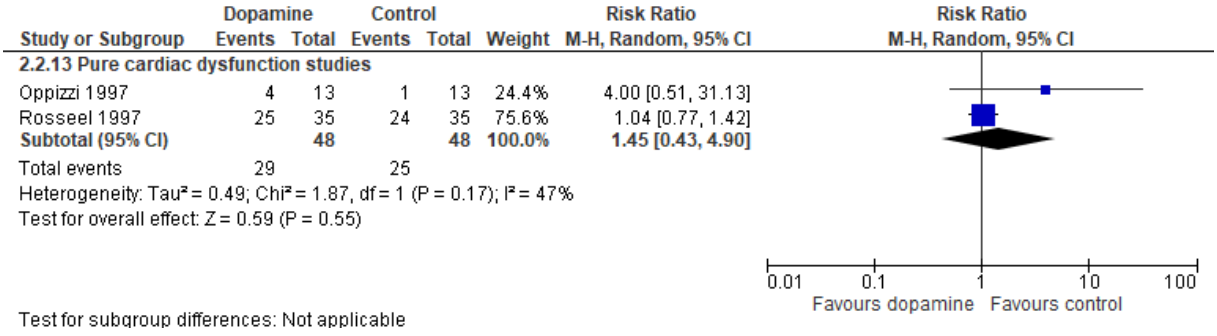
E-Figures 1.3.8-1.3.10: subgroup analysis 3 – trials subdivided by dose



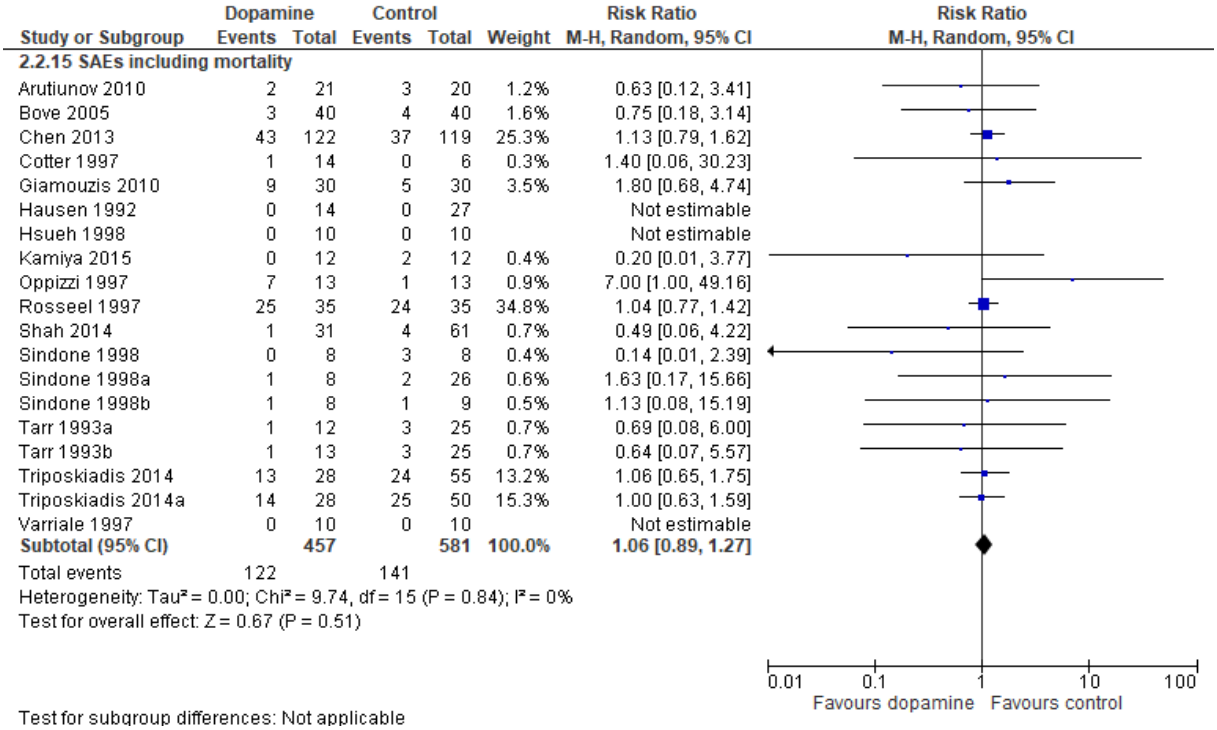
E-Figures 1.3.11-1.3.12: subgroup analysis 4 – trials subdivided by clinical setting



E-Figure 1.3.13: sensitivity analysis – trials including only patients with cardiac dysfunction

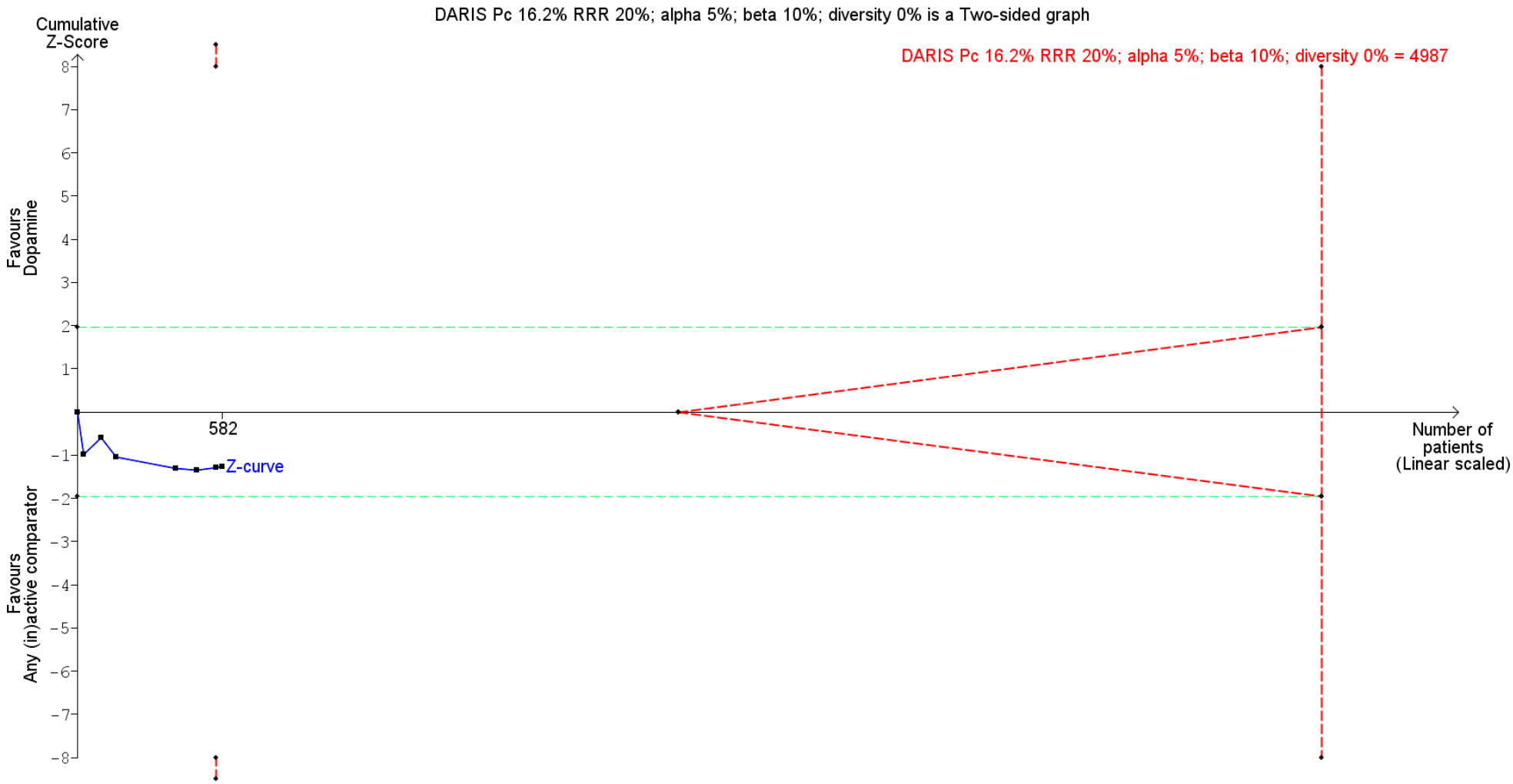


E-Figure 1.3.14: sensitivity analysis – SAEs in all trials including mortality



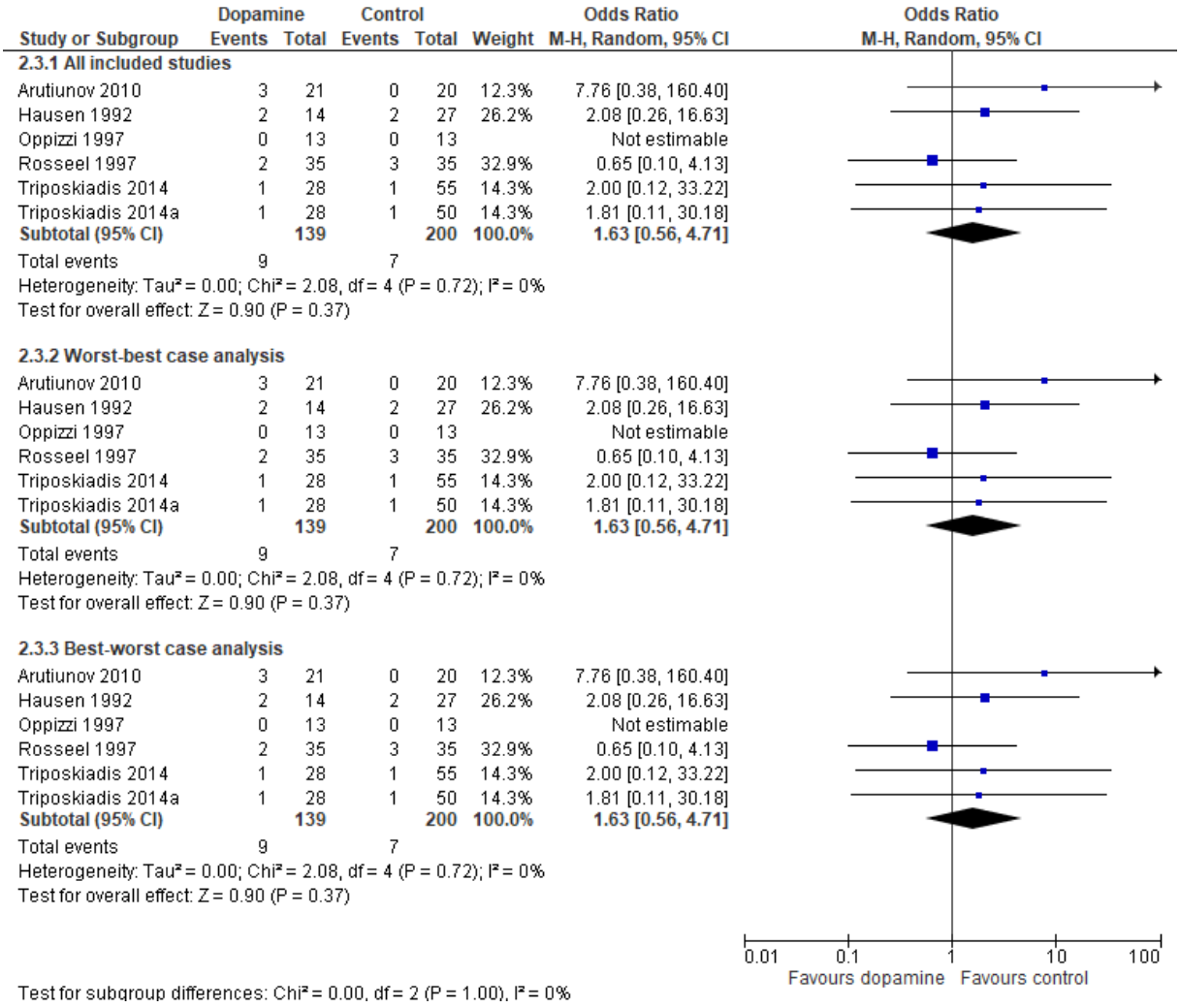
1.6. Trial sequential analysis of serious adverse events

E-Figure 1.4: the TSA is based on seven trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

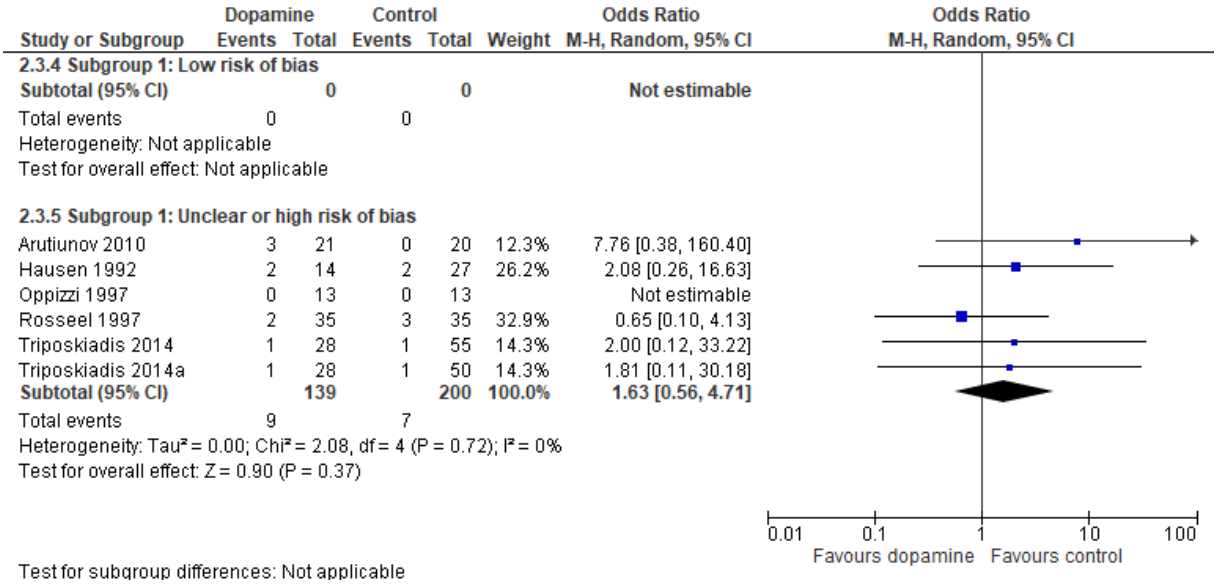


1.7. Forest plots of myocardial infarction

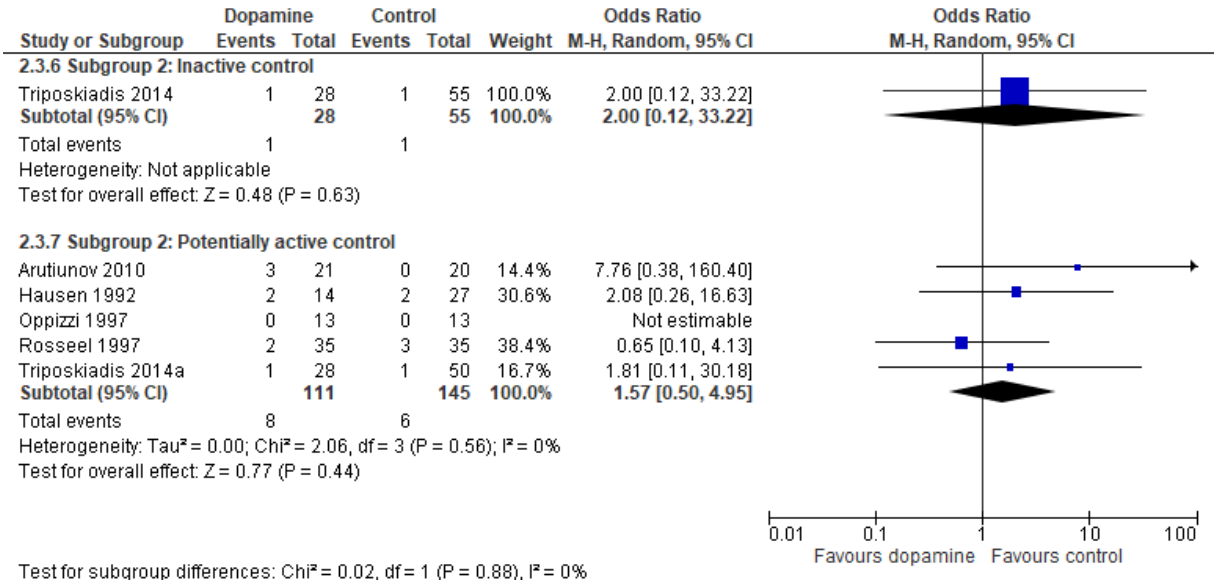
E-Figures 1.5.1-1.5.3: all trials with worst-best and best-worst case analyses



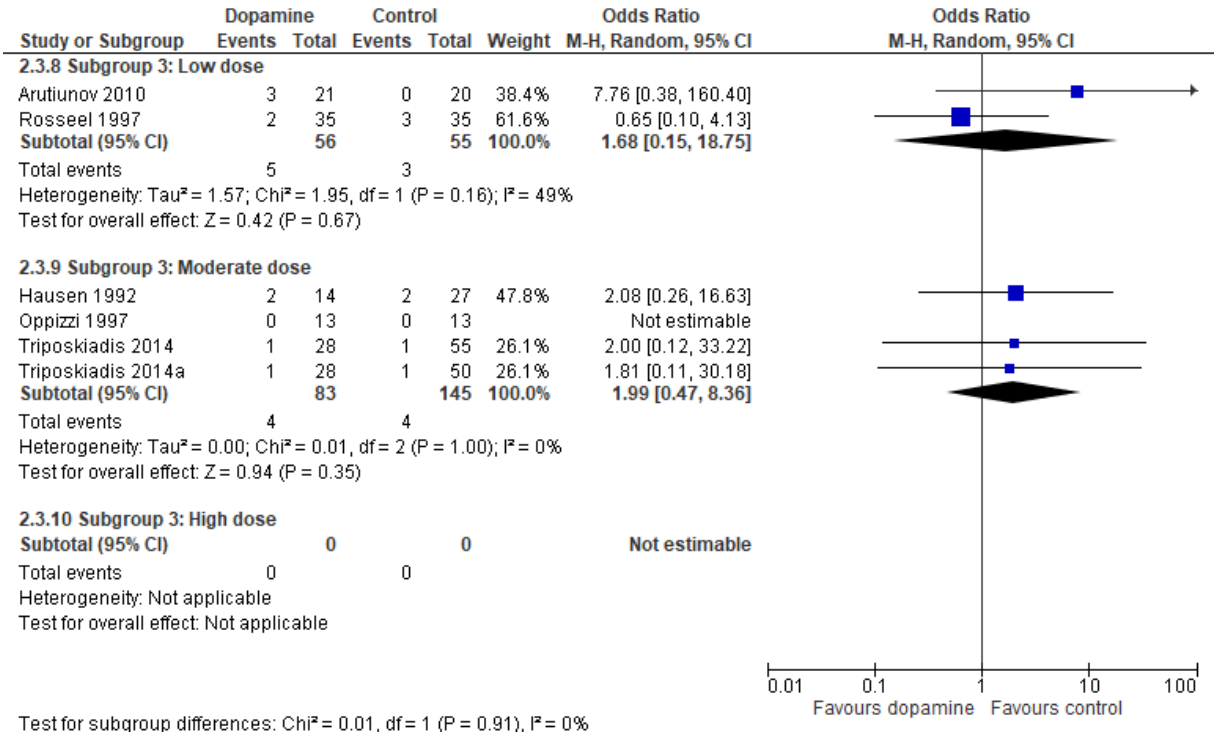
E-Figures 1.5.4-1.5.5: subgroup analysis 1 - trials subdivided by risk of bias



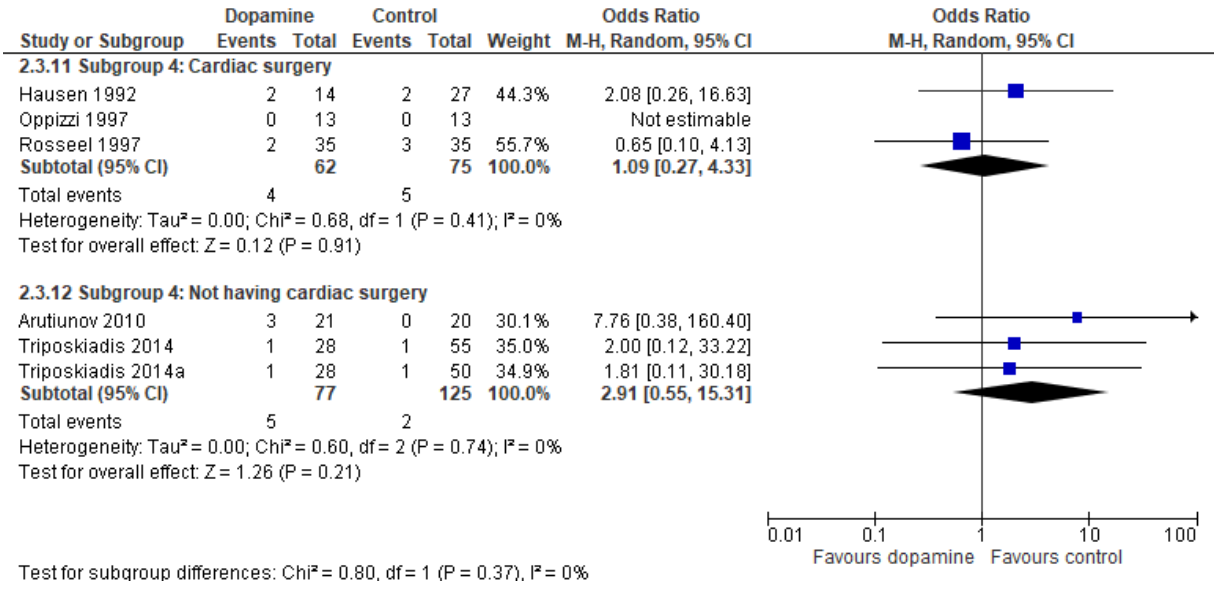
E-Figures 1.5.6-1.5.7: subgroup analysis 2 – trials subdivided by comparator intervention



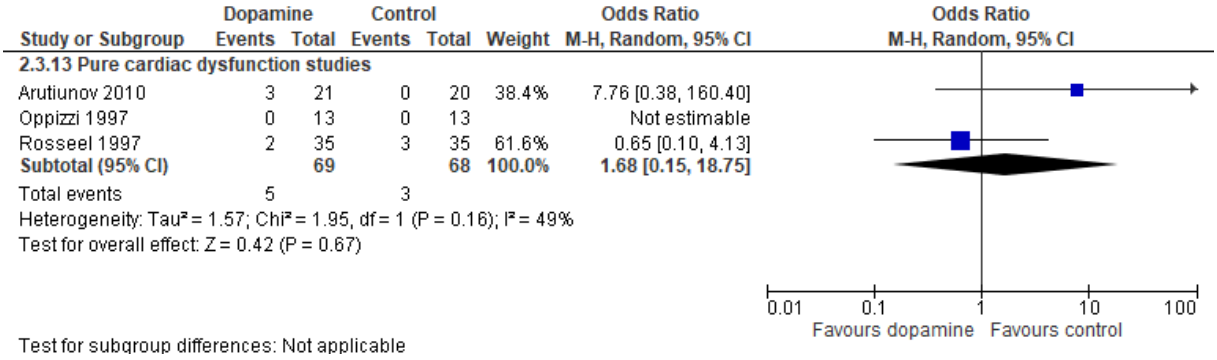
E-Figures 1.5.8-1.5.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 1.5.11-1.5.12: subgroup analysis 4 – trials subdivided by clinical setting

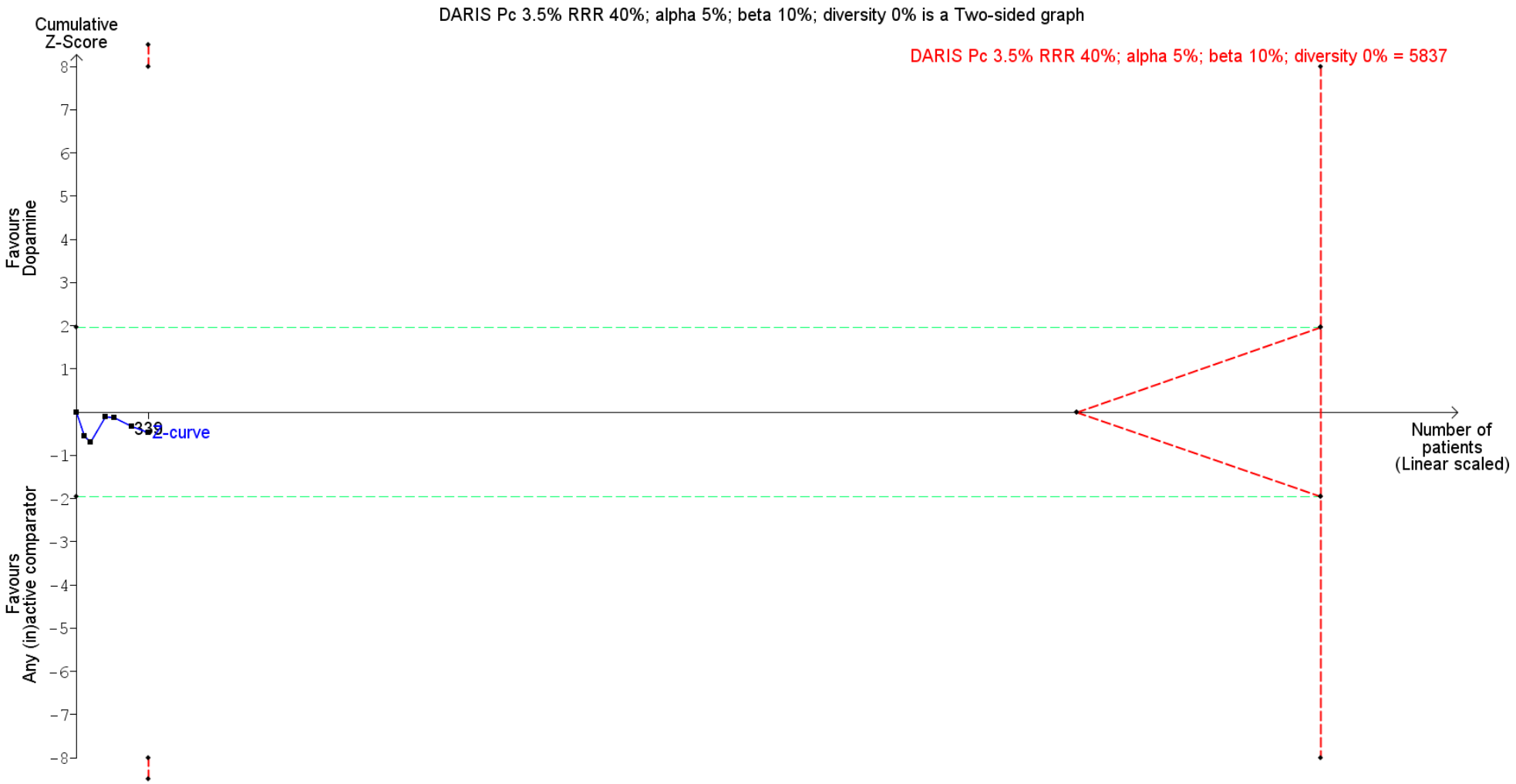


E-Figure 1.5.13: sensitivity analysis – trials including only patients with cardiac dysfunction



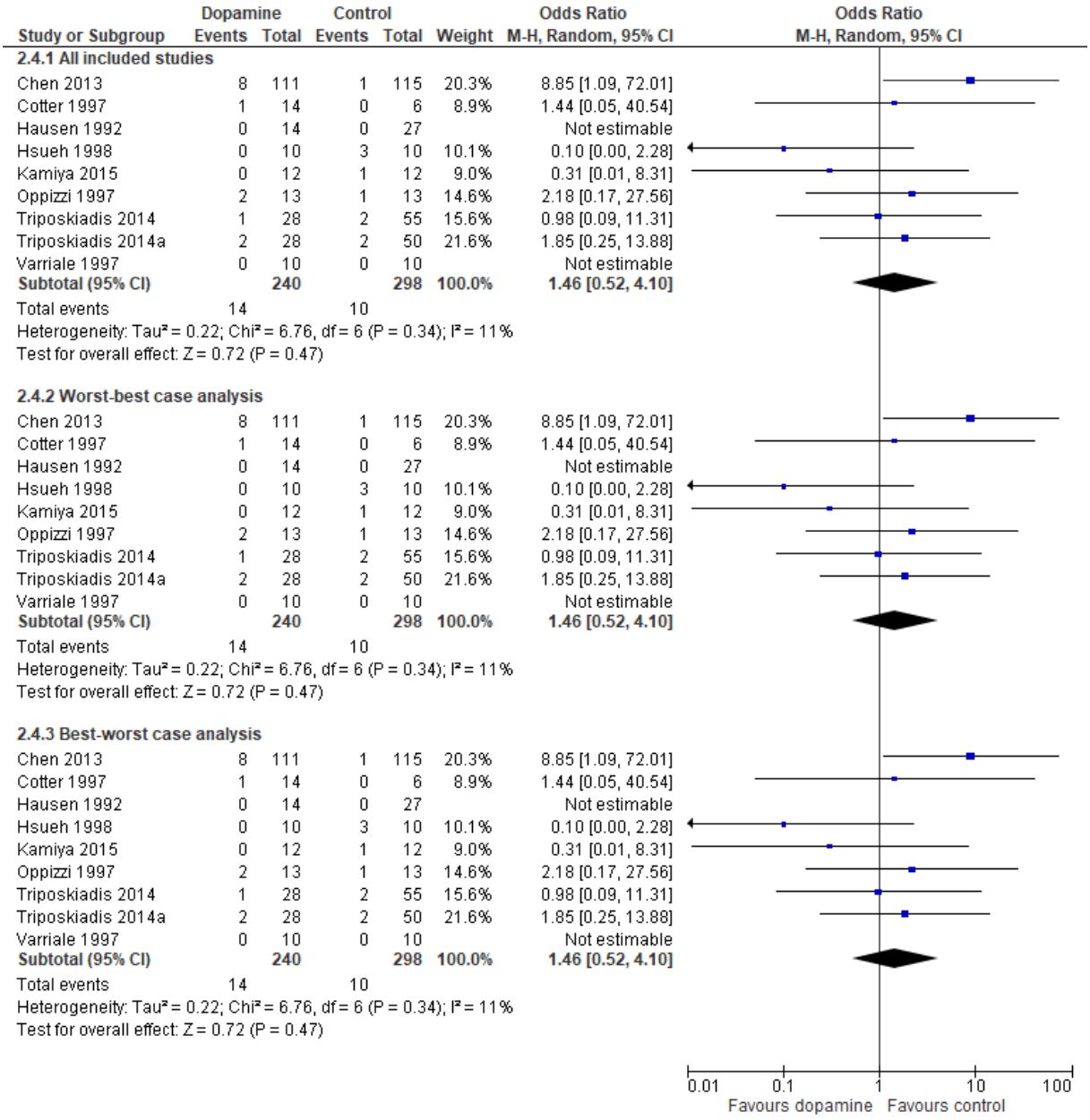
1.8. Trial sequential analysis of myocardial infarction

E-Figure 1.6: the TSA is based on six trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

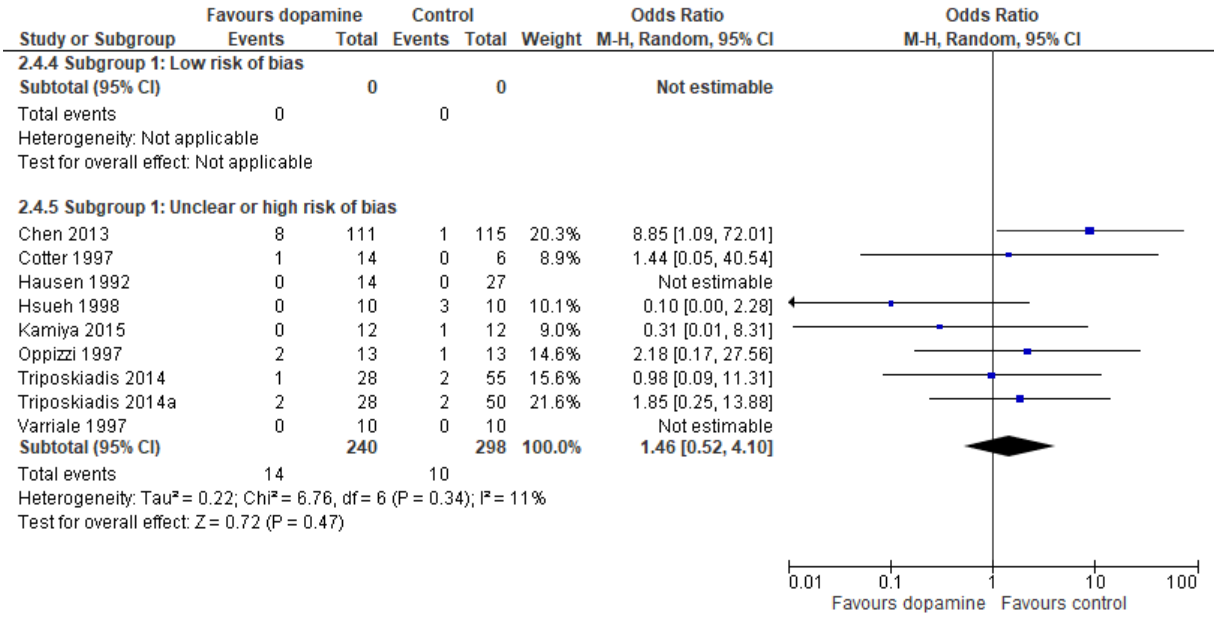


1.9. Forest plots of ventricular tachyarrhythmias

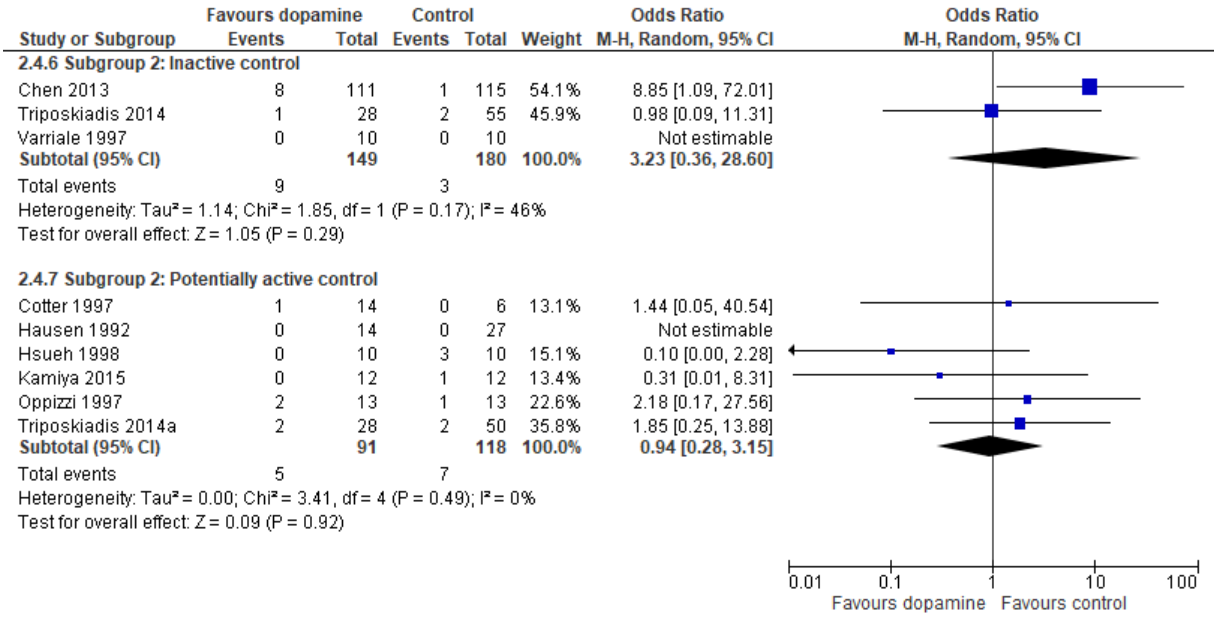
E-Figures 1.7.1-1.7.3: all trials with worst-best and best-worst case analyses



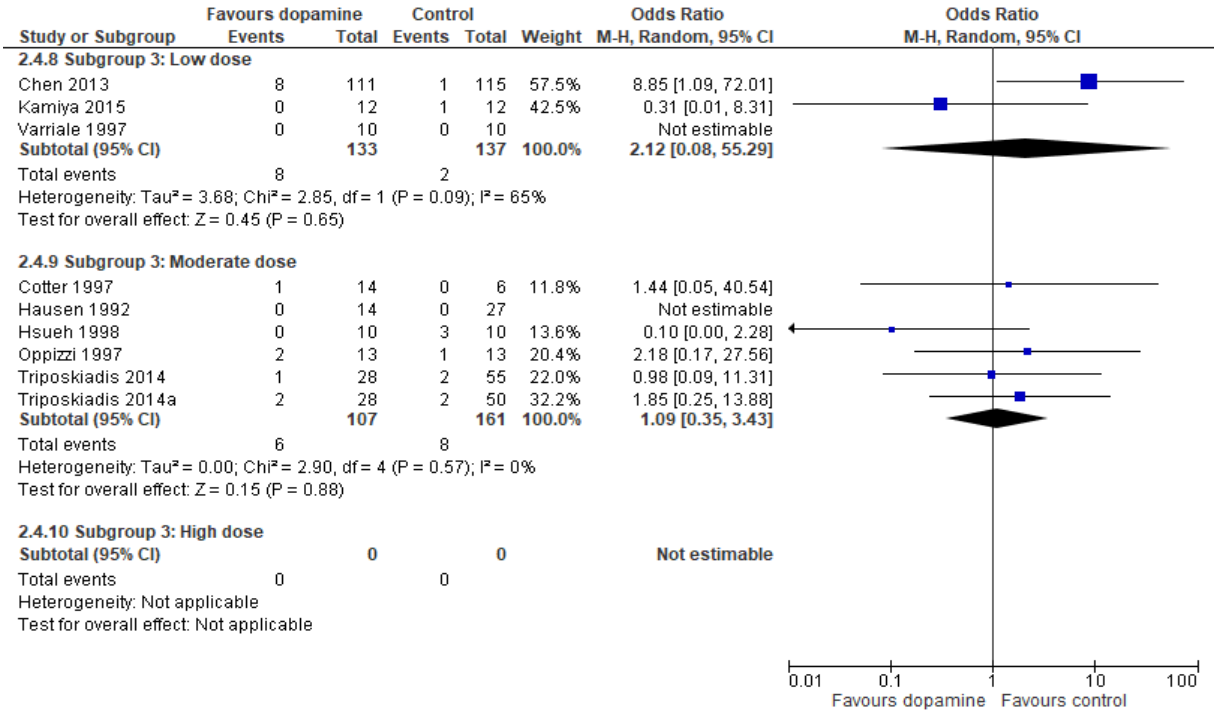
E-Figures 1.7.4-1.7.5: subgroup analysis 1 - trials subdivided by risk of bias



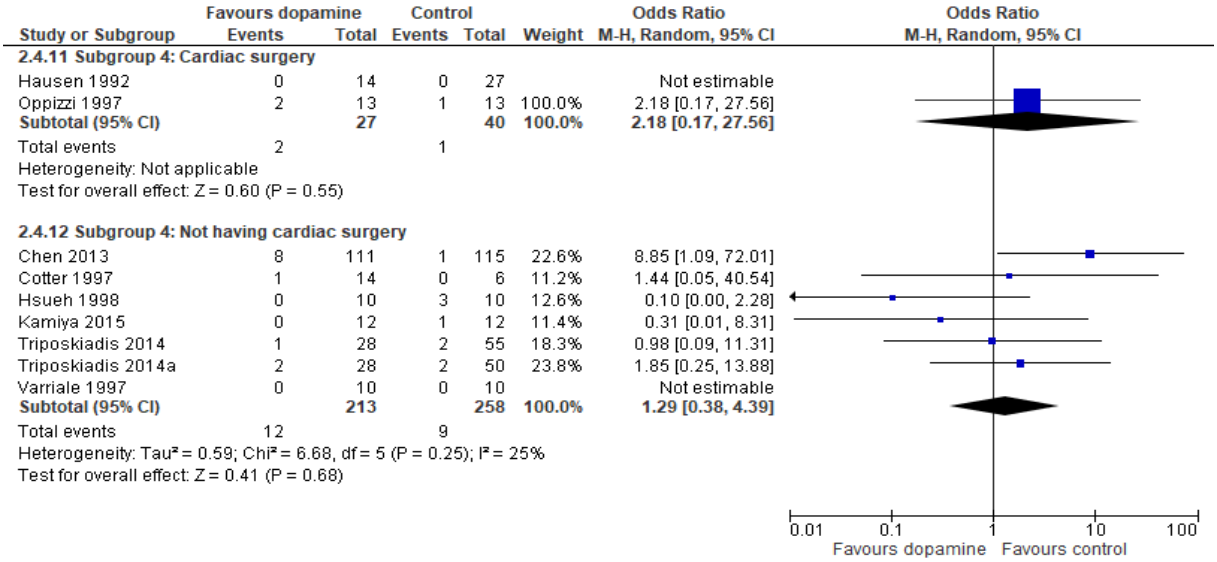
E-Figures 1.7.6-1.7.7: subgroup analysis 2 – trials subdivided by comparator intervention



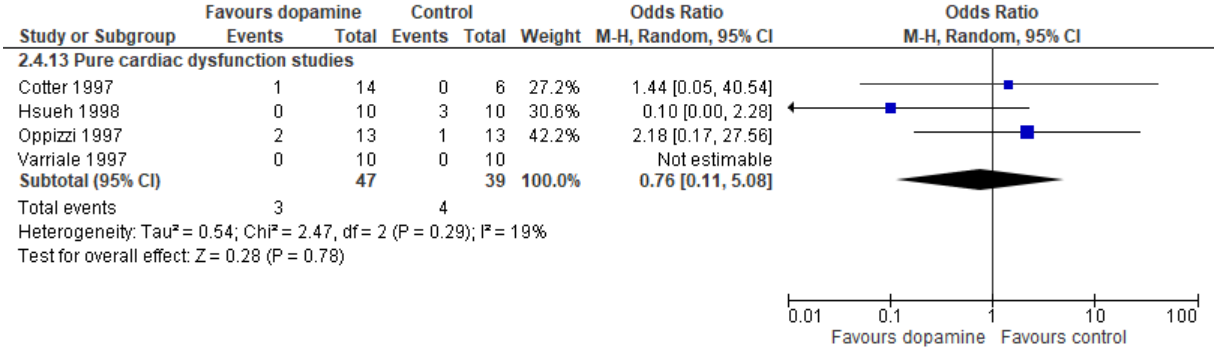
E-Figures 1.7.8-1.7.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 1.7.11-1.7.12: subgroup analysis 4 – trials subdivided by clinical setting

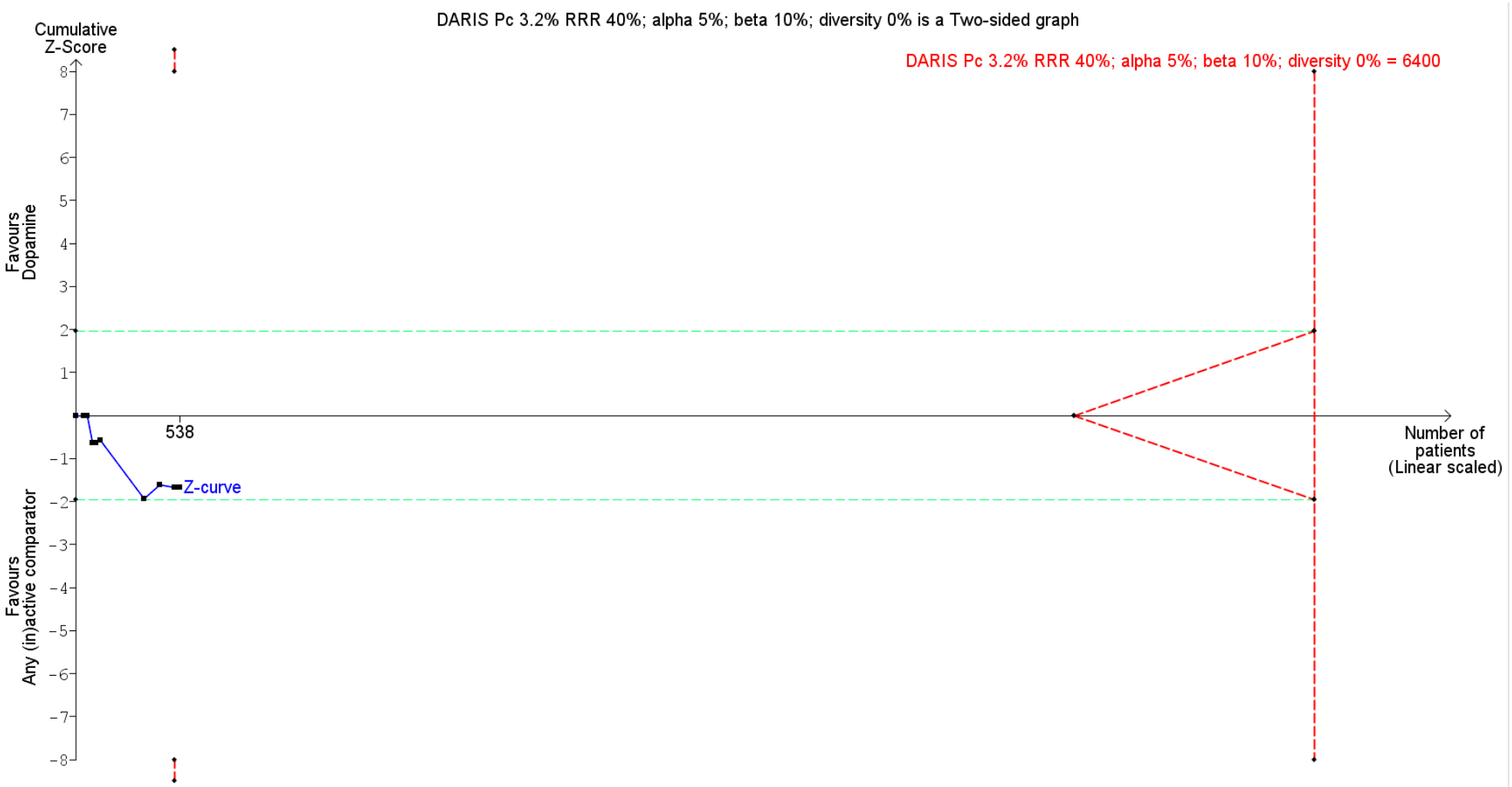


E-Figure 1.7.13: sensitivity analysis – trials including only patients with cardiac dysfunction



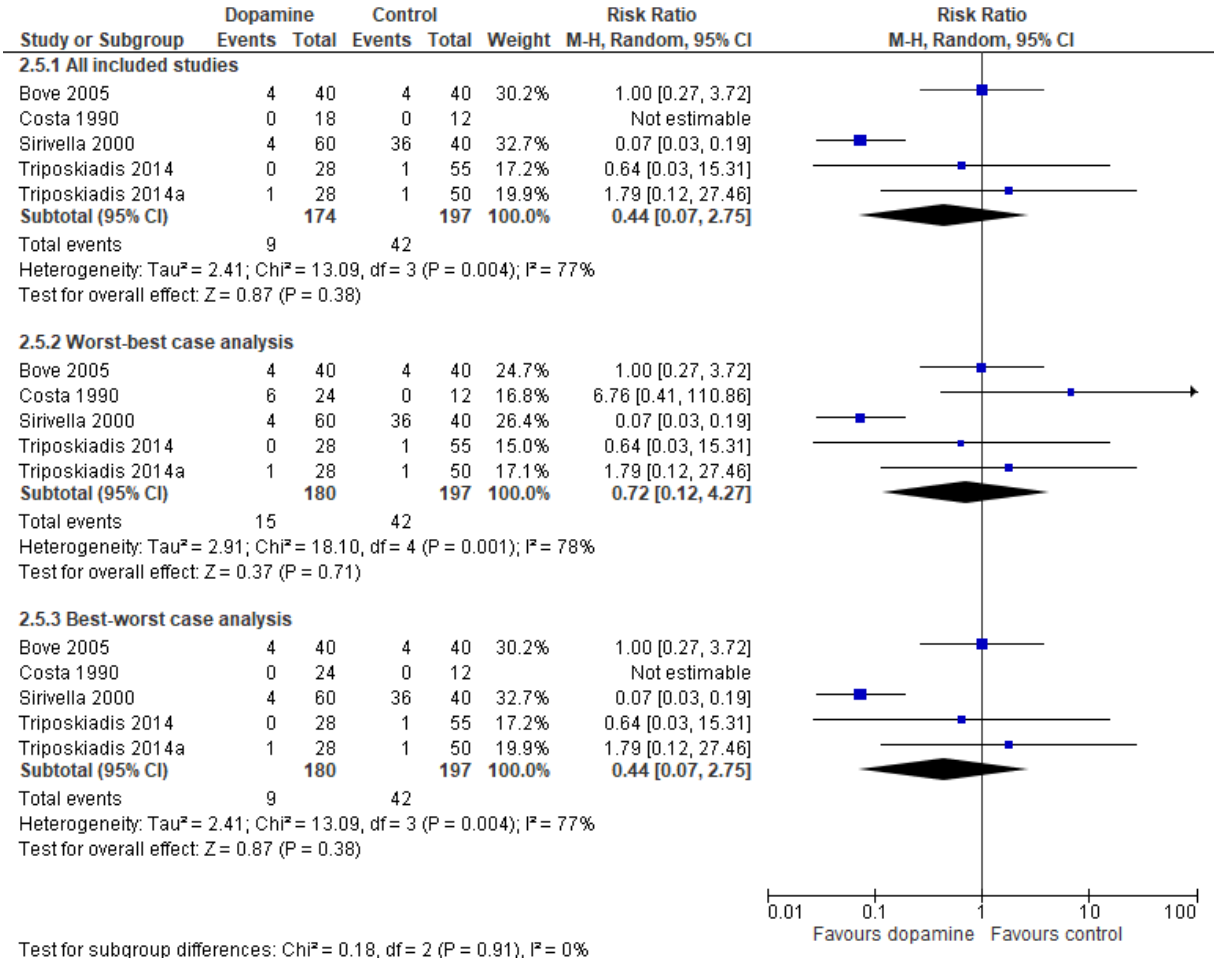
1.10. Trial sequential analysis of ventricular tachyarrhythmias

E-Figure 1.8: the TSA is based on eight trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

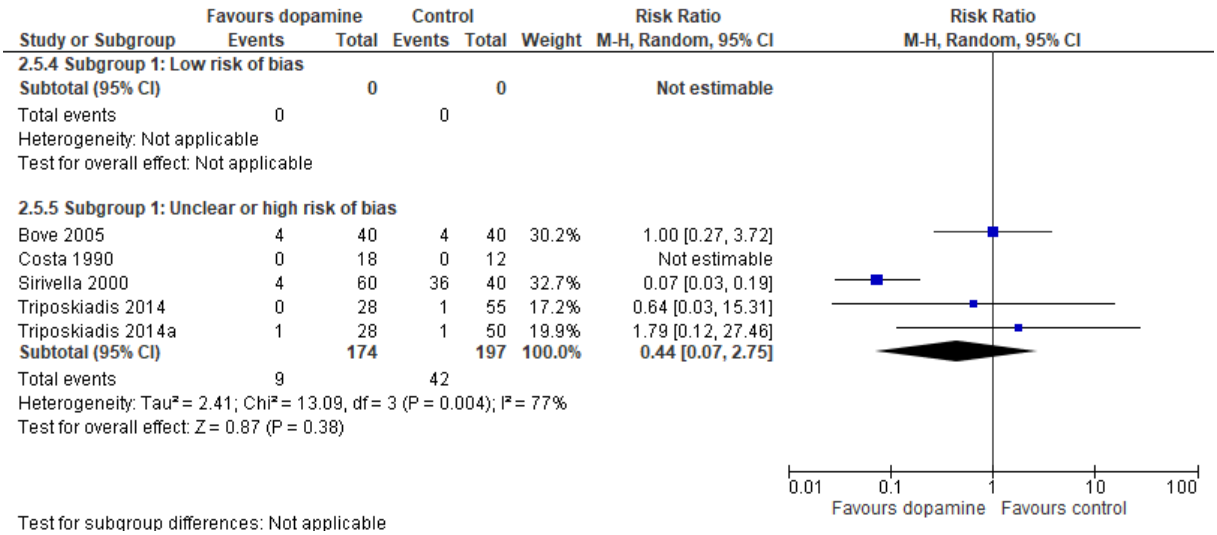


1.11. Forest plots of renal replacement therapy

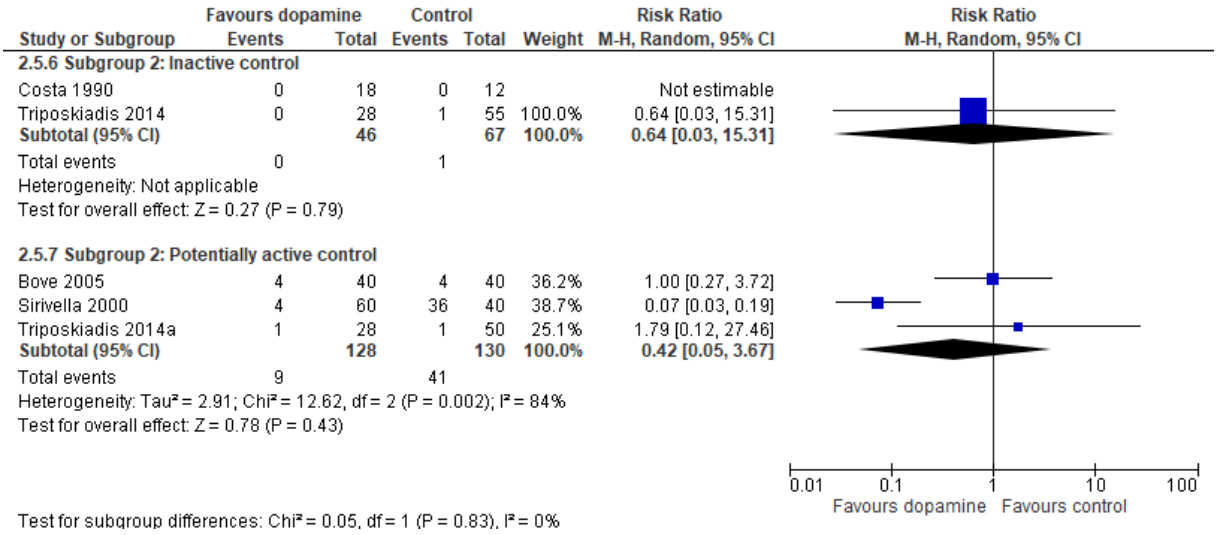
E-Figures 1.9.1-1.9.3: all trials with worst-best and best-worst case analyses



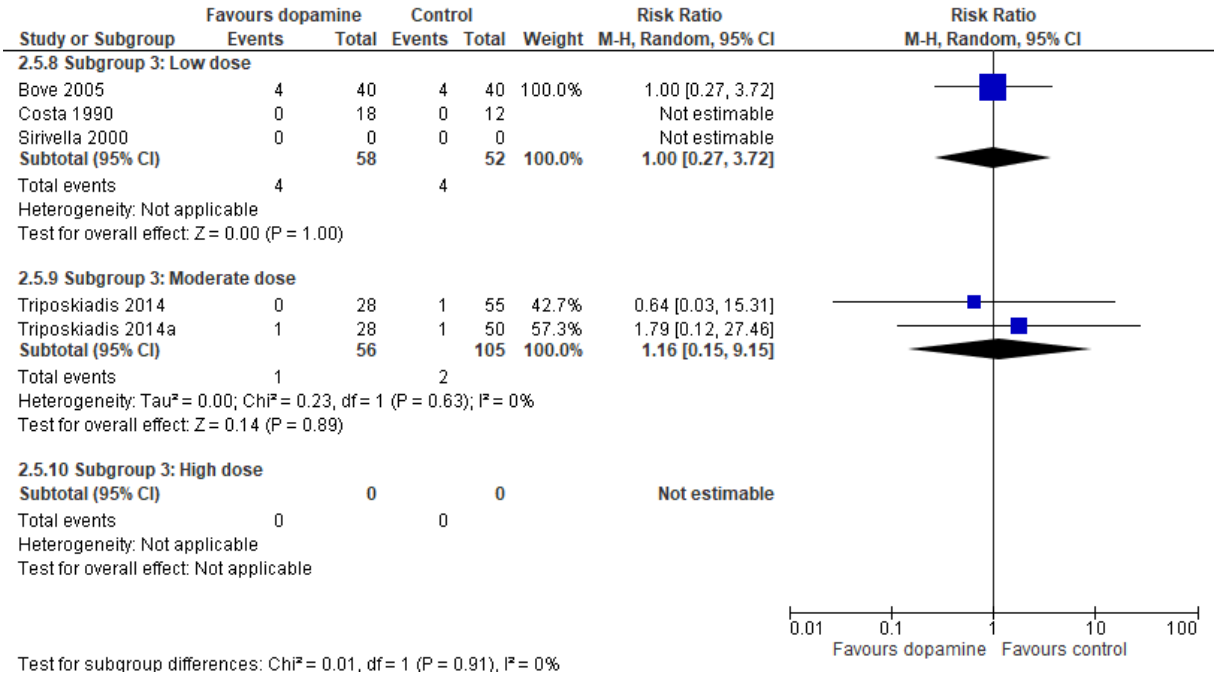
E-Figures 1.9.4-1.9.5: subgroup analysis 1 - trials subdivided by risk of bias



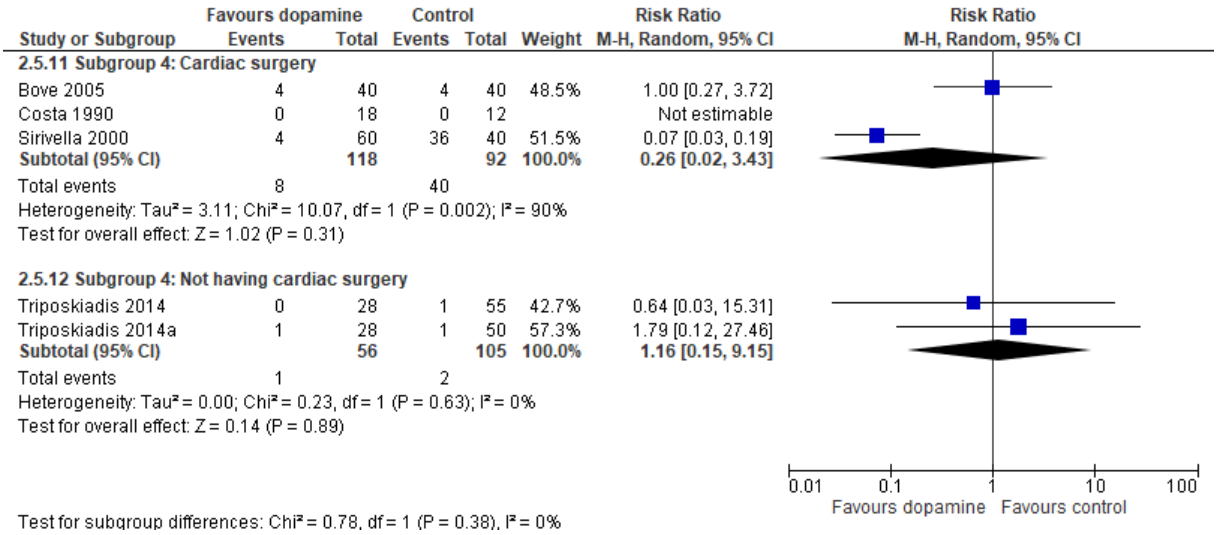
E-Figures 1.9.6-1.9.7: subgroup analysis 2 – trials subdivided by comparator intervention



E-Figures 1.9.8-1.9.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 1.9.11-1.9.12: subgroup analysis 4 – trials subdivided by clinical setting

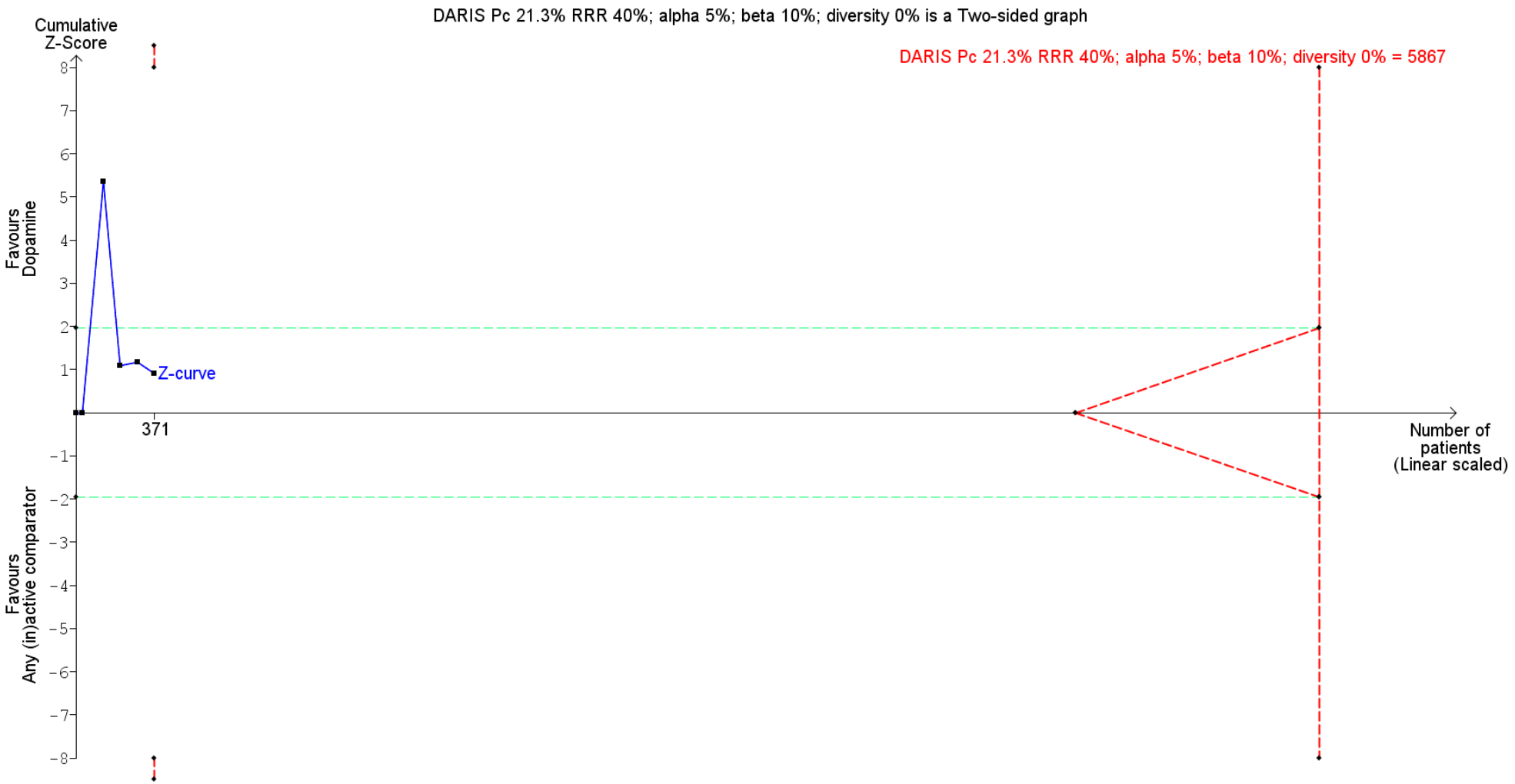


E-Figure 1.9.13: sensitivity analysis – trials including only patients with cardiac dysfunction

There was no data for this outcome in trials including only patients with cardiac dysfunction.

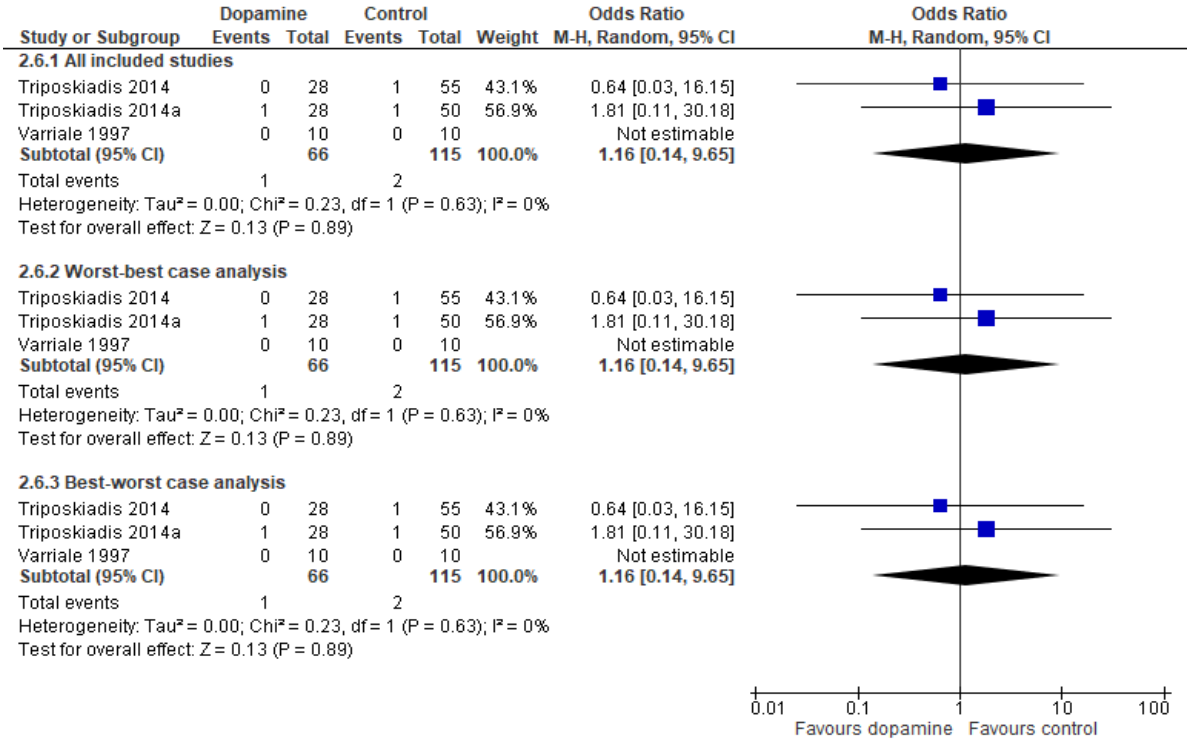
1.12. Trial sequential analysis of renal replacement therapy

E-Figure 2.13: the TSA is based on four trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

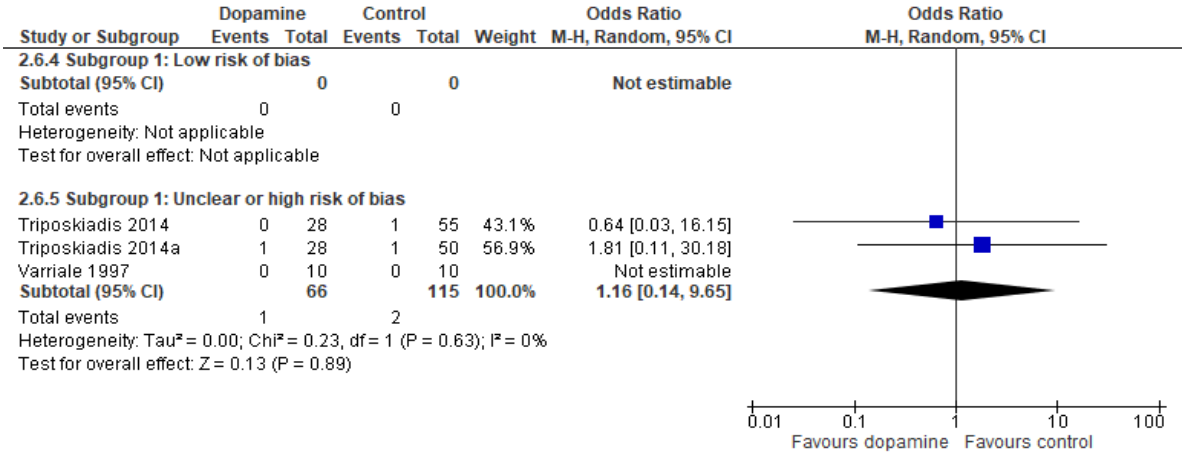


1.13. Forest plots of atrial tachyarrhythmias

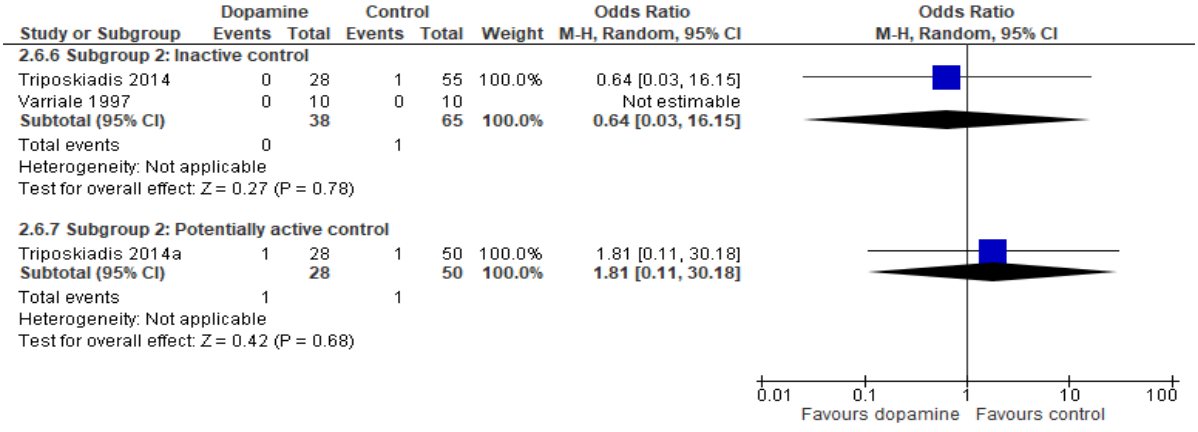
E-Figures 1.11.1-1.11.3: all trials with worst-best and best-worst case analyses



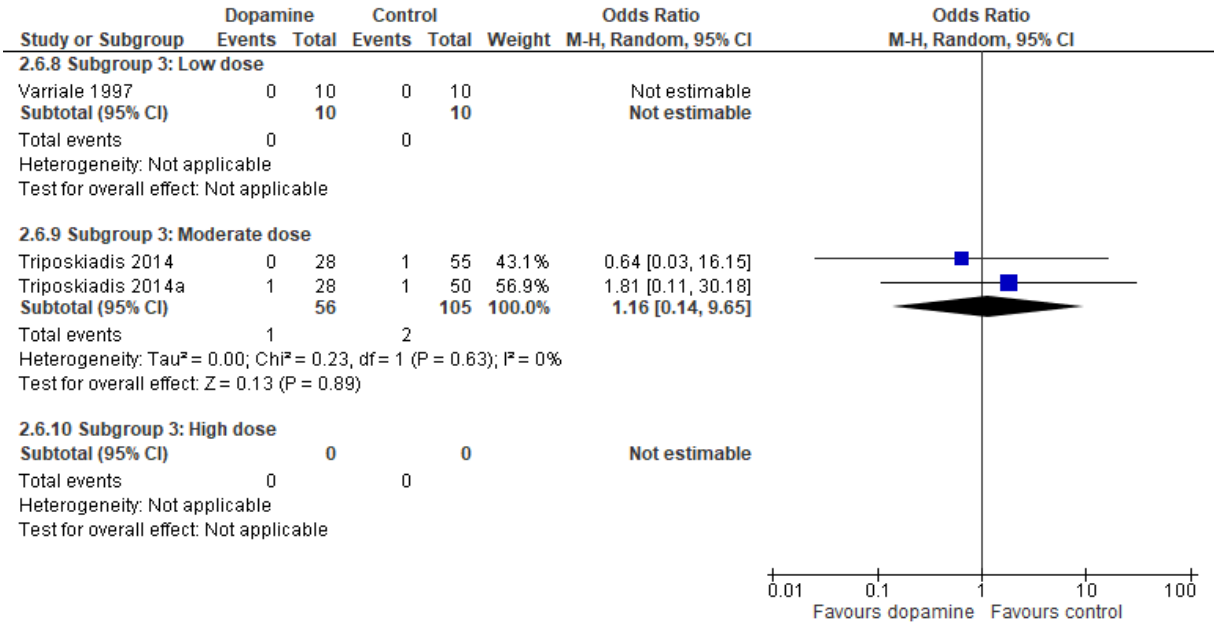
E-Figures 1.11.4-1.11.5: subgroup analysis 1 - trials subdivided by risk of bias



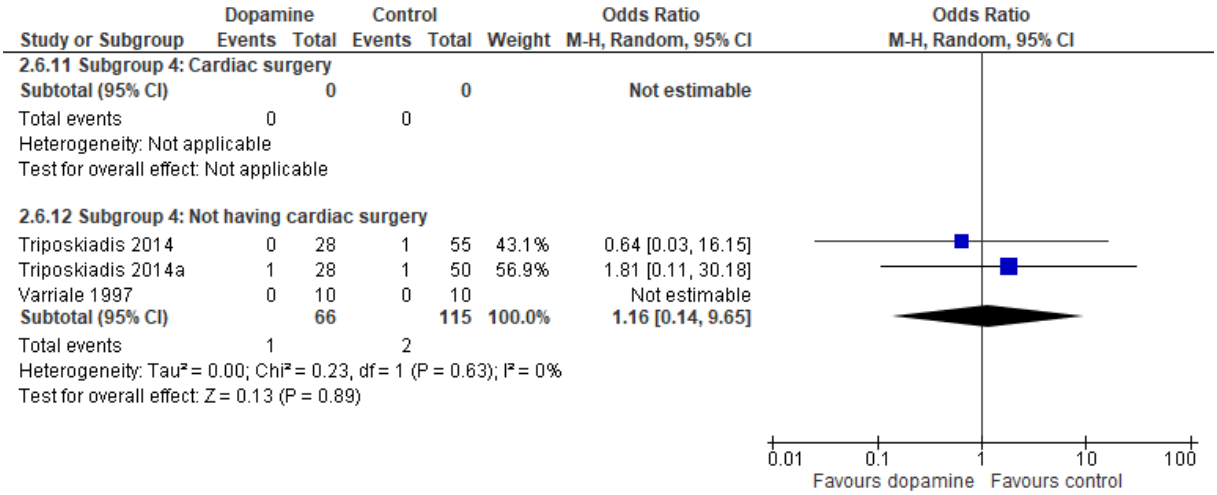
E-Figures 1.11.6-1.11.7: subgroup analysis 2 – trials subdivided by comparator intervention



E-Figures 1.11.8-1.11.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 1.11.11-1.11.12: subgroup analysis 4 – trials subdivided by clinical setting

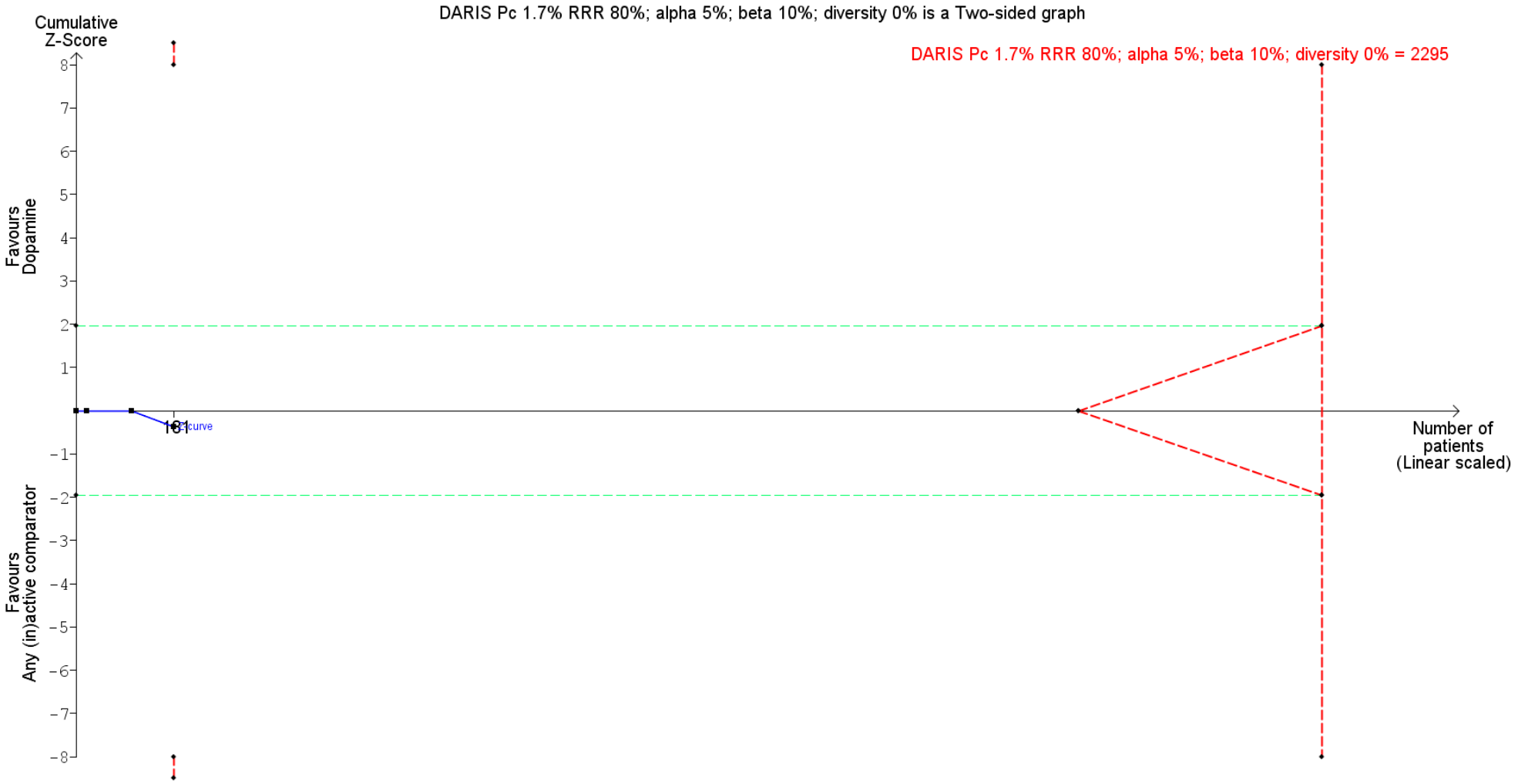


E-Figure 1.11.13: sensitivity analysis – trials including only patients with cardiac dysfunction

There was no data for this outcome in trials including only patients with cardiac dysfunction.

1.14. Trial sequential analysis of atrial tachyarrhythmias

E-Figure 1.12: the TSA is based on two trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

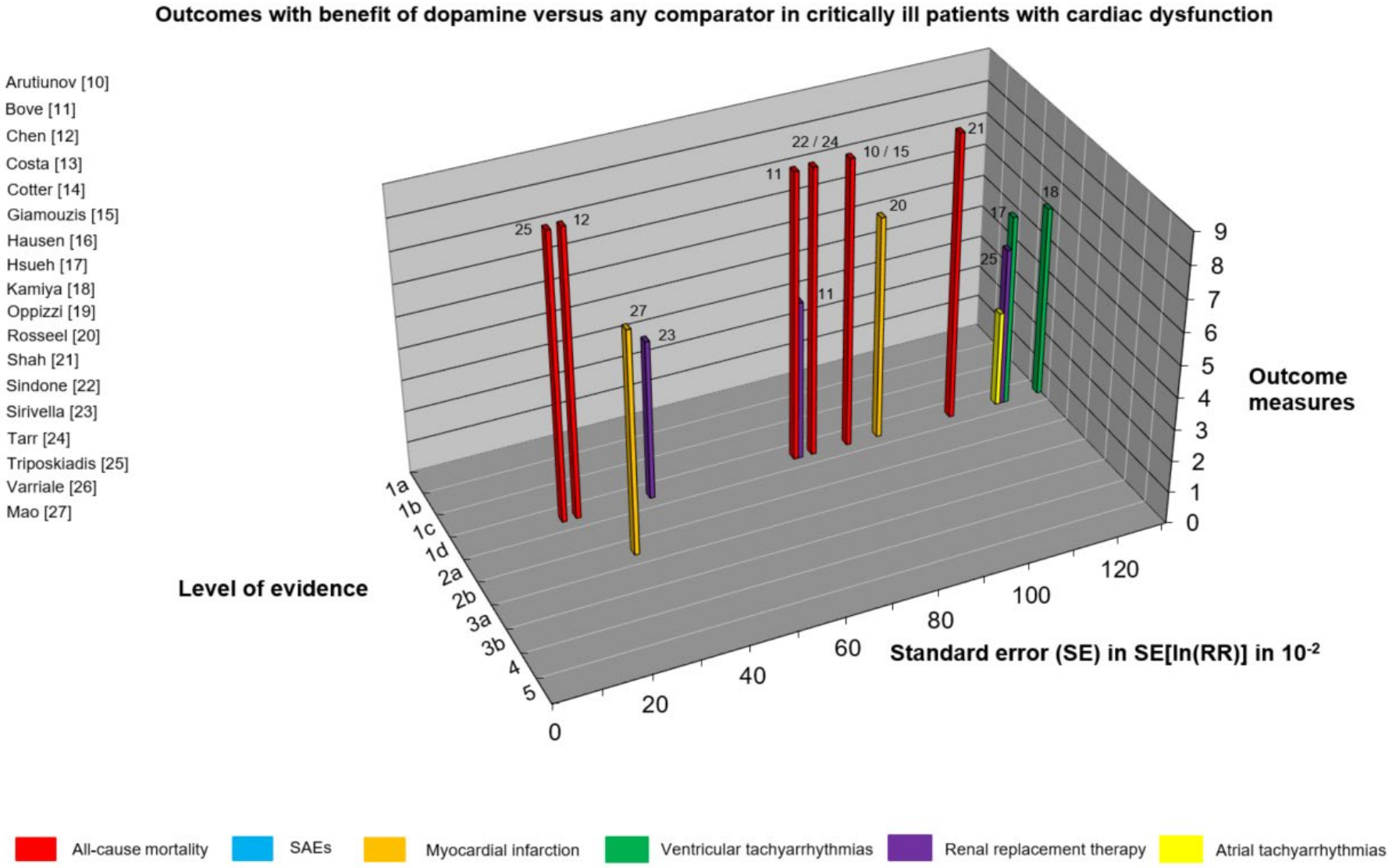


1.15. E-Table 2. Reported harmfull outcomes in observational studies

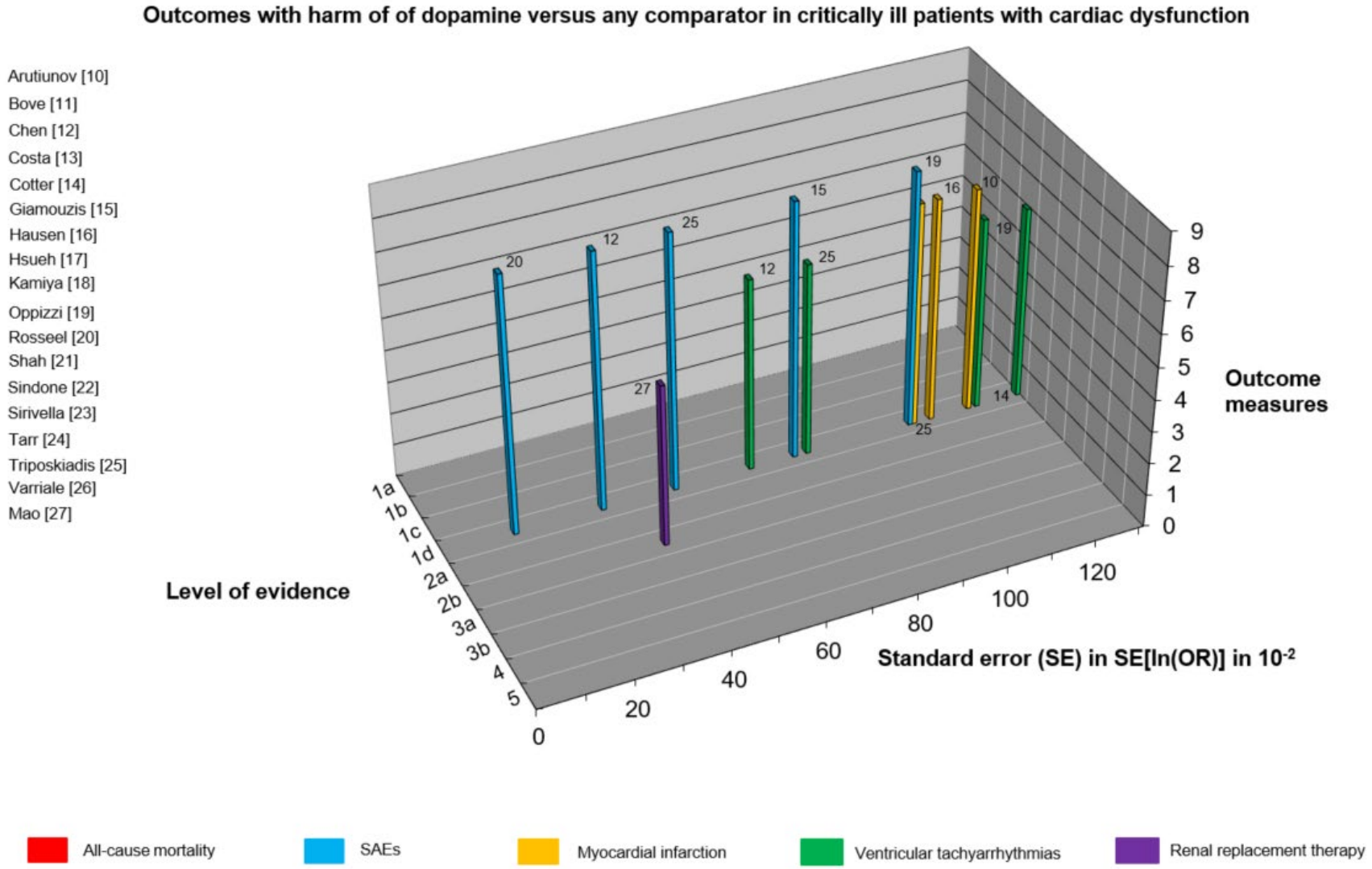
	Studies	Patients	Events	Odds ratio	95% CI
Serious adverse events	1	30	7	1.33	0.36 to 4.97
Myocardial infarction	1	1758	42	0.67	0.36 to 1.26
Ventricular tachyarrhythmias	1	30	7	3.25	0.52 to 20.4
Renal replacement therapy	1	1758	24	2.02	0.86 to 4.74
Atrial tachyarrhythmias	0	-	-	-	-

Abbreviations: CI, confidence interval.

1.16. Manhattan matrix plot with beneficial outcomes



1.17. Manhattan matrix plot with harmful outcomes



1.18. Funnel plots for small trial bias including publication bias

Fig. 1.16.1. Funnel plot of comparison: dopamine versus any (in-)active control for mortality at maximum follow-up

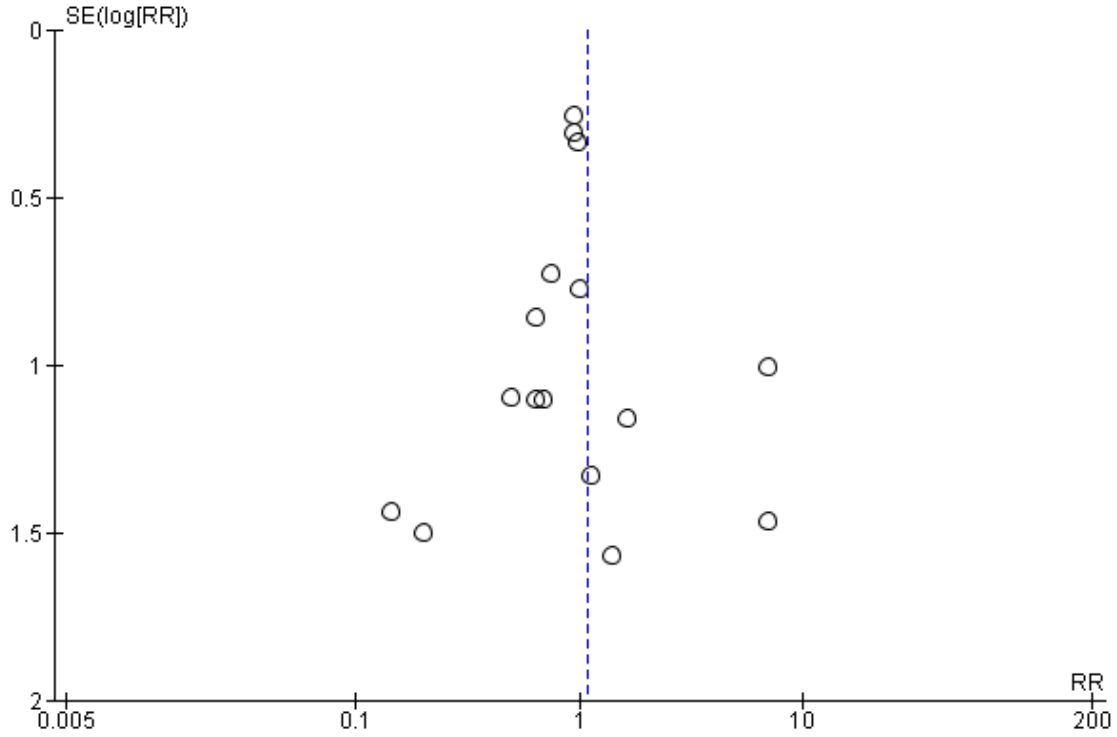


Fig 1.16.2. Funnel plot of comparison: dopamine versus any (in-)active control for SAEs

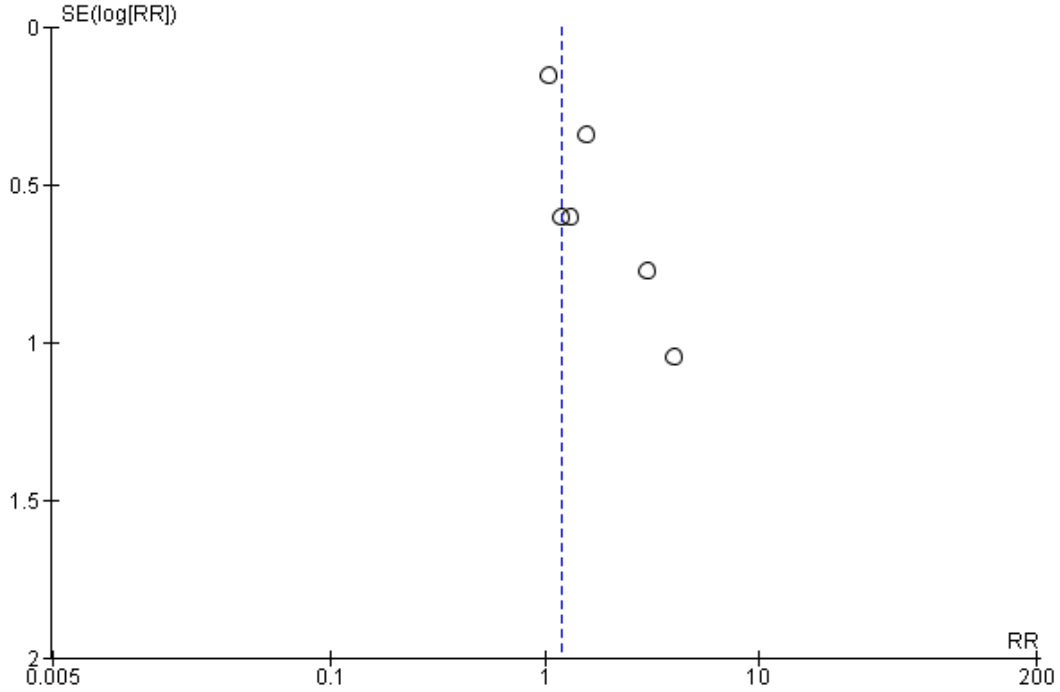


Fig 1.16.3. Funnel plot of comparison: dopamine versus any (in-)active control for myocardial infarction

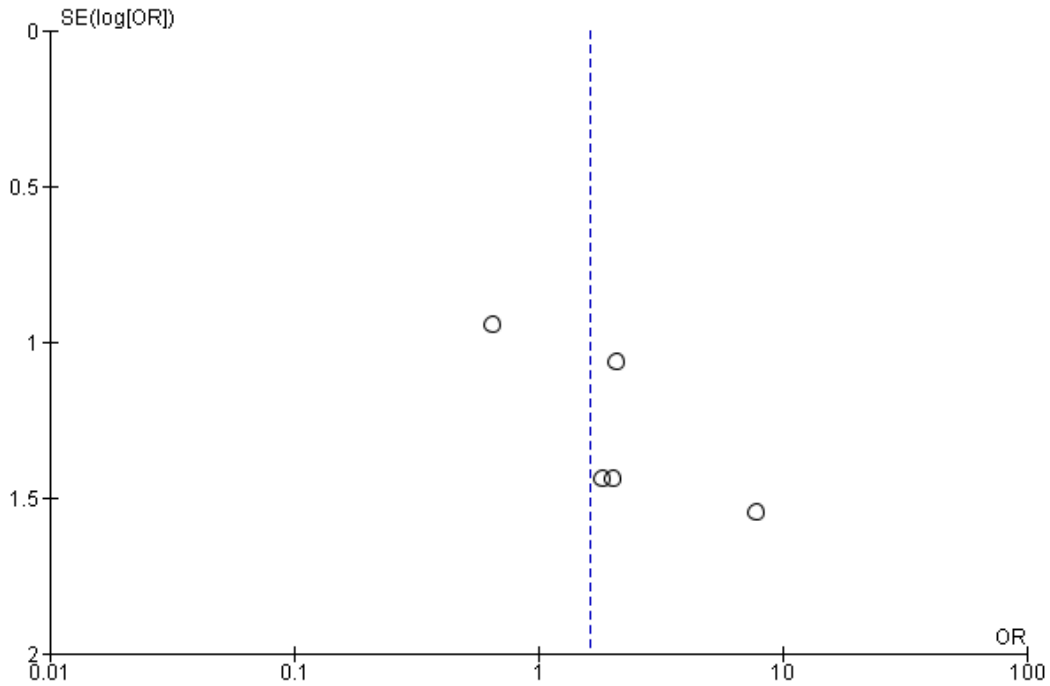


Fig 1.16.4. Funnel plot of comparison: dopamine versus any (in-)active control for ventricular tachyarrhythmias

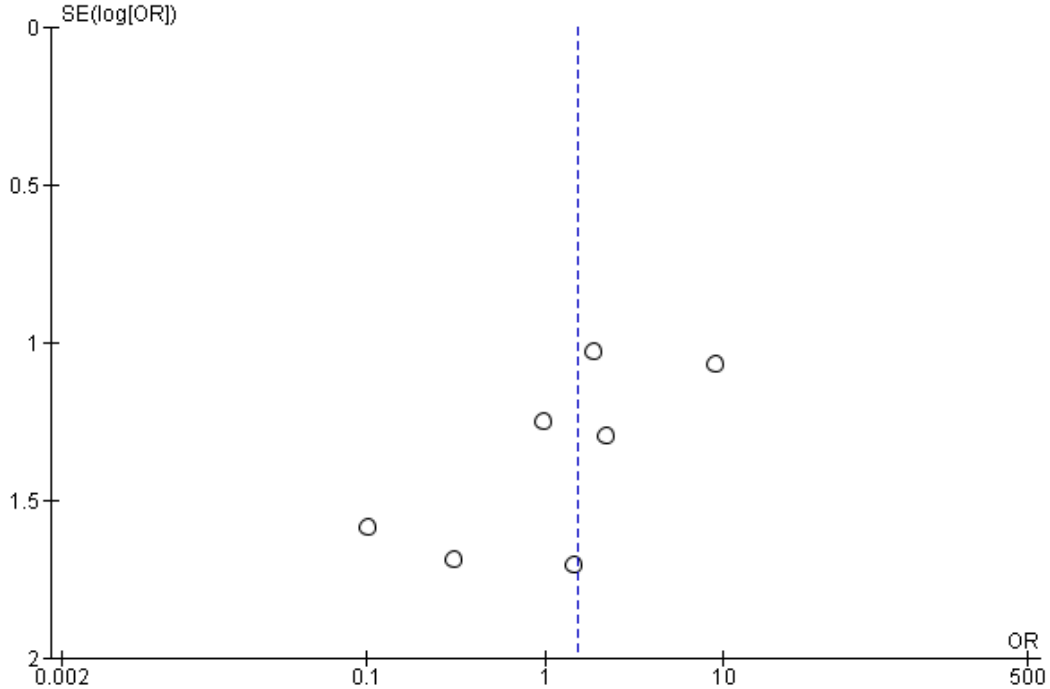


Fig. 1.16.5. Funnel plot of comparison: dopamine versus any (in-)active control for renal replacement therapy

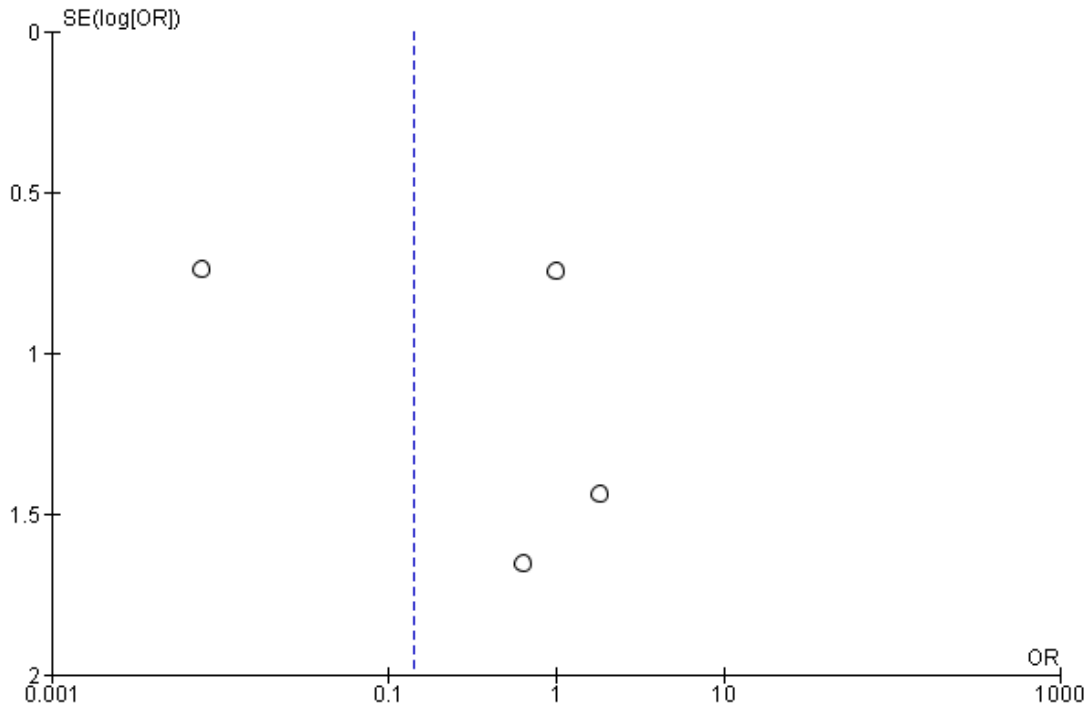
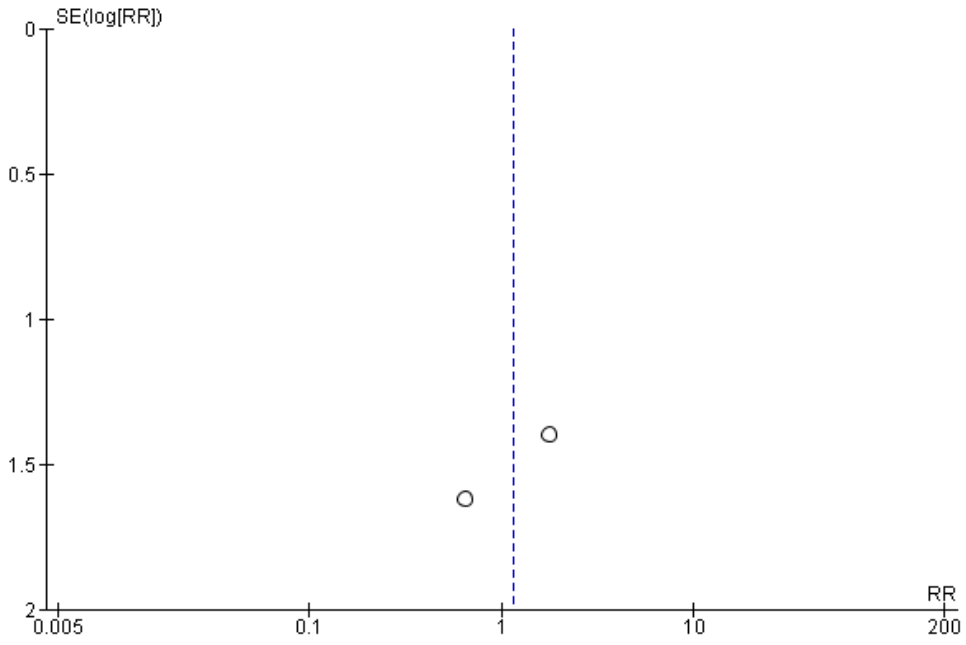


Fig. 1.16.6. Funnel plot of comparison: dopamine versus any (in-)active control for atrial tachyarrhythmias



2. Post-hoc analysis

In this post-hoc selection strategy, we also included trials in which a considerable proportion of patients (in most cases: more than 25%) had cardiac dysfunction or were expected to have cardiac dysfunction based on observational studies. We based this post-hoc strategy on observational studies that show cardiac dysfunction measured by LVEF may be operator dependent and may have considerable inter-observer variability [18-20]. Therefore, excluding trials that only have a small proportion of patients with normal cardiac function might introduce selection bias.

With this selection criterion, we also added trials that did not report on degree of cardiac dysfunction, however, in which a considerable proportion of patients were expected to have cardiac dysfunction based on observational studies. This post-hoc selection strategy included patients undergoing all-cause cardiac [21-24] and vascular surgery [25,26], patients with septic shock [27,28], or patients with liver cirrhosis [29-31], unless these trials specifically excluded patients with cardiac dysfunction.

Data (i.e. RRs or ORs, 95% CIs) is reported in this appendix if substantially different from the main comparison or if demonstrating statistically significant differences.

2.1. E-Table 3: Characteristics of included trials

The post-hoc analysis included an additional 23 trials and 3629 patients [1-5,8,12-14,17,32-53], resulting in 40 trials and 4182 patients (e-Table 2.7). We added ten trials randomising patients with septic shock (9 trials; n = 444) or circulatory shock (1 trial; n = 1679) and all but one administered high-dose dopamine (supplements e-Table 3.1). Only mortality proportions could be analysed with the TSA using our prespecified parameters.

All-cause mortality was reported in 37 of the 40 trials (3971 patients; 1254 events), the occurrence of SAEs in 11 trials (861 patients; 169 events); 11 trials on myocardial infarction (2302 patients; 62 events), 16 trials on ventricular tachyarrhythmias (2416 patients; 68 events), 15 trials on renal replacement therapy (2723 patients; 193 events), and seven trials on atrial tachyarrhythmias (2009 patients; 311 events).

E-Table 2.1: Characteristics of the included trials

Author	Year	N	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
Soliman *et al. [54]*	2017	150	Cardiac surgery	3.0 µg/kg/min	Dexmedetomidine 0.4 µg/kg/min	Primary: none Secondary: adverse events, i.e. 30-day mortality, renal replacement therapy
Kanchi *et al. [53]*	2017	60	Cardiac surgery	2.0 µg/kg/min	Placebo	Primary: none Other: mortality (in-hospital), renal replacement therapy
Gatot *et al.* [36]	2004	89	Cardiac surgery	5.0 µg/kg/min (none needed inotropic support)	Placebo (5% received adrenaline or noradrenaline)	Primary: cardiac and hemodynamic status (of which: arrhythmias, MI)
Carcoana *et al.* [33]	2003	135	Cardiac surgery	2.0 µg/kg/min **(1)** 2.0 µg/kg/min + mannitol 1 g/kg **(2)** ("use of vasoactive drugs did not differ among the four groups")	Placebo **(1)** Mannitol 1 g/kg added to CPB prime **(2)**	Primary: none Secondary: significant clinical events, i.e. mortality (in-hospital), renal replacement therapy
Woo *et al.* [50]	2002	50	Cardiac surgery	3.0 µg/kg/min	Placebo	Primary: none Other: mortality (in-hospital), neurologic complications
Sumeray *et al.* [49]	2001	48	Cardiac surgery	2.5 µg/kg/min	Placebo	Primary: none

Author	Year	N	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
						Secondary: significant clinical events, i.e. mortality (in-hospital), arrhythmias, renal replacement therapy
Lassnigg *et al.* [39]	2000	126	Cardiac surgery	2.0 µg/kg/min (adrenaline for inotropic support; proportion not mentioned)	Placebo **(1)** Furosemide 0.5 µg/kg/min **(2)** (adrenaline for inotropic support; proportion not mentioned)	Primary: none Secondary: mortality (in-hospital), renal replacement therapy
Schneider *et al.* [46]	1999	100	Cardiac surgery	2.0 µg/kg/min + CPB low flow (1.5 L/min/m^2) **(1)** 2.0 µg/kg/min + CPB high flow (2.4 L/min/m^2) **(2)** (22% received noradrenaline)	Placebo + CPB low flow (1.5 L/min/m^2) **(1)** Placebo + CPB high flow (2.4 L/min/m^2) **(2)** (2% received noradrenaline)	Primary: none Other: complications including mortality (in-hospital)
Sharpe *et al.* [47]	1999	30	Cardiac surgery	4.0 µg/kg/min (10% received dobutamine)	Placebo **(1)** (20% received adrenaline; 10% received dobutamine) Dopexamine 1-2 µg/kg/min **(2)** (10% received dobutamine)	Primary: none Other: mortality (in-ICU), MI, arrhythmias
Sinclair *et al.* [48]	1997	30	Cardiac surgery	2.5 µg/kg/min	Dopexamine 2 µg/kg/min	Primary: none Other: mortality (in-hospital), SAE's
Myles *et al.* [44]	1993	52	Cardiac surgery	3.0 µg/kg/min (36% received adrenaline or noradrenaline)	Placebo (42% received adrenaline or noradrenaline)	Primary: none Other: mortality (7 days), renal replacement therapy
Hausen *et al.* [17]	1992	41	Cardiac surgery	5-7 µg/kg/min + glyceroltrinitrate 1 µg/kg/min (57% received adrenaline)	Enoximone 5-20 µg/kg/min **(1)** (62% received adrenalin) Piroximone 3-6 µg/kg/min **(2)** (43% received adrenaline)	Primary: none Other: mortality (mean 6 ± 3 months), MI, arrhythmias
Birnbaum *et al.* [32]	1990	20	Cardiac surgery	3-4 µg/kg/min	Enoximone bolus 2x 0.5 mg/kg, followed by 5 µg/kg/min	Primary: none Other: mortality (peri-operative), MI, arrhythmias, renal replacement therapy
Hua *et al.* [38]	2013	32	Septic shock	Up to 20 µg/kg/min + dobutamine up to 20 µg/kg/min	Terlipressin 1.3 µg/kg/min + dobutamine up to 20 µg/kg/min	Primary: mortality (28 days) Secondary: none
Chen *et al.* [34]	2012	80	Septic shock	Up to 20 µg/kg/min (cointerventions not specified)	Noradrenaline up to 2 µg/kg/min (cointerventions not specified)	Primary: none Other: mortality (In-hospital), cardiogenic adverse events (MI, arrhythmias)

Author	Year	N	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
Zhuangyu *et al.* [51]	2011	90	Septic shock	1-15 µg/kg/min (cointerventions not specified)	Noradrenaline 0.05-0.5 µg/kg/min (cointerventions not specified)	Primary: none Other: mortality (In-hospital)
De Backer *et al.* [35]	2010	1679	Circulatory shock	Up to 20 µg/kg/min (18% received open-label noradrenaline; 1.5% adrenaline; 15% dobutamine)	Noradrenaline up to 0.19 µg/kg/min (13% received open-label noradrenaline; 1.1% adrenaline; 19% dobutamine)	Primary: mortality (28 days) Secondary: mortality (in-ICU, in-hospital, 28 days, 6 months, 12 months). Other: adverse events, i.e. arrhythmia, MI, skin necrosis, ischemia in limbs or distal extremities, or secondary infections
Liu *et al.* [40]	2010	50	Septic shock	1.0-45 µg/kg/min (cointerventions not specified)	Noradrenaline 0.05-0.5 µg/kg/min (cointerventions not specified)	Primary: none Other: mortality (28 days)
Gao *et al.* [37]	2008	44	Septic shock	≥2 µg/kg/min (cointerventions not specified)	Noradrenaline ≥0.1 µg/kg/min (cointerventions not specified)	Primary: none Other: mortality (in-hospital)
Mathur *et al.* [43]	2007	50	Septic shock	10-25 µg/kg/min	Noradrenaline 0.5-2.5 µg/kg/min	Primary: none Other: mortality (in-hospital)
Schmoelz *et al.* [45]	2006	64	Septic shock	3 µg/kg/min + noradrenalin at least 0.05 µg/kg/5.18min	Placebo + noradrenaline at least 0.05 µg/kg/min **(1)** Dopexamine 2 µg/kg/min + noradrenaline at least 0.05 µg/kg/min **(2)**	Primary: none Other: mortality (28 days), renal replacement therapy
Marik *et al.* [41]	1994	20	Septic shock	26 ± 3.8 µg/kg/min	Noradrenaline 0.18 ± 0.06 µg/kg/min	Primary: none Other: mortality (in-hospital)
Martin *et al.* [42]	1993	32	Septic shock	2.5-25 µg/kg/min (69% crossed over; 6% received adrenaline)	Noradrenaline 0.5-5.0 µg/kg/min (6% crossed over and received adrenaline)	Primary: none Other: mortality (in-hospital)

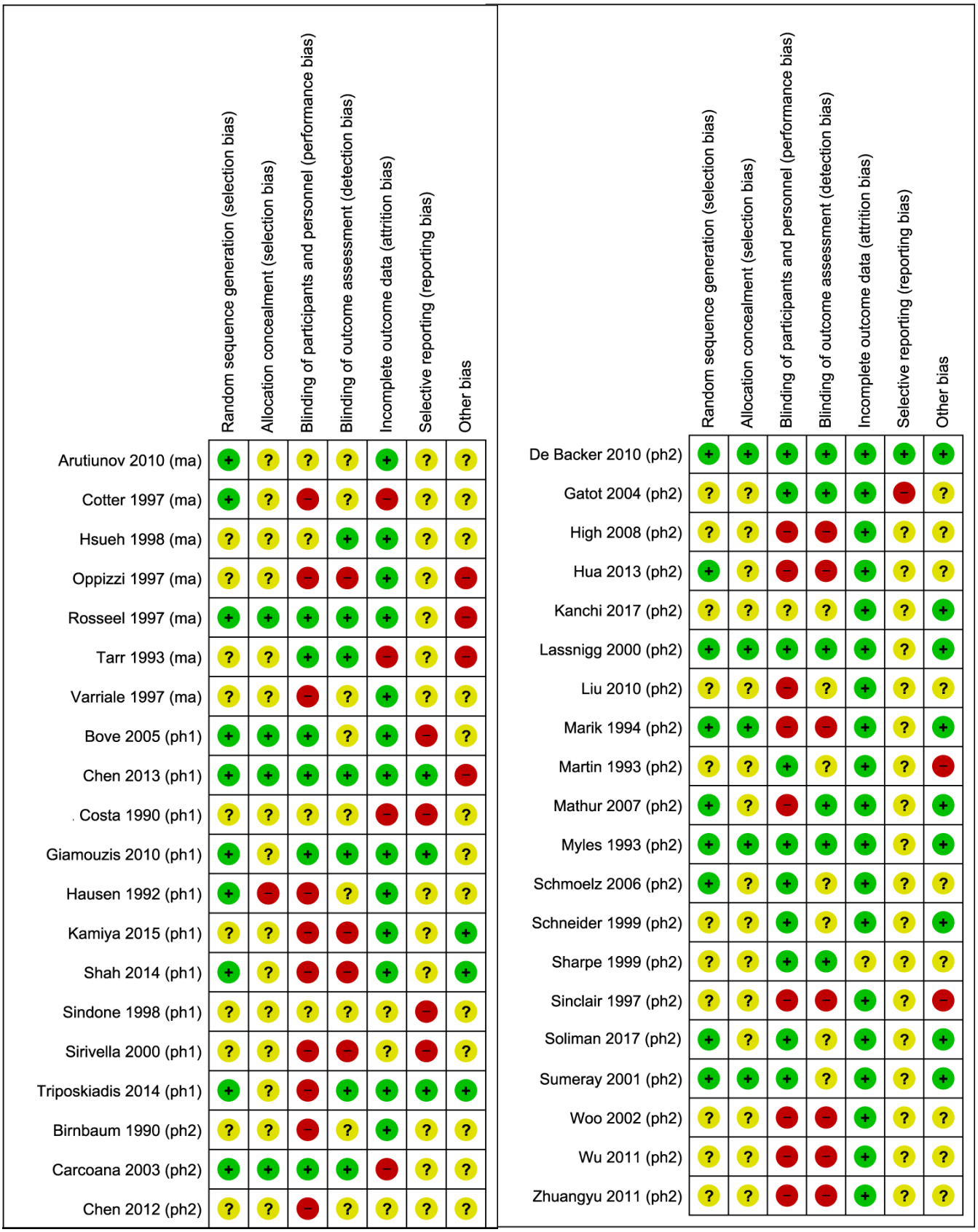
* The timing of starting the experimental administration differed between these two treatment arms. Abbreviations: AHF, acute heart failure; CHF, chronic heart failure; kg, kilograms; mg, milligrams; µg, micrograms; h, hours; min, minute; dd, die de/daily dose; SAEs, serious adverse events; MI, myocardial infarction; ICU, intensive care unit.

2.2. Risk of bias

Risk of bias description of the included trials

All but one of the 40 trials were at overall high risk of bias (appendix e-Figure 3.2). Random sequence generation was at high risk of bias in 21 of the trials (53%). Allocation concealment was at high risk of bias in 31 of the trials (78%). Twenty-four trials (60%) did not blind their participants and/or personnel, and 26 trials (68%) used unblinded outcome assessors. Eight trials (20%) provided incomplete outcome data. Thirty-six trials (90%) were at high risk of bias for selective outcome reporting. High risk of other bias was present in 28 trials (70%), either because they did not provide a statement on conflicts of interest or financial disclosures (n = 22), had a cross-over design with possible carry-over effect (n = 3), or had vested interests (n = 3).

E-Figure 3.2: risk of bias graph of the included trials



2.3. All-cause mortality

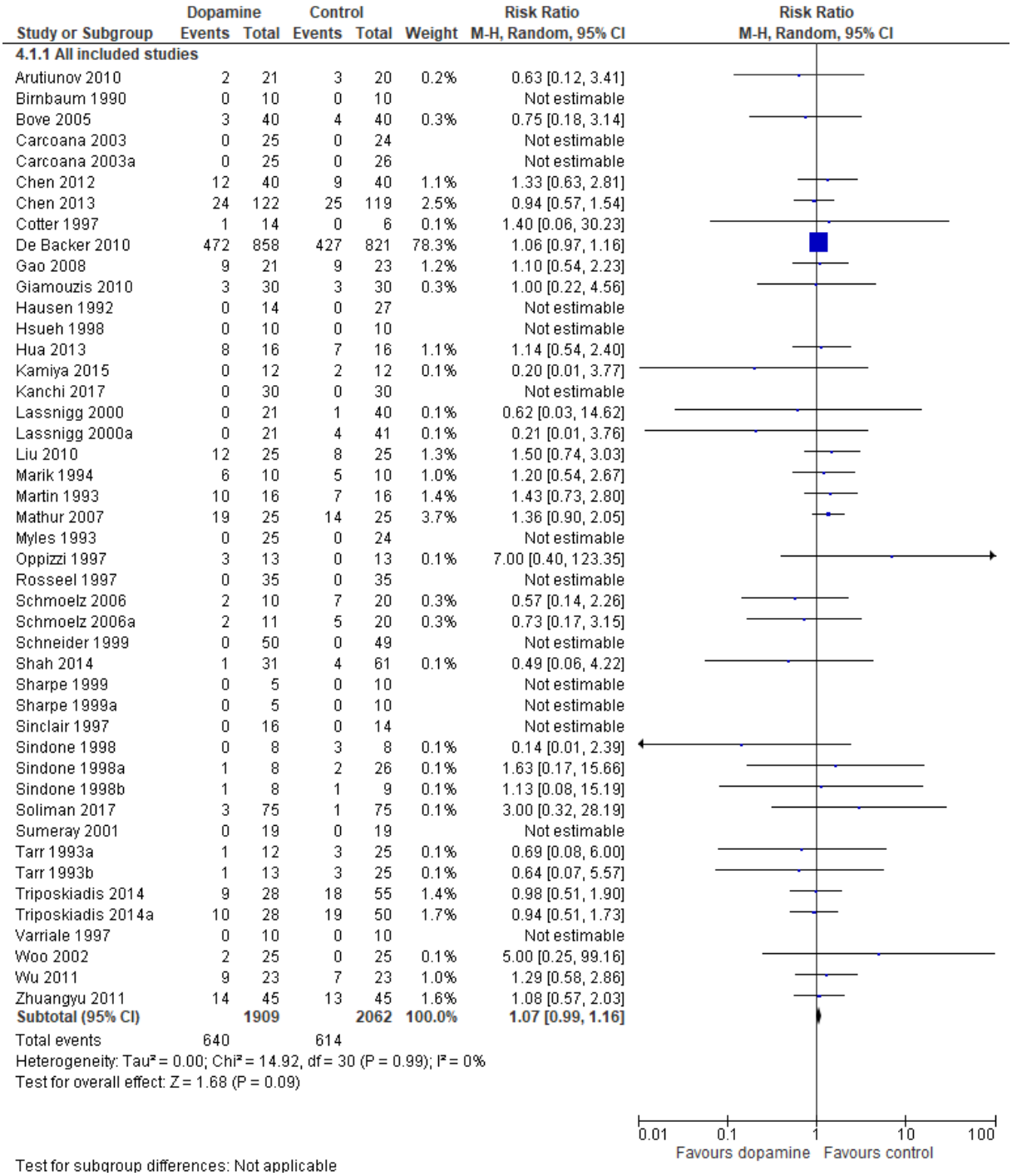
When compared with any control, dopamine was not significantly associated with mortality (e-Table 2). Dopamine seemed inferior on mortality proportion when compared with a potentially active control intervention (e-Figure 4). This effect did not seem to depend on dose or clinical setting, as the tests for interactions were not statistically significant (supplements 3.4). TSA on all 37 trials showed that it is unlikely to reach a beneficial effect of dopamine with further trials, because the cumulative Z-curve would have to cross the futility area (e-Figure 5). The excess mortality was largely attribue-Table to the trials that administered high-dose dopamine; these ten trials accounted for 87% of weight in the entire analysis (supplements e-Figure 3.4.1). All but one of these trials compared dopamine with noradrenaline and two trials allowed other cardioactive co-interventions with dobutamine or open-label noradrenaline (1743 patients; weight 80%; supplements e-Table 3.1). There was a discrepancy between the meta-analysed RR and RD: we observed an RD of 0.0 for dopamine versus a potentially active, inactive or any control intervention (supplements 3.4), whereas the RR's showed a potential harmful effect of dopamine (e-Table 2).

2.4. Other outcomes

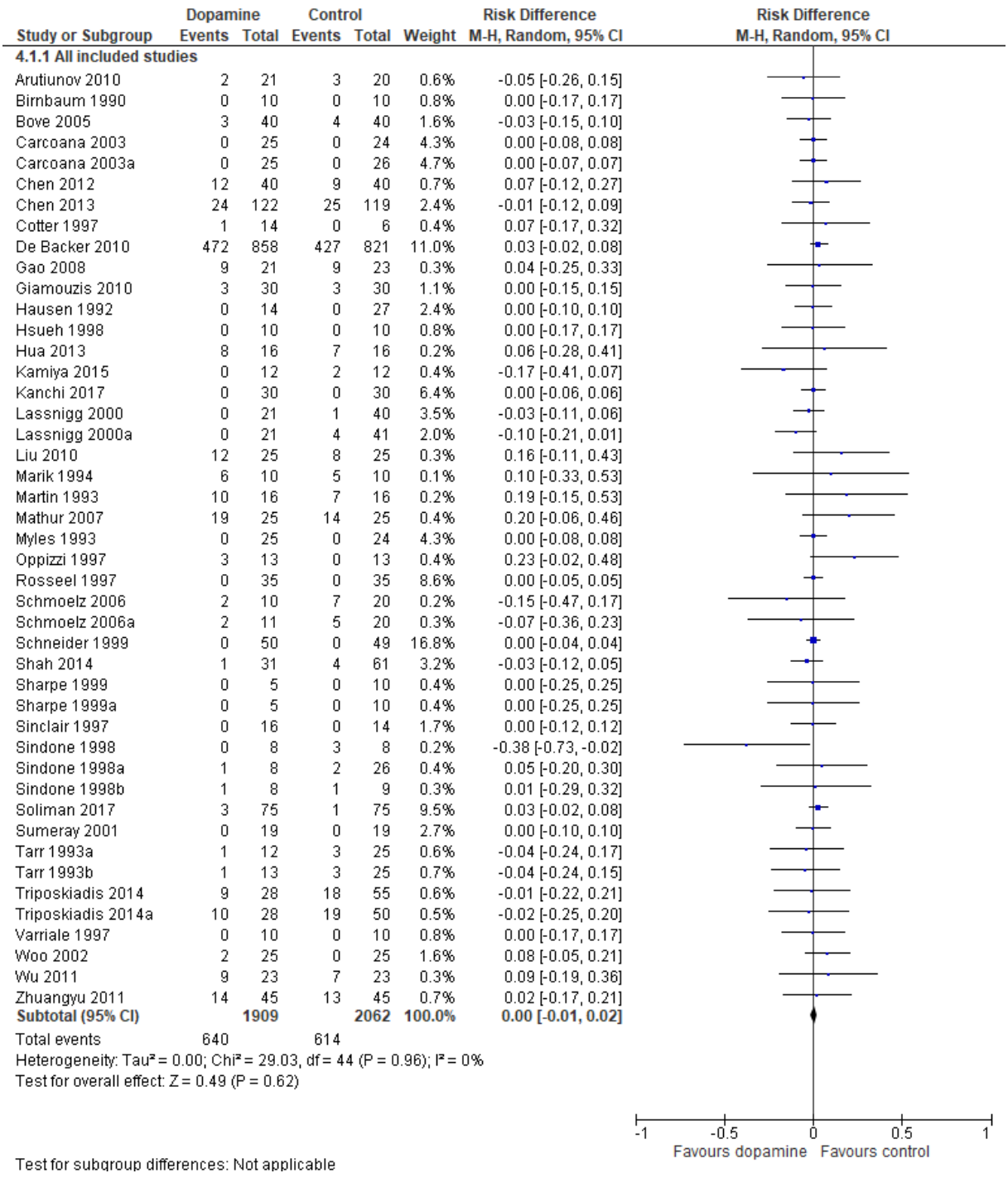
When compared with any control intervention, dopamine was associated with an increased proportion of SAEs and ventricular or atrial tachyarrhythmias (e-Table 2). The increased occurrence of atrial tachyarrhythmias were only confined to trials that compared dopamine with any potentially active control, as the tests of interaction was significant (p = 0.001) when compared to placebo or no intervention (e-Table 2). Again, these increased event proportions were largely attribue-Table to trials that administered high-dose dopamine, which accounted for 64% of the weight for all ventricular, and 44% of the weight for all atrial tachyarrhythmias occurrences (supplements 3.9 and 3.11).

2.5. Forest plots of mortality

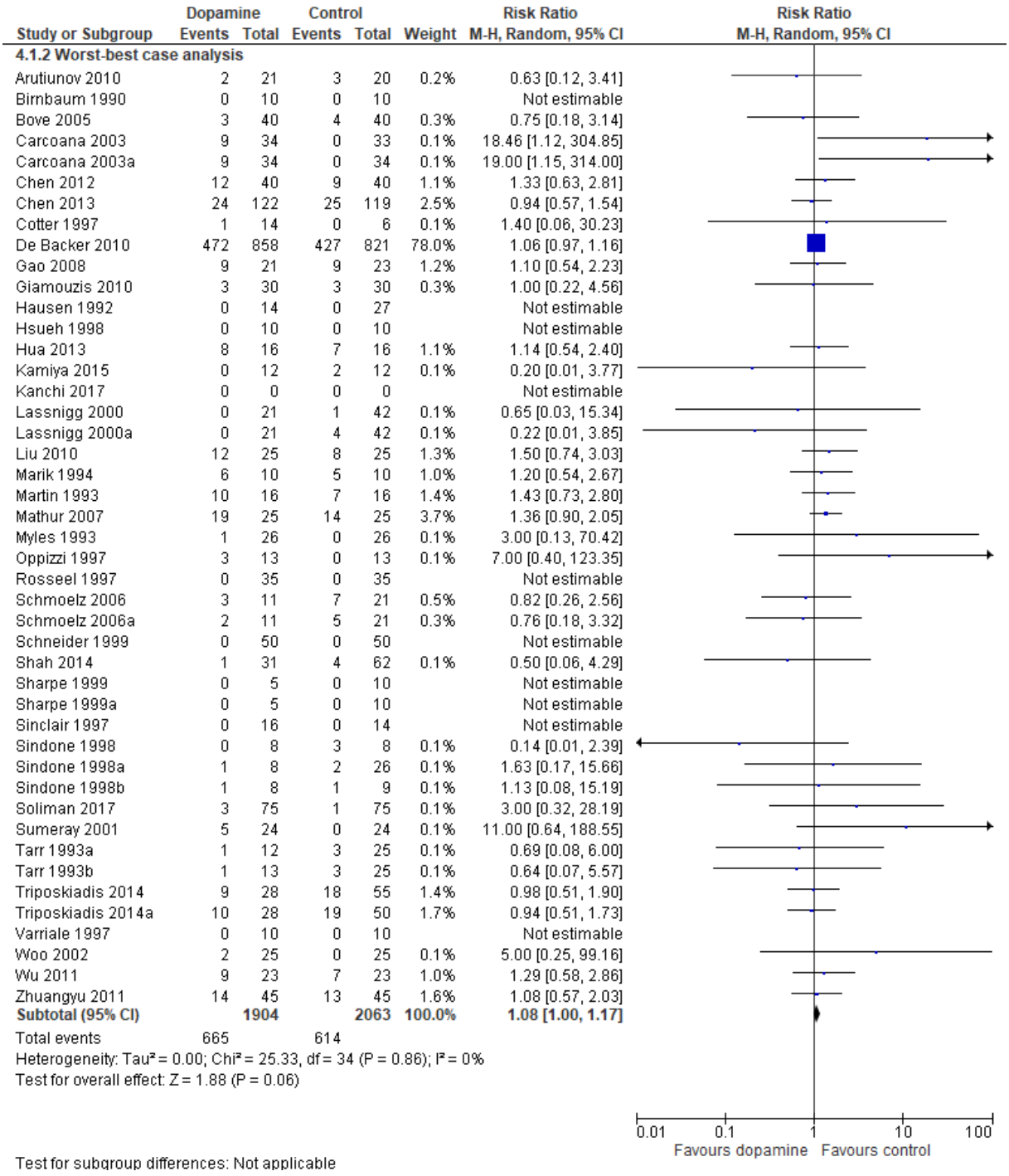
E-Figures 2.5.1a: all trials with relative risk



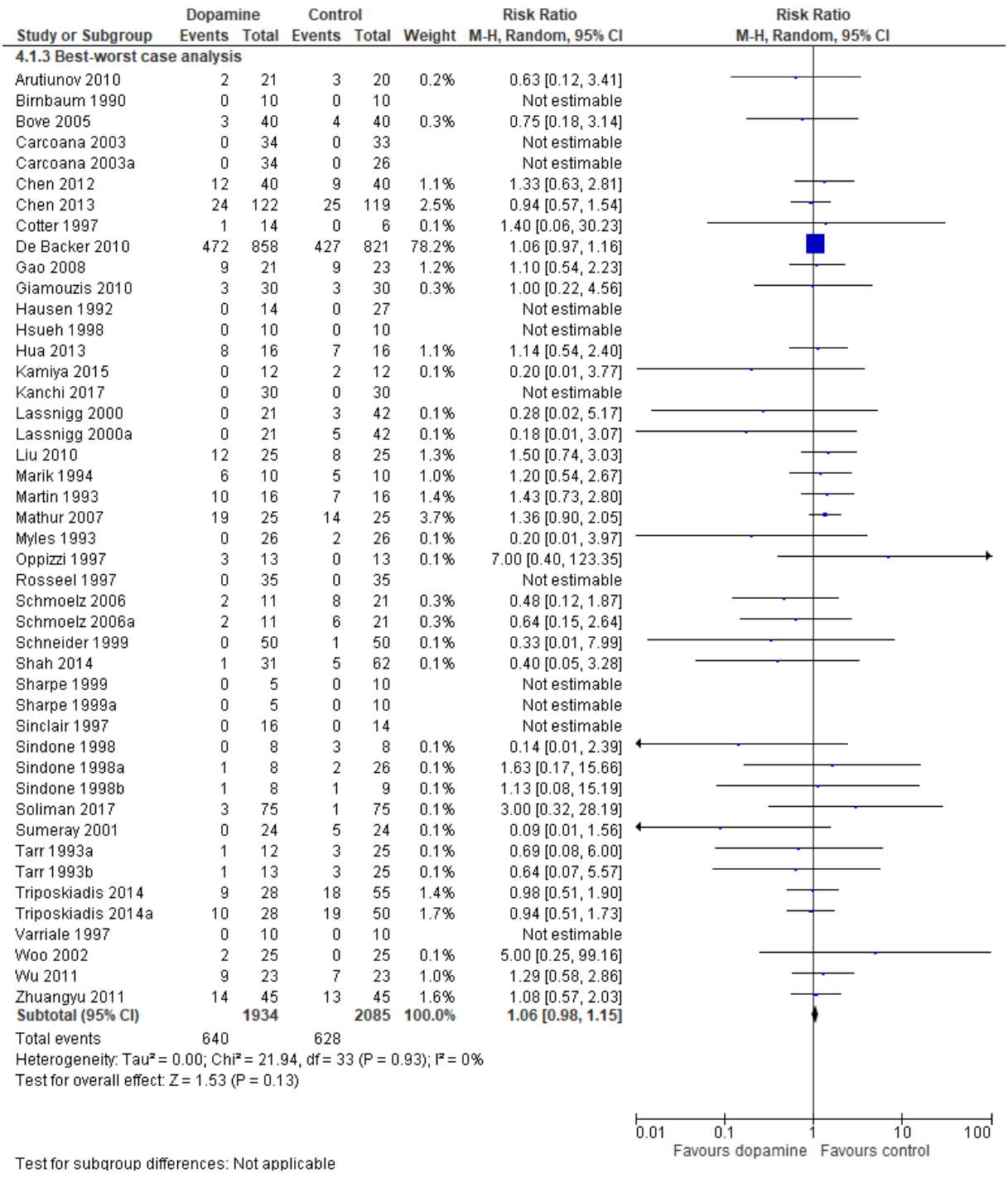
E-Figures 2.5.1b: all trials with risk differences



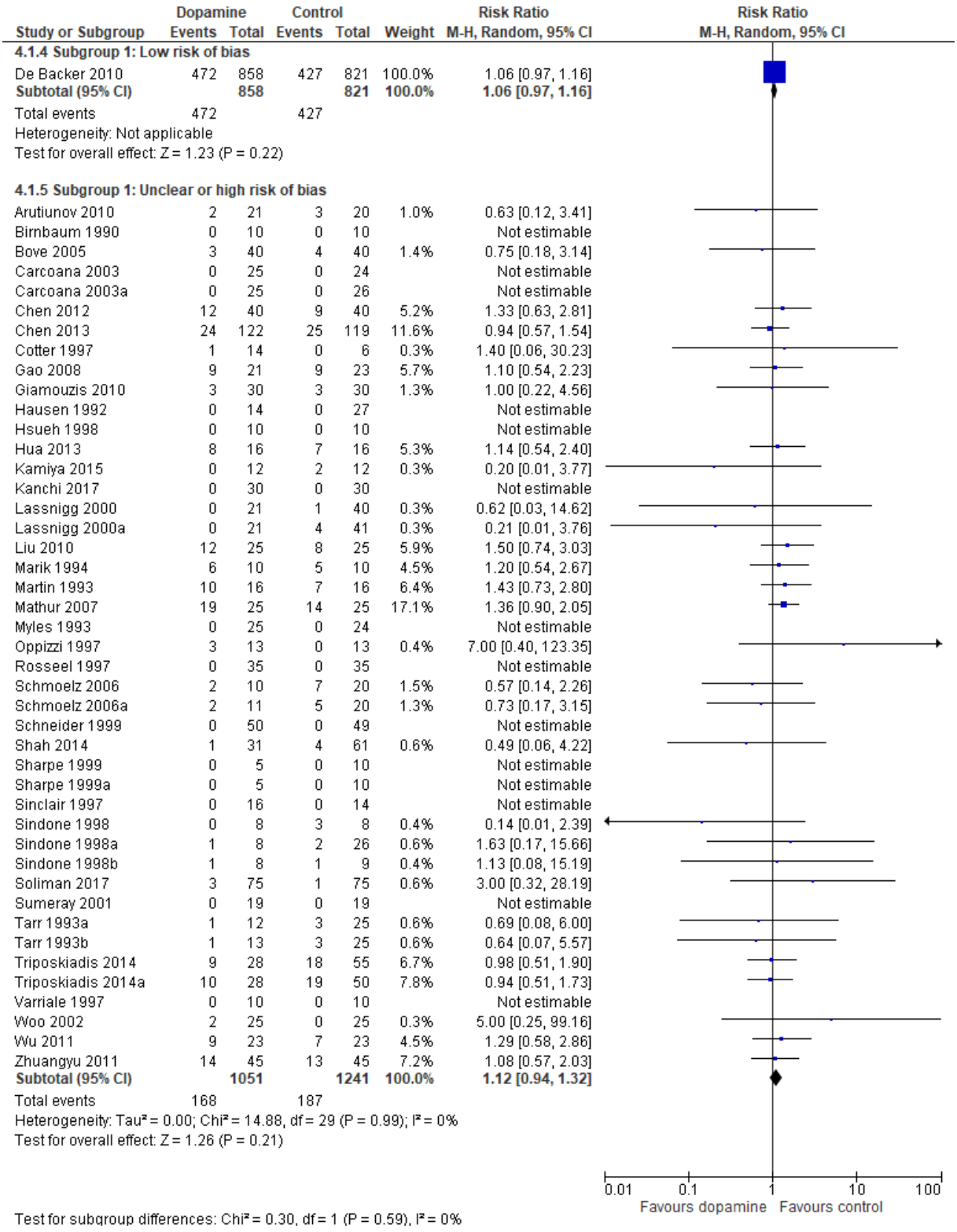
E-Figure 2.5.2: worst-best case analysis



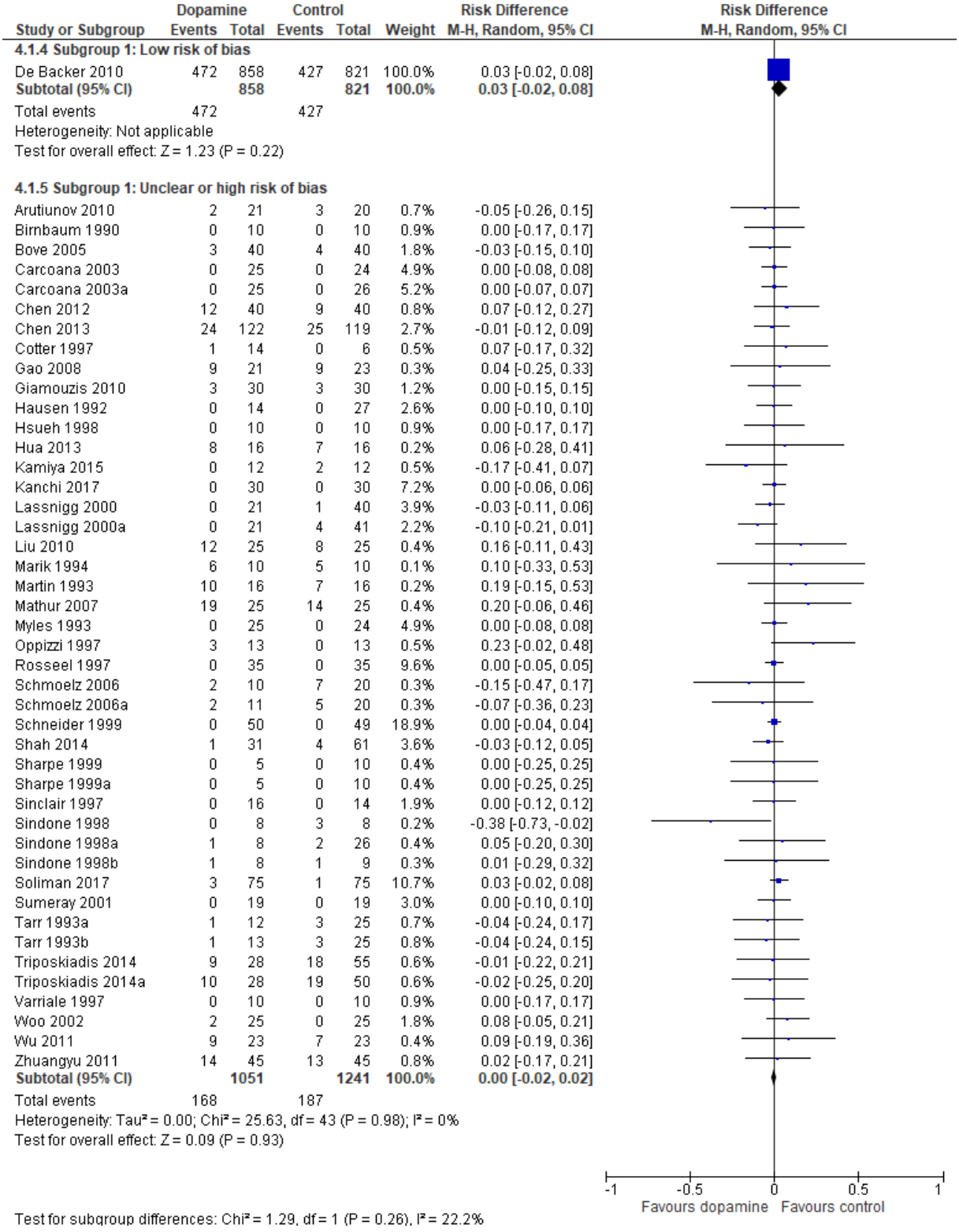
E-Figure 2.5.3: best-worst case analysis



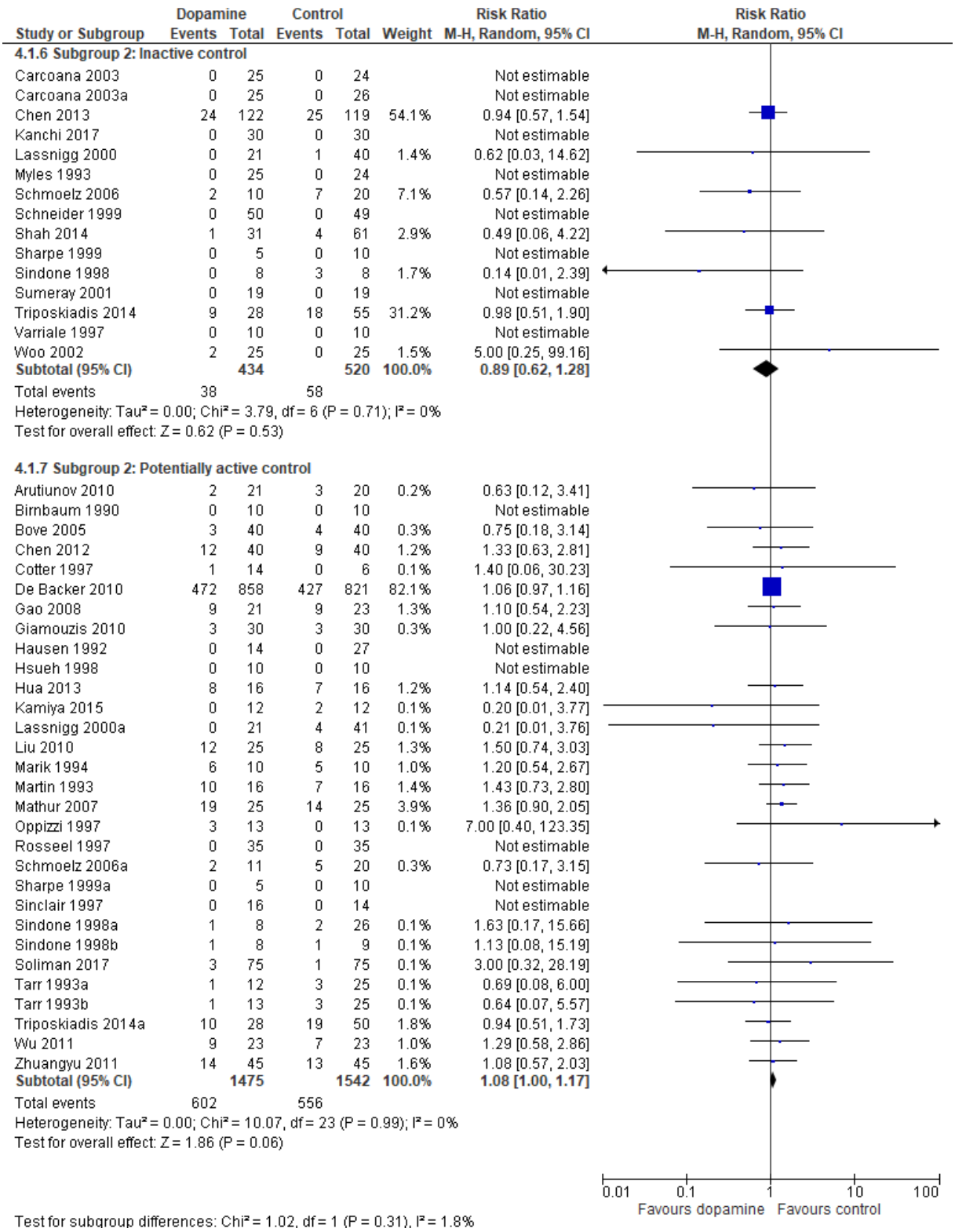
E-Figures 2.5.4-2.5.5: subgroup analysis 1 - trials subdivided by risk of bias



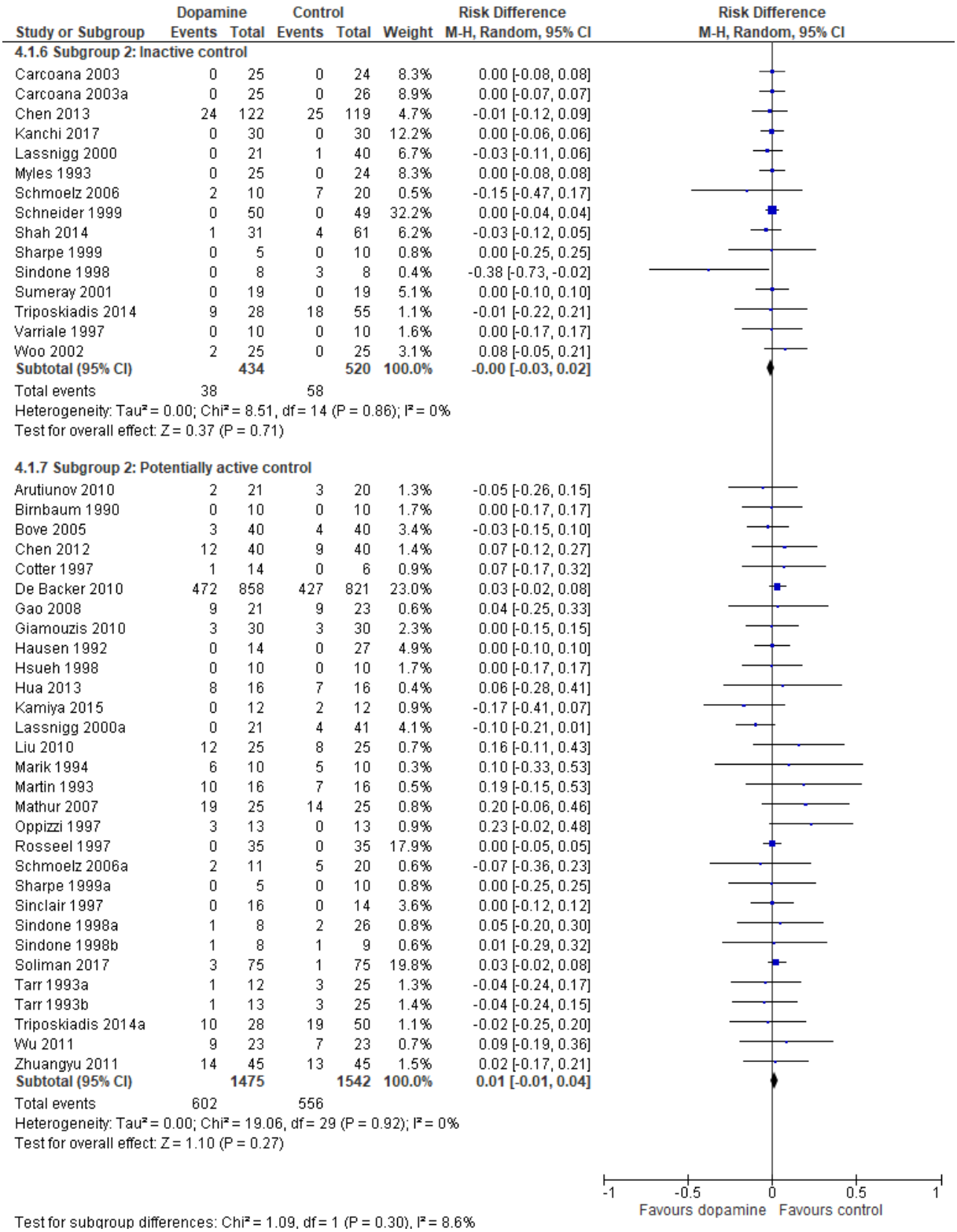
E-Figures 2.5.4-2.5.5: risk differences



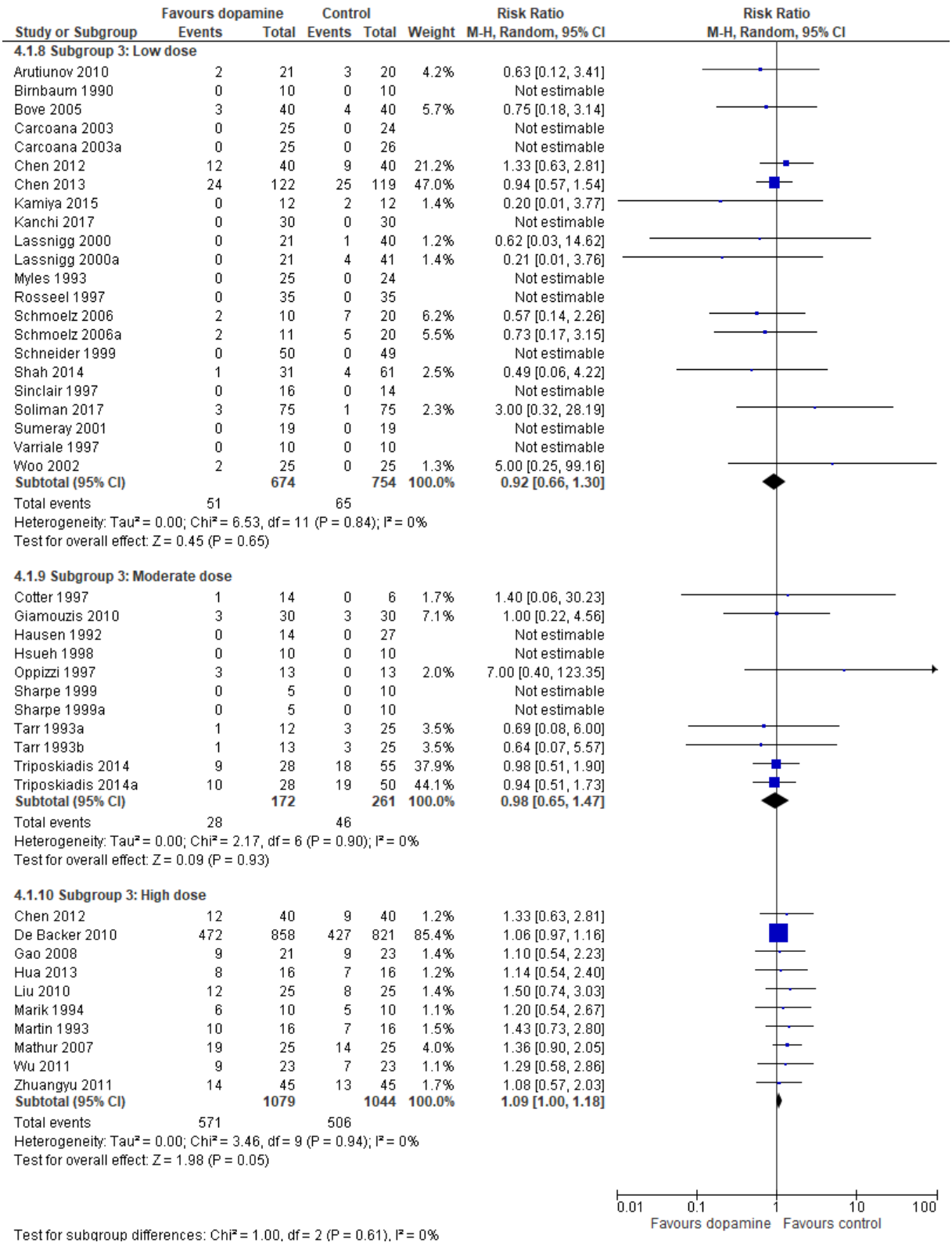
E-Figures 2.5.6-2.5.7: subgroup analysis 2 – trials subdivided by comparator intervention



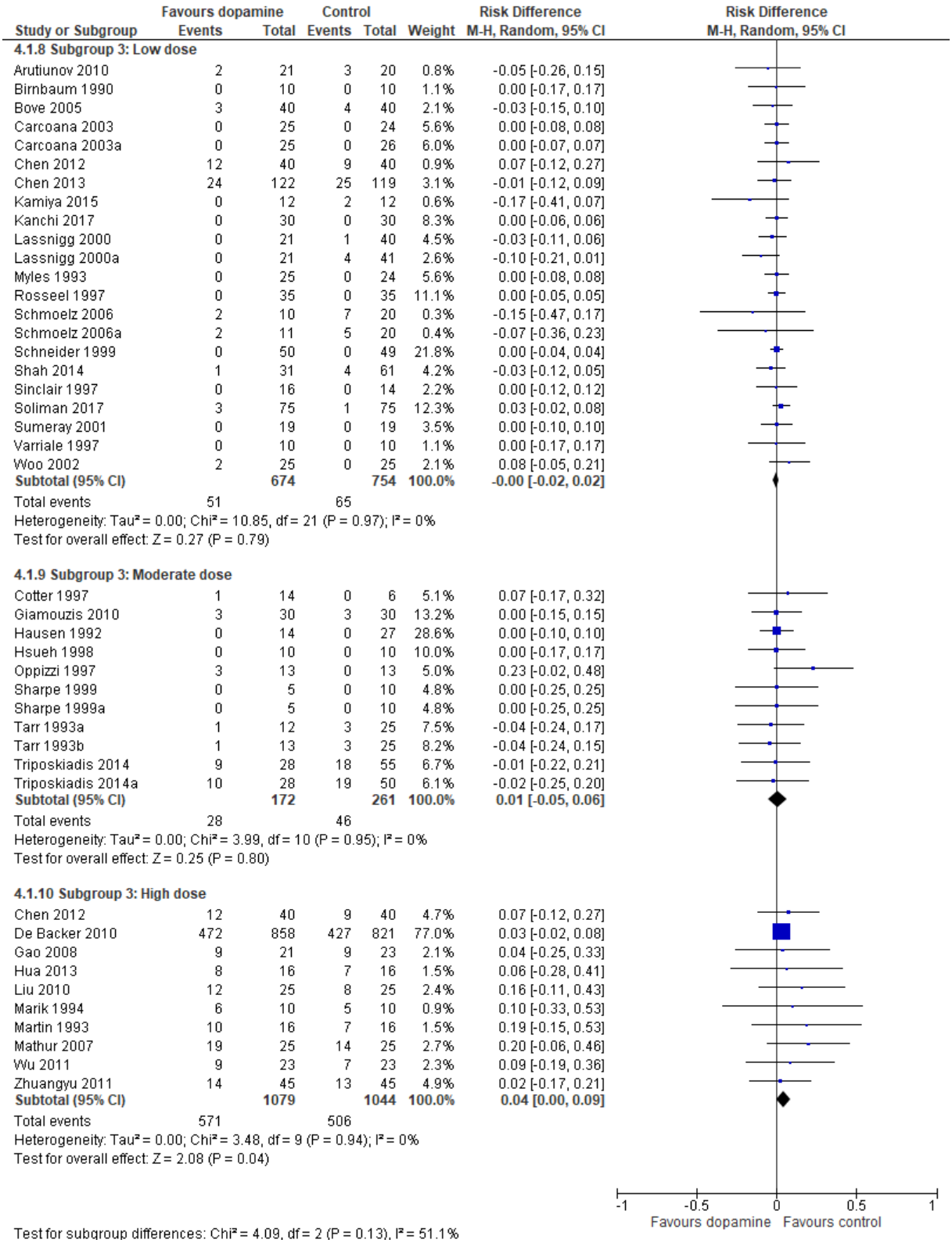
E-Figures 2.5.6-2.5.7: risk differences



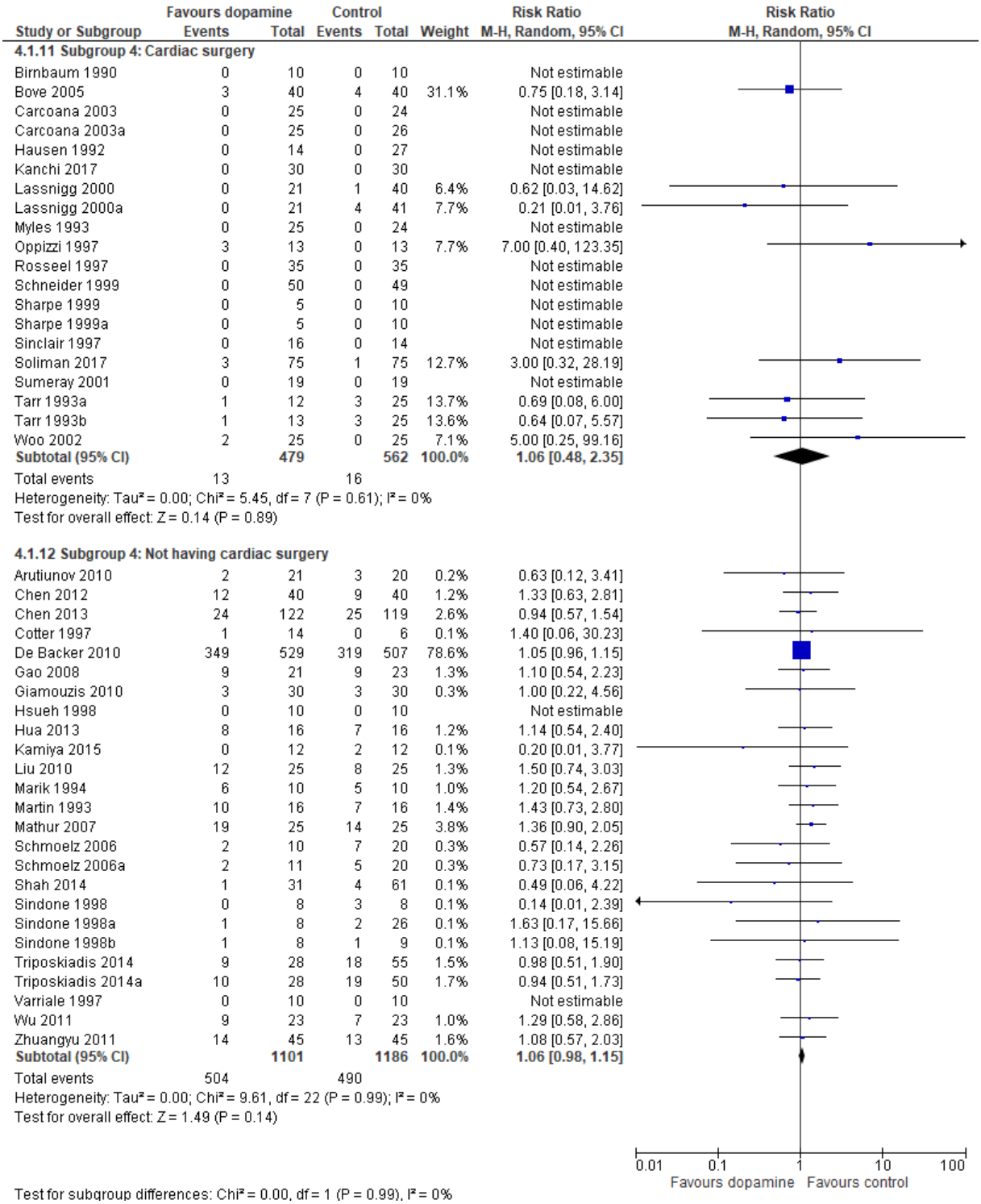
E-Figures 2.5.8-2.5.10: subgroup analysis 3 – trials subdivided by dose



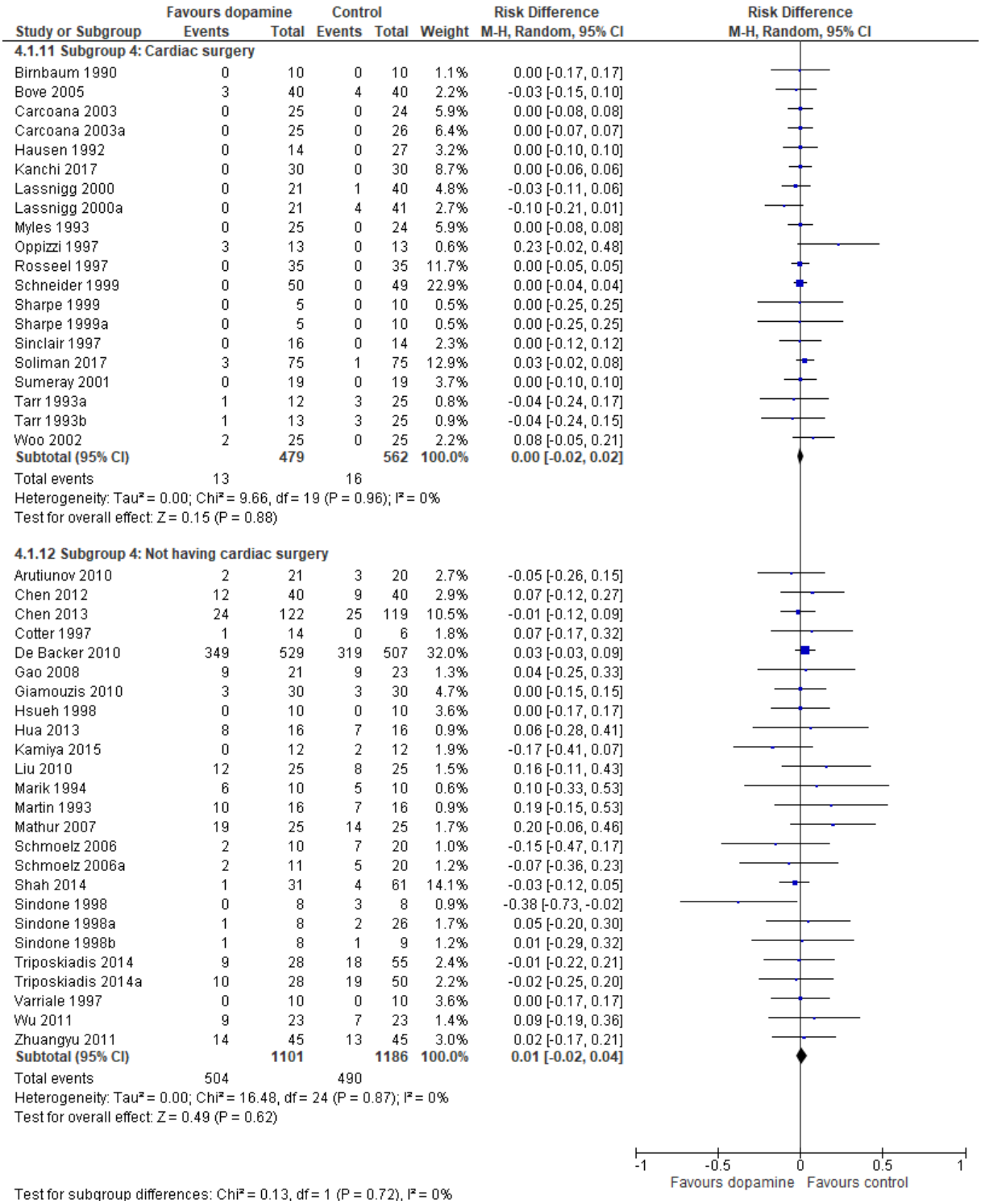
E-Figures 2.5.8-2.5.10: risk differences



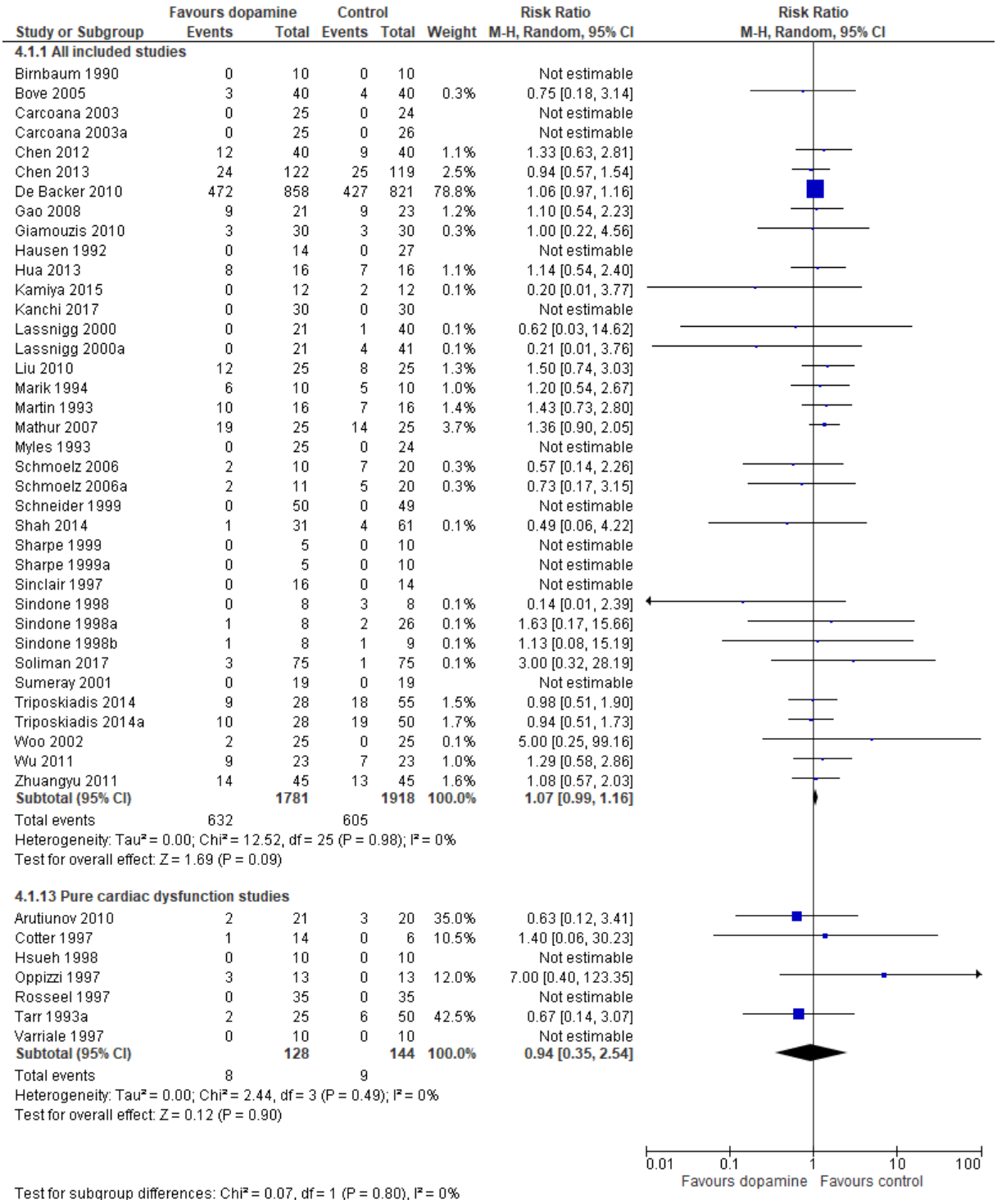
E-Figures 2.5.11-2.5.12: subgroup analysis 4 – trials subdivided by clinical setting



E-Figures 2.5.11-2.5.12: risk differences

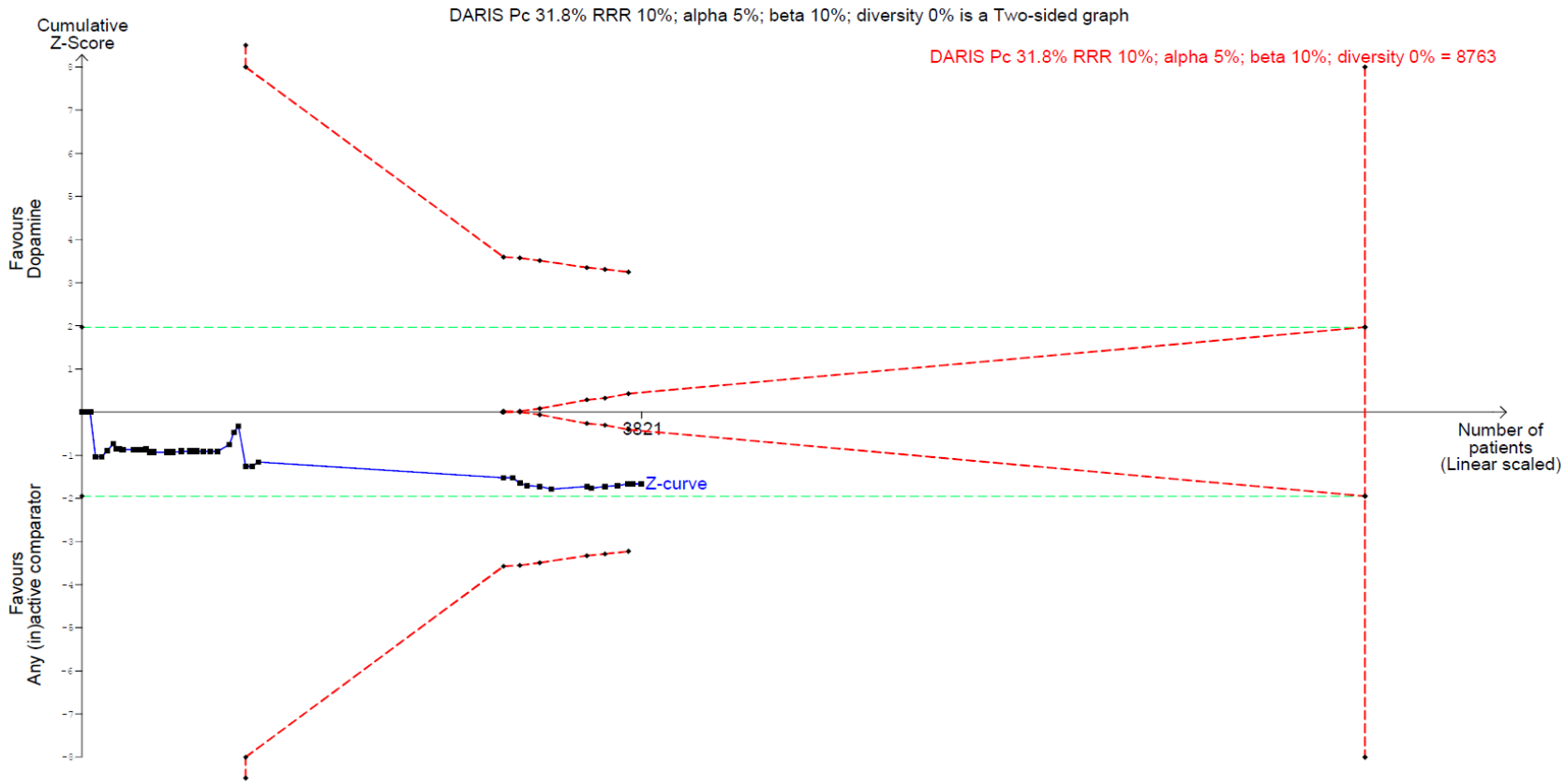


E-Figures 2.5.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction



2.6. Trial sequential analysis of mortality

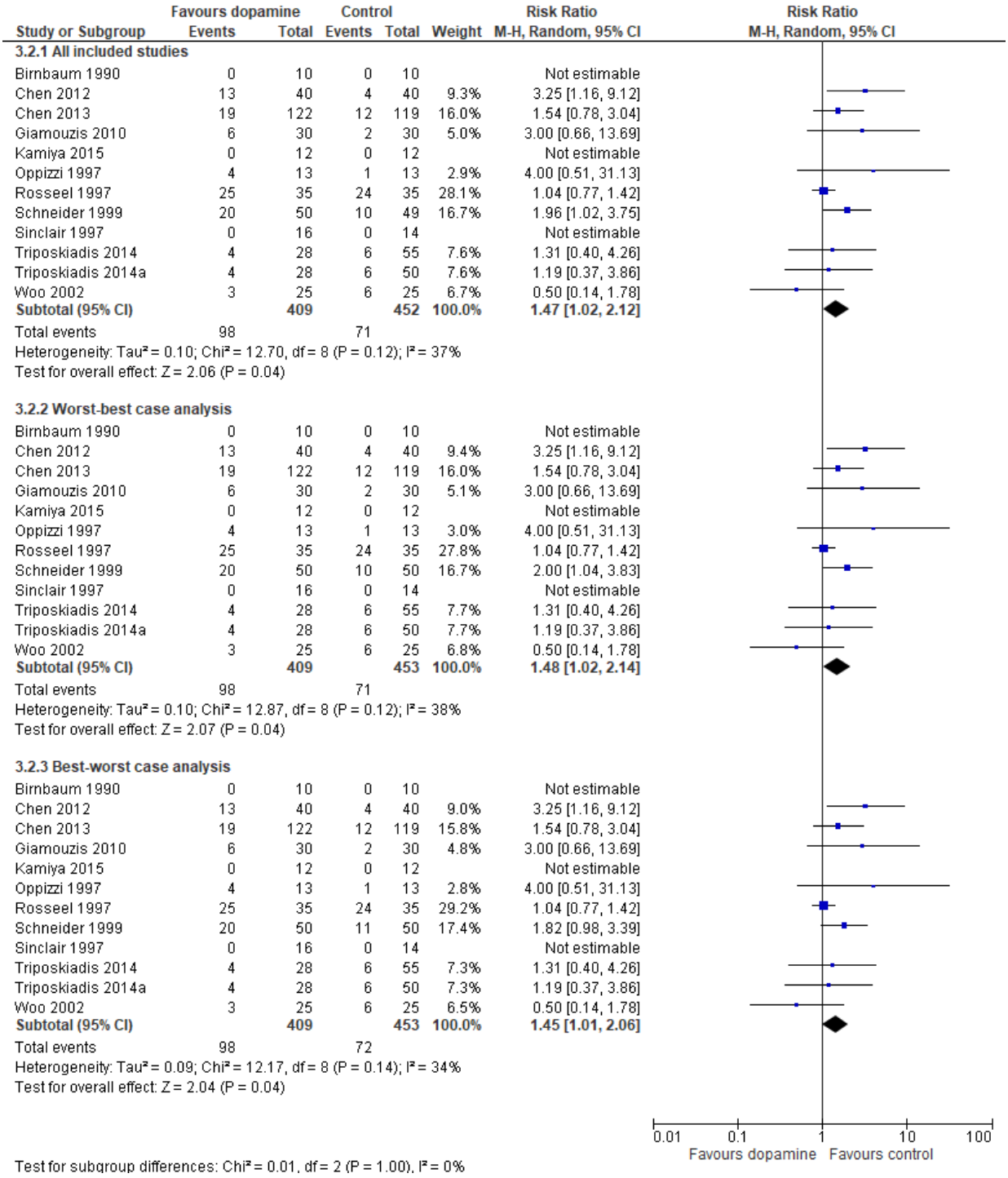
E-Figure 2.6: the TSA is based on 11 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.



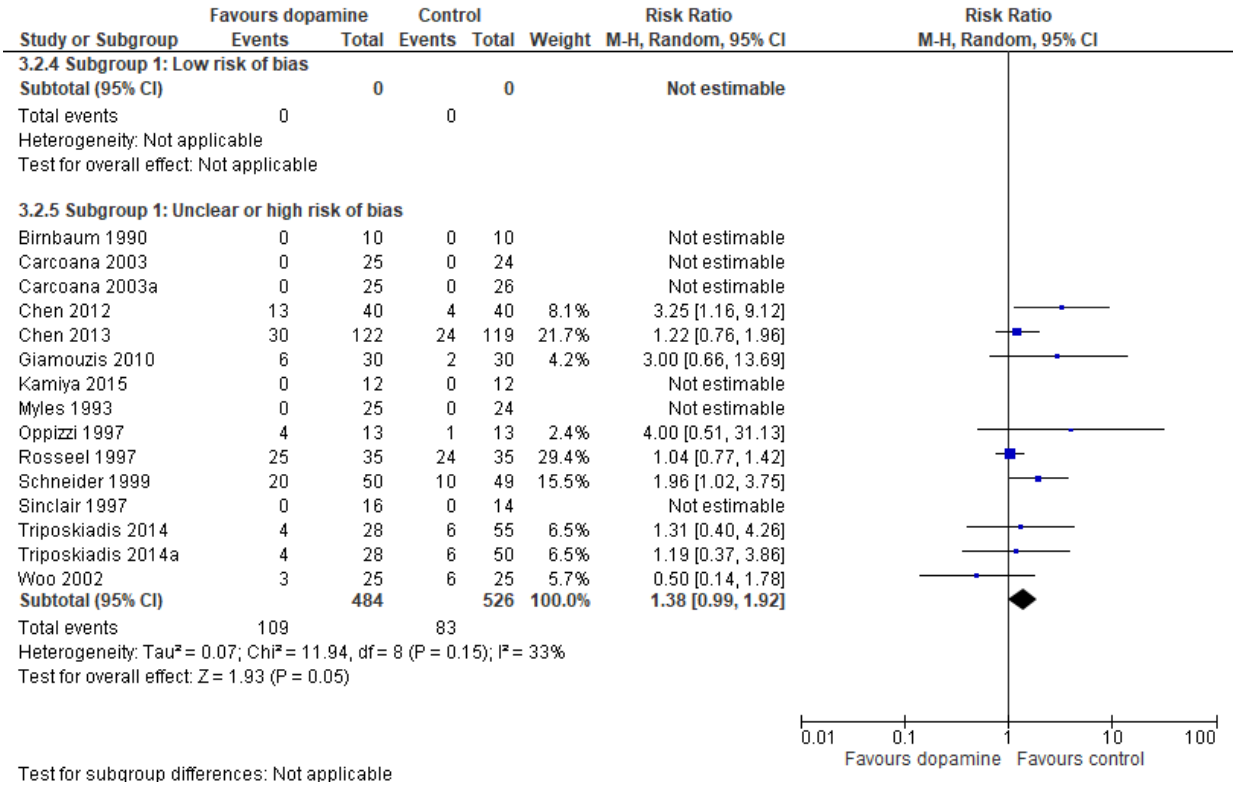
E-Figure legend. A diversity-adjusted required information size (RIS) of 8,763 patients was calculated using the predefined α = 0.05 (two-sided), β = 0.10 (power 90%), D^2 = 0%, an anticipated relative risk reduction of 10% and an event proportion of 31.8% in the control arm. The *blue cumulative z-curve* was constructed using a random effects model. The *horizontal green dotted lines* represent the conventional boundary's for benefit (positive) or harm (negative). The *horizontal red dotted lines* represent the trial sequential boundary's for benefit (positive), harm (negative) or futility (middle triangular area).

2.7. Forest plots of serious adverse events

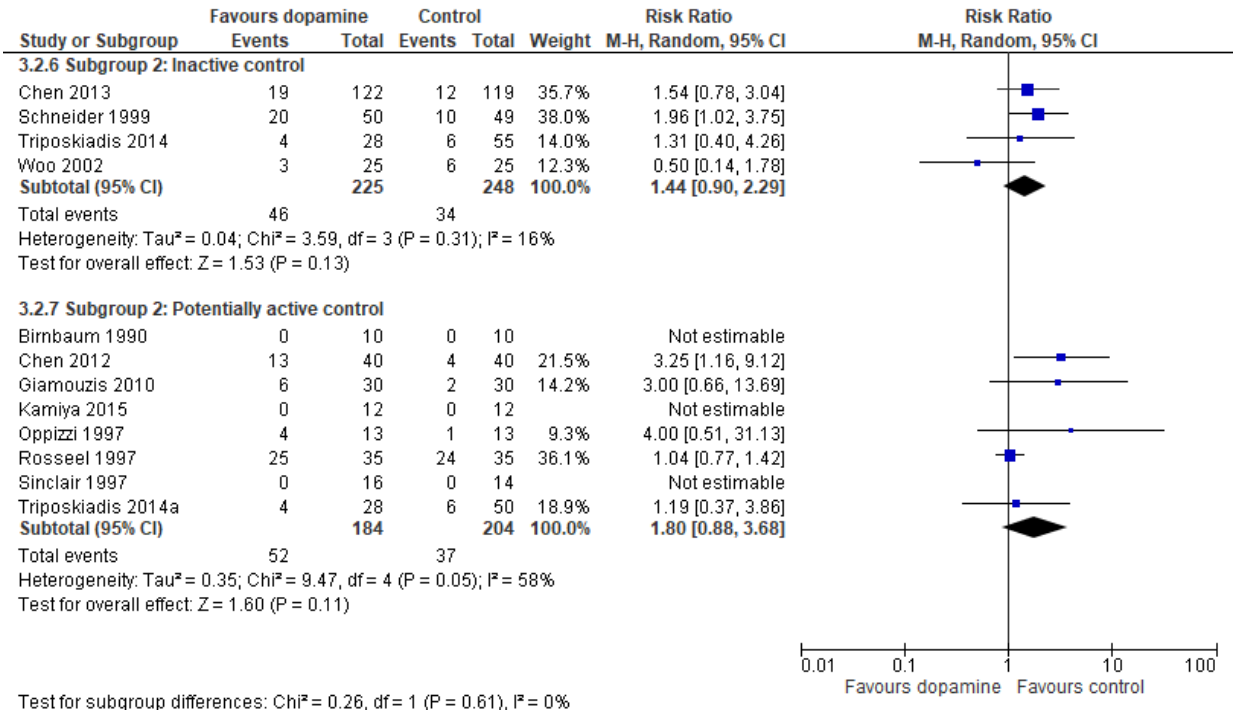
E-Figures 2.7.1-2.7.3: all trials with worst-best and best-worst case analyses



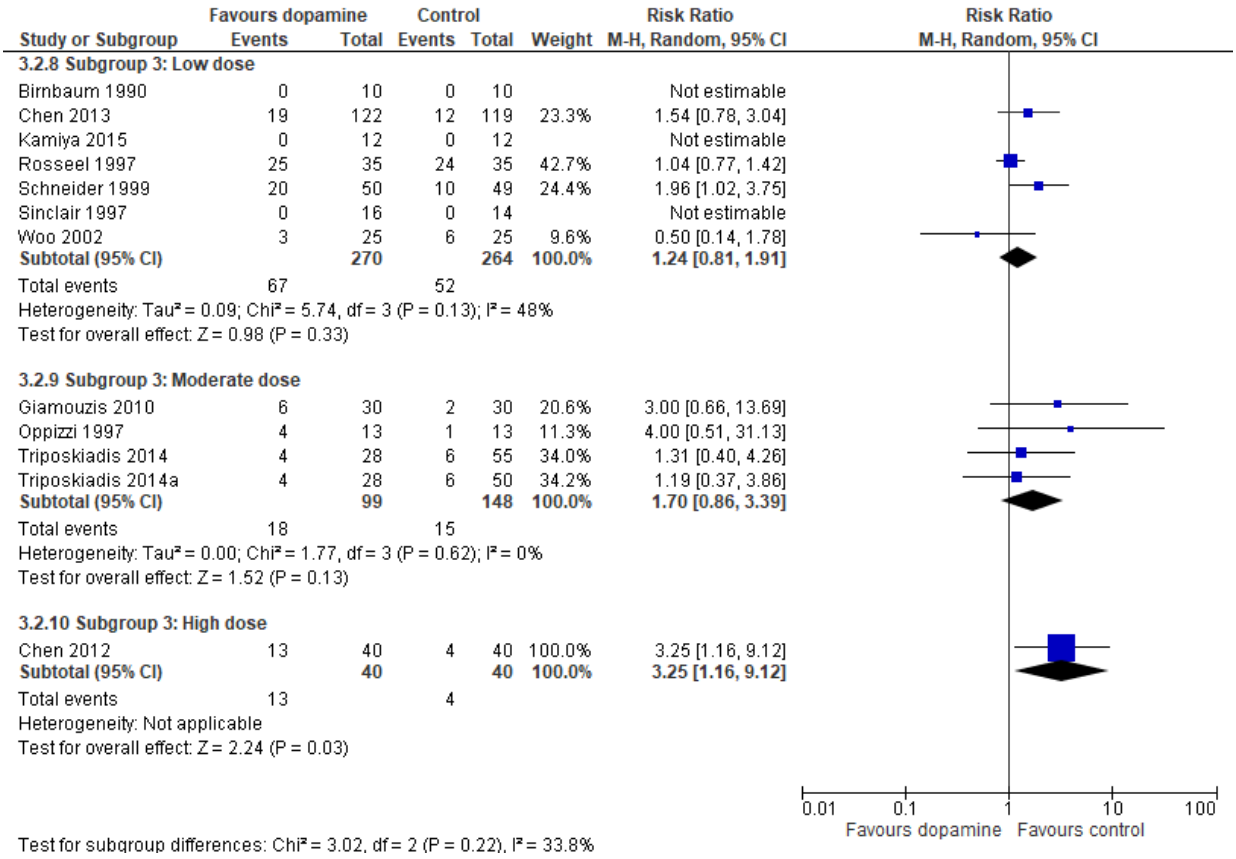
E-Figures 2.7.4-2.7.5: subgroup analysis 1 - trials subdivided by risk of bias



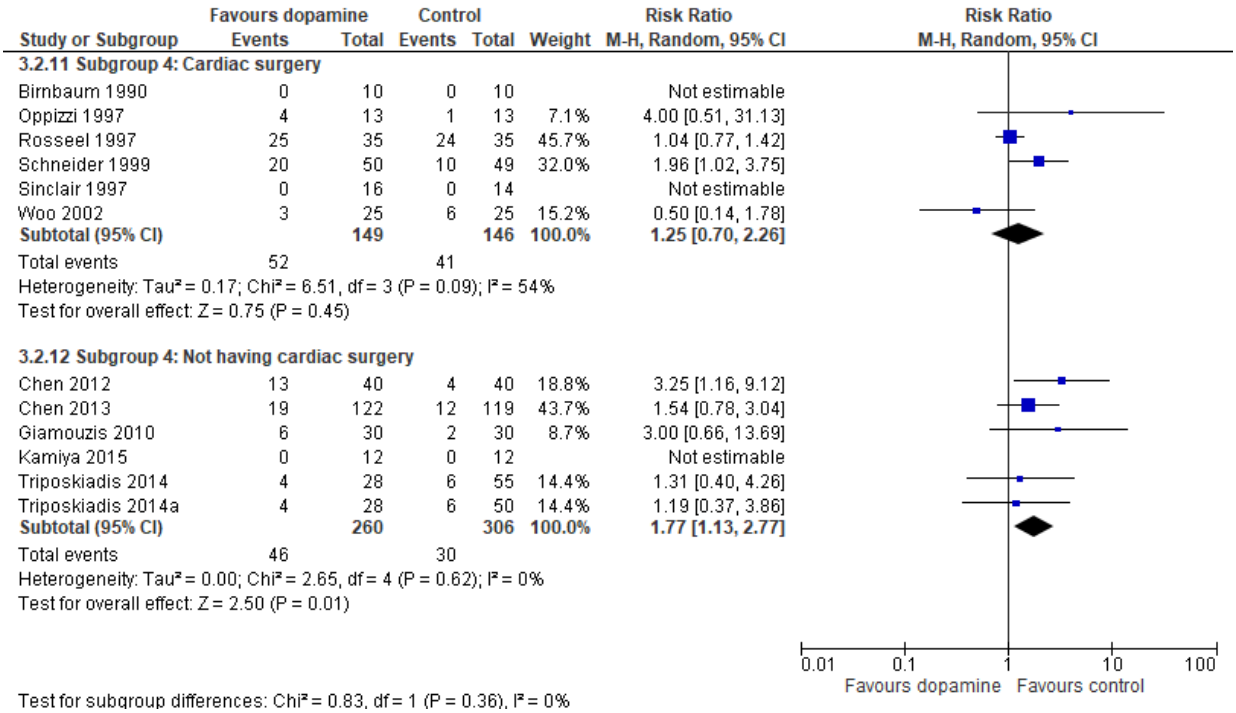
E-Figures 2.7.6-2.7.7: subgroup analysis 2 – trials subdivided by comparator intervention



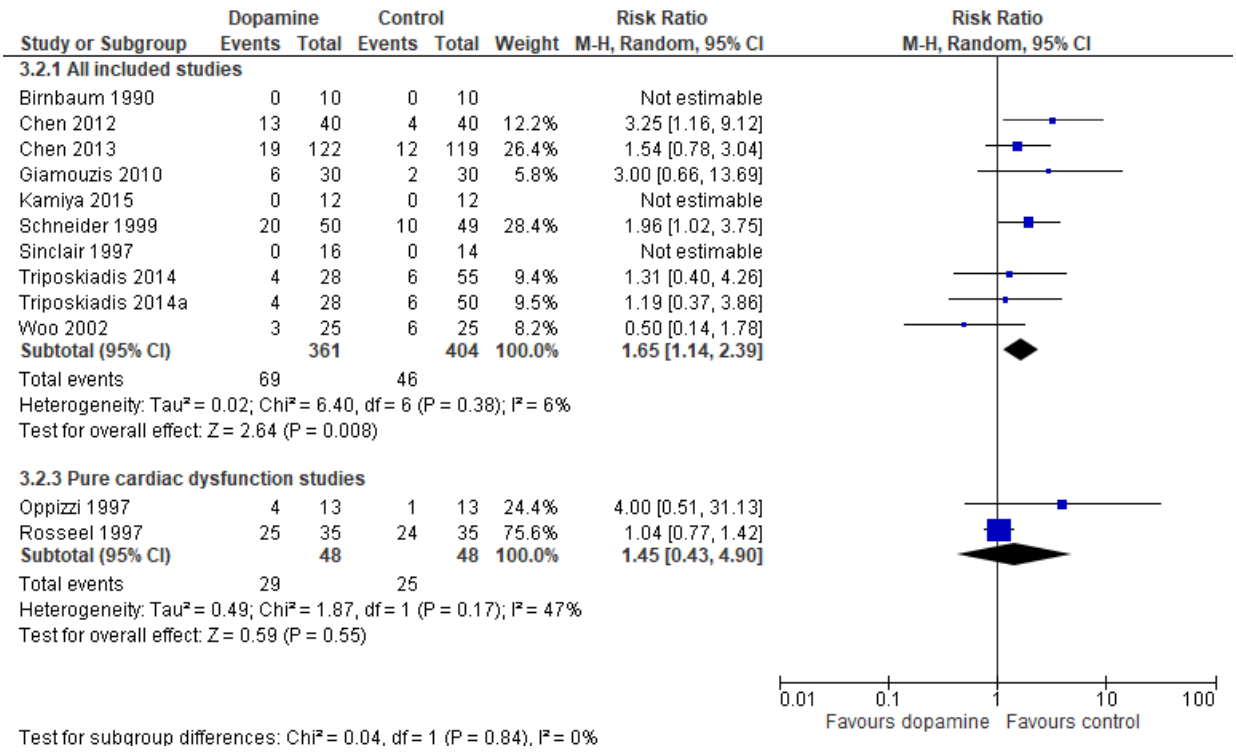
E-Figures 2.7.8-2.7.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 2.7.11-2.7.12: subgroup analysis 4 – trials subdivided by clinical setting

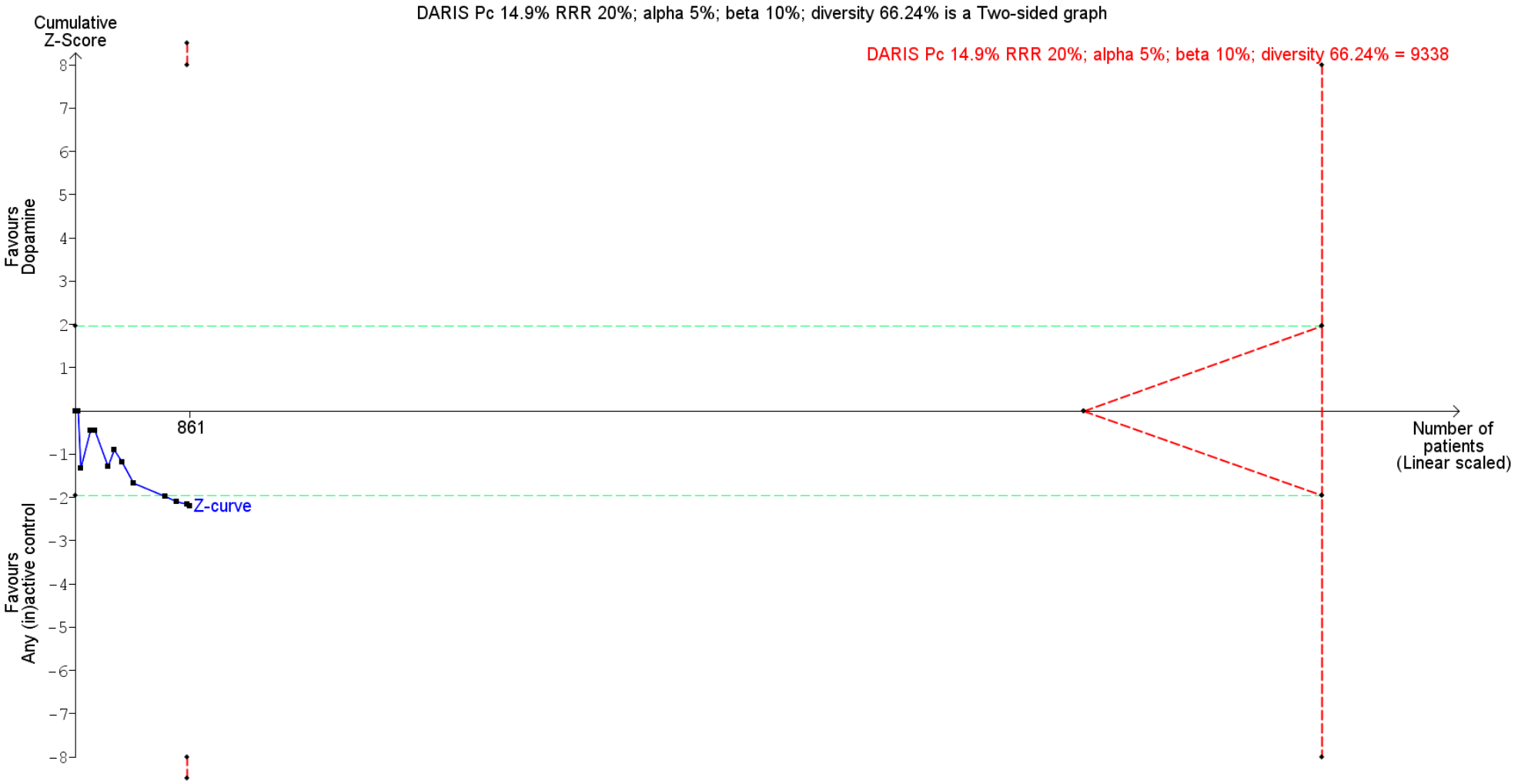


E-Figures 2.7.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction



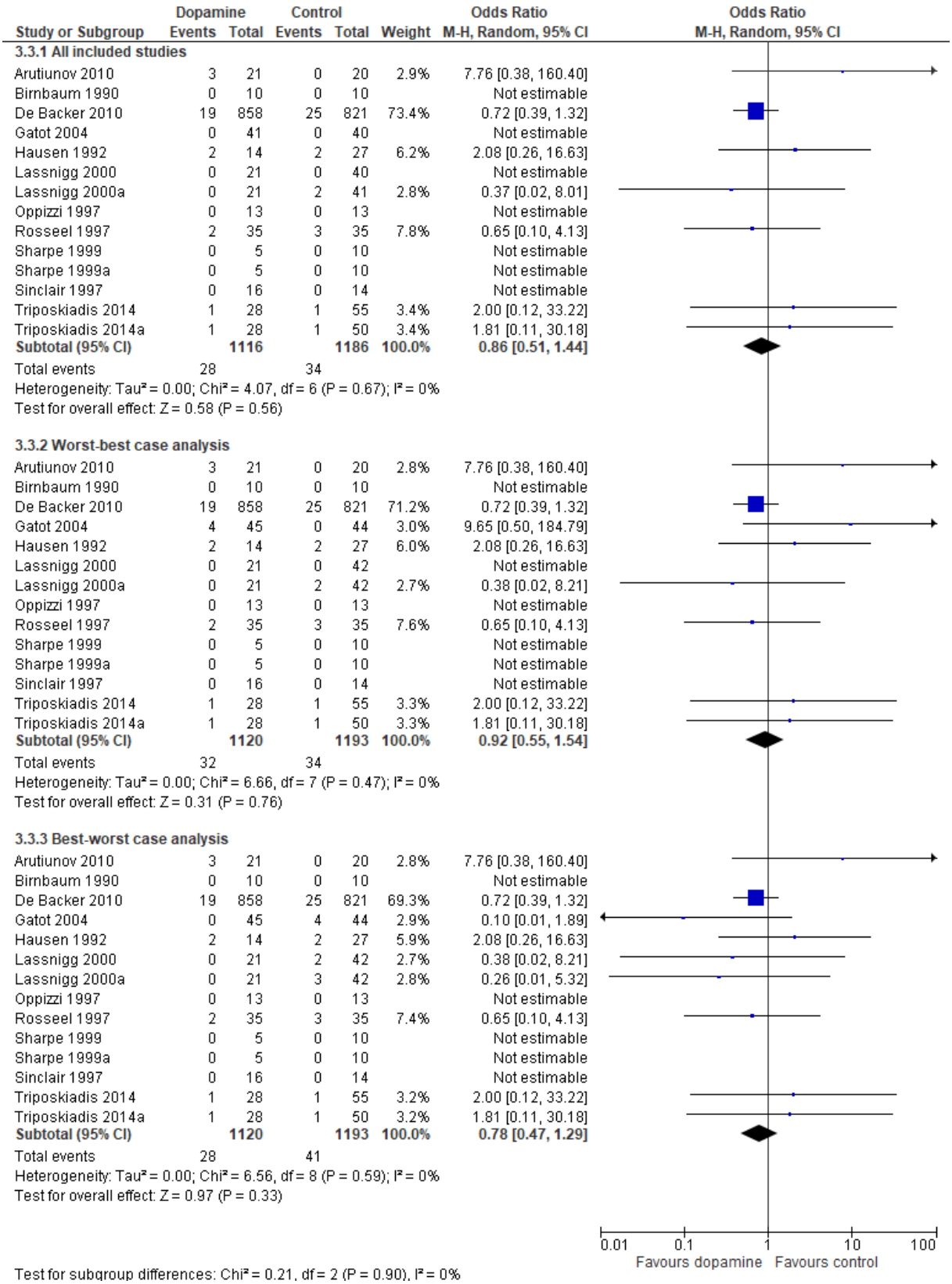
2.8. Trial sequential analysis of serious adverse events

E-Figure 2.8: the TSA is based on 11 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

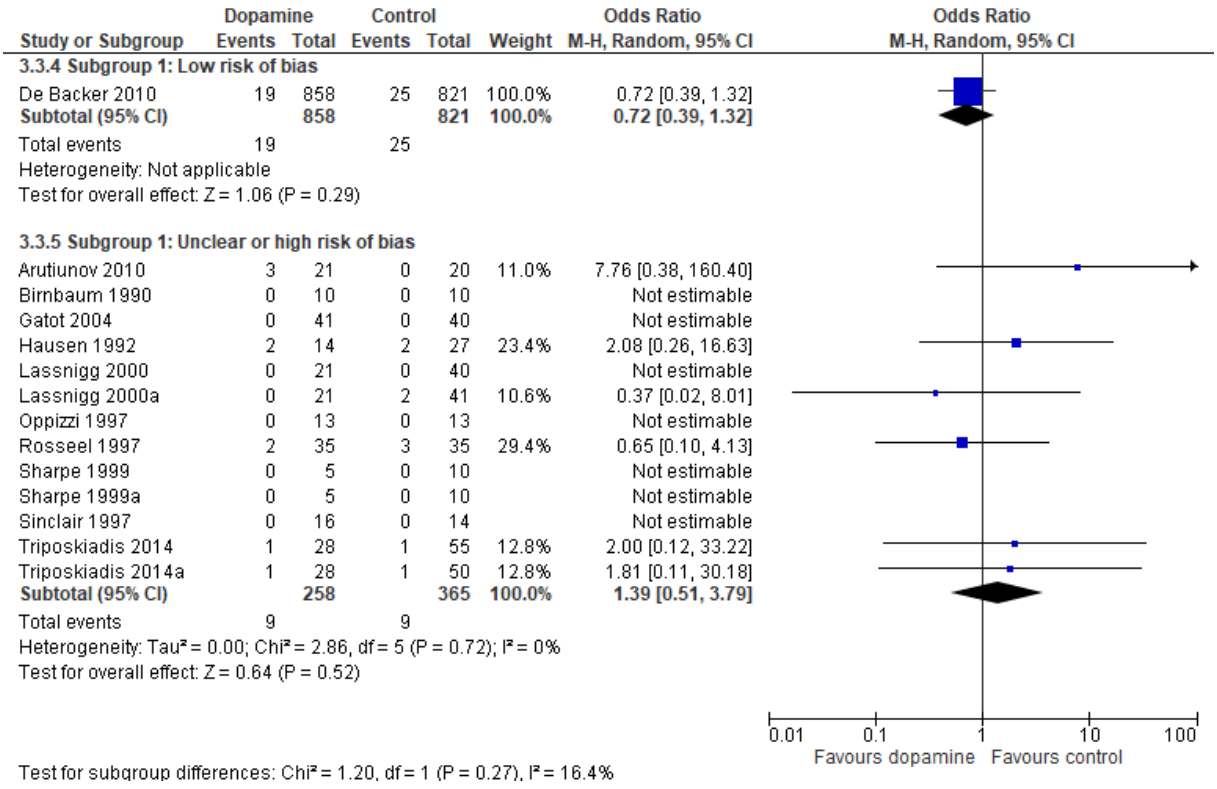


2.9. Forest plots of myocardial infarction

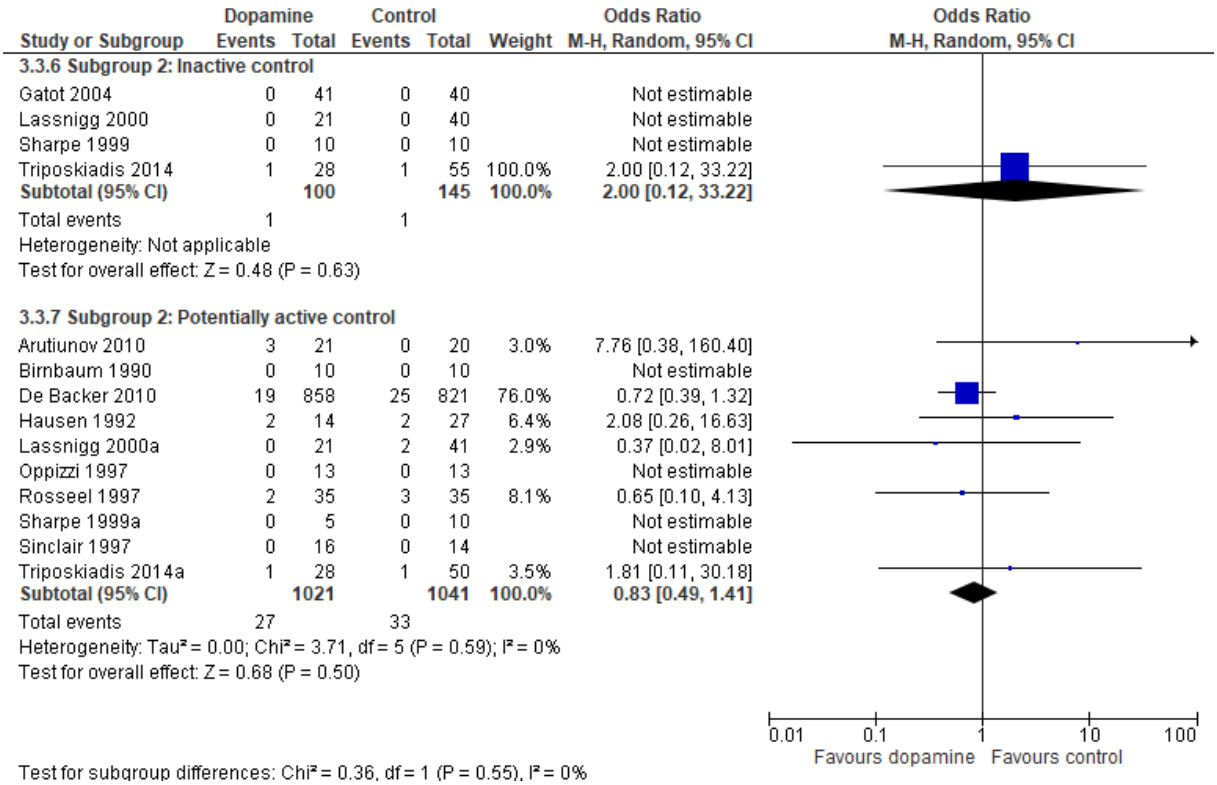
E-Figures 2.9.1-2.9.3: all trials with worst-best and best-worst case analyses



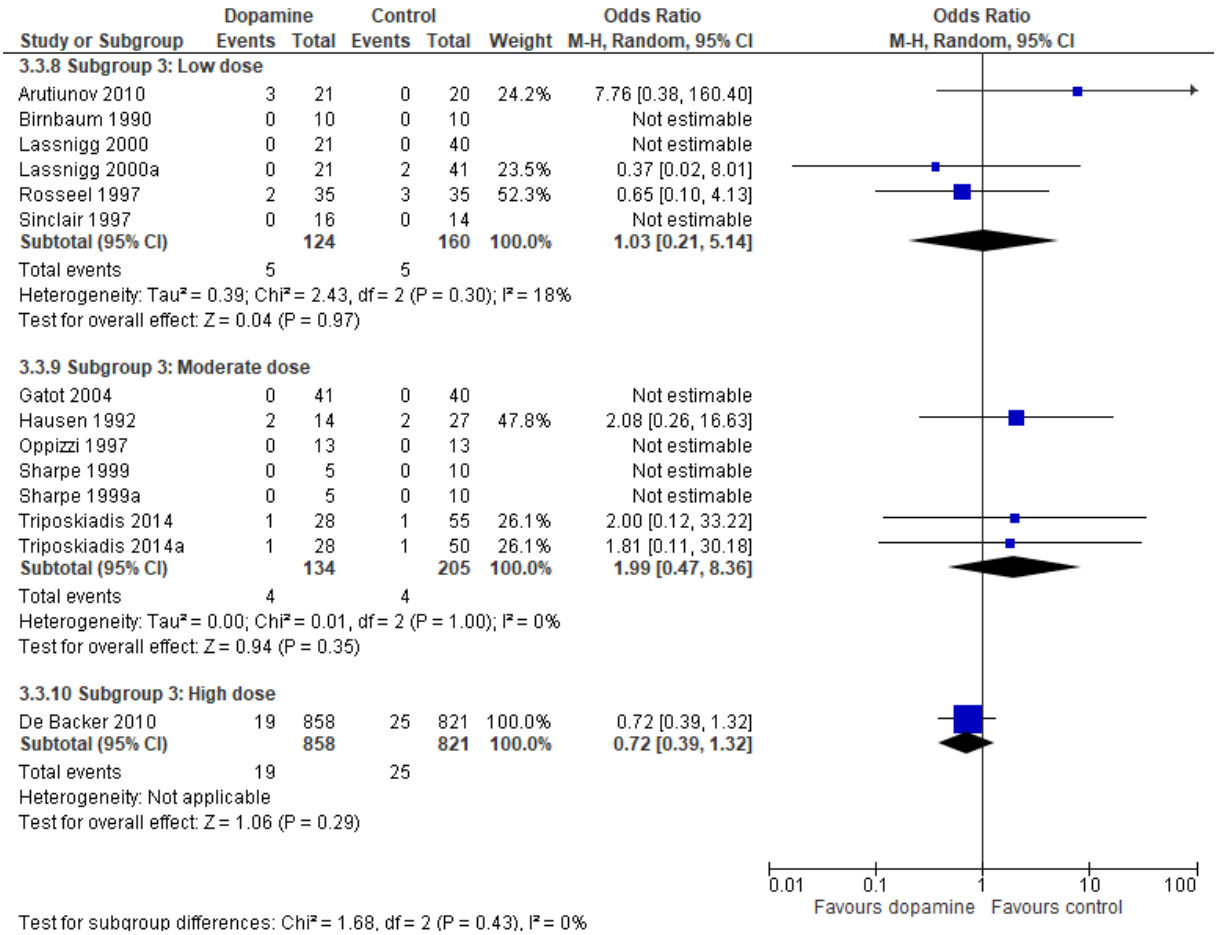
E-Figures 2.9.4-2.9.5: subgroup analysis 1 - trials subdivided by risk of bias



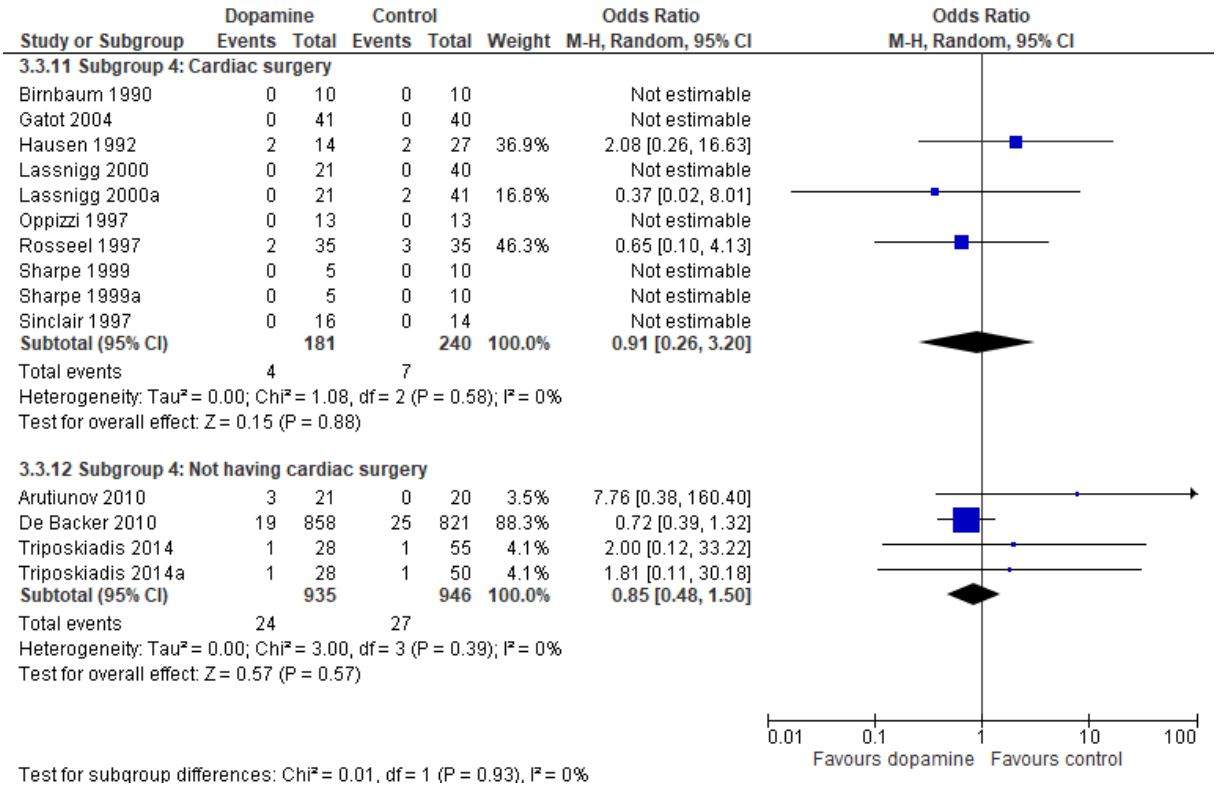
E-Figures 2.9.6-2.9.7: subgroup analysis 2 – trials subdivided by comparator intervention



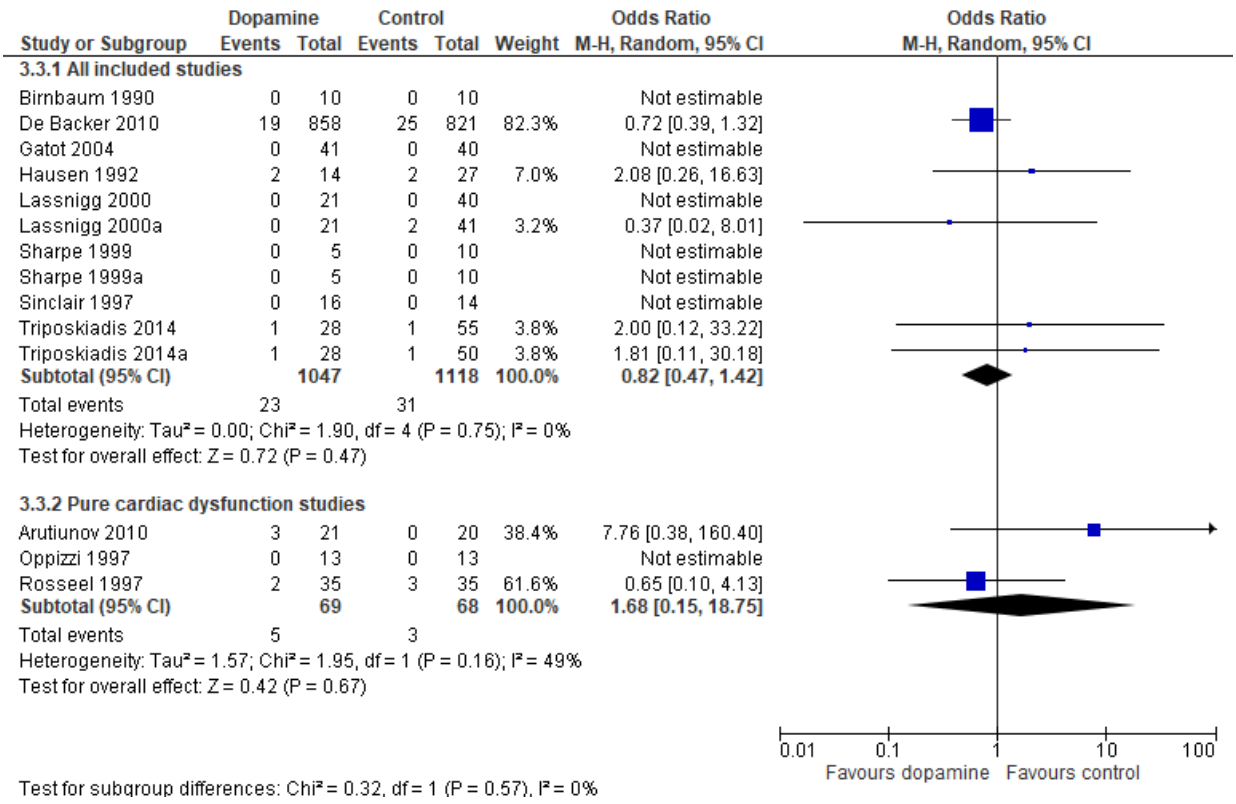
E-Figures 2.9.8-2.9.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 2.9.11-2.9.12: subgroup analysis 4 – trials subdivided by clinical setting

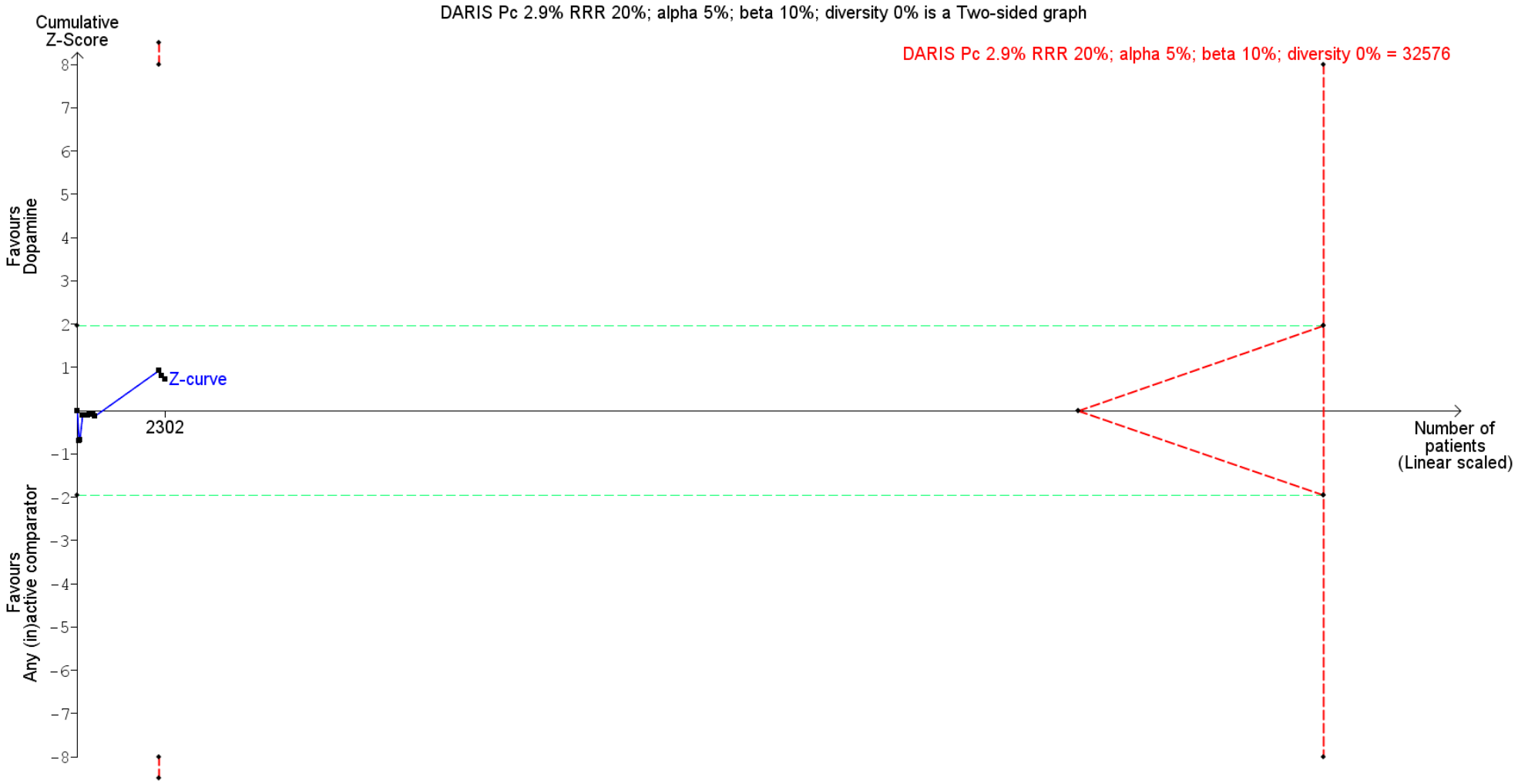


E-Figures 2.9.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction



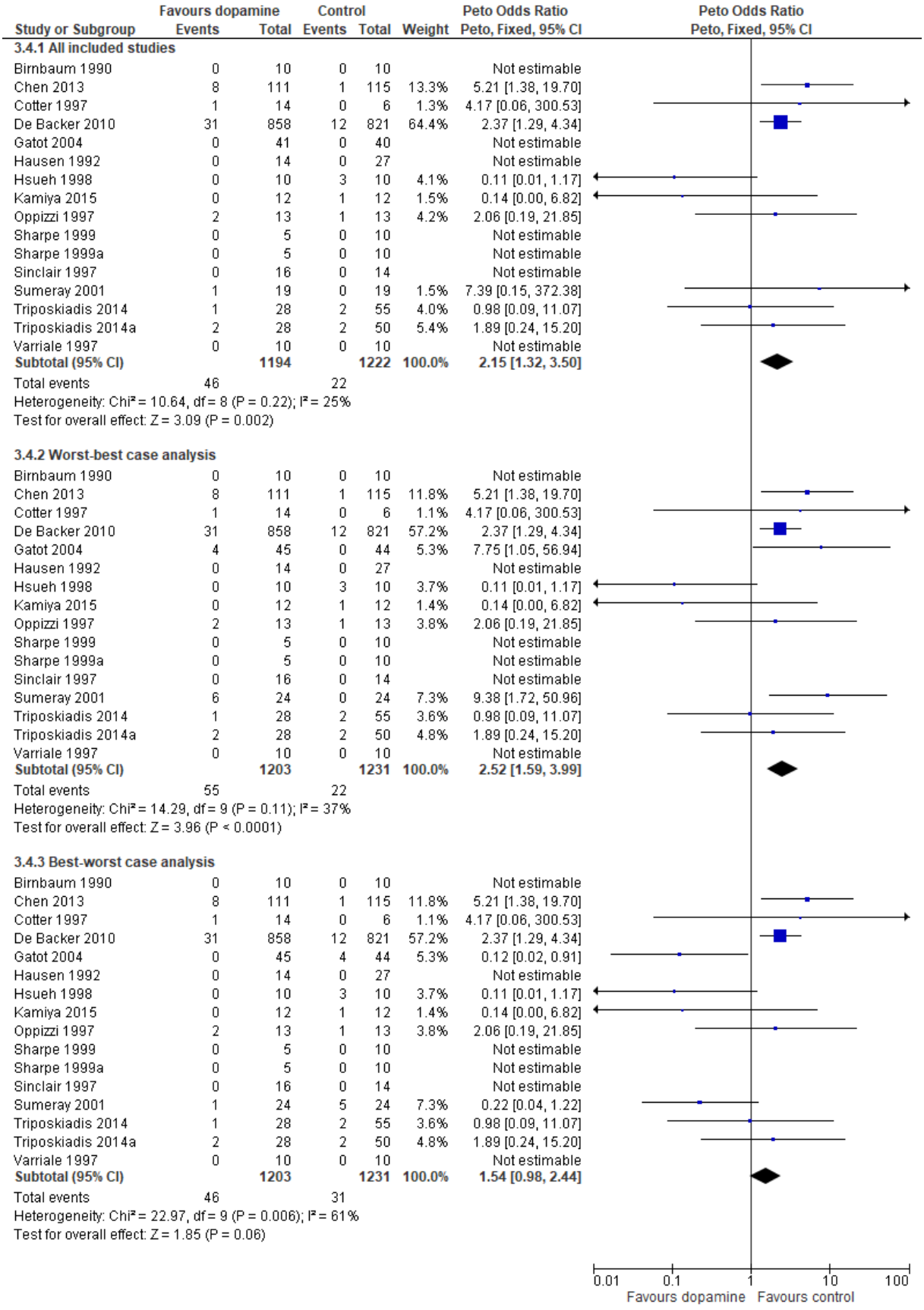
2.10. Trial sequential analysis of myocardial infarction

E-Figure 2.10: the TSA is based on 11 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

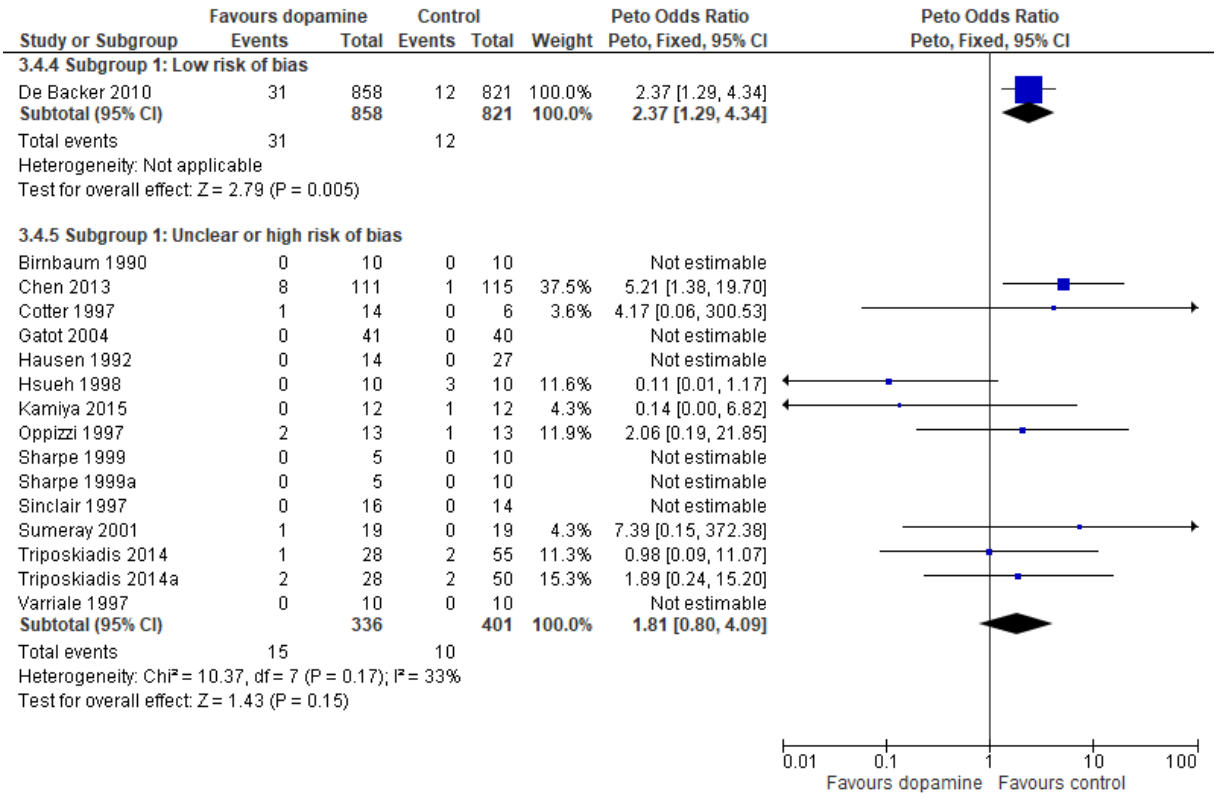


2.11. Forest plots of ventricular tachyarrhythmias

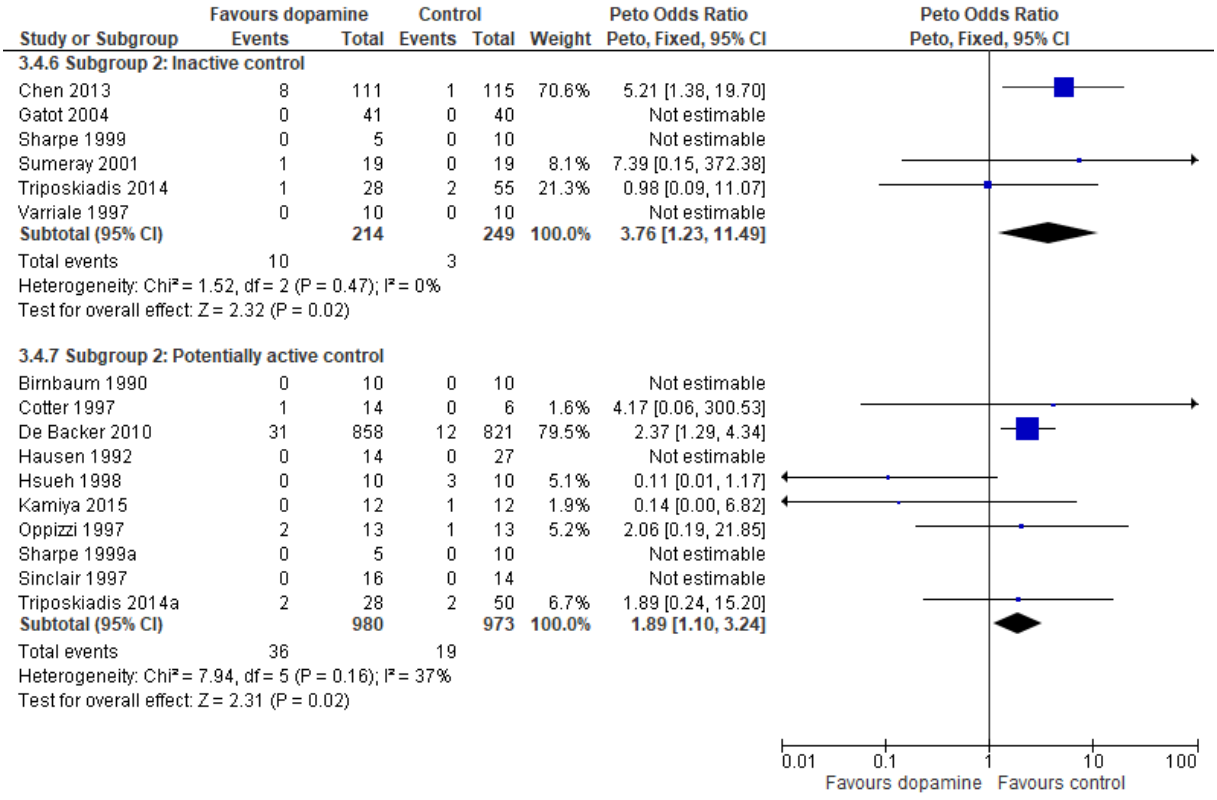
E-Figures 2.11.1-2.11.3: all trials with worst-best and best-worst case analyses



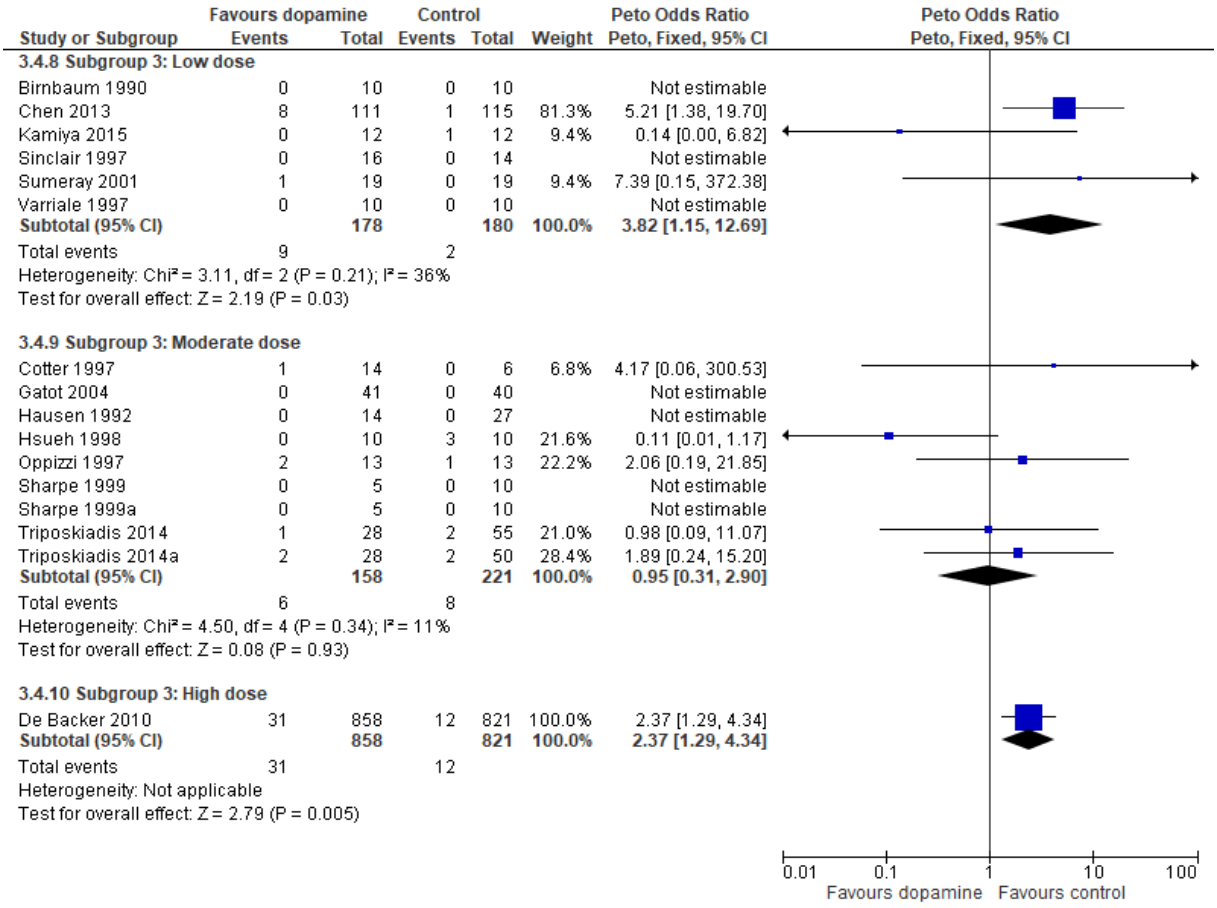
E-Figures 2.11.4-2.11.5: subgroup analysis 1 - trials subdivided by risk of bias



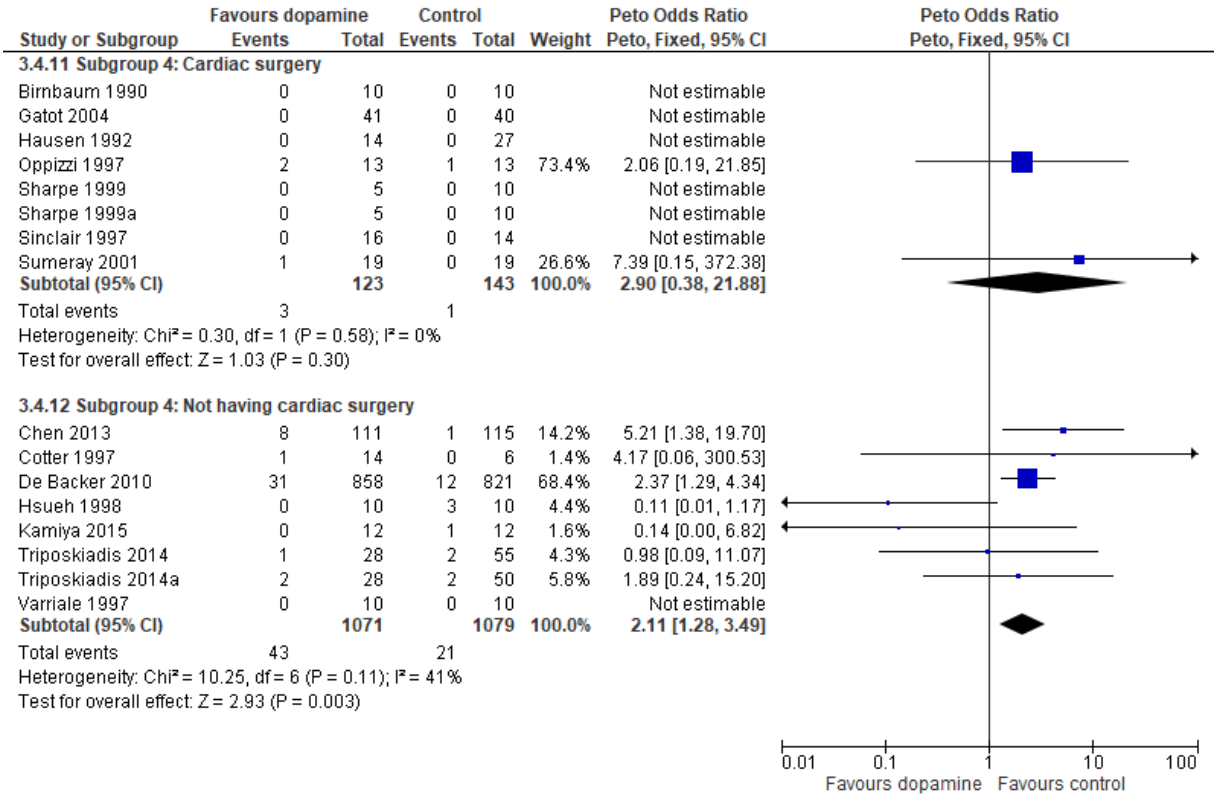
E-Figures 2.11.6-2.11.7: subgroup analysis 2 – trials subdivided by comparator intervention



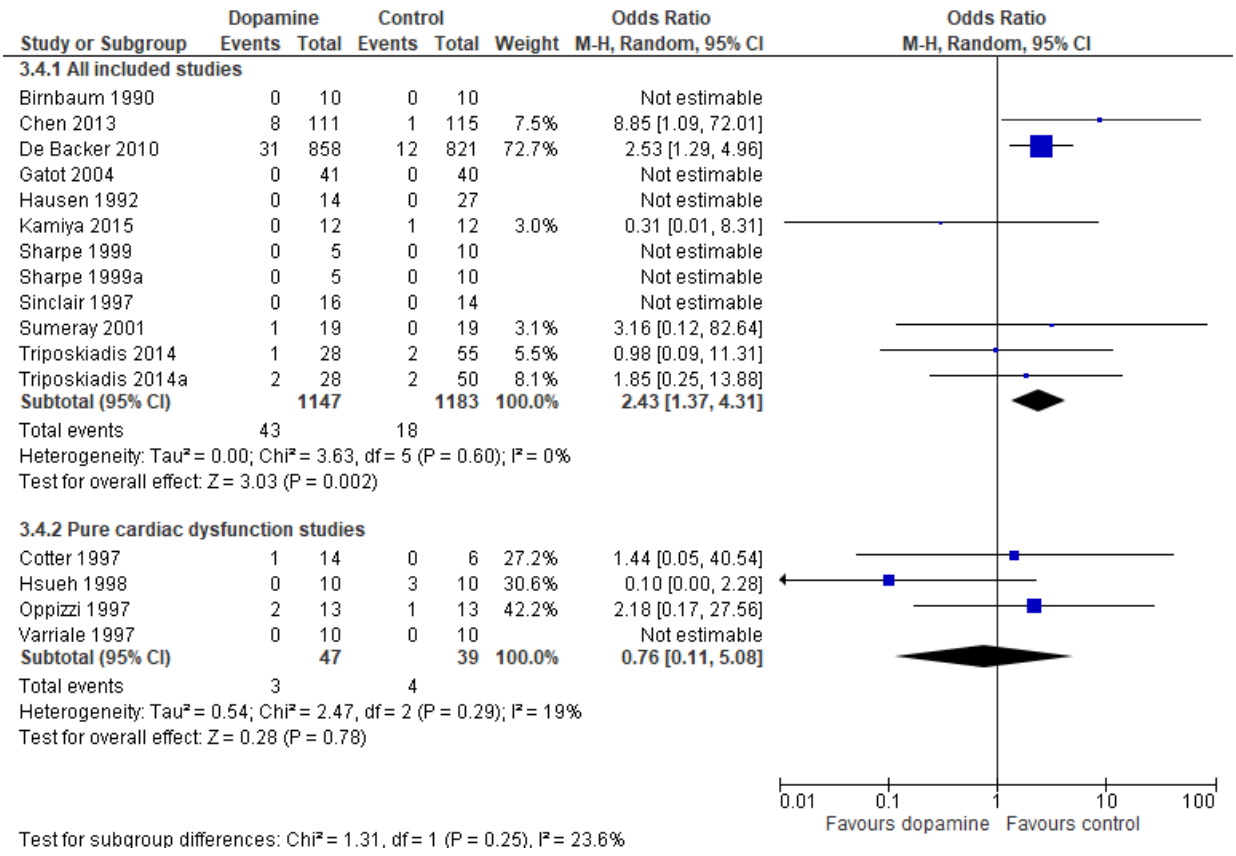
E-Figures 2.11.8-2.11.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 2.11.11-2.11.12: subgroup analysis 4 – trials subdivided by clinical setting

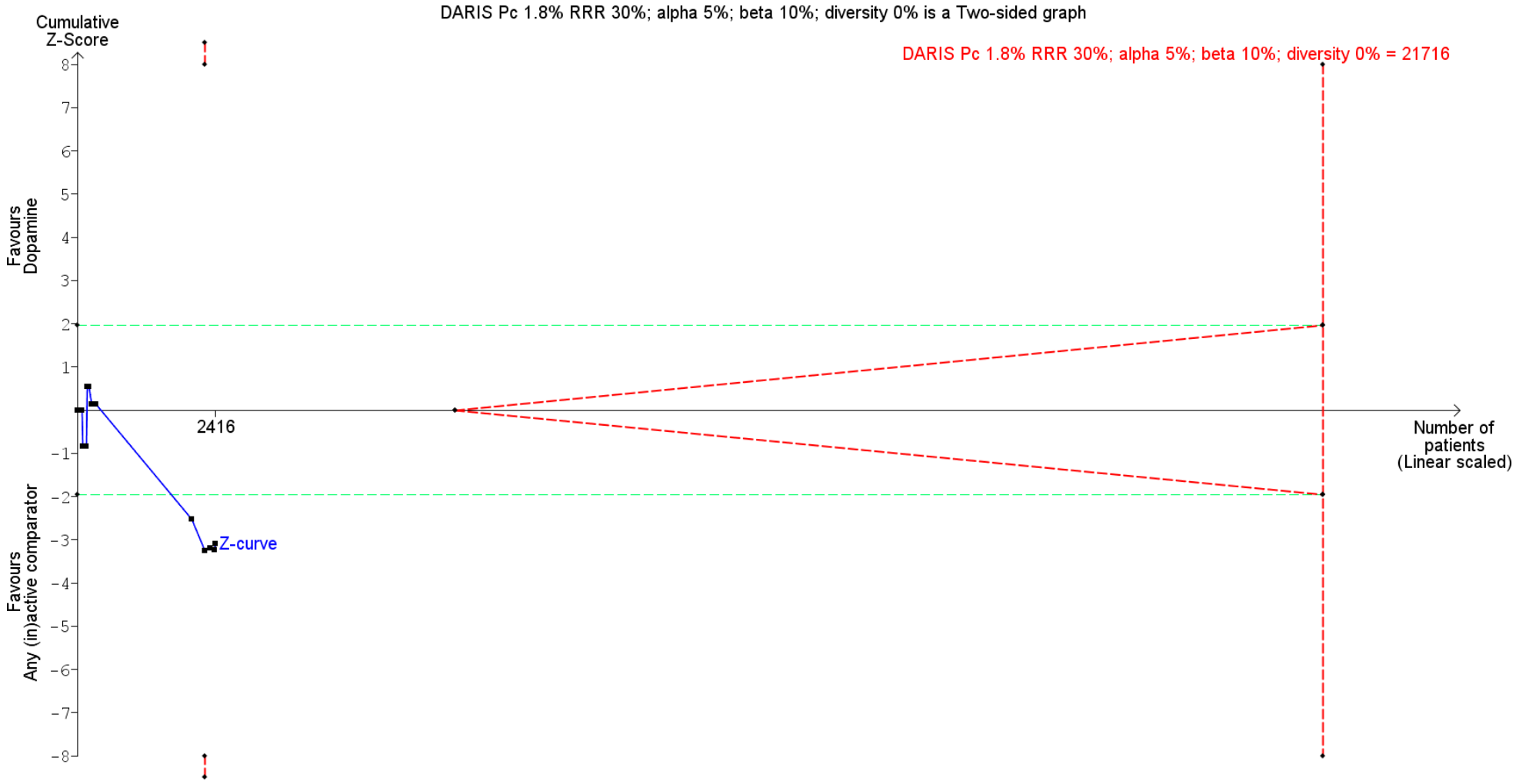


E-Figures 2.11.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction



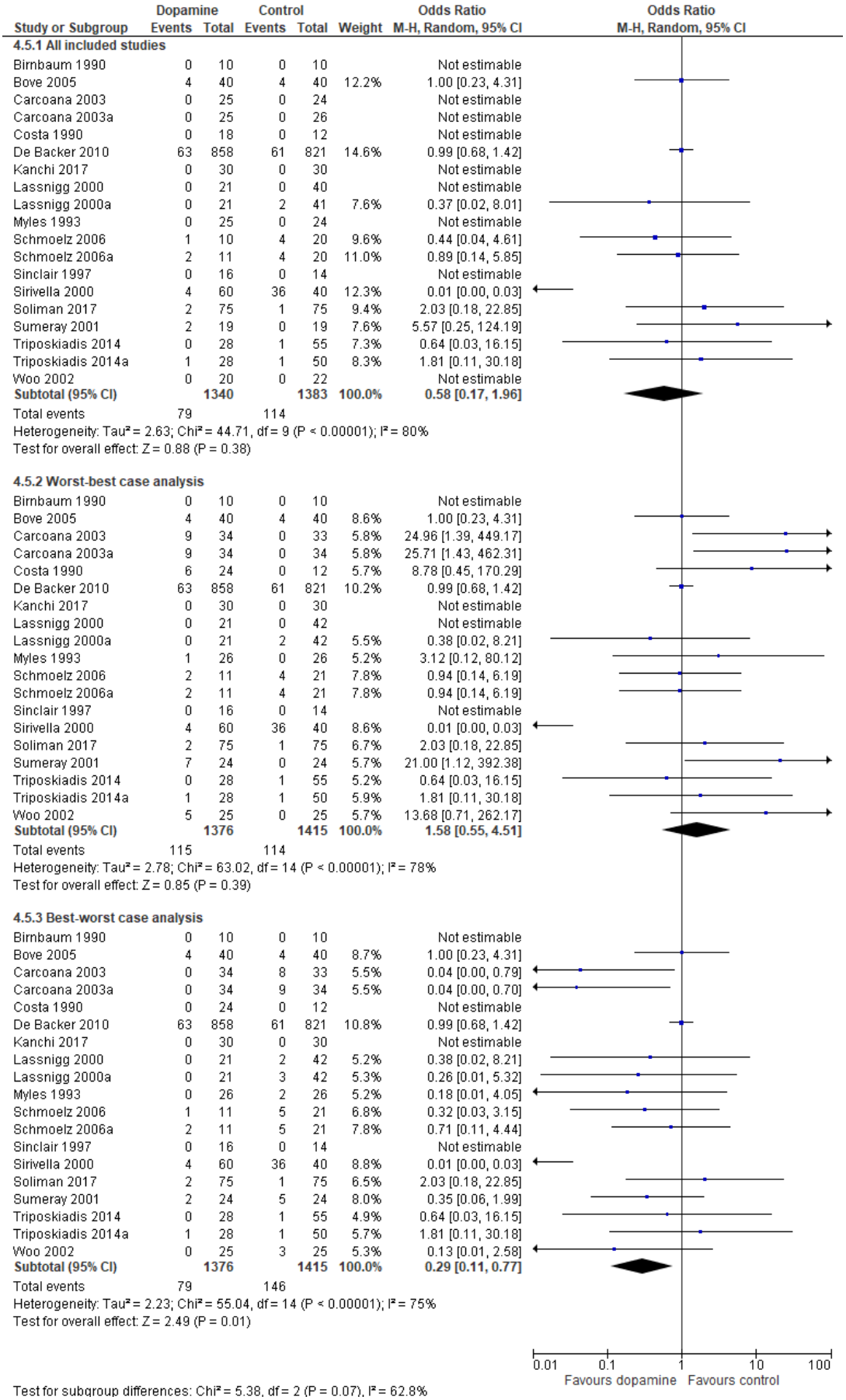
2.12. Trial sequential analysis of ventricular tachyarrhythmias

E-Figure 2.12: the TSA is based on 14 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

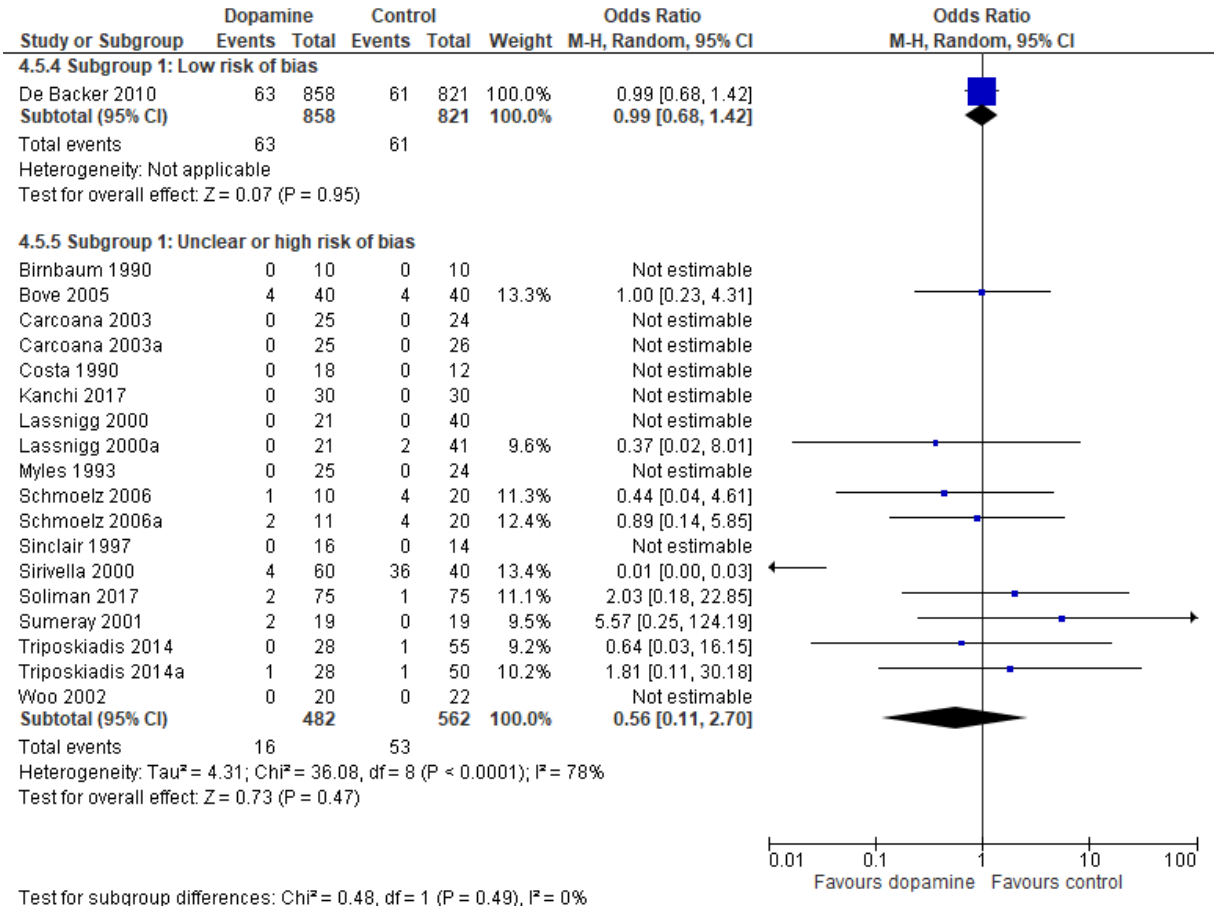


2.13. Forest plots of renal replacement therapy

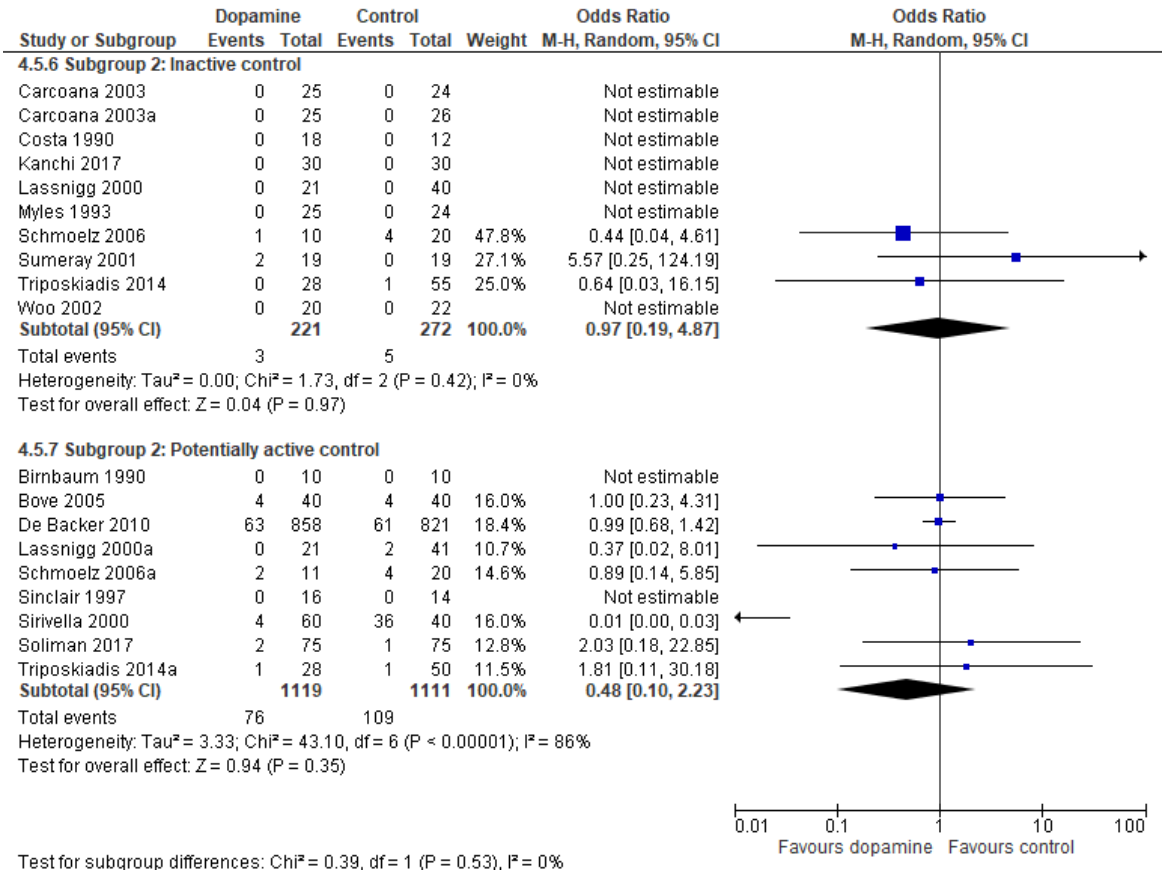
E-Figures 2.13.1-2.13.3: all trials with worst-best and best-worst case analyses



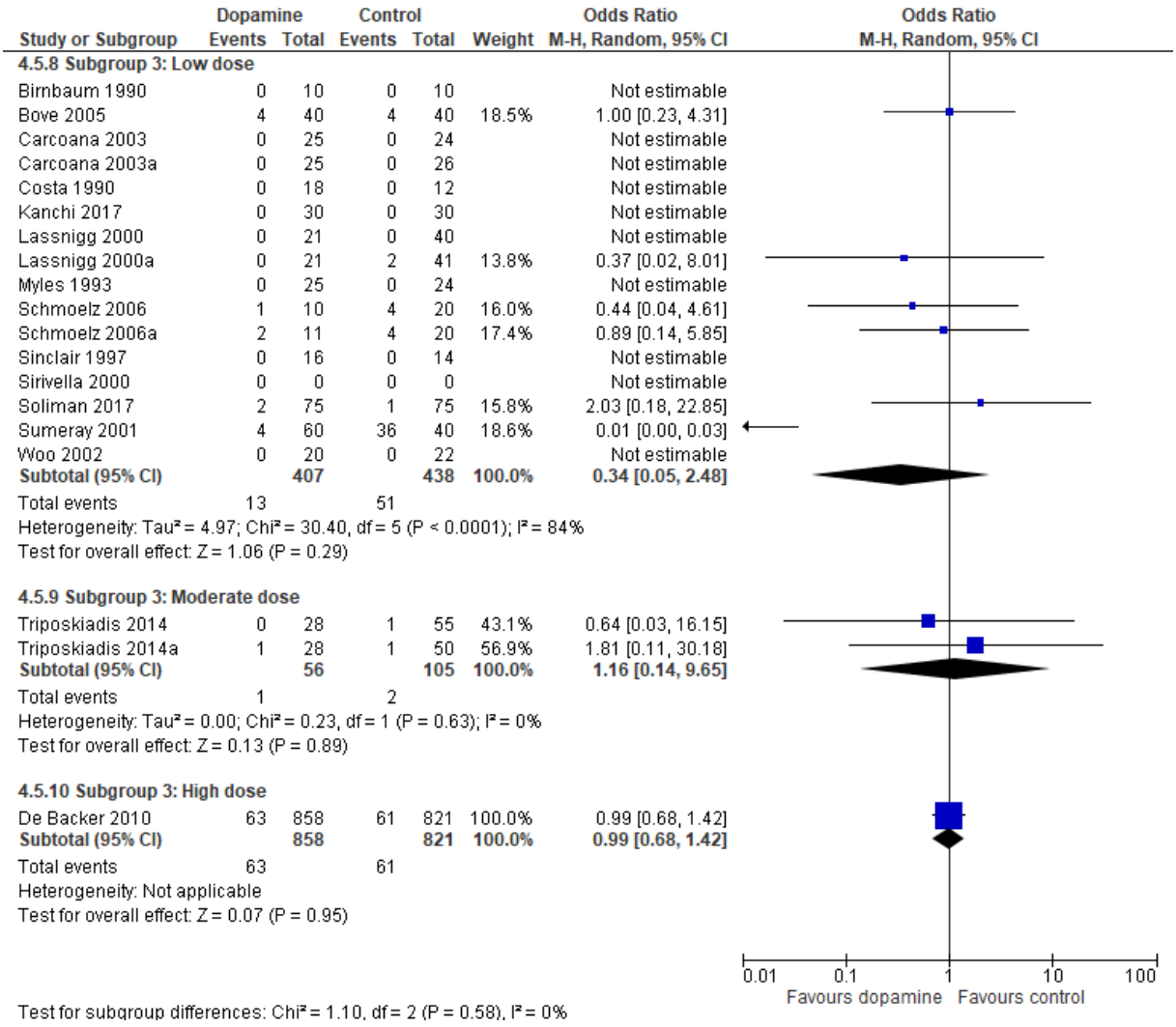
E-Figures 2.13.4-2.13.5: subgroup analysis 1 - trials subdivided by risk of bias



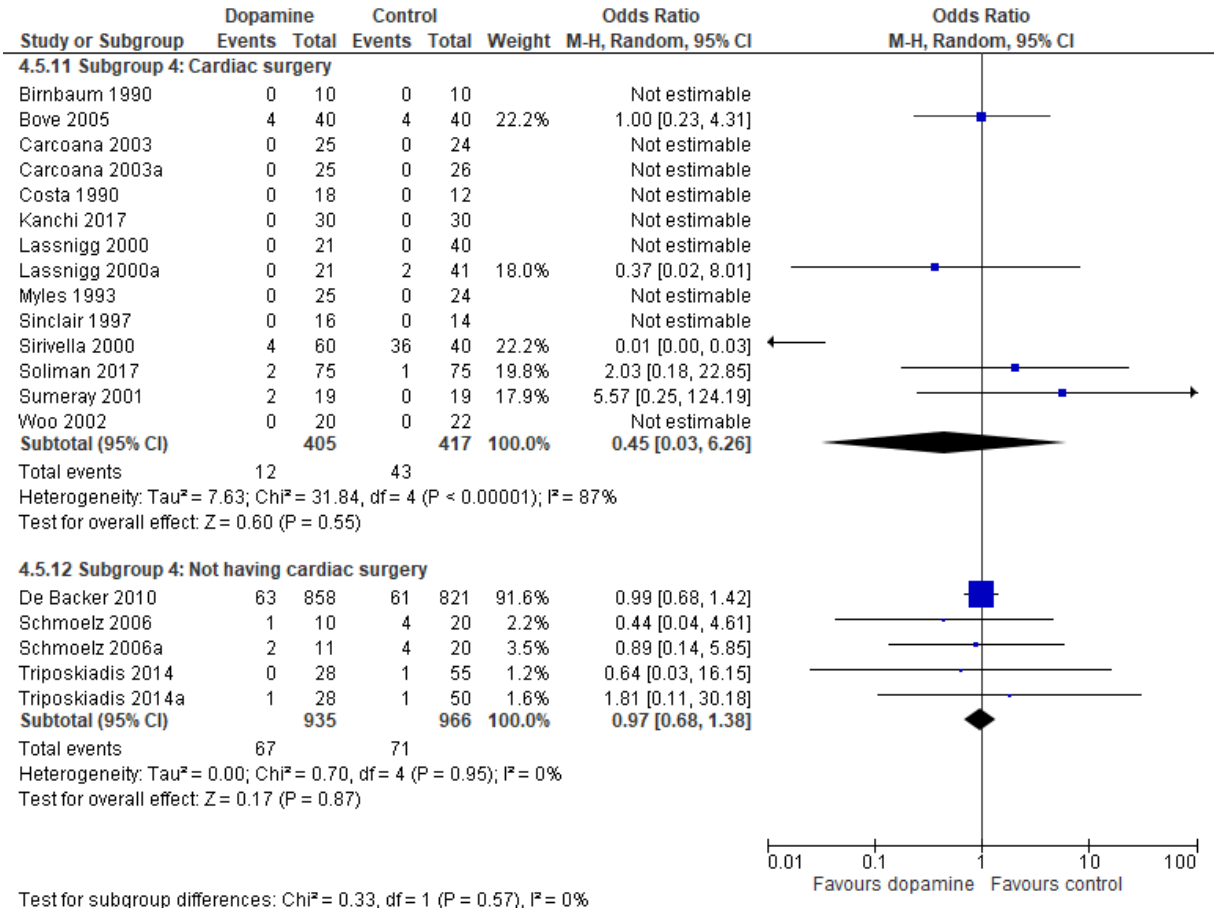
E-Figures 2.13.6-2.13.7: subgroup analysis 2 – trials subdivided by comparator intervention



E-Figures 2.13.8-2.13.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 2.13.11-2.13.12: subgroup analysis 4 – trials subdivided by clinical setting

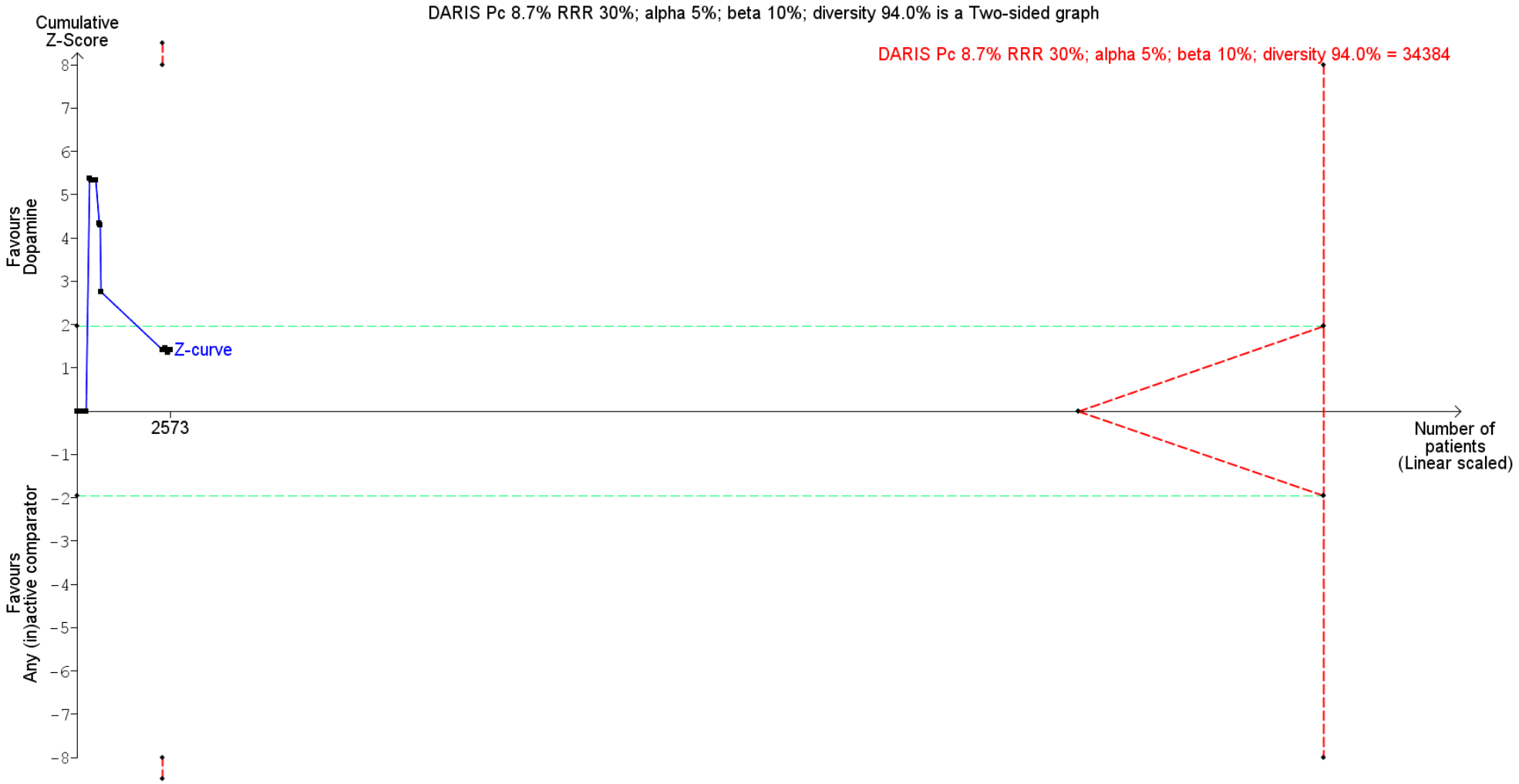


E-Figures 2.13.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

Not possible because all seven trials on patients with documented cardiac dysfunction did not report renal replacement therapy proportions.

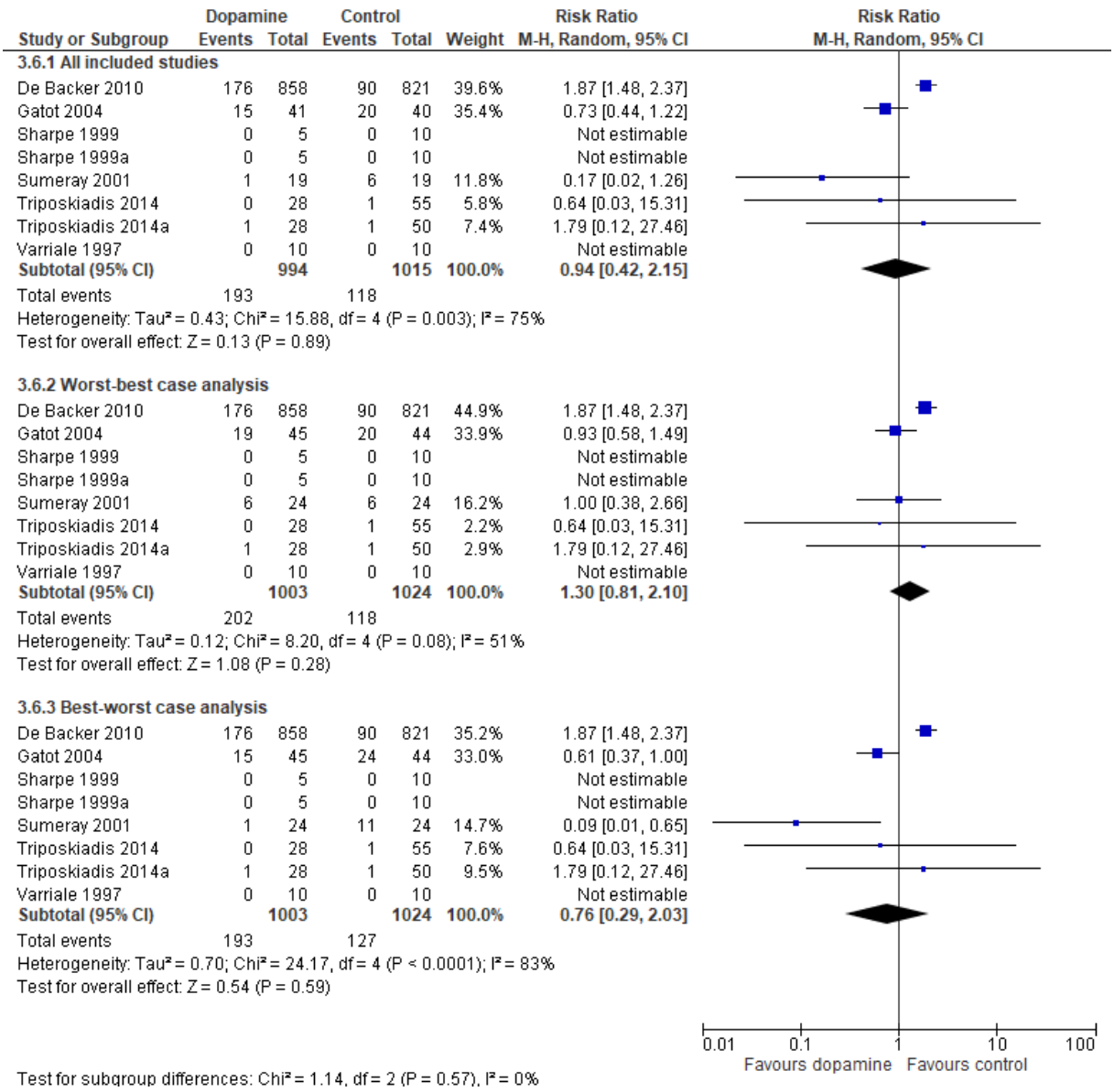
2.14. Trial sequential analysis of renal replacement therapy

E-Figure 2.14: the TSA is based on 14 trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.

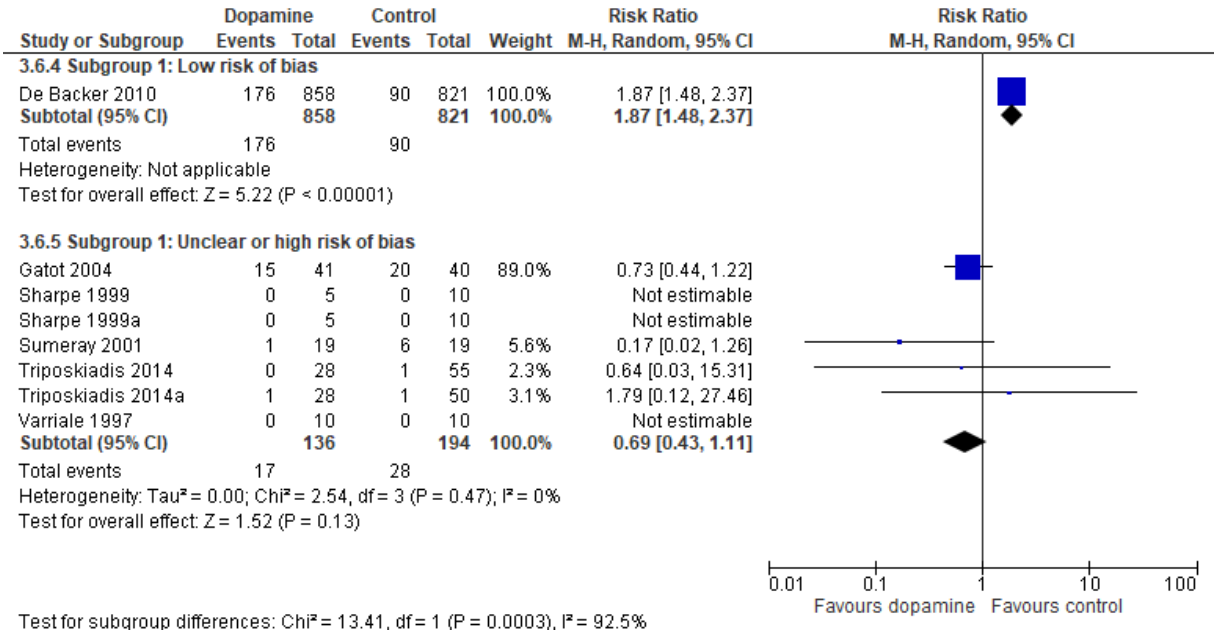


2.15. Forest plots of atrial tachyarrhythmias

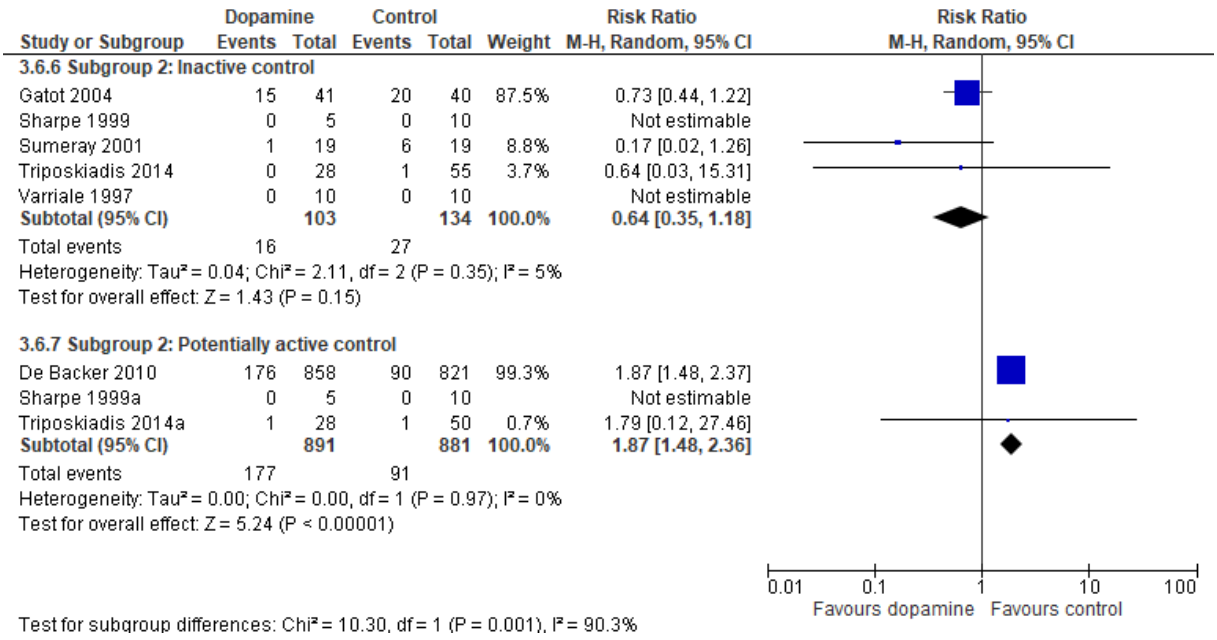
E-Figures 2.15.1-2.15.3: all trials with worst-best and best-worst case analyses



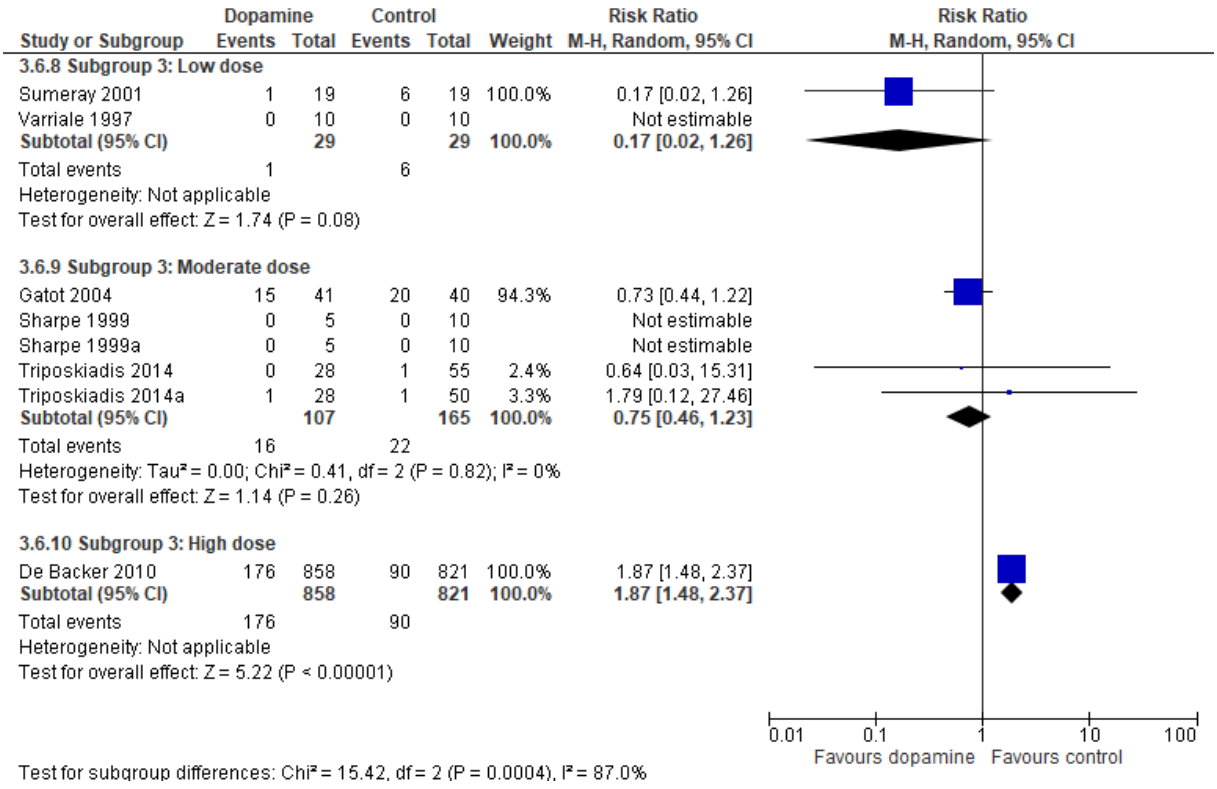
E-Figures 2.15.4-2.15.5: subgroup analysis 1 - trials subdivided by risk of bias



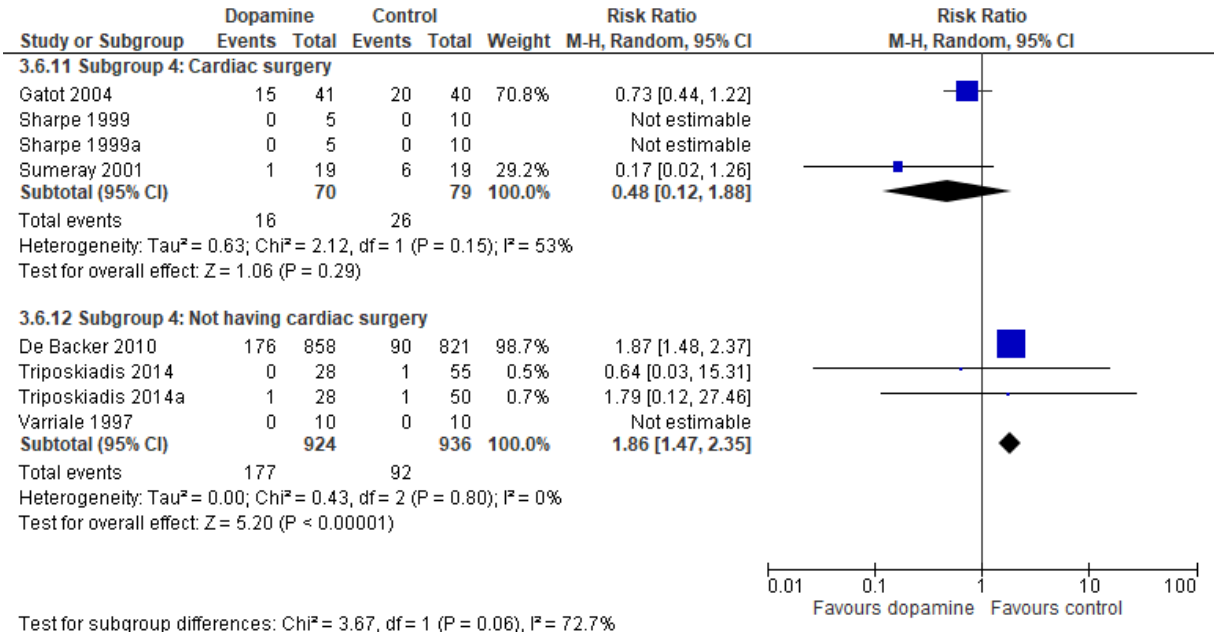
E-Figures 2.15.6-2.15.7: subgroup analysis 2 – trials subdivided by comparator intervention



E-Figures 2.15.8-3.9.10: subgroup analysis 3 – trials subdivided by dose



E-Figures 2.15.11-3.9.12: subgroup analysis 4 – trials subdivided by clinical setting

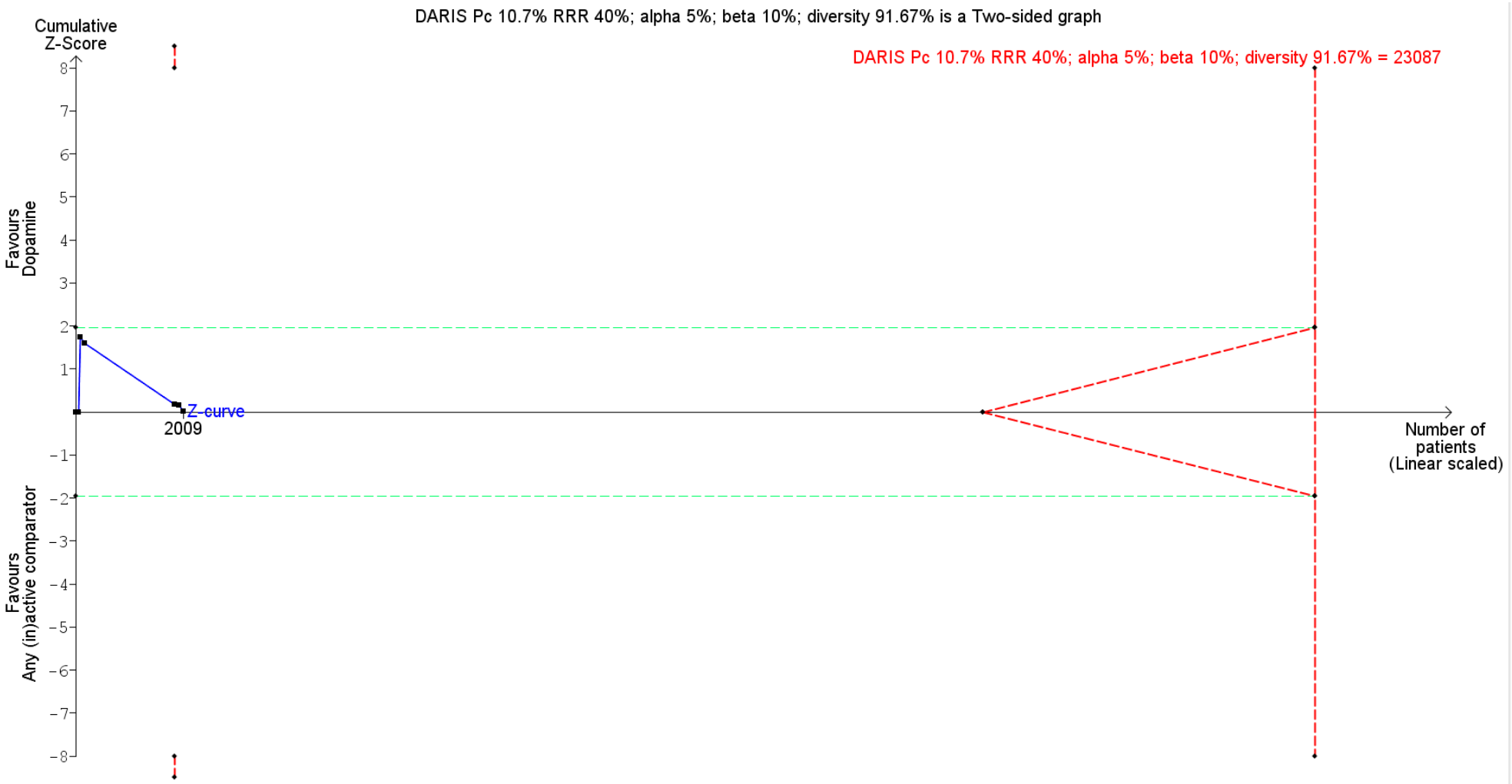


E-Figures 2.15.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

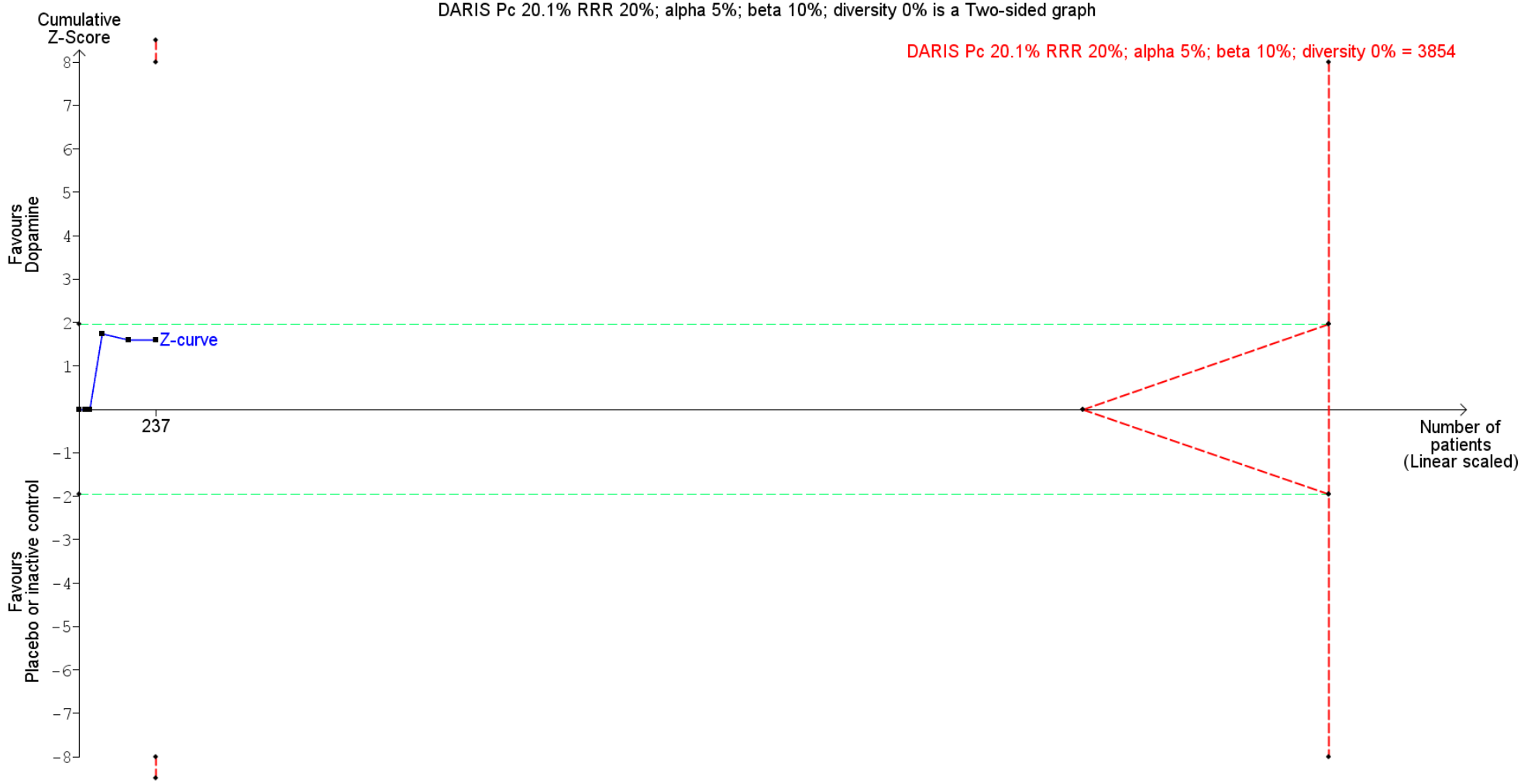
Not possible because all seven trials on patients with documented cardiac dysfunction did not report the occurrence of atrial tachyarrhythmias.

2.16. Trial sequential analyses of atrial tachyarryhythmias

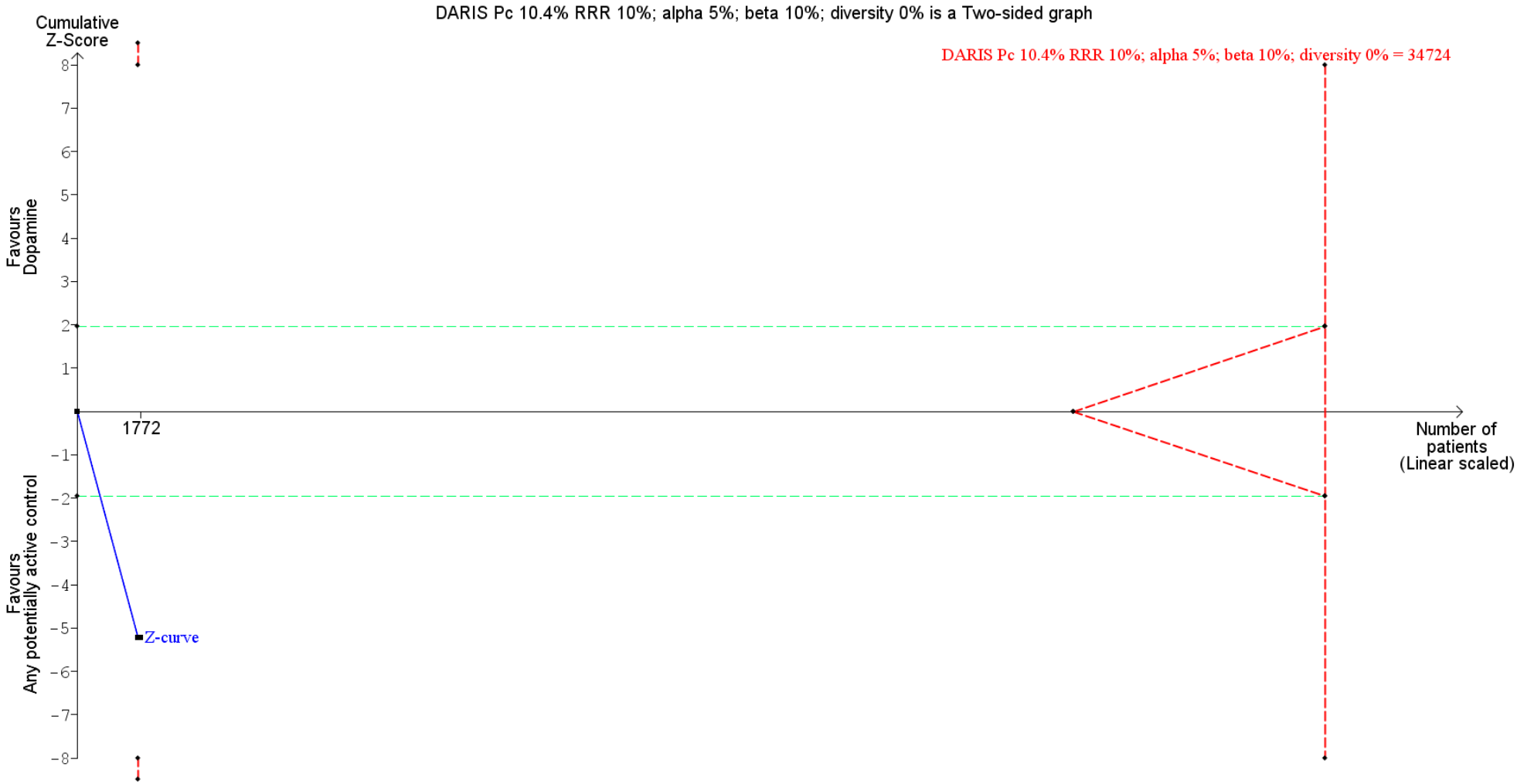
E-Figure 2.16.1: the TSA is based on six trials, which is the meta-analysed effect of dopamine versus any (in)active comparator intervention.



E-Figure 2.16.2: the TSA is based on five trials, which is the meta-analysed effect of dopamine versus placebo or inactive control.



E-Figure 2.16.3: the TSA is based on three trials, which is the meta-analysed effect of dopamine versus any potentially active control.



2.17. E-Table 4: GRADEpro summary of finding e-Table of the outcomes of interest

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopamine	Any (in)active comparator	Relative (95% CI)	Absolute (95% CI)		
Mortality at maximum follow-up - All included studies												
40	randomised trials	serious [a]	not serious	serious [b]	serious [c]	dose response gradient	640/1909 (33.5%)	614/2062 (29.8%)	**RR 1.07** (0.99 to 1.16)	**21 more per 1.000** (from 3 fewer to 48 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse events - All included studies												
12	randomised trials	very serious [d]	serious [e]	serious [b]	serious [f]	dose response gradient	98/409 (24.0%)	71/452 (15.7%)	**RR 1.44** (1.03 to 2.00)	**69 more per 1.000** (from 5 more to 157 more)	⊕◯◯◯ VERY LOW	CRITICAL
Myocardial infarction - All included studies												
11	randomised trials	not serious [a]	not serious	serious [b]	serious [f]	none	28/1116 (2.5%)	34/1186 (2.9%)	**OR 0.82** (0.48 to 1.40)	**5 fewer per 1.000** (from 11 more to 15 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Ventricular tachyarrhythmias - All included studies												
16	randomised trials	not serious [a]	not serious	serious [b]	serious [f]	none	46/1194 (3.9%)	22/1222 (1.8%)	**Peto's OR 2.15** (1.32 to 3.50)	**20 more per 1.000** (from 6 more to 42 more)	⊕⊕◯◯ LOW	IMPORTANT
Renal replacement therapy - All included studies												
14	randomised trials	not serious [a]	very serious [g]	serious [b]	serious [f]	none	79/1340 (5.9%)	114/1383 (8.2%)	**OR 0.60** (0.24 to 1.23)	**31 fewer per 1.000** (from 24 more to 59 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Atrial tachyarrhythmias - All included studies												
7	randomised trials	not serious [a]	not serious	serious [b]	serious [f]	dose response gradient	193/994 (19.4%)	118/1015 (11.6%)	**RR 1.58** (1.28 to 1.95)	**67 more per 1.000** (from 33 fewer to 110 more)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT

Abbreviations: CI, confidence interval; RR, risk ratio; OR, odds ratio. Explanations: a. There was only one large trial at low risk of bias present (n = 1679); many bias domains and especially allocation concealment is not described in the trials; b. There was considerable difference in population types (i.e. heart failure, cardiac surgery and septic shock), incidence of cardiac dysfunction, and both dosing and length of administration of the study drugs; c. Many trials with few patients and few events; nearly 50% of the DARIS accrued; d. There were no trials with low risk of bias in this domain; many bias domains and especially allocation concealment is not described in the trials; e. There was considerable clinical diversity and statistical heterogeneity; f. Many trials did not report these serious adverse events; in total less than 30% of the DARIS was accrued; g. There was considerable statistical heterogeneity, which was caused by one study with a high risk of bias. The heterogeneity disappeared after removing the trial as a sensitivity analysis.

3. Risk of bias description for each domain per study

Arutiunov et al. 2010 [6]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed according to the e-Table of random numbers".
Allocation concealment (selection bias)	Unclear risk	Comment: Probably done.
Blinding of participants and personnel (performance bias)	Unclear risk	Not described.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	Not stated.
Selective reporting (reporting bias)	Unclear risk	No incomplete outcome data.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Birnbaum et al. 1990 [32]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "divided randomly into two groups". Comment: unclear, since early reports of the same investigators do also not describe their method of randomization
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, since early reports of the same investigators also did not include a statement on allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. Probably not. Comment: low risk on mortality, high risk on other outcomes.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Bove et al. 2005 [13]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by permuting blocks of size 40".

		Comment: probably low risk, because a meta-analysis of the same research group describes the use of "Computer-generated random numbers" in this trial.
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomization were contained in a set of sealed envelopes". Comment: Probably done properly, however there is no information on sequentially numbering and opacity. In addition, a meta-analysis of the same research group describes the allocation concealment as "adequate".
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind trial". Comment: probably done, since a meta analyses of the same investigators describe this study as "low risk" of performance bias.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. Comment: probably unclear, since a meta analyses of the same investigators describe this study as "unclear" of detection bias. Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "All participants who underwent random allocation were analyzed according to group assignment". Comment: probably low risk.
Selective reporting (reporting bias)	High risk	The authors did not register the trial or prepublished the trial design. ARF was measured on at least three occasions, but only one (with statistically insignificant results) is reported.
Other bias	Unclear risk	Quote: "Fenoldopam (Corlopam) was provided free of charge by the producer (Elan Pharma Italia SPA)" Comment: influence of the sponsor on the trial is not addressed.

Carcoana et al. 2003 [33]

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "use of computer-generated random-number tables". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated by the Department of Investigational Pharmacy". Comment: probably done properly. Unclear information on the sequential numbering, opacity and sealing of envelopes, but it was likely concealed allocation due to the central allocation. A similar trial by these investigators included the same phrase yet did not describe the opacity and sealing.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "supplied by the Department of Investigational Pharmacy in a blinded manner". Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "supplied by the Department of Investigational Pharmacy in a blinded manner". Comment: probably done.
Incomplete outcome data (attrition bias)	High risk	Quote: "Of the 135 patients enrolled, 35 patients were removed because of a change in...". Comment: probably high risk, as excluding 26% of the randomized patients could result in substantial inequality in patient characteristics between both groups.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Chaiyaroj et al. 1999 [55]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	**High risk - REMOVED**	Quote: "randomly assigned to one of two groups according to odd or even unit registry numbers". Comment: high risk, as randomization on patient number is 'quasi-random'. **QUASI RANDOMISED TRIAL**
Allocation concealment (selection bias)	High risk	Not described. Probably not performed properly as the method of randomization was 'quasi-random'.
Blinding of participants and personnel (performance bias)	High risk	Quote: "blinded prospective randomized study". Comment: Probably not done, because control group did not receive a placebo and therefore the personnel was probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not. Comment: low risk for mortality (not reported), high risk for other outcomes.
Incomplete outcome data (attrition bias)	High risk	"Two patients were excluded from the study because of unse-Table hemodynamics following cardiopulmonary bypass". Comment: no events were observed in the study group and these two excluded patients have a high chance of needing renal replacement therapy.
Selective reporting (reporting bias)	High risk	The authors did not register the trial or prepublished the trial design. The primary outcome of this meta-analysis (mortality) is not reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Chen et al. 2012 [34]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided into two groups" Comment: unclear information on selection bias.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	Blinding was not applied.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated, probably not. Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Unclear risk	Not specified.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Chen et al. 2013 [4]

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A permuted block randomization scheme stratified by clinical site was performed using an automated web-based system". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "A permuted block randomization scheme stratified by clinical site was performed using an automated web-based system". Comment: probably done, as an automated web-based system also ensures allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote from supplements: "Clinical personnel, investigators, and the patients will be blinded" and "For each of the two strategies (nesiritide vs. placebo and dopamine vs. placebo), the treatment assignments will be double-blinded". Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote from supplements: "Clinical personnel, investigators, and the patients will be blinded" and "The primary safety endpoint will be change in serum cystatin C from randomization to 72 hours, based on a standardized, blinded core lab assessment" and "All patients will have a telephone visit at day 60 to assess vital status and any potential rehospitalizations. Mortality data will be collected at 6 months via telephone call" Comment: Although it is unclear if the outcome assessors of mortality and rehospitalizations were blinded for the treatment group, they had a 100% follow-up and these hard endpoints are probably low risk.
Incomplete outcome data (attrition bias)	Low risk	<10% of all randomized patients were excluded due to various reasons. Quote supplements: "Handling of Dropouts and Missing Data: If patient did not die before the 6-month follow-up, they will be considered to be a censored observation as of last contact". Comment: probably low risk.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported and prespecified in a protocol.
Other bias	High risk	Seen manuscripts quote on: "All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Funding/Support: This work was supported by grants from the National Heart, Lung, and Blood Institute (NHLBI)" Comment: high risk of industry bias.

Costa et al. 1990 [12]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "'Randomly divided into three groups". Comment: no description of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Quote: "Because six patients were disqualified from the study, groups D and DN included nine patients each." Comment: probably high risk, as excluding 17% of the randomized patients could result in substantial inequality in patient characteristics between both groups.
Selective reporting (reporting bias)	High risk	The authors did not register the trial or prepublished the trial design. The primary outcome of this meta-analysis (mortality) is not reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Cotter et al. 1997 [9]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized by lottery into three groups". Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	High risk	Quote: "It was decided to discontinue the study because of the severe adverse side effects". Comment: probably high risk, however data was used in our meta-analysis: the mention of early stopping of a trial has been removed, because (i) simulation evidence suggests that inclusion of stopped early trials in meta-analyses will not lead to substantial bias, and (ii) exclusion of stopped early trials has the potential to bias meta-analyses towards the null (as well as leading to loss of precision).
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. Despite describing the prespecified outcomes; the outcome adverse events is very short and one might argue that more adverse events were to be expected considering the population studied.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

De Backer et al. 2010 [35]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Qoute: "Randomization was performed in computer-generated, permuted blocks of 6 to 10". Quote (clinicaltrials.gov): "Randomization by blocks for each participating ICU, using a computer generated list to allocate treatments A or B, put in sealed envelopes near the drug supplies". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Treatment assignments and a five-digit reference number were placed in sealed, opaque envelopes, which were opened by the person responsible for the preparation of the trial-drug solutions". Quote (clinicaltrials.gov): "In each ICU, sealed envelopes including treatment allocation and a five digit number will be available. The envelope will be opened by the person responsible for preparation of the dopamine and norepinephrine solutions. The random number and treatment allocation will be written on a hidden book, available only for the person responsible for preparation of the dopamine and norepinephrine solutions". Comment: probably done.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The doctors and nurses administering the drugs, as well as the local investigators and research personnel who collected data, were unaware of the treatment assignments". Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The doctors and nurses administering the drugs, as well as the local investigators and research personnel who collected data, were unaware of the treatment assignments". Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: "data on the outcome during the stay in the hospital were available for 1656 patients (98.6%)". Comment: probably low risk, because of high incidence of primary outcome (50%) and small percentage of missing data.
Selective reporting (reporting bias)	Low risk	All measured outcomes were reported and prespecified in a protocol.
Other bias	Low risk	Quote: "Supported in part by the European Society of Intensive Care through support from the European Critical Care Research Network. Dr. Aldecoa reports receiving consulting fees from Covidien. No other potential conflict of interest relevant to this article was reported." Quote: "the mention of early stopping of a trial has been removed, because (i) simulation evidence suggests that inclusion of stopped early trials in meta-analyses will not lead to substantial bias, and (ii) exclusion of stopped early trials has the potential to bias meta-analyses towards the null (as well as leading to loss of precision)". Comment: probably low risk of other bias.

Dzhaiani et al. 2011 [56]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	**High risk – REMOVED**	Quote: "divided by simple randomization into 2 groups." (even numbers 1st group, uneven 2nd group). Comment: not random and predice-Table allocation. **QUASI RANDOMISED TRIAL**
Allocation concealment (selection bias)	High risk	Quote: "divided by simple randomization into 2 groups." (even numbers 1st group, uneven 2nd group). Comment: not random and predice-Table allocation.
Blinding of participants and personnel (performance bias)	High risk	Quote: "A pilot prospective one-center open-ended randomized trial". Comment: not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not described. Probably not blinded because it was an open-label trial.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Gao et al. 2008 [37]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "44 patients included in this study were randomly divided into two groups". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done.
Incomplete outcome data (attrition bias)	Low risk	Data and follow-up of all patients were reported.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. Also, the trial does not state their primary and secondary outcomes.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Gatot et al. 2004 [36]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly and blindly assigned". Comment: method of randomization unclear. Comment: unclear, as a similar trial by these investigators included the same phrase yet did not elaborate on method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as a similar trial by these investigator report: "Treatment allocation was made with the sealed envelope method", however they do not report anything on opacity and numbering.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Dopamine and saline were provided in code uniformly appearing 10 mL syringes. The content of the syringes was unknown to the caring staff and to the investigators." Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Dopamine and saline were provided in code uniformly appearing 10 mL syringes. The content of the syringes was unknown to the caring staff and to the investigators." Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: ""A total of 89 patients were initially enrolled in the study. Four patients were excluded from the study - two due to reoperation for postoperative bleeding, one due to high blood pressure and postoperative atrial fibrillation, and one due to mechanical ventilation for more than 24 hours". Comment: Small percentage of drop-out and plausible reasons for exclusion. Probably low risk.
Selective reporting (reporting bias)	High risk	The authors did not register the trial or prepublished the trial design. The primary outcome of this meta-analysis (mortality) is not reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Giamouzis et al. 2010 [5]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subsequently allocated to one of two treatment strategies in a double-blind randomized fashion". Comment: Probably done properly, as a similar trial by these investigators state that "Randomization was based on a sequence of binary numbers. In detail, for each consecutive patient of our clinic we assigned a sequence of random binary numbers (ie, 1,1,1,0,1,0,1,1,0,1…) that assisted to allocate participants into the 2 treatment arms. For example if a patient was assigned to number 1, he/she was treated with levosimendan, if he/she was assigned to number 0, he/she was not treated with levosimendan. No blocking or stratification was performed. The treatment code was not known to the physician of the study. The randomization system was created by a special software (STATA, STATA Corp, College Station, Texas 77845 USA, data command: sample # [if exp] [in range] [, count by (groupvars)])".
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were subsequently allocated" Comment: unclear information on this risk of bias. Similar trials by these investigators also do not elaborate on their allocation concealment.

Blinding of participants and personnel (performance bias)	Low risk	Quote: "randomized double-blind study" Comment: Probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All measurements were performed by one investigator in each hospital who was blinded with respect to treatment allocation" Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: "One hundred eighty-seven consecutive ADHF patients were screened for the study... A total of 60 patients fulfilled all inclusion criteria and were enrolled in the study". Comment: probably low risk, as all allocated patients completed the trial and withdrawals were before randomization and according to the exclusion criteria.
Selective reporting (reporting bias)	Low risk	Quote: "All primary and secondary outcomes were prespecified in the protocol". Comment: probably low risk, as all outcome measures are reported and the protocol was registered at clinicaltrials.gov.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Hausen et al. 1992 [17]

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were allocated to either group according to randomization tables provided by the Statistical Program for the Social Sciences (SPSS)." Comment: probably done.
Allocation concealment (selection bias)	High risk	Quote: "Patients were allocated to either group according to randomization tables provided by the Statistical Program for the Social Sciences (SPSS)." Comment: probably high risk. The researchers could probably access these randomization tables and therefore were aware of the allocation. Furthermore, no details on allocation method described and previous trials from the same researchers also do not elaborate on allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. probably not done. Comment: low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "There are no reports regarding late death in any case". Comment: probably none lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. Also, the trial does not state their primary and secondary outcomes.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Hsueh et al. 1998 [7]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized to either". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated. Dosages of both interventions were similar.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The ECGs were further edited and analyzed by an experienced cardiologist not involved in the study". Comment: not involved in the study means that this outcome assessor was probably not aware of the assigned treatment.
Incomplete outcome data (attrition bias)	Low risk	Data and follow-up of all patients were reported.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All hemodynamic variables in methods section are described in the results.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Hua et al. 2005 [38]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to one of two study groups using a computer-generated random number table". Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality outcomes, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "None of the enrolled patients died during the study period" and "Of the 72 patients with ARDS and shock who met the inclusion criteria of the study, 40 were excluded due to prior catecholamine therapy (n = 27), severe cardiovascular disorders (n = 6), and severe liver or renal dysfunction (n = 7)." Comment: no patients lost to follow-up. Probably low risk, as all allocated patients completed the trial and withdrawals were before allocation.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes mentioned in methods section are described in the results.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Kamiya et al. 2015 [1]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to". Comment:No further details described and previous trials from the same researchers also do not elaborate on allocation concealment.
Allocation concealment (selection bias)	Unclear risk	No details on allocation method described and previous trials from the same researchers also do not elaborate on allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Quote: "This study was a prospective, open-labeled". Comment: personnel was not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality outcomes, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Data and follow-up of all patients were reported.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes described in the methods section, including mortality and SAEs, are described in the results.
Other bias	Low risk	Quote: "The authors report no conflicts of interest".

Kanchi et al. 2017 [53]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to". Comment:No further details described and previous trials from the same researchers also do not elaborate on allocation concealment.
Allocation concealment (selection bias)	Unclear risk	No details on allocation method described and previous trials from the same researchers also do not elaborate on allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Quote: "This study was a prospective, open-labeled". Comment: personnel was not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality outcomes, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Data and follow-up of all patients were reported.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes described in the methods section, including mortality and SAEs, are described in the results.
Other bias	Low risk	Quote: "The authors report no conflicts of interest".

Lassnigg et al. 2000 [39]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "block randomization (sealed envelopes)". Email first author: "Computer generated block randomization (statgraphics old version)" Comment: probably low risk.
Allocation concealment (selection bias)	Low risk	Quote: "block randomization (sealed envelopes)". Email first author: "Opaque envelopes were used and drugs were prepared by the director of the study (PI) not involved in any patient evaluation or data collection." Comment: probably low risk.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study medications and placebo were provided in uniformly appearing 50-ml syringes blinded to attending physicians and nurses involved in intra- and postoperative care." Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote from personal correspondence: "The caregivers and the study personal were blinded to the study medication". Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: "Three patients were excluded after randomization. One patient in group F and two in group P required reoperation because of bleeding" and "None of the three patients who were excluded developed ARI". Comment: Only 3 of the 126 allocated excluded due to plausible reasons. Clinical outcomes of excluded patients are clearly described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes mentioned in methods are reported in results section.
Other bias	Low risk	Email first author: "No conflict of interest. No pharmaceutical company involved in any stage of the trial. Drugs available in routine care at that time were used."

Liu et al. 2010 [40]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No statement on randomization and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. Probably not done. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	All patients seemed to have completed the follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. No primary or secondary outcome measures reported in the methods section.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Marik et al. 1994 [41]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized using a random-number generator to receive". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Email first author: "white sealed envelopes (non translucent) were used". Comment: unclear, as two similar trials by these investigators also do not report additional information on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably high risk.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	All patients seemed to have completed the follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes mentioned in methods are reported in results section.
Other bias	Low risk	Email from first author (prof. Marik): "There were NO conflicts of interest".

Martin et al. 1993 [42]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not described. Comment: unclear, as two similar trials by these investigators also do not report additional information on their randomization method.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as two similar trials by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "At no time was the physician in charge of the patient aware of the drug being infused". Comment: probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "Fifteen patients were discharged from the hospital". Comment: probably all patients had complete follow-up until hospital discharge.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. No primary or secondary outcome measures reported in the methods section.
Other bias	High risk	Possible carry-over effect in cross-over design. The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Mathur et al. 2007 [43]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomization not described. Comment: probably done properly, as one similar trial by these investigators report to have used "a computer-generated table" for randomization sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Quote: "The person who manipulated the syringe pump knew what drug the patient was receiving and what were the set aliquots for that drug." Comment: not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The outcome assessors were blinded to the drug the patient was receiving." Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Probably all patients had complete follow-up until hospital discharge.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome mentioned in methods ("goal of therapy achieved") is reported in results section.
Other bias	Low risk	Quote: "Source of Support: Nil, Conflict of Interest: None declared". Comment: probably low risk.

Myles et al. 1993 [44]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised into either group according to a e-Table of random numbers" Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "randomised into either group according to a e-Table of random numbers, arranged by the hospital Pharmacy Department". Comment: probably done properly, as central allocation was used.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "It was a prospective, double-blind, randomised trial". Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The coded 50 ml syringes were prepared by pharmacy, with the contents remaining unknown by the investigators until the end of the trial". Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: "There were three withdrawals (one patient withdrew consent before commencement of surgery after discussion with their spouse, one patient was haemofiltered during cardiopulmonary bypass to correct dilutional anaemia, one patient required an intra-aortic balloon pump following return to the operating theatre for continued bleeding and pericardia! tamponade)." Comment: Only 3 of the 52 allocated were withdrawn and reasons are well described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcomes mentioned in methods are reported in results section.
Other bias	Low risk	Email author: "there were no conflicts of interest."

Oppizzi et al. 1997 [11]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to 2 groups". Comment: unclear, as one similar trial by these investigators also did not elaborate on their method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably high risk.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Probably all patients had complete follow-up until hospital discharge.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcomes mentioned in methods are well defined and reported in results section.
Other bias	High risk	Possible carry-over effect in cross-over design. The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Patel et al. 2010 [57]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	**High risk - REMOVED**	Quote: "Randomized by day of month". Comment: high risk, as randomization on day of the month is 'quasi-random'. QUASI RANDOMISED TRIAL
Allocation concealment (selection bias)	High risk	Quote: "Randomization was based on whether the patient presented on an odd or even calendar day of the month". Comment: allocation could not be concealed with this quasi-randomization scheme.
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label comparison of DA versus NE" Comment: high risk, as the care givers were aware of the instituted intervention.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not.
Incomplete outcome data (attrition bias)	Low risk	Probably all patients had complete follow-up until hospital discharge.
Selective reporting (reporting bias)	Low risk	The authors registered the trial prior to the start of the study. The outcomes mentioned in methods are well defined and reported in results section.
Other bias	Low risk	Quote: "The dopamine versus norepinephrine trial was not funded. None of the authors have any financial involvement or commercial association that might pose a real or perceived conflict of interest in connection with this study." Comment: probably low risk.

Rosseel et al. 1997 [15]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "to a randomisation list with balanced blocks of four within each centre". Comment: Probably done properly.
Allocation concealment (selection bias)	Low risk	Quote: "The drugs were supplied by the hospital pharmacist as a blinded, prepared infusion according to a randomisation list with balanced blocks of four within each centre." Comment: Probably done properly, as central allocation was used.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The randomisation list with the patient study number and the matching study medication was not revealed to the investigator or anyone else involved in the study in order to maintain the blind." Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The randomisation list with the patient study number and the matching study medication was not revealed to the investigator or anyone else involved in the study in order to maintain the blind." Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Probably all patients had complete follow-up until hospital discharge.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcomes mentioned in methods are well defined and reported in results section.
Other bias	High risk	The last author is employed at Speywood Pharmaceuticals. Comment: probably high risk.

Schmoelz et al. 2006 [45]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was performed using a computer-generated randomization table". Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: "the drug infusions were prepared by a study nurse who was not involved in the care of the patients". Comment: unclear, study nurse could be aware of the prognosis of the patient. Another trial from this research group also did not include a statement on allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "the drug infusions were prepared by a study nurse who was not involved in the care of the patients". Comment: probably blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described. Comment: unclear. Low risk for mortality and renal replacement therapy.
Incomplete outcome data (attrition bias)	Low risk	Quote: "One patient from each group was excluded from the trial because of a protocol violation". Comment: only 3/61 excluded and reason for exclusion is described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The hypotheses and endpoints mentioned in methods are well defined and reported in results section.
Other bias	Unclear risk	Study supported by grant from the Elan Corporation (drug firm).

		Comment: it is unclear to what extent the Elan Corporation was involved in the trial

Schneider et al. 1999 [46]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated". Comment: unclear information, as a previous trial of the same group also did not describe their method of randomization.
Allocation concealment (selection bias)	Unclear risk	Quote: "contents of a sealed envelope in a 2 x 2 factorial structure". Comment: unclear information on opacity and sequential opening. A previous trial of the same group also did not elaborate on their allocation concealment method.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Clinicians involved with the case were blinded to the study drug". Comment: probably done.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described. Comment: unclear. Low risk for mortality, high risk for SEAs.
Incomplete outcome data (attrition bias)	Low risk	Quote: "One patient (group 2) had to be withdrawn from the study because of damage to the gastric tonometer balloon". Comment: only 1/101 included patients is withdraw after allocation and the reason is well described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and include both mortality and SAEs.
Other bias	Low risk	Quote: "This study was supported by grants from the Australian and New Zealand College of Anaesthetists and the Australian Society of Anaesthetists". Comment: probably low risk.

Shah et al. 2014 [2]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "they were randomized into three groups". Comment: Probably done properly, as a similar trial by these investigators state that they used a "simple random method" for randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "One patient each expired in the infusion þ dopamine group and bolus group during first 24 h of index hospitalization and one patient in infusion group got discharged against medical advice within 24 h of admission. These three patients were excluded." Comment: only 3/93 excluded and reasons for withdrawal are well described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and reported in results section.
Other bias	Low risk	Quote: "Conflict of interest: All authors have none to declare".

Sharpe et al. 1999 [47]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were prospectively randomized". Comment: unclear, as a similar trial by these investigators also did not elaborate on their method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "An unmarked syringe of the study agent was then infused at a predetermined rate." Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All observations were made by a single blinded observer". Comment: probably done.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "All patients left intensive care on the first postoperative day". Comment: no lost to follow-up in this short period of time, however one might argue that this follow-up period is too short for a reliable assessment of mortality.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and reported in results section.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Sinclair et al. 1997 [48]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated". Comment: unclear, as a similar trial by these investigators also did not elaborate on their method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Quote: "allocated to receive an infusion of either dopexamine 2.0 mg/kg per min, or dopamine 2.5 mg/kg per min" Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Quote: "Urinary analysis was blinded to which pharmacological agent the patient had received." Comment: assessors of the clinical outcome were probably not blinded.
Incomplete outcome data (attrition bias)	Low risk	All patients were follow-up until the end of the follow-up period (In-hospital).
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and reported in results section.
Other bias	High risk	Quote: "Our work was supported, in part, by a grant from Speywood Pharmaceuticals (UK) Ltd". Comment: probably high risk of industry bias.

Sindone et al. 1998 [8]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described in abstract.
Allocation concealment (selection bias)	Unclear risk	Not described in abstract.
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated in abstract.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated in abstract.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear from abstract.
Selective reporting (reporting bias)	High risk	High risk: one treatment arm terminated prematurely.
Other bias	Unclear risk	The abstract does not contain a statement on conflicts of interest or financial disclosures.

Sirivella et al. 2000 [14]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized either to receive". Comment: unclear, as a similar trial by these investigators also did not elaborate on their method of randomization.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Quote: "Criteria for dialysis were the same in both groups, and were established and carried out by the nephrologists of this institution; in none of the patients was the dialysis given either prematurely or postponed because of bias." Comment: the nephrologists were probably aware of the treatment allocation.
Incomplete outcome data (attrition bias)	Unclear risk	No patients seemed to be lost to follow-up. However one might argue that the follow-up period is too short to assess the true number of mortality and SAEs.
Selective reporting (reporting bias)	High risk	The authors did not register the trial or prepublished the trial design. The primary outcome of this meta-analysis (mortality) is not reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Soliman et al. 2017 [54]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization through a process of coin-tossing" Comment: low risk according to the Cochrane handbook.
Allocation concealment (selection bias)	Unclear risk	Quote: "simple randomization through a process of coin-tossing" Comment: unclear description of allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study medication was prepared in 50 ml syringe by nursing staff and given to the anesthetist blindly" Comment: probably low risk
Blinding of outcome assessment (detection bias)	Unclear risk	Not described.
Incomplete outcome data (attrition bias)	Low risk	All included patients completed the study and none seemed to be lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and reported in results section.
Other bias	Low risk	Quote: "There are no conflicts of interest."

Sumeray et al. 2001 [49]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised patients according to a e-Table of random numbers". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "The Pharmacy Department (UCLH) randomised patients". Comment: probably done properly as allocation was performed centrally.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Participating physicians and nursing staff were blinded to the syringe contents until the conclusion of the trial".
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated. Probably not done. Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Low risk	Quote: "2 patients were excluded due to technical error with baseline GFR measurement".. and "data sets were incomplete for 7 patients discharged prior to the second GFR measurement". Comment: Only 2/46 were excluded after allocation and reasons for exclusion are well described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. The outcome measures are mentioned in methods and reported in results section.
Other bias	Low risk	Quote: "This study was supported by grants from North Thames NHS R&D Responsive Funding Group, the Royal College of Surgeons of Edinburgh and the Society of Cardiothoracic Surgeons of Great Britain and Ireland". Comment: probably low risk.

Tarr et al. 1993 [16]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated". Comment: unclear, as a similar trial by these investigators also did not elaborate on their method of randomization

Allocation concealment (selection bias)	Unclear risk	Not described. Comment: unclear, as one similar trial by these investigators also did not include a statement on their allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "ideal values and accepe-Table ranges were set for each individual patient.... by an anaesthetist outside of the study group, who was blinded to the patient's drug allocation." Comment: probably done.
Blinding of outcome assessment (detection bias)	Low risk	Not stated. Probably not done. Comment: Low risk for mortality.
Incomplete outcome data (attrition bias)	High risk	This trial excluded patients who not responded to therapy.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. Follow-up on mortality was only reported for all included patients (not only the succesfully treated patients).
Other bias	High risk	Possible carry-over effect in cross-over design. The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Triposkiadis et al. 2014 [3]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients with ADHF were randomly assigned in a 1:1:1 ratio to: a) HDF, b) LDFD, or c) LDF arms using randomization method based on random number generation." Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: "were subsequently randomized". Comment: unclear information on this risk of bias. Similar trials by these investigators also do not elaborate on their allocation concealment.
Blinding of participants and personnel (performance bias)	High risk	Quote: "single blind, randomized trial". Comment: the paper only describes that outcome assessors were blinded, treating physicians were probably aware of the assigned intervention.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "An investigator in each hospital who was blinded to the treatment allocation performed all measurements" and: "Investigators locally at the participating sites adjudicated all outcomes events and adverse events". Comment: probably done.
Incomplete outcome data (attrition bias)	Low risk	Quote: "Four hundred and twenty-seven consecutive patients were screened. Of the 212 who had oxygen saturation b90% and qualified for participation, 51 patients were further excluded (14 severe aortic stenosis, 11 acute coronary syndrome, 8 severe mitral regurgitation, and 17 refused to participate). A total of 161 patients fulfilled all criteria and were enrolled" and: "No patient was lost to follow-up". Comment: probably low risk, as all allocated patients completed the trial and withdrawals were before allocation according to the exclusion criteria.
Selective reporting (reporting bias)	Low risk	The authors registered the trial prior to the start of the study. All measured outcomes mentioned in the methods section were reported.
Other bias	Low risk	Quote: "The study was not sponsored by industry support and was funded locally." Comment: probably done.

Varriale et al. 1997 [10]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized consecutively to one of two treatment strategies". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized consecutively to one of two treatment strategies". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated.
Incomplete outcome data (attrition bias)	Low risk	All included patients completed the study and none seemed to be lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcome measures are reported
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Woo et al. 2002 [50]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized into two groups". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomized into two groups". Comment: no details on allocation method described and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	No statement on blinding. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	No statement on blinding. Comment: probably not blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Forty-two of the 50 patients enrolled completed the study". Comment: Reasons for exclusion of the 8 patients (< 10%) are well described.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcome measures are reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Wu et al. 2011 [52]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "received dopamine or noradrenaline randomly". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done.
Incomplete outcome data (attrition bias)	Low risk	All included patients completed the study and none seemed to be lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. All outcome measures are reported.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

Zhuangyu et al. 2005 [51]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided into two groups". Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Allocation concealment (selection bias)	Unclear risk	Not described. Comment: insufficient information and no previous trials from the same researchers are available for additional information.
Blinding of participants and personnel (performance bias)	High risk	Blinding not described, however dosing schemes of both interventions differed. Comment: probably not blinded.
Blinding of outcome assessment (detection bias)	High risk	Not stated. Probably not done.
Incomplete outcome data (attrition bias)	Low risk	All included patients completed the study and none seemed to be lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	The authors did not register the trial or prepublished the trial design. No outcome measures reported in the methods section.
Other bias	Unclear risk	The manuscript does not contain a statement on conflicts of interest or financial disclosures.

4. References

1. Kamiya M, Sato N, Nozaki A, Akiya M, Okazaki H, Takahashi Y, et al. Renal effects of added low-dose dopamine in acute heart failure patients with diuretic resistance to natriuretic peptide. J Cardiovasc Pharmacol 2015 March 01;65(3):282-288.

2. Shah RA, Subban V, Lakshmanan A, Narayanan S, Udhayakumaran K, Pakshirajan B, et al. A prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure. Indian Heart J 2014 June 01;66(3):309-316.

3. Triposkiadis FK, Butler J, Karayannis G, Starling RC, Filippatos G, Wolski K, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. Int J Cardiol 2014 Mar 1;172(1):115-121.

4. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA 2013 Dec 18;310(23):2533-2543.

5. Giamouzis G, Butler J, Starling RC, Karayannis G, Nastas J, Parisis C, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail 2010 Dec;16(12):922-930.

6. Arutiunov GP, Arutiunov AG, Volkova AL. Study evaluating the impact of a combination of inotropic support and heart rate control on prognosis and stabilization rate in patients with decompensated chronic heart failure (LEGION). Ter Arkh 2010;82(3):47-52.

7. Hsueh CW, Lee WL, Chen CK, Ho HY, Chen CP, Huang JL, et al. Dopamine and dobutamine have different effects on heart rate variability in patients with congestive heart failure. Zhonghua Yi Xue Za Zhi (Taipei) 1998 April 01;61(4):199-209.

8. Sindone, A, MacDonald, P, K, A. Haemodynamic, neurohumoral and symptomatic effects of dobutamine, dopamine and milrinone in severe heart failure. Aust N Z J Med 1998;28:113.

9. Cotter G, Weissgarten J, Metzkor E, Moshkovitz Y, Litinski I, Tavori U, et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. Clin Pharmacol Ther 1997 August 01;62(2):187-193.

10. Varriale P, Mossavi A. The benefit of low-dose dopamine during vigorous diuresis for congestive heart failure associated with renal insufficiency: does it protect renal function? Clin Cardiol 1997 July 01;20(7):627-630.

11. Oppizzi M, Montorsi E, Tosoni A, Casati V, Venturino M, Franco A, et al. The effectiveness of enoximone in patients with serious left ventricular dysfunction submitted for aorto-coronary bypass. Minerva Anestesiol 1997 February 01;63(1-2):17-27.

12. Costa P, Ottino GM, Matani A, Pansini S, Canavese C, Passerini G, et al. Low-dose dopamine during cardiopulmonary bypass in patients with renal dysfunction. J Cardiothorac Anesth 1990 August 01;4(4):469-473.

13. Bove T, Landoni G, Calabro MG, Aletti G, Marino G, Cerchierini E, et al. Renoprotective action of fenoldopam in high-risk patients undergoing cardiac surgery: a prospective, double-blind, randomized clinical trial. Circulation 2005 June 21;111(24):3230-3235.

14. Sirivella S, Gielchinsky I, Parsonnet V. Mannitol, furosemide, and dopamine infusion in postoperative renal failure complicating cardiac surgery. Ann Thorac Surg 2000 February 01;69(2):501-506.

15. Rosseel PM, Santman FW, Bouter H, Dott CS. Postcardiac surgery low cardiac output syndrome: dopexamine or dopamine? Intensive Care Med 1997 September 01;23(9):962-968.

16. Tarr TJ, Moore NA, Frazer RS, Shearer ES, Desmond MJ. Haemodynamic effects and comparison of enoximone, dobutamine and dopamine following mitral valve surgery. Eur J Anaesthesiol Suppl 1993;8:15-24.

17. Hausen B, Heublein B, Vogelpohl J, von der Leyen H, Haverich A. Comparison of enoximone and piroximone in patients after mitral valve operation: a prospective and controlled clinical study. J Cardiovasc Pharmacol 1992 March 01;19(3):299-307.

18. Johri AM, Picard MH, Newell J, Marshall JE, King ME, Hung J. Can a teaching intervention reduce interobserver variability in LVEF assessment: a quality control exercise in the echocardiography lab. JACC Cardiovasc Imaging 2011 August 01;4(8):821-829.

19. Cole GD, Dhutia NM, Shun-Shin MJ, Willson K, Harrison J, Raphael CE, et al. Defining the real-world reproducibility of visual grading of left ventricular function and visual estimation of left ventricular ejection fraction: impact of image quality, experience and accreditation. Int J Cardiovasc Imaging 2015 October 01;31(7):1303-1314.

20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015 Mar;16(3):233-270.

21. Rao V, Ivanov J, Weisel RD, Ikonomidis JS, Christakis GT, David TE. Predictors of low cardiac output syndrome after coronary artery bypass. J Thorac Cardiovasc Surg 1996 Jul;112(1):38-51.

22. Maganti M, Badiwala M, Sheikh A, Scully H, Feindel C, David TE, et al. Predictors of low cardiac output syndrome after isolated mitral valve surgery. J Thorac Cardiovasc Surg 2010 October 01;140(4):790-796.

23. Algarni KD, Maganti M, Yau TM. Predictors of low cardiac output syndrome after isolated coronary artery bypass surgery: trends over 20 years. Ann Thorac Surg 2011 November 01;92(5):1678-1684.

24. Pieri M, Belletti A, Monaco F, Pisano A, Musu M, Dalessandro V, et al. Outcome of cardiac surgery in patients with low preoperative ejection fraction. BMC Anesthesiol 2016 October 18;16(1):97.

25. Matyal R, Hess PE, Subramaniam B, Mitchell J, Panzica PJ, Pomposelli F, et al. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. J Vasc Surg 2009 July 01;50(1):70-76.

26. Flu WJ, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, et al. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. Anesthesiology 2010 June 01;112(6):1316-1324.

27. Jardin F, Fourme T, Page B, Loubieres Y, Vieillard-Baron A, Beauchet A, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. Chest 1999 November 01;116(5):1354-1359.

28. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008 June 01;36(6):1701-1706.

29. Keller H, Bezjak V, Stegaru B, Buss J, Holm E, Heene DL. Ventricular function in cirrhosis and portasystemic shunt: a two-dimensional echocardiographic study. Hepatology 1988 June 01;8(3):658-662.

30. Grose RD, Nolan J, Dillon JF, Errington M, Hannan WJ, Bouchier IA, et al. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. J Hepatol 1995 March 01;22(3):326-332.

31. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. Ann Gastroenterol 2015 March 01;28(1):31-40.

32. Birnbaum DE, Preuner JG, Gieseke R, Trenk D, Jaehnchen E. Enoximone versus dopamine in patients being weaned from cardiopulmonary bypass. Cardiology 1990;77 Suppl 3:7.

33. Carcoana OV, Mathew JP, Davis E, Byrne DW, Hayslett JP, Hines RL, et al. Mannitol and dopamine in patients undergoing cardiopulmonary bypass: a randomized clinical trial. Anesth Analg 2003 November 01;97(5):1222-1229.

34. Chen H, Zeng Z. Comparison of the effect and complication between dopamine and norepinephrine on treatment of the septic shock. Jiangxi Medical Journal 2012;47:565-567.

35. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010 Mar 4;362(9):779-789.

36. Gatot I, Abramov D, Tsodikov V, Yeshayahu M, Orman S, Gavriel A, et al. Should we give prophylactic renal-dose dopamine after coronary artery bypass surgery? J Card Surg 2004 April 01;19(2):128-133.

37. Gao J, Li X, Wang A. Impact of dopamine and norepinephrine on renal perfusion in patients with septic shock. Journal of Hebei Medicine 2008;30:1188-1121.

38. Hua F, Wang X, Zhu L. Terlipressin decreases vascular endothelial growth factor expression and improves oxygenation in patients with acute respiratory distress syndrome and shock. J Emerg Med 2013 February 01;44(2):434-439.

39. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 2000 January 01;11(1):97-104.

40. Liu P, Chen T, Zhang Y. Comparison evaluation of resuscitation effect of norepinephrine and dopamine on the treatment of septic shock. Clinical Education of General Practice 2010;8:265-267.

41. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA 1994 Nov 2;272(17):1354-1357.

42. Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest 1993 Jun;103(6):1826-1831.

43. Mathur S, Dhunna R, Chakraborty A. Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography. Indian J Crit Care Med 2007;11(4):186-191.

44. Myles PS, Buckland MR, Schenk NJ, Cannon GB, Langley M, Davis BB, et al. Effect of "renal-dose" dopamine on renal function following cardiac surgery. Anaesth Intensive Care 1993 February 01;21(1):56-61.

45. Schmoelz M, Schelling G, Dunker M, Irlbeck M. Comparison of systemic and renal effects of dopexamine and dopamine in norepinephrine-treated septic shock. J Cardiothorac Vasc Anesth 2006 Apr;20(2):173-178.

46. Schneider M, Valentine S, Hegde RM, Peacock J, March S, Dobb GJ. The effect of different bypass flow rates and low-dose dopamine on gut mucosal perfusion and outcome in cardiac surgical patients. Anaesth Intensive Care 1999 February 01;27(1):13-19.

47. Sharpe DA, Mitchel IM, Kay EA, McGoldrick JP, Munsch CM, Kay PH. Enhancing liver blood flow after cardiopulmonary bypass: the effects of dopamine and dopexamine. Perfusion 1999 Jan;14(1):29-36.

48. Sinclair DG, Houldsworth PE, Keogh B, Pepper J, Evans TW. Gastrointestinal permeability following cardiopulmonary bypass: a randomised study comparing the effects of dopamine and dopexamine. Intensive Care Med 1997 May 01;23(5):510-516.

49. Sumeray M, Robertson C, Lapsley M, Bomanji J, Norman AG, Woolfson RG. Low dose dopamine infusion reduces renal tubular injury following cardiopulmonary bypass surgery. J Nephrol 2001 October 01;14(5):397-402.

50. Woo EB, Tang AT, el-Gamel A, Keevil B, Greenhalgh D, Patrick M, et al. Dopamine therapy for patients at risk of renal dysfunction following cardiac surgery: science or fiction? Eur J Cardiothorac Surg 2002 July 01;22(1):106-111.

51. Zhuangyu Y. Affect of norepinephrine and dopamine on infectious tissue oxygen metabolism and hemodynamics in patients with shock. Shandong Medicine Journal 2011;51:93-94.

52. Wu Y, Zhang N, Wu Y, Zheng Y, You X, Cao Z, et al. Effects of dopamine, norepinephrine and dobutamine on gastric mucosal pH of septic shock patients. Exp Ther Med 2016 August 01;12(2):975-978.

53. Kanchi M, Manjunath R, Massen J, Vincent L, Belani K. Neutrophil gelatinase-associated lipocalin as a biomarker for predicting acute kidney injury during off-pump coronary artery bypass grafting. Ann Card Anaesth 2017 September 01;20(3):297-302.

54. Soliman R, Hussien M. Comparison of the renoprotective effect of dexmedetomidine and dopamine in high-risk renal patients undergoing cardiac surgery: A double-blind randomized study. Ann Card Anaesth 2017 December 01;20(4):408-415.

55. Chaiyaroj S, Tatoulis J. Low-dose dopamine in coronary artery bypass patients with preoperative renal dysfunction. Asian Cardiovasc Thorac Ann 1999;7(1):9-12.

56. Dzhaiani NA, Kositsyna IV, Gnidkina NA, Tereshchenko SN. Efficacy of levosimendan vs dopamine in patients with resistant cardiac failure. Ter Arkh 2011;83(6):53-59.

57. Patel GP, Grahe JS, Sperry M, Singla S, Elpern E, Lateef O, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock 2010 Apr;33(4):375-380.