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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Trial	Year	Inclusion criteria	Exclusion criteria	Outcomes
Acute heart fa	ilure			
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 m² 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

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

	•	Chemical markers of renal impairment: urea nitrogen ≥25 mg/dL and creatinine ≥1.5 mg/dL.		
Shah [2]	:	Age \geq 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 \geq 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]		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 <i>LVEF</i> <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]	•	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 m² 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 >¹/₃ 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 m² 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)
Sindone [8] Cardiac surgery	1998		 Not described (abstract only) 	Mortality (1 year)
	1998 2000	 HF of NYHA class IV Manifested with either acute oliguric or anuric renal failure in the postoperative period 	 Acute renal failure associated with inadequate cardiac output and tissue perfusion 	Mortality (1 year) Renal replacement therapy
Cardiac surgery		 HF of NYHA class IV Manifested with either acute oliguric or anuric 	 Acute renal failure associated with inadequate 	
Cardiac surgery Sirivella [14]	2000	 HF of NYHA class IV Manifested with either acute oliguric or anuric renal failure in the postoperative period Adequate cardiac output and tissue perfusion Cardiac surgery requiring cardiopulmonary bypass Preoperative renal dysfunction: creatinine 	 Acute renal failure associated with inadequate cardiac output and tissue perfusion Preoperative renal replacement therapy Usage of enflurane 	Renal replacement therapy

			 Pregnancy 	
Hausen [17]	1992	 Age >18 years Mitral valve operation Mitral valve disease CI <2.5 L/min/m² pre-operatively at rest 	Revascularization proceduresAortic 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

						Test for
	Trials*	Patients	Events	RR or OR	95% CI	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. threearm 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.

Forest plots of mortality 1.3.

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

Study or Subgroup	Dopam Events		Contro Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
2.1.1 All included stu							
Arutiunov 2010	2	21	3	20	3.0%	0.63 [0.12, 3.41]	
3ove 2005	3	40	4	40	4.2%	0.75 [0.18, 3.14]	
Chen 2013	24	122	25	119	34.1%	0.94 [0.57, 1.54]	_ _
Cotter 1997	1	14	0	6	0.9%	1.40 [0.06, 30.23]	
Jiamouzis 2010	3	30	3	30	3.7%	1.00 [0.22, 4.56]	
Hausen 1992	ō	14	Ō	27		Not estimable	
Hsueh 1998	ō	10	ŏ	10		Not estimable	
Kamiya 2015	Ő	12	2	12	1.0%	0.20 [0.01, 3.77]	
Oppizzi 1997	3	13	Ô	13	1.0%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35	1.070	Not estimable	
Shah 2014	1	31	4	61	1.8%		
	0	8	4	8		0.49 [0.06, 4.22]	•
Sindone 1998 Sindone 1998	1	8	2	26	1.1%	0.14 [0.01, 2.39] 1.63 [0.17, 15.66]	
Sindone 1998a		8			1.7%		
Sindone 1998b	1		1	9	1.3%	1.13 [0.08, 15.19]	
Farr 1993a	1	12	3	25	1.8%	0.69 [0.08, 6.00]	
Farr 1993b	1	13	3	25	1.8%	0.64 [0.07, 5.57]	
Friposkiadis 2014	9	28	18	55	19.7%	0.98 [0.51, 1.90]	
Friposkiadis 2014a	10	28	19	50	22.9%	0.94 [0.51, 1.73]	
/arriale 1997	0	10	0	10	400.00	Not estimable	
Subtotal (95% CI)		457		581	100.0%	0.91 [0.68, 1.21]	•
Fotal events	60		90				
Heterogeneity: Tau² = Fest for overall effect:				(P = 0.9	97); I² = 0%	6	
			0				
2.1.2 Worst-best cas	-		2	20	2.00	0 60 (0 40 0 44)	
Arutiunov 2010	2	21	3	20	3.0%	0.63 [0.12, 3.41]	
Bove 2005	3	40	4	40	4.2%	0.75 [0.18, 3.14]	
Chen 2013	24	122	25	119	34.1%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.9%	1.40 [0.06, 30.23]	
∋iamouzis 2010	3	30	3	30	3.7%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	1.0%	0.20 [0.01, 3.77]	
Oppizzi 1997	3	13	0	13	1.0%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
3hah 2014	1	31	4	62	1.8%	0.50 [0.06, 4.29]	
Sindone 1998	0	8	3	8	1.1%	0.14 [0.01, 2.39]	·
Sindone 1998a	1	8	2	26	1.7%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	1.3%	1.13 [0.08, 15.19]	
Farr 1993a	1	12	3	25	1.8%	0.69 [0.08, 6.00]	
Farr 1993b	1	13	3	25	1.8%	0.64 [0.07, 5.57]	
Triposkiadis 2014	9	28	18	55	19.7%	0.98 [0.51, 1.90]	
Triposkiadis 2014	10	28	19	50	22.9%		
/arriale 1997	0	10	19	10	22.370	0.94 [0.51, 1.73] Not estimable	1
Subtotal (95% CI)	U	457	U		100.0%	0.91 [0.68, 1.21]	▲
	20	437		JOZ	100.0%	0.51 [0.00, 1.21]	T
Fotal events	60		90	~ ~ ~	07).17 0.0	r	
Heterogeneity: Tau² = Fest for overall effect:				(F = 0.)	97), I" = 0%	0	
2.1.3 Best-worst cas	o analysis						
Arutiunov 2010	2	21	3	20	3.0%	0.63 [0.12, 3.41]	
3ove 2005	3	40	4	40	4.2%	0.75 [0.18, 3.14]	
Chen 2013	24	122	25	119	34.1%	0.94 [0.57, 1.54]	_ _
Cotter 1997	1	14	0	6	0.9%	1.40 [0.06, 30.23]	
Jiamouzis 2010	3	30	3	30	3.7%	1.00 [0.22, 4.56]	
Hausen 1992	Ő	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	1.0%	0.20 [0.01, 3.77]	
,	3	12	2 0	12			
Oppizzi 1997					1.0%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35	4.000	Not estimable	
Shah 2014	1	31	5	62	1.9%	0.40 [0.05, 3.28]	
Sindone 1998	0	8	3	8	1.1%	0.14 [0.01, 2.39]	·
Bindone 1998a	1	8	2	26	1.7%	1.63 [0.17, 15.66]	
	1	8	1	9	1.3%	1.13 [0.08, 15.19]	
Sindone 1998b	1	12	3	25	1.8%	0.69 [0.08, 6.00]	
Sindone 1998b Farr 1993a		13	3	25	1.8%	0.64 [0.07, 5.57]	
Sindone 1998b	1		18	55	19.7%	0.98 [0.51, 1.90]	_ + _
Sindone 1998b Farr 1993a	1 9	28			22.9%	0.94 [0.51, 1.73]	
3indone 1998b Farr 1993a Farr 1993b		28 28	19	50	22.370		
Sindone 1998b Farr 1993a Farr 1993b Friposkiadis 2014	9		19 0	50 10	22.370		
Sindone 1998b Farr 1993a Farr 1993b Friposkiadis 2014 Friposkiadis 2014a	9 10	28		10	100.0%	Not estimable	•
Sindone 1998b Farr 1993a Farr 1993b Friposkiadis 2014 Friposkiadis 2014a Aarriale 1997 Subtotal (95% CI)	9 10 0	28 10	0	10			•
Sindone 1998b Farr 1993a Farr 1993b Friposkiadis 2014 Friposkiadis 2014a Aarriale 1997 Subtotal (95% CI) Fotal events	9 10 0 60	28 10 457	0 91	10 582	100.0%	Not estimable 0.90 [0.67, 1.21]	•
Sindone 1998b Farr 1993a Farr 1993b Friposkiadis 2014 /arriale 1997 S ubtotal (95% CI) Fotal events Heterogeneity: Tau ² =	9 10 0 60 : 0.00; Chi ^a	28 10 457 ² = 6.08	0 91 3, df = 14 ;	10 582	100.0%	Not estimable 0.90 [0.67, 1.21]	•
Sindone 1998b "arr 1993a "riposkiadis 2014 Triposkiadis 2014 "arriale 1997 Subtotal (95% CI) Total events	9 10 0 60 : 0.00; Chi ^a	28 10 457 ² = 6.08	0 91 3, df = 14 ;	10 582	100.0%	Not estimable 0.90 [0.67, 1.21]	•
iindone 1998b 'arr 1993a 'riposkiadis 2014 'riposkiadis 2014a 'arriale 1997 Jubtotal (95% CI) 'otal events leterogeneity: Tau ² =	9 10 0 60 : 0.00; Chi ^a	28 10 457 ² = 6.08	0 91 3, df = 14 ;	10 582	100.0%	Not estimable 0.90 [0.67, 1.21]	

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

	Dopam		Cont			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.4 Subgroup 1: Lo	w risk of l						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	•						
Test for overall effect:	Not applic	able					
2.1.5 Subgroup 1: Un	clear or h	igh ris	k of bias				
Arutiunov 2010	2	21	3	20	3.0%	0.63 [0.12, 3.41]	
Bove 2005	3	40	4	40	4.2%	0.75 [0.18, 3.14]	
Chen 2013	24	122	25	119	34.1%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.9%	1.40 [0.06, 30.23]	
Giamouzis 2010	3	30	3	30	3.7%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	1.0%	0.20 [0.01, 3.77]	
Oppizzi 1997	3	13	0	13	1.0%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
Shah 2014	1	31	4	61	1.8%	0.49 [0.06, 4.22]	
Sindone 1998	0	8	3	8	1.1%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	1.7%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	1.3%	1.13 [0.08, 15.19]	
Tarr 1993a	1	12	3	25	1.8%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	1.8%	0.64 [0.07, 5.57]	
Triposkiadis 2014	9	28	18	55	19.7%	0.98 [0.51, 1.90]	
Triposkiadis 2014a	10	28	19	50	22.9%	0.94 [0.51, 1.73]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		457		581	100.0%	0.91 [0.68, 1.21]	•
Total events	60		90				
Heterogeneity: Tau² =				(P = 0.	97); I² = 0	%	
Test for overall effect:	Z=0.66 (P = 0.5	1)				
							0.01 0.1 1 10 10
Fest for subaroup diff	ferences: t	Not an	hlicable				Favours dopamine Favours control

Test for subgroup differences: Not applicable

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

	Doparr		Cont			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.6 Subgroup 2: Ina	active con	trol					
Chen 2013	24	122	25	119	60.1%	0.94 [0.57, 1.54]	
Shah 2014	1	31	4	61	3.3%	0.49 [0.06, 4.22]	
Sindone 1998	0	8	3	8	1.9%	0.14 [0.01, 2.39]	•
Triposkiadis 2014	9	28	18	55	34.7%	0.98 [0.51, 1.90]	_
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		199		253	100.0%	0.90 [0.61, 1.33]	+
Total events	34		50				
Heterogeneity: Tau ² =	: 0.00; Chi	² = 2.0!	9, df = 3 (P = 0.5	5); I ² = 0%		
Test for overall effect:	Z=0.53 (P = 0.5	9)				
2.1.7 Subgroup 2: Po	tentially a	ctive c	ontrol				
Arutiunov 2010	2	21	3	20	7.0%	0.63 [0.12, 3.41]	
Bove 2005	3	40	4	40	9.6%	0.75 [0.18, 3.14]	
Cotter 1997	1	14	0	6	2.1%	1.40 [0.06, 30.23]	
Giamouzis 2010	3	30	3	30	8.5%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	2.3%	0.20 [0.01, 3.77]	
Oppizzi 1997	3	13	0	13	2.4%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
Sindone 1998a	1	8	2	26	3.8%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	2.9%	1.13 [0.08, 15.19]	
Tarr 1993a	1	12	3	25	4.2%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	4.2%	0.64 [0.07, 5.57]	
Triposkiadis 2014a	10	28	19	50	52.9%	0.94 [0.51, 1.73]	
Subtotal (95% CI)		258		328	100.0%	0.92 [0.59, 1.43]	•
Total events	26		40				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 3.79	5, df = 10	(P = 0.	96); l² = 0	%	
Test for overall effect:	Z=0.39 (P = 0.7	0)				
							0.01 0.1 1 10 10
Test for subaroup difi							Favours dopamine Favours control

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

	Dopan		Cont			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.8 Subgroup 3: Lov							
Arutiunov 2010	2	21	3	20	6.8%	0.63 [0.12, 3.41]	
Bove 2005	3	40	4	40	9.4%	0.75 [0.18, 3.14]	
Chen 2013	24	122	25	119	77.3%	0.94 [0.57, 1.54]	
Kamiya 2015	0	12	2	12	2.2%	0.20 [0.01, 3.77]	
Rosseel 1997	0	35	0	35		Not estimable	
Shah 2014	1	31	4	61	4.2%	0.49 [0.06, 4.22]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		271		297	100.0%	0.84 [0.54, 1.30]	•
Total events	30		38				
Heterogeneity: Tau ² =	0.00; Chi	² = 1.49	9, df = 4 (P = 0.8	3); I 2 = 0%	6	
Test for overall effect:	Z = 0.78 (P = 0.4	4)				
2.1.9 Subgroup 3: Mo	derate do	ose					
Cotter 1997	1	14	0	6	1.7%	1.40 [0.06, 30.23]	
Giamouzis 2010	3	30	3	30	7.1%	1.00 [0.22, 4.56]	
Hausen 1992	Ō	14	Ō	27		Not estimable	
Hsueh 1998	Ō	10	Ō	10		Not estimable	
Oppizzi 1997	3	13	0	13	2.0%	7.00 [0.40, 123.35]	
Tarr 1993a	1	12	3	25	3.5%	0.69 [0.08, 6.00]	
Tarr 1993b	. 1	13	3	25	3.5%	0.64 [0.07, 5.57]	
Triposkiadis 2014	. 9	28	18	55	37.9%	0.98 [0.51, 1.90]	_
Triposkiadis 2014a	10	28	19	50	44.1%	0.94 [0.51, 1.73]	
Subtotal (95% CI)		162			100.0%	0.98 [0.65, 1.47]	•
Total events	28		46				1
Heterogeneity: Tau ² =		r = 2.13		P = 0.9	0): I 2 = 0.9	6	
Test for overall effect:				, = 0.0	0/11 = 0 /	•	
			-,				
2.1.10 Subgroup 3: Hi	igh dose						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:		cable					
							F
							0.01 0.1 1 10 10
Test for subaroup diff	erences:	Chi² = í	126 df=	1 (P =	0.61) P=	0%	Favours dopamine Favours control

Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), l² = 0%

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

	Dopam		Cont			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.11 Subgroup 4: C	ardiac su	rgery					
Bove 2005	3	40	4	40	47.0%	0.75 [0.18, 3.14]	
Hausen 1992	0	14	0	27		Not estimable	
Oppizzi 1997	3	13	0	13	11.7%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
Tarr 1993a	1	12	3	25	20.7%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	20.6%	0.64 [0.07, 5.57]	
Subtotal (95% CI)		127		165	100.0%	0.93 [0.35, 2.48]	
Total events	8		10				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 2.26	6, df = 3 (P = 0.5	2); I ² = 0%	6	
Test for overall effect:	Z=0.15 (P = 0.8	8)				
2.1.12 Subgroup 4: N	lot having	cardia	c surger	у			
Arutiunov 2010	2	21	3	20	3.3%	0.63 [0.12, 3.41]	
Chen 2013	24	122	25	119	37.4%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	1.0%	1.40 [0.06, 30.23]	
Giamouzis 2010	3	30	3	30	4.1%	1.00 [0.22, 4.56]	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	1.1%	0.20 [0.01, 3.77]	
Shah 2014	1	31	4	61	2.0%	0.49 [0.06, 4.22]	
Sindone 1998	0	8	3	8	1.2%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	1.8%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	1.4%	1.13 [0.08, 15.19]	
Triposkiadis 2014	9	28	18	55	21.6%	0.98 [0.51, 1.90]	+
Triposkiadis 2014a	10	28	19	50	25.1%	0.94 [0.51, 1.73]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		330		416	100.0%	0.90 [0.67, 1.23]	•
Total events	52		80				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 3.69	9, df = 10	(P = 0.1)	96); I² = 0	%	
Test for overall effect:	Z=0.64 (P = 0.5	2)				
Test for subaroup dif	foronoo.	268 - 1	000 df_	1 /D -	0.000 17-	0.07	Favours dopamine Favours control

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), l² = 0%

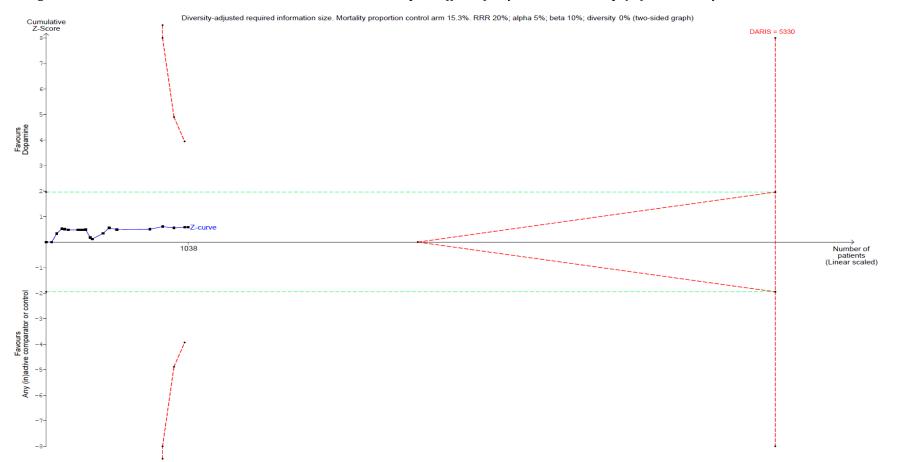
E-Figure 1.1.13: sensitivity analysis – trials including only patients with cardiac dysfunction

	Dopan	nine	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	I M-H, Random, 95% CI	
2.1.13 Pure cardiac	: dysfuncti	on stud	lies					
Arutiunov 2010	2	21	3	20	35.0%	0.63 [0.12, 3.41]]	
Cotter 1997	1	14	0	6	10.5%	1.40 [0.06, 30.23]]	
Hsueh 1998	0	10	0	10		Not estimable	9	
Oppizzi 1997	3	13	0	13	12.0%	7.00 [0.40, 123.35]]	
Rosseel 1997	0	35	0	35		Not estimable	9	
Tarr 1993a	2	25	6	50	42.5%	0.67 [0.14, 3.07]]	
Varriale 1997	0	10	0	10		Not estimable	9	
Subtotal (95% CI)		128		144	100.0%	0.94 [0.35, 2.54]	-	
Total events	8		9					
Heterogeneity: Tau ²	= 0.00; Ch	i² = 2.4	4, df = 3 ((P = 0.4)	9); I ² = 09	6		
Test for overall effec	t: Z = 0.12	(P = 0.9	30)					
								100
								100

Test for subgroup differences: Not applicable

0.01 0.1 1 10 Favours dopamine Favours control

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.

Forest plots of serious adverse events 1.5.

2.2.1 All included studies Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Siamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Camiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Ossseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.20 [0.91, 1.57] Total events 62 51 - - - - Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); P = 2% Test for overall effect Z = 1.29 (P = 0.20) - Not estimable Dipizzi 1997 4 13 1.3 1.8% 4.00 [0.51, 31.13] - Subtotal (95% Cl) 268 314 10.0% 1.20 [0.91, 1.57] - - Total events 62 51		Dopan		Cont			Risk Ratio	Risk Ratio
Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2015 0 12 0 12 Not estimable Oppizi 1997 4 13 1 13 18% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% Cl) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 ($P = 0.40$); $P = 2\%$ Test for overall effect Z = 1.29 ($P = 0.20$) 2.2.2 Worst-best case analysis Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2010 6 31 2 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 55 5.3% 1.19 [0.37, 3.86] Subtotal (95% Cl) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 ($P = 0.40$); $P = 2\%$ Test for overall effect Z = 1.29 ($P = 0.20$) 2.2.3 Best-worst case analysis Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2010 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% Cl) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 ($P = 0.40$); $P = 2\%$ Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% Cl) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 ($P = 0.40$); $P = 2\%$ Test for overall effect Z = 1.29 ($P = 0.20$)	Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Karniya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 14.2] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 50 5.3% 1.13 [0.0, 7, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity. Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); P = 2% Test for overall effect $Z = 1.29$ ($P = 0.20$) 2.2.2 Worst-best case analysis Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.69] Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); P = 2% Test for overall effect $Z = 1.29$ (P = 0.20) Triposkiadis 2014 4 2.28 6 50 5.3% Triposkiadis 2014 4 2.28 6 50 5.3% Triposkiadis 2014 4 2.28 6 50 5.3% Triposkiadis 2014 4 2.29 (P = 0.20) Triposkiadis 2014								
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Test for overall effect: $Z = 1.29$ (P = 0.20) 2.2.3 Best-worst case analysis Chen 2013 19 122 12 119 15.7% 1.54 [0.78, 3.04] Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] 1.20 [0.91, 1.57] Total events 62 51 51 1.29 (P = 0.20) 1.20 [0.91, 1.57]								
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Giamouzis 2010 6 30 2 30 3.2% 3.00 [0.66, 13.69] Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 50 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); l ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	2.2.3 Best-worst cas	e analysi	s					
Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); I ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Chen 2013	19	122	12	119	15.7%	1.54 [0.78, 3.04]	+ •
Kamiya 2015 0 12 0 12 Not estimable Oppizzi 1997 4 13 1 13 1.8% 4.00 [0.51, 31.13] Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); I ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Giamouzis 2010	6	30	2	30	3.2%		
Rosseel 1997 25 35 24 35 68.8% 1.04 [0.77, 1.42] Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); i ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Kamiya 2015	0	12	0	12			
Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau² = 0.00; Chi² = 5.09, df = 5 (P = 0.40); i² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Oppizzi 1997	4	13	1	13	1.8%	4.00 [0.51, 31.13]	
Triposkiadis 2014 4 28 6 55 5.3% 1.31 [0.40, 4.26] Triposkiadis 2014a 4 28 6 50 5.3% 1.19 [0.37, 3.86] Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau² = 0.00; Chi² = 5.09, df = 5 (P = 0.40); i² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Rosseel 1997	25	35	24	35	68.8%	1.04 [0.77, 1.42]	+
Subtotal (95% CI) 268 314 100.0% 1.20 [0.91, 1.57] Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); I ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Triposkiadis 2014	4	28	6	55	5.3%		
Total events 62 51 Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); I ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Triposkiadis 2014a	4	28	6	50	5.3%	1.19 [0.37, 3.86]	
Heterogeneity: Tau ² = 0.00; Chi ² = 5.09, df = 5 (P = 0.40); l ² = 2% Test for overall effect: Z = 1.29 (P = 0.20)	Subtotal (95% CI)		268		314	100.0%	1.20 [0.91, 1.57]	◆
Test for overall effect: Z = 1.29 (P = 0.20)	Total events	62		51				
					P = 0.4	0); I² = 2%	6	
'0.01 0.'1 i 1'0								
								0.01 0.1 1 10 1

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

Test for subgroup differences: $Chi^2 = 0.00$, df = 2 (P = 1.00), $I^2 = 0\%$

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

	Dopam	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.2.4 Subgroup 1: Lov	w risk of t	oias					
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
2.2.5 Subgroup 1: Un	clear or h	igh ris	k of bias				
Chen 2013	30	122	24	119	25.9%	1.22 [0.76, 1.96]	
Giamouzis 2010	6	30	2	30	2.5%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	1.4%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	61.8%	1.04 [0.77, 1.42]	+
Triposkiadis 2014	4	28	6	55	4.2%	1.31 [0.40, 4.26]	
Triposkiadis 2014a	4	28	6	50	4.2%	1.19 [0.37, 3.86]	
Subtotal (95% CI)		268		314	100.0%	1.15 [0.91, 1.47]	•
Total events	73		63				
Heterogeneity: Tau ² =	0.00; Chi ^a	² = 3.96	6, df = 5 (P = 0.5	5); I² = 0%		
Test for overall effect:	Z=1.15 (P = 0.2	!5)				
							0.01 0.1 i 10 100
Test for subgroup diff	erences: N	Vot app	plicable				Favours dopamine Favours control

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

	Dopam	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.2.6 Subgroup 2: Ina	ctive con	trol					
Chen 2013	19	122	12	119	75.2%	1.54 [0.78, 3.04]	-+ -
Triposkiadis 2014 Subtotal (95% CI)	4	28 150	6	55 174	24.8% 100.0%	1.31 [0.40, 4.26] 1.48 [0.82, 2.67]	•
Total events	23		18				
Heterogeneity: Tau ² =	0.00; Chi	= 0.08	6, df = 1 (P = 0.8	1); I² = 0%		
Test for overall effect:	Z=1.31 (P = 0.1	9)				
2.2.7 Subgroup 2: Pot	tentially a	ctive c	ontrol				
Giamouzis 2010	6	30	2	30	12.3%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	7.3%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	62.0%	1.04 [0.77, 1.42]	🖷 -
Triposkiadis 2014a Subtotal (95% CI)	4	28 118	6	50 140	18.4% 100.0%	1.19 [0.37, 3.86] 1.34 [0.75, 2.40]	
Total events	39		33				
Heterogeneity: Tau ² =	0.12; Chi	² = 4.16	6, df = 3 (P = 0.2	5); i² = 28'	%	
Test for overall effect:	•						
Test for subgroup diff							0.01 0.1 1 10 100 Favours dopamine Favours control

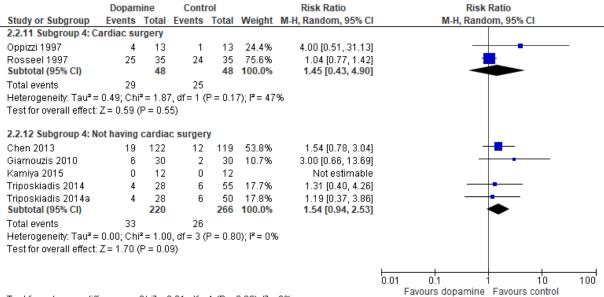
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0\%$

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

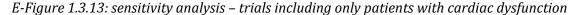
	Dopam	nine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
2.2.8 Subgroup 3: Lov	w dose						
Chen 2013	19	122	12	119	26.8%	1.54 [0.78, 3.04]	
Kamiya 2015	0	12	0	12		Not estimable	
Rosseel 1997	25	35	24	35	73.2%	1.04 [0.77, 1.42]	
Subtotal (95% CI)		169		166	100.0%	1.16 [0.78, 1.71]	◆
Total events	44		36				
Heterogeneity: Tau² =	0.03; Chi	i ² = 1.43	2, df = 1 (l	P = 0.2	3); I² = 29	%	
Test for overall effect:	Z=0.73 ((P = 0.4	6)				
2.2.9 Subgroup 3: Mo	derate do	ose					
Giamouzis 2010	6	30	2	30	20.6%	3.00 [0.66, 13.69]	
Hsueh 1998	0	10	0	10		Not estimable	
Oppizzi 1997	4	13	1	13	11.3%	4.00 [0.51, 31.13]	
Triposkiadis 2014	4	28	6	55	34.0%	1.31 [0.40, 4.26]	
Triposkiadis 2014a	4	28	6	50	34.2%	1.19 [0.37, 3.86]	
Subtotal (95% CI)		109		158	100.0%	1.70 [0.86, 3.39]	★
Total events	18		15				
Heterogeneity: Tau ² =	0.00; Chi	² = 1.7	7, df = 3 (l	P = 0.6	2); I ² = 0%	6	
Test for overall effect:	Z=1.52 ((P = 0.1	3)				
2.2.10 Subgroup 3: Hi	igh dose						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
	. ,						
							0.01 0.1 1 10 100
							Favours dopamine Favours control
Fest for subgroup diff	erences:	Chi² = I).92, df =	1 (P =	0.34), I ^z =	0%	r avours dopannine Favours control

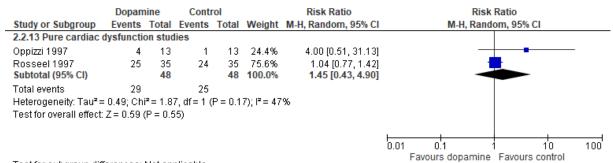
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), l² = 0%

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



Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), $I^2 = 0\%$





Test for subgroup differences: Not applicable

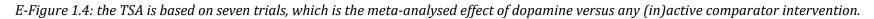
E-Figure 1.3.14: sensitivity analysis – SAEs in all trials including mortality

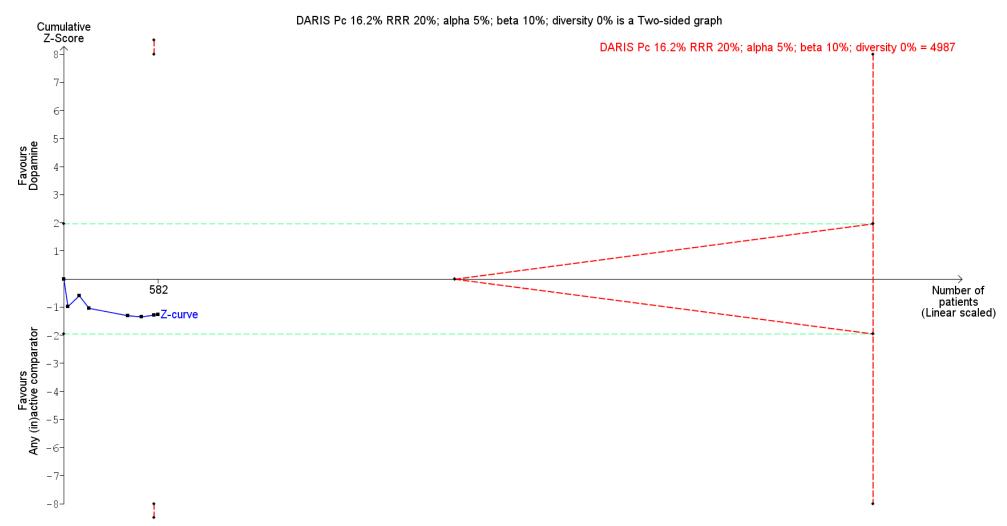
	Dopam	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.2.15 SAEs including	g mortality	1					
Arutiunov 2010	2	21	3	20	1.2%	0.63 [0.12, 3.41]	
Bove 2005	3	40	4	40	1.6%	0.75 [0.18, 3.14]	
Chen 2013	43	122	37	119	25.3%	1.13 [0.79, 1.62]	-
Cotter 1997	1	14	0	6	0.3%	1.40 [0.06, 30.23]	
Giamouzis 2010	9	30	5	30	3.5%	1.80 [0.68, 4.74]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Kamiya 2015	0	12	2	12	0.4%	0.20 [0.01, 3.77]	
Oppizzi 1997	7	13	1	13	0.9%	7.00 [1.00, 49.16]	
Rosseel 1997	25	35	24	35	34.8%	1.04 [0.77, 1.42]	+
Shah 2014	1	31	4	61	0.7%	0.49 [0.06, 4.22]	
Sindone 1998	0	8	3	8	0.4%	0.14 [0.01, 2.39]	·
Sindone 1998a	1	8	2	26	0.6%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.5%	1.13 [0.08, 15.19]	
Tarr 1993a	1	12	3	25	0.7%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	0.7%	0.64 [0.07, 5.57]	
Triposkiadis 2014	13	28	24	55	13.2%	1.06 [0.65, 1.75]	_ _
Triposkiadis 2014a	14	28	25	50	15.3%	1.00 [0.63, 1.59]	-+-
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		457		581	100.0%	1.06 [0.89, 1.27]	•
Total events	122		141				
Heterogeneity: Tau ² =	: 0.00; Chi ^a	²= 9.74	4, df = 15	(P = 0.	84); I ^z = 0	%	
Test for overall effect:	Z = 0.67 (P = 0.5	1)				
							0.01 0.1 1 10 100

Favours dopamine Favours control

Test for subgroup differences: Not applicable

1.6. Trial sequential analysis of serious adverse events





1.7. Forest plots of myocardial infarction

	Dopam		Cont			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.3.1 All included stu	dies						
Arutiunov 2010	3	21	0	20	12.3%	7.76 [0.38, 160.40]	
lausen 1992	2	14	2	27	26.2%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	32.9%	0.65 [0.10, 4.13]	
Triposkiadis 2014	1	28	1	55	14.3%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	14.3%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		139		200	100.0%	1.63 [0.56, 4.71]	-
Total events	9		7				
Heterogeneity: Tau ² =	: 0.00; Chi	²= 2.08	3, df = 4 (P = 0.7	2); I ^z = 0%	6	
Fest for overall effect:	Z=0.90 (P = 0.3	7)				
2.3.2 Worst-best cas	e analysi	s					
Arutiunov 2010	3	21	0	20	12.3%	7.76 [0.38, 160.40]	
Hausen 1992	2	14	2	27	26.2%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	32.9%	0.65 [0.10, 4.13]	
Friposkiadis 2014	1	28	1	55	14.3%	2.00 [0.12, 33.22]	
riposkiadis 2014a	1	28	1	50	14.3%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		139		200	100.0%	1.63 [0.56, 4.71]	-
Fotal events	9		7				
Heterogeneity: Tau ² =	0.00; Chi	² = 2.08	3, df = 4 (P = 0.7	2); I² = 0%	6	
Test for overall effect:	Z=0.90 (P = 0.3	7)				
2.3.3 Best-worst cas	e analysi	5					
Arutiunov 2010	3	21	0	20	12.3%	7.76 [0.38, 160.40]	
Hausen 1992	2	14	2	27	26.2%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	32.9%	0.65 [0.10, 4.13]	
Friposkiadis 2014	1	28	1	55	14.3%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	14.3%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		139		200	100.0%	1.63 [0.56, 4.71]	
Total events	9		7				
Heterogeneity: Tau ² =	0.00; Chi	= 2.08	3, df = 4 (P = 0.7	2); I ² = 0%	6	
Test for overall effect:							
							0.01 0.1 1 10 1

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

Test for subgroup differences: $Chi^2 = 0.00$, df = 2 (P = 1.00), $I^2 = 0\%$

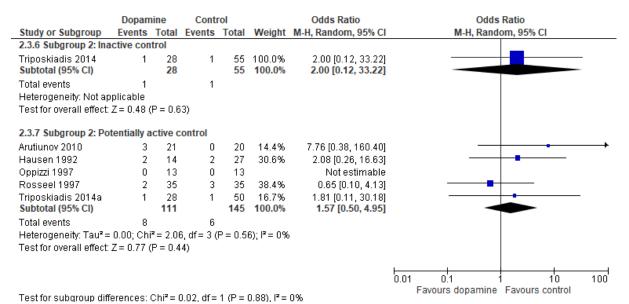
E-Figures 1.5.4-1.5.5: subgroup analysis 1 - trials subdivided by risk of bias

	Dopam	ine	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.3.4 Subgroup 1: Lo	w risk of b	ias					
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applic	able					
2.3.5 Subgroup 1: Un	clear or hi	igh ris	k of bias				
Arutiunov 2010	3	21	0	20	12.3%	7.76 [0.38, 160.40]	_ >
Hausen 1992	2	14	2	27	26.2%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	32.9%	0.65 [0.10, 4.13]	
Triposkiadis 2014	1	28	1	55	14.3%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	14.3%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		139		200	100.0%	1.63 [0.56, 4.71]	-
Total events	9		7				
Heterogeneity: Tau ² =	: 0.00; Chi ^a	²= 2.08	3, df = 4 (l	P = 0.7	2); I² = 0%	6	
Test for overall effect:	Z = 0.90 (i	P = 0.3	7)				
							Favours dopamine Favours control
Test for subgroup diff	foroncoe · N	Jot and	dicable				r aroaro aopaninio il avodio control

Test for subgroup differences: Not applicable

Favours dopamine Favours control

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

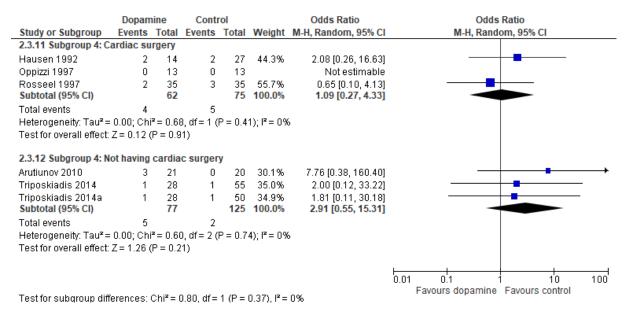


E-Figures 1.5.8-1.5.10: subgroup analysis 3 – trials subdivided by dose

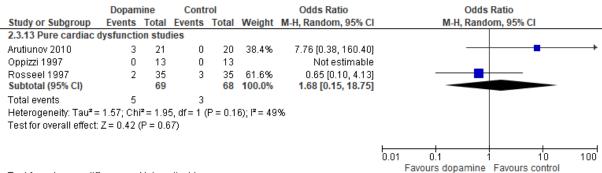
	Dopan	nine	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.3.8 Subgroup 3: Lo	w dose						
Arutiunov 2010	3	21	0	20	38.4%	7.76 [0.38, 160.40]	
Rosseel 1997	2	35	3	35	61.6%	0.65 [0.10, 4.13]	
Subtotal (95% CI)		56		55	100.0%	1.68 [0.15, 18.75]	
Total events	5		3				
Heterogeneity: Tau ² =	•		• •	P = 0.1	6); I² = 49	%	
Test for overall effect	Z = 0.42 ((P = 0.6	7)				
2.3.9 Subgroup 3: Mo	oderate de	ose					
Hausen 1992	2	14	2	27	47.8%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Triposkiadis 2014	1	28	1	55	26.1%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	26.1%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		83		145	100.0%	1.99 [0.47, 8.36]	
Total events	4		4				
Heterogeneity: Tau ² =	•			P = 1.0	0); I² = 0%	6	
Test for overall effect	: Z = 0.94 ((P = 0.3	5)				
2.3.10 Subgroup 3: H	ligh dose						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect	Not appli	cable					
							0.01 0.1 1 10 10
							Favours dopamine Favours control

Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), l² = 0%

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

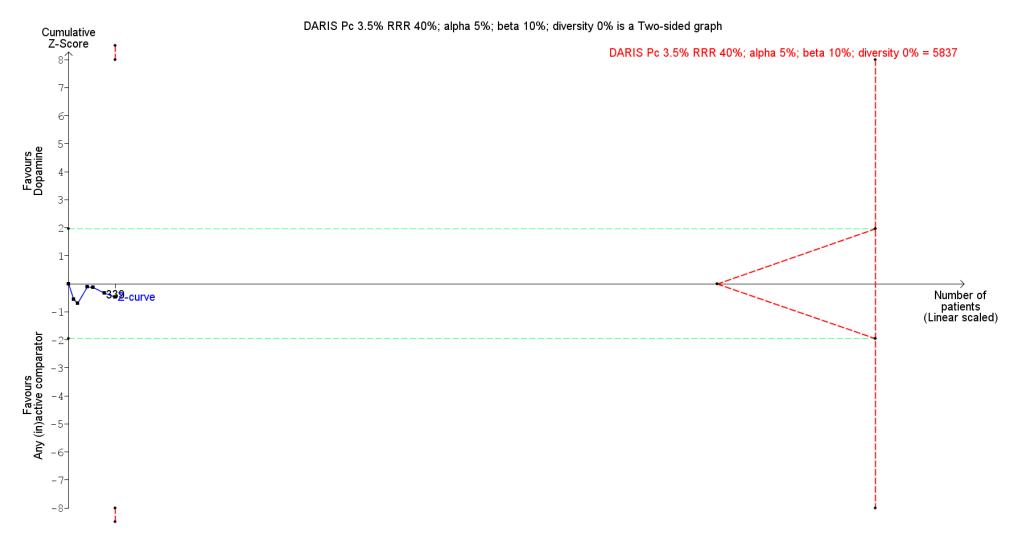


Test for subgroup differences: Not applicable

Favours dopamine Favours contro

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

	Dopan		Cont			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.4.1 All included stu							
Chen 2013	8	111	1	115	20.3%	8.85 [1.09, 72.01]	
Cotter 1997	1	14	0	6	8.9%	1.44 [0.05, 40.54]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	3	10	10.1%	0.10 [0.00, 2.28]	· · · · · · · · · · · · · · · · · · ·
Kamiya 2015	0	12	1	12	9.0%	0.31 [0.01, 8.31]	
Oppizzi 1997	2	13	1	13	14.6%	2.18 [0.17, 27.56]	
Triposkiadis 2014	1	28	2	55	15.6%	0.98 [0.09, 11.31]	
Triposkiadis 2014a	2	28	2	50	21.6%	1.85 [0.25, 13.88]	
/arriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		240		298	100.0%	1.46 [0.52, 4.10]	-
Total events	14		10				
Heterogeneity: Tau ² =	0.22; Chi	i ^z = 6.76	6, df = 6 (P = 0.3	4); I ² = 11	%	
Test for overall effect:	Z = 0.72 ((P = 0.4	7)				
2.4.2 Worst-best cas	e analvsi	s					
Chen 2013	8	111	1	115	20.3%	8.85 [1.09, 72.01]	_
Cotter 1997	1	14	O	6	8.9%	1.44 [0.05, 40.54]	
Hausen 1992	O	14	Ŭ	27	0.070	Not estimable	
Hsueh 1998	0	10	3	10	10.1%	0.10 [0.00, 2.28]	· · · · · · · · · · · · · · · · · · ·
Kamiya 2015	0	12	1	12	9.0%	0.31 [0.01, 8.31]	e
Oppizzi 1997	2	13	1	13	14.6%	2.18 [0.17, 27.56]	
Triposkiadis 2014	1	28	2	55	15.6%	0.98 [0.09, 11.31]	
Triposkiadis 2014	2	28	2	50	21.6%	1.85 [0.25, 13.88]	
/arriale 1997	2	10	2	10	21.0%	Not estimable	
Subtotal (95% CI)	0	240	0		100.0%	1.46 [0.52, 4.10]	
Total events	14	240	10	230	100.070	1.40 [0.52, 4.10]	
Heterogeneity: Tau² =		2 - 6 70		0-00	4V-12 - 1.1	ox.	
Test for overall effect:				r – 0.5	4),1 - 11	70	
2.4.3 Best-worst cas	o analvei						
	-		4	445	20.20	0.05 14 00 70 041	
Chen 2013	8	111	1	115	20.3%	8.85 [1.09, 72.01]	
Cotter 1997	1	14	0	6	8.9%	1.44 [0.05, 40.54]	
Hausen 1992	0	14	0	27	40.40	Not estimable	
Hsueh 1998 Kamina 2016	0	10	3	10	10.1%	0.10 [0.00, 2.28]	
Kamiya 2015	0	12	1	12	9.0%	0.31 [0.01, 8.31]	
Oppizzi 1997 Triana dia dia 2014	2	13	1	13	14.6%	2.18 [0.17, 27.56]	
Triposkiadis 2014	1	28	2	55	15.6%	0.98 [0.09, 11.31]	
Triposkiadis 2014a	2	28	2	50	21.6%	1.85 [0.25, 13.88]	
/arriale 1997	0	10	0	10	400.05	Not estimable	
Subtotal (95% CI)		240		298	100.0%	1.46 [0.52, 4.10]	
Total events	14		10				
Heterogeneity: Tau ² =	•			P = 0.3	4); I ² = 11	%	
Test for overall effect:	Z = 0.72 ((P = 0.4	7)				
							0.01 0.1 1 10

0.01 0.1 1 10 Favours dopamine Favours control

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

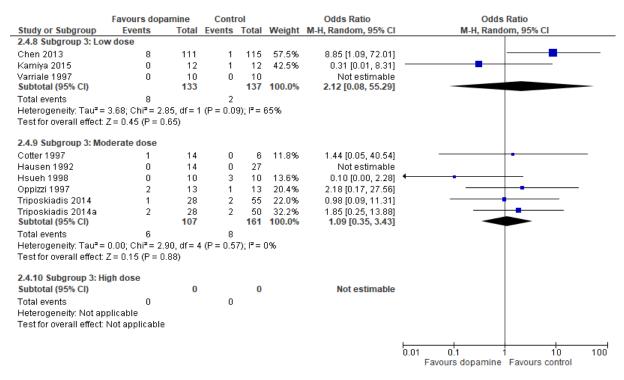
Chudu an Culturation	Favours dopa		Contr		14/	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.4.4 Subgroup 1: Lov Subtotal (95% Cl)	v risk of bias	0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not app	plicable						
Test for overall effect: I	Not applicable						
2.4.5 Subgroup 1: Und	lear or high ris	k of bia	s				
Chen 2013	8	111	1	115	20.3%	8.85 [1.09, 72.01]	
Cotter 1997	1	14	0	6	8.9%	1.44 [0.05, 40.54]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	3	10	10.1%	0.10 [0.00, 2.28]	• • • · · · · · · · · · · · · · · · · ·
Kamiya 2015	0	12	1	12	9.0%	0.31 [0.01, 8.31]	
Oppizzi 1997	2	13	1	13	14.6%	2.18 [0.17, 27.56]	
Triposkiadis 2014	1	28	2	55	15.6%	0.98 [0.09, 11.31]	
Triposkiadis 2014a	2	28	2	50	21.6%	1.85 [0.25, 13.88]	
/arriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		240		298	100.0%	1.46 [0.52, 4.10]	-
Total events	14		10				
Heterogeneity: Tau ² =	0.22; Chi ² = 6.7	6, df = 6	(P = 0.34	4); I ² = 1	11%		
Test for overall effect: 2	Z = 0.72 (P = 0.4	7)					
							0.01 0.1 1 10 100 Favours dopamine Favours control

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

	Favours dopa		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.4.6 Subgroup 2: Ina	ictive control						
Chen 2013	8	111	1	115	54.1%	8.85 [1.09, 72.01]	
Triposkiadis 2014	1	28	2	55	45.9%	0.98 [0.09, 11.31]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		149		180	100.0%	3.23 [0.36, 28.60]	
Total events	9		3				
Heterogeneity: Tau ² =	1.14; Chi ² = 1.8	5, df = 1	(P = 0.1)	7); I ² = -	46%		
Test for overall effect:	Z = 1.05 (P = 0.)	29)					
2.4.7 Subgroup 2: Po Cotter 1997 Hausen 1992 Hsueh 1998 Kamiya 2015	tentially active (1 0 0 0	14 14 10 12	0 0 3 1	6 27 10 12	13.1% 15.1% 13.4%	1.44 (0.05, 40.54) Not estimable 0.10 (0.00, 2.28) 0.31 (0.01, 8.31)	· · · · · · · · · · · · · · · · · · ·
Oppizzi 1997	2	13	1	13	22.6%	2.18 [0.17, 27.56]	
Triposkiadis 2014a Subtotal (95% CI)	2	28 91	2	50	35.8% 100.0%	1.85 [0.25, 13.88] 0.94 [0.28, 3.15]	
Total events	5		7				
Heterogeneity: Tau² = Test for overall effect:			(P = 0.4)	9); I² = I	0%		

24

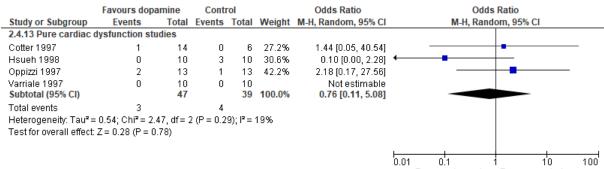
E-Figures 1.7.8-1.7.10: subgroup analysis 3 - trials subdivided by dose



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

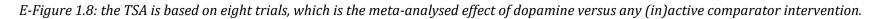
	Favours dopar		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.4.11 Subgroup 4: C	ardiac surgery						
Hausen 1992	0	14	0	27		Not estimable	
Oppizzi 1997	2	13	1	13	100.0%	2.18 [0.17, 27.56]	
Subtotal (95% CI)		27		40	100.0%	2.18 [0.17, 27.56]	
Total events	2		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.60 (P = 0.5	5)					
2.4.12 Subgroup 4: N	ot having cardia	c surge	ery				
Chen 2013	8	111	1	115	22.6%	8.85 [1.09, 72.01]	
Cotter 1997	1	14	0	6	11.2%	1.44 [0.05, 40.54]	
Hsueh 1998	0	10	3	10	12.6%	0.10 [0.00, 2.28]	←
Kamiya 2015	0	12	1	12	11.4%	0.31 [0.01, 8.31]	
Triposkiadis 2014	1	28	2	55	18.3%	0.98 [0.09, 11.31]	+
Triposkiadis 2014a	2	28	2	50	23.8%	1.85 [0.25, 13.88]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		213		258	100.0%	1.29 [0.38, 4.39]	
Total events	12		9				
Heterogeneity: Tau ² =	0.59; Chi ² = 6.68	3. df = 5	(P = 0.2	5); I ² = (25%		
Test for overall effect:		-					
		-					
							i0.01 0.1 i 10 10

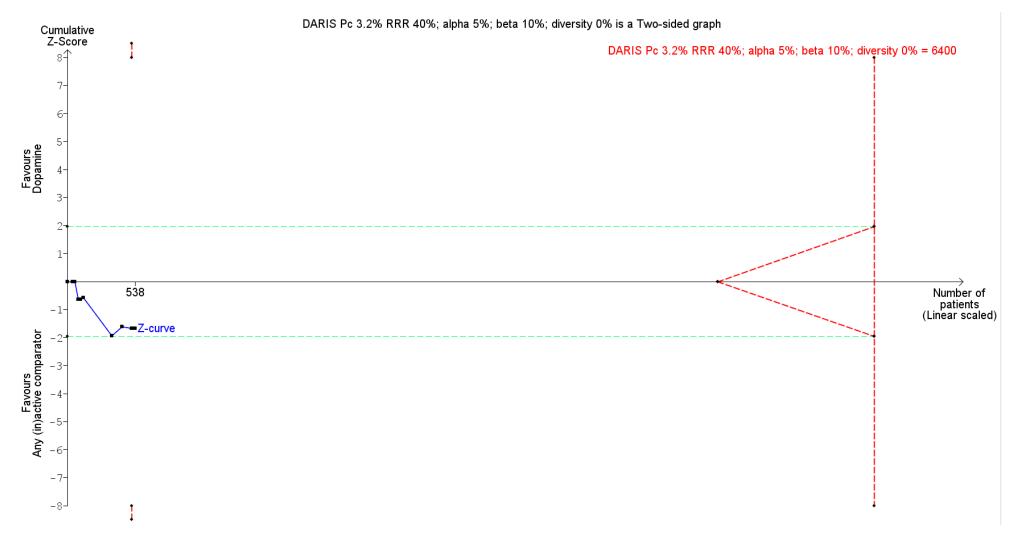
E-Figure 1.7.13: sensitivity analysis - trials including only patients with cardiac dysfunction



Favours dopamine Favours control

1.10. Trial sequential analysis of ventricular tachyarrhythmias





1.11. Forest plots of renal replacement therapy

	Dopan	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.5.1 All included stu	dies						
Bove 2005	4	40	4	40	30.2%	1.00 [0.27, 3.72]	
Costa 1990	0	18	0	12		Not estimable	
Sirivella 2000	4	60	36	40	32.7%	0.07 [0.03, 0.19]	_
Triposkiadis 2014	0	28	1	55	17.2%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	19.9%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		174		197	100.0%	0.44 [0.07, 2.75]	
Total events	9		42				
Heterogeneity: Tau ² =	= 2.41; Chi	² = 13.0	09, df = 3	(P = 0.	004); I ² =	77%	
Test for overall effect:	Z=0.87 (P = 0.3	8)				
2.5.2 Worst-best cas	se analysi	s					
Bove 2005	4	40	4	40	24.7%	1.00 [0.27, 3.72]	_
Costa 1990	6	24	0	12	16.8%	6.76 [0.41, 110.86]	
Sirivella 2000	4	60	36	40	26.4%	0.07 [0.03, 0.19]	_
Triposkiadis 2014	0	28	1	55	15.0%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	17.1%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		180		197	100.0%	0.72 [0.12, 4.27]	
Total events	15		42				
Heterogeneity: Tau ² =	= 2.91; Chi	² = 18.1	10, df = 4	(P = 0.	001); I ^z =	78%	
Test for overall effect:	Z=0.37 (P = 0.7	1)				
2.5.3 Best-worst cas	se analysi	s					
Bove 2005	4	40	4	40	30.2%	1.00 [0.27, 3.72]	+
Costa 1990	0	24	0	12		Not estimable	
Sirivella 2000	4	60	36	40	32.7%	0.07 [0.03, 0.19]	_
Triposkiadis 2014	0	28	1	55	17.2%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	19.9%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		180		197	100.0%	0.44 [0.07, 2.75]	
Total events	9		42				
Heterogeneity: Tau ² =	= 2.41; Chi	² = 13.0	09, df = 3	(P = 0.	004); I ^z =	77%	
Test for overall effect:	Z=0.87 (P = 0.3	8)				
							0.01 0.1 i 10 10

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

Test for subgroup differences: $Chi^2 = 0.18$, df = 2 (P = 0.91), $l^2 = 0\%$

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

	Favours dopar	nine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
2.5.4 Subgroup 1: Lo	w risk of bias						
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Not applicable						
2.5.5 Subgroup 1: Un	clear or high ris	k of bia	S				
Bove 2005	4	40	4	40	30.2%	1.00 [0.27, 3.72]	+
Costa 1990	0	18	0	12		Not estimable	
Sirivella 2000	4	60	36	40	32.7%	0.07 [0.03, 0.19]	_
Triposkiadis 2014	0	28	1	55	17.2%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	19.9%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		174		197	100.0%	0.44 [0.07, 2.75]	
Total events	9		42				
Heterogeneity: Tau ² =	= 2.41; Chi ² = 13.0	09, df=	3 (P = 0.0	004); I ^z	= 77%		
Test for overall effect:	Z = 0.87 (P = 0.3	8)					
							0.01 0.1 1 10 100
							Favours dopamine Favours control
Tast for subgroup diff	foroncoc: Not on	alieabla					· ····································

Test for subgroup differences: Not applicable

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

	Favours dopa	mine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.5.6 Subgroup 2: Ina	active control						
Costa 1990	0	18	0	12		Not estimable	
Triposkiadis 2014 Subtotal (95% CI)	0	28 46	1	55 67	100.0% 100.0%	0.64 [0.03, 15.31] 0.64 [0.03, 15.31]	
Total events Heterogeneity: Not ap Test for overall effect:	•	79)	1				
2.5.7 Subgroup 2: Po	tentially active	control					
Bove 2005	4	40	4	40	36.2%	1.00 [0.27, 3.72]	+
Sirivella 2000	4	60	36	40	38.7%	0.07 [0.03, 0.19]	_
Triposkiadis 2014a Subtotal (95% CI)	1	28 128	1	50 130	25.1% 100.0%	1.79 [0.12, 27.46] 0.42 [0.05, 3.67]	
Total events	9		41				
Heterogeneity: Tau ² = Test for overall effect:	•		2 (P = 0.1	002); I²	= 84%		
Test for subaroun diff	foroncas: Chiž -	0.05 df	– 1 (P – 1	183) 19	°- 0%		0.01 0.1 1 10 100 Favours dopamine Favours control

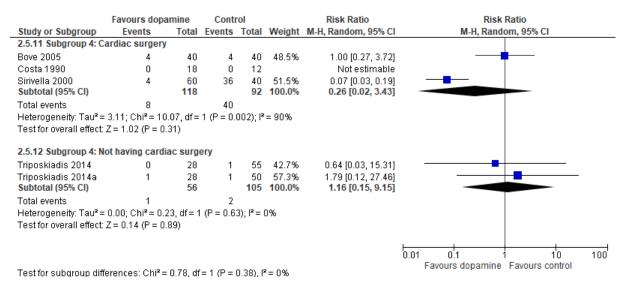
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), $l^2 = 0\%$

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

	Favours dopa	mine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
2.5.8 Subgroup 3: Lov	wdose						
Bove 2005	4	40	4	40	100.0%	1.00 [0.27, 3.72]	
Costa 1990	0	18	0	12		Not estimable	T
Sirivella 2000	0	0	0	0		Not estimable	
Subtotal (95% CI)		58		52	100.0%	1.00 [0.27, 3.72]	
Total events	4		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.00 (P = 1.	00)					
2.5.9 Subgroup 3: Mo	derate dose						
Triposkiadis 2014	0	28	1	55	42.7%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	57.3%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		56		105	100.0%	1.16 [0.15, 9.15]	
Total events	1		2				
Heterogeneity: Tau ² =	0.00; Chi ² = 0.2	3, df = 1	(P = 0.6	3); I 2 = ()%		
Test for overall effect:	Z = 0.14 (P = 0.	89)					
2.5.10 Subgroup 3: Hi	igh dose						
Subtotal (95% CI)	•	0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	-		÷				
Test for overall effect:							
							Favours dopamine Favours control
Test for subaroun diff	orondos: Chiž –	0.01 df	= 1 (P = 1)	0 Q1) P	- 0%		r avouro dopartinto i r avouro control

Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.91), $l^2 = 0\%$

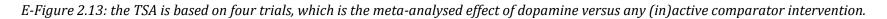
E-Figures 1.9.11-1.9.12: subgroup analysis 4 – trials subdivided by clinical setting

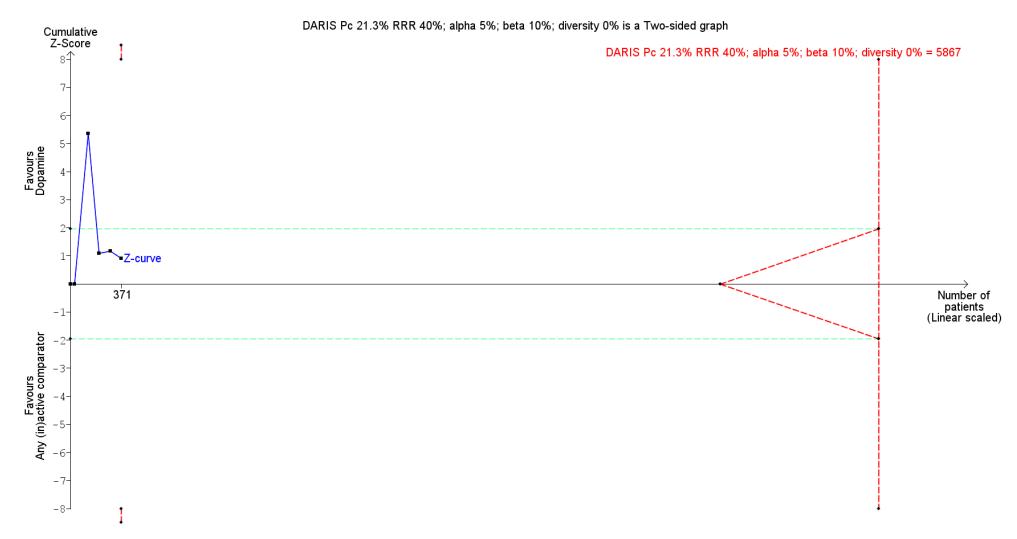


E-Figure 1.9.13: sensitivity analysis - trials including only patients with cardiac dysfunction

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

1.12. Trial sequential analysis of renal replacement therapy





1.13. Forest plots of atrial tachyarrhythmias

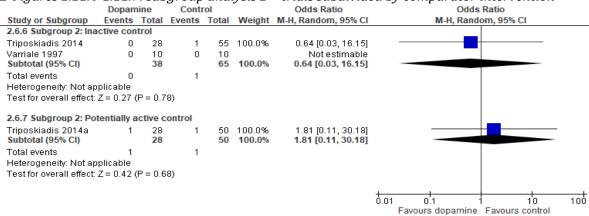
E-Figures 1.11.1-1.11.3: all trials with worst-best and best-worst case analyses

	Dopan		Cont			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.6.1 All included stu	idies						
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]	
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30.18]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		66		115	100.0%	1.16 [0.14, 9.65]	
Total events	1		2				
Heterogeneity: Tau² =				P = 0.6	3); I² = 0%	6	
Test for overall effect:	Z = 0.13 ((P = 0.8	9)				
2.6.2 Worst-best cas	se analysi	s					
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]	
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30.18]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		66		115	100.0%	1.16 [0.14, 9.65]	
Total events	1		2				
Heterogeneity: Tau ² =	= 0.00; Chi	r = 0.23	3, df = 1 (P = 0.6	3); I ^z = 0%	b	
Test for overall effect:	Z = 0.13 ((P = 0.8	9)				
2.6.3 Best-worst cas	se analysi	s					
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]	
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30.18]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		66		115	100.0%	1.16 [0.14, 9.65]	
Total events	1		2				
Heterogeneity: Tau ² =	= 0.00; Chi	r = 0.23	3, df = 1 (P = 0.6	3); I² = 0%	b .	
Test for overall effect:	Z = 0.13 ((P = 0.8	9)				
							0.01 0.1 1 10 10
							Favours dopamine Favours control

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

	Dopam	ine	Contr	rol		Odds Ratio		Odds Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random,	95% CI	
2.6.4 Subgroup 1: Lo	w risk of	bias								
Subtotal (95% CI)		0		0		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	oplicable									
Test for overall effect:	Not appli	cable								
2.6.5 Subgroup 1: Un	clear or h	igh ris	k of bias							
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]				
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30.18]			l	
Varriale 1997	0	10	0	10		Not estimable				
Subtotal (95% CI)		66		115	100.0%	1.16 [0.14, 9.65]				
Total events	1		2							
Heterogeneity: Tau ² =	= 0.00; Chi	z = 0.23	3, df = 1 (P = 0.6	3); I ^z = 0%	, 0				
Test for overall effect:	Z=0.13 (P = 0.8	9)							
							+			+
							Ó.01	0.1 İ	1'0	100
								Favours dopamine Favours	vours control	

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



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

	Dopam	nine	Contr	rol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
2.6.8 Subgroup 3: Lov	w dose							
Varriale 1997 Subtotal (95% CI)	0	10 10	0	10 10		Not estimable Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appli	cable						
2.6.9 Subgroup 3: Mo	derate do	ose						
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]		
Triposkiadis 2014a Subtotal (95% CI)	1	28 56	1	50 105	56.9% 100.0%	1.81 [0.11, 30.18] 1.16 [0.14, 9.65]		
Total events	1		2					
Heterogeneity: Tau ² = Test for overall effect: .				P = 0.6	3); I² = 0%	6		
2.6.10 Subgroup 3: Hi	gh dose							
Subtotal (95% CI)		0		0		Not estimable		
Total events Heterogeneity: Not ap	0 plicable		0					
Test for overall effect:	Not appli	cable						
							+	
							Ó.01	
								Favours dopamine Favours control

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

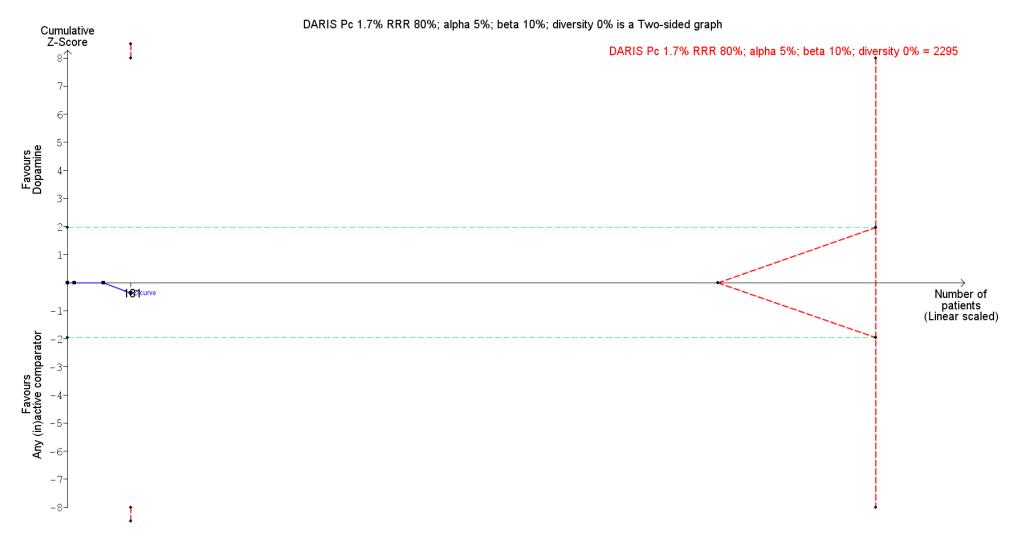
	Dopam	ine	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.6.11 Subgroup 4: Ca	ardiac su	rgery					
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	able					
2.6.12 Subgroup 4: No	ot having	cardia	c surger	у			
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]	
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30.18]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		66		115	100.0%	1.16 [0.14, 9.65]	
Total events	1		2				
Heterogeneity: Tau ² =	0.00; Chi	² = 0.20	3, df = 1 (l	P = 0.6	3); I² = 0%	6	
Test for overall effect: J	Z = 0.13 (P = 0.8	9)				
							Favours dopamine Favours control

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.

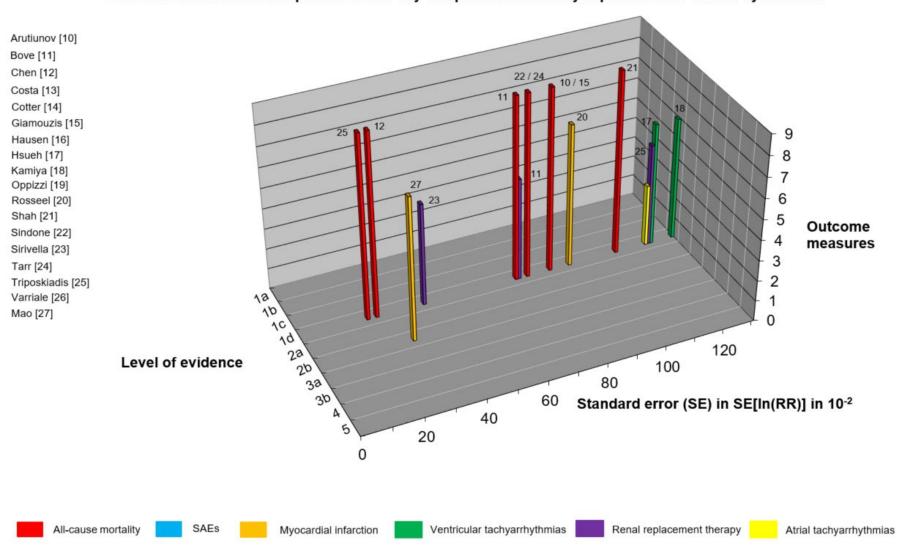


	Studies	Patients	Events	Odds ratio	95% CI
Serious adverse events	1	30	7	1.33	0.36 to 4.97
Myocardial infarction	1	1758	42	0.67	0.36 to 1.26
Ventricular tachyarrhythmias	1	30	7	3.25	0.52 to 20.4
Renal replacement therapy	1	1758	24	2.02	0.86 to 4.74
Atrial tachyarrhythmias	0	-	-	-	-

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

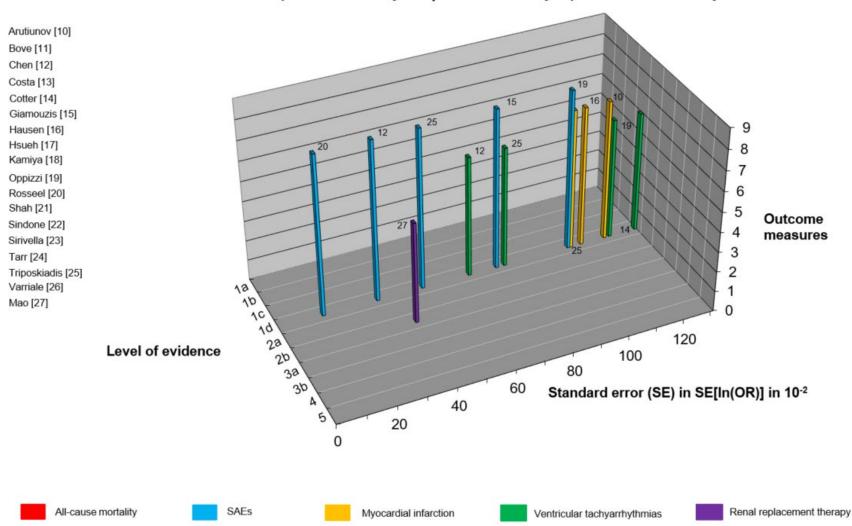
Abbreviations: CI, confidence interval.

1.16. Manhattan matrix plot with beneficial outcomes



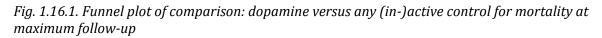
Outcomes with benefit of dopamine versus any comparator in critically ill patients with cardiac dysfunction

1.17. Manhattan matrix plot with harmful outcomes



Outcomes with harm of of dopamine versus any comparator in critically ill patients with cardiac dysfunction

1.18. Funnel plots for small trial bias including publication bias



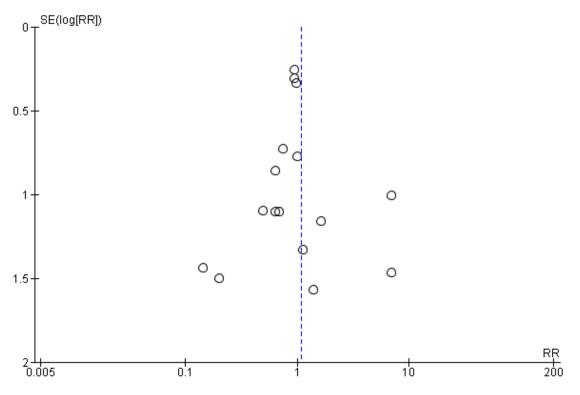
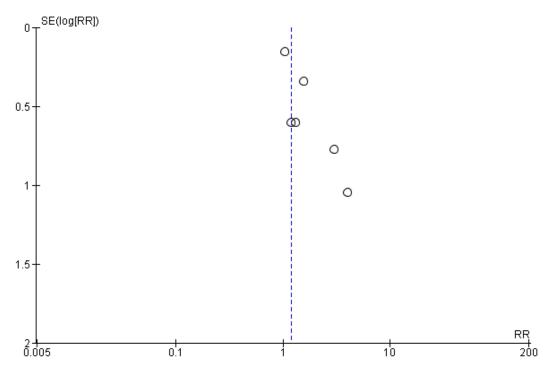


Fig 1.16.2. Funnel plot of comparison: dopamine versus any (in-)active control for SAEs



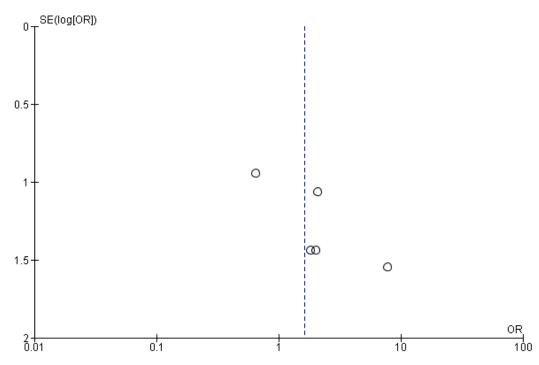


Fig 1.16.3. Funnel plot of comparison: dopamine versus any (in-)active control for myocardial infarction

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

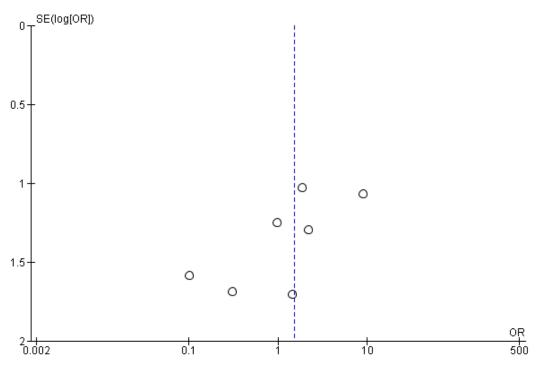


Fig. 1.16.5. Funnel plot of comparison: dopamine versus any (in-)active control for renal replacement therapy

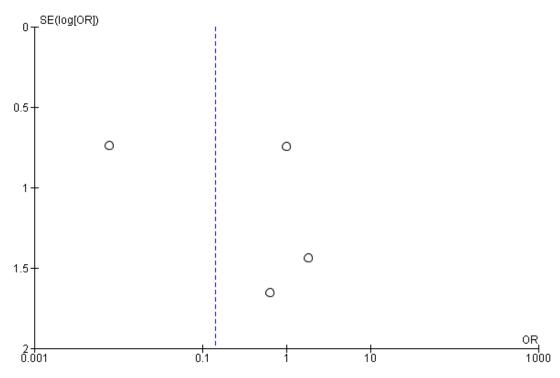
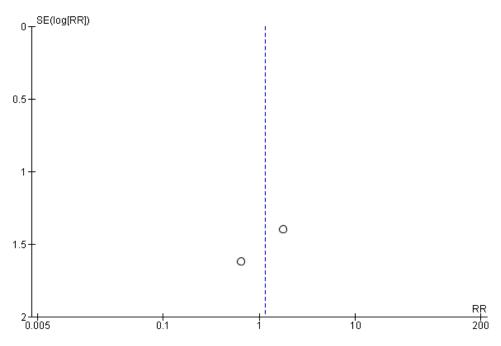


Fig. 1.16.6. Funnel plot of comparison: dopamine versus any (in-)active control for atrial tachyarrhythmias



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).

Author	Year	Ν	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
Soliman <i>et</i> 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 <i>et</i> al. [53]	2017	60	Cardiac surgery	2.0 μg/kg/min	Placebo	Primary: none Other: mortality (in-hospital), renal replacement therapy
Gatot <i>et</i> <i>al.</i> [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 <i>et al.</i> [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 <i>et al.</i> [50]	2002	50	Cardiac surgery	3.0 μg/kg/min	Placebo	Primary: none Other: mortality (in-hospital), neurologic complications
Sumeray <i>et al.</i> [49]	2001	48	Cardiac surgery	2.5 μg/kg/min	Placebo	Primary: none

E-Table 2.1: Characteristics of the included trials

Author	Year	Ν	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
						Secondary: significant clinical events, i.e. mortality (in-hospital), arrhythmias, renal replacement therapy
Lassnigg <i>et</i> <i>al.</i> [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 <i>et al.</i> [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 <i>et</i> <i>al.</i> [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 <i>et</i> <i>al.</i> [48]	1997	30	Cardiac surgery	2.5 μg/kg/min	Dopexamine 2 μg/kg/min	Primary: none Other: mortality (in-hospital), SAE's
Myles <i>et</i> 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 <i>et</i> <i>al.</i> [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 <i>et al.</i> [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 <i>et al.</i> [28]	2013	32	Septic shock	Up to 20 μ g/kg/min + dobutamine	Terlipressin 1.3 µg/kg/min +	Primary: mortality (28 days)
[38] Chen <i>et al.</i> [34]	2012	80	Shock Septic shock	up to 20 μg/kg/min Up to 20 μg/kg/min (cointerventions not specified)	dobutamine up to 20 μg/kg/min Noradrenaline up to 2 μg/kg/min (cointerventions not specified)	Secondary: none Primary: none Other: mortality (In-hospital), cardiogenic adverse events (MI, arrhythmias)

Author	Year	Ν	Clinical setting	Dopamine infusion rate	Comparator	Patient relevant outcomes
Zhuangyu <i>et al.</i> [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 <i>et al.</i> [35]	2010	1679	Circulato ry 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 <i>et al.</i> [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 <i>et al.</i> [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 <i>et</i> <i>al.</i> [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 <i>et al.</i> [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 <i>et</i> <i>al.</i> [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 <i>et</i> <i>al.</i> [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).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias		Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arutiunov 2010 (ma)	•	?	?	?	•	?	?	De Backer 2010 (ph2)	•	•	•	•	•	•	•
Cotter 1997 (ma)	•	?	•	?		?	?	Gatot 2004 (ph2)	?	?	•	•	•	•	?
Hsueh 1998 (ma)	?	?	?	•	+	?	?	High 2008 (ph2)	?	?	•	•	•	?	?
Oppizzi 1997 (ma)	?	?	•		+	?	•	Hua 2013 (ph2)	•	?	•	•	•	?	?
Rosseel 1997 (ma)	+	•	•	•	+	?	•	Kanchi 2017 (ph2)	?	?	?	?	•	?	•
Tarr 1993 (ma)	?	?	•	+		?	•	Lassnigg 2000 (ph2)	•	•	•	•	•	?	•
Varriale 1997 (ma)	?	?		?	+	?	?	Liu 2010 (ph2)	?	?	•	?	•	?	?
Bove 2005 (ph1)	+	•	•	?	+	•	?	Marik 1994 (ph2)	•	•	•	•	•	?	•
Chen 2013 (ph1)	•	•	•	+	+	+	•	Martin 1993 (ph2)	?	?	•	?	•	?	•
. Costa 1990 (ph1)	?	?	?	?	•	•	?	Mathur 2007 (ph2)	•	?	•	•	•	?	•
Giamouzis 2010 (ph1)	•	?	•	+	+	•	?	Myles 1993 (ph2)	•	•	•	•	•	?	•
Hausen 1992 (ph1)	•	•	•	?	•	?	?	Schmoelz 2006 (ph2)	•	?	•	?	•	?	?
Kamiya 2015 (ph1)	?	?	•	•	+	?	•	Schneider 1999 (ph2)	?	?	•	?	•	?	•
Shah 2014 (ph1)	•	?	•	•	+	?	•	Sharpe 1999 (ph2)	?	?	•	•	?	?	?
Sindone 1998 (ph1)	?	?	?	?	?	•	?	Sinclair 1997 (ph2)	?	?	•	•	•	?	
Sirivella 2000 (ph1)	?	?	•	•	?	•	?	Soliman 2017 (ph2)	•	?	•	?	•	?	•
Triposkiadis 2014 (ph1)	•	?	•	•	+	+	•	Sumeray 2001 (ph2)	•	•	•	?	•	?	•
Birnbaum 1990 (ph2)	?	?	•	?	+	?	?	Woo 2002 (ph2)	?	?	•	•	•	?	?
Carcoana 2003 (ph2)	+	•	•	+	•	?	?	Wu 2011 (ph2)	?	?	•	•	•	?	?
Chen 2012 (ph2)	?	?	•	?	?	?	?	Zhuangyu 2011 (ph2)	?	?	•	-	•	?	?

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

Study of Subgroup	Dopan		Contr		Moight	Risk Ratio	Risk Ratio
Study or Subgroup 4.1.1 All included stu		Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
		24	2	20	0.20	0 60 60 40 0 441	
Arutiunov 2010	2	21	3	20	0.2%	0.63 [0.12, 3.41]	-
Birnbaum 1990	0	10	0	10	0.00	Not estimable	
Bove 2005	3	40	4	40	0.3%	0.75 [0.18, 3.14]	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Chen 2012	12	40	9	40	1.1%	1.33 [0.63, 2.81]	
Chen 2013	24	122	25	119	2.5%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.1%	1.40 [0.06, 30.23]	
De Backer 2010	472	858	427	821	78.3%	1.06 [0.97, 1.16]	
Эао 2008	9	21	9	23	1.2%	1.10 [0.54, 2.23]	
Giamouzis 2010	3	30	3	30	0.3%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
lua 2013	8	16	7	16	1.1%	1.14 [0.54, 2.40]	
Kamiya 2015	0	12	2	12	0.1%	0.20 [0.01, 3.77]	
(anchi 2017	0	30	0	30		Not estimable	
assnigg 2000.	0	21	1	40	0.1%	0.62 [0.03, 14.62]	
assnigg 2000a	0	21	4	41	0.1%	0.21 [0.01, 3.76]	
_iu 2010	12	25	8	25	1.3%	1.50 [0.74, 3.03]	
Aarik 1994	6	10	5	10	1.0%	1.20 [0.54, 2.67]	
Aartin 1993	10	16	7	16	1.4%	1.43 [0.73, 2.80]	
Aathur 2007	19	25	14	25	3.7%	1.36 [0.90, 2.05]	+ - -
Ayles 1993	0	25	0	24	0.1.70	Not estimable	
	3	13	Ő	13	0.1%	7.00 [0.40, 123.35]	
Rosseel 1997	Ŭ	35	Ő	35	0.170	Not estimable	
Schmoelz 2006	2	10	7	20	0.3%	0.57 [0.14, 2.26]	
Schmoelz 2006a	2	11	5	20	0.3%	0.73 [0.17, 3.15]	
Schneider 1999	0	50	0	49	0.5 /0	Not estimable	
Shah 2014	1	31	4	49 61	0.1%	0.49 [0.06, 4.22]	
	0	5	4 0	10	0.1%		
Sharpe 1999 Sharpa 1999		5	0			Not estimable	
Sharpe 1999a	0			10		Not estimable	
Sinclair 1997	0	16	0	14	0.400	Not estimable	
Sindone 1998	0	8	3	8	0.1%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	0.1%	1.63 [0.17, 15.66]	
Bindone 1998b	1	8	1	9	0.1%	1.13 [0.08, 15.19]	
Soliman 2017	3	75	1	75	0.1%	3.00 [0.32, 28.19]	
Sumeray 2001	0	19	0	19		Not estimable	
Farr 1993a	1	12	3	25	0.1%	0.69 [0.08, 6.00]	
arr 1993b	1	13	3	25	0.1%	0.64 [0.07, 5.57]	
riposkiadis 2014	9	28	18	55	1.4%	0.98 [0.51, 1.90]	-+-
Triposkiadis 2014a	10	28	19	50	1.7%	0.94 [0.51, 1.73]	-+-
/arriale 1997	0	10	0	10		Not estimable	
Voo 2002	2	25	0	25	0.1%	5.00 [0.25, 99.16]	
Vu 2011	9	23	7	23	1.0%	1.29 [0.58, 2.86]	-+
Zhuangyu 2011	14	45	13	45	1.6%	1.08 [0.57, 2.03]	
Subtotal (95% CI)		1909		2062	100.0%	1.07 [0.99, 1.16]	•
Fotal events Heterogeneity: Tau² = Fest for overall effect:) (P = ().99); I² = (0%	

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E-Figures 2.5.1b: all trials with risk differences

Study or Subgroup	Dopan		Contr		Woight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% Cl
4.1.1 All included stu		Total	Events	TUtai	weight	m-n, Kanuoin, 95% Ci	m-n, Kandolii, 55% Ci
Arutiunov 2010	2	21	3	20	0.6%	0.0510.26.0.151	
	0	10	0	10	0.8%	-0.05 [-0.26, 0.15]	
Birnbaum 1990	3	40	4	40	0.8%	0.00 [-0.17, 0.17]	
Bove 2005	0	40 25	4		4.3%	-0.03 [-0.15, 0.10]	
Carcoana 2003				24		0.00 [-0.08, 0.08]	
Carcoana 2003a	0	25	0	26	4.7%	0.00 [-0.07, 0.07]	
Chen 2012	12	40	9	40	0.7%	0.07 [-0.12, 0.27]	
Chen 2013	24	122	25	119	2.4%	-0.01 [-0.12, 0.09]	
Cotter 1997	1	14	0	6	0.4%	0.07 [-0.17, 0.32]	
De Backer 2010	472	858	427	821	11.0%	0.03 [-0.02, 0.08]	
Gao 2008	9	21	9	23	0.3%	0.04 [-0.25, 0.33]	
Giamouzis 2010	3	30	3	30	1.1%	0.00 [-0.15, 0.15]	
Hausen 1992	0	14	0	27	2.4%	0.00 [-0.10, 0.10]	
Hsueh 1998	0	10	0	10	0.8%	0.00 [-0.17, 0.17]	
Hua 2013	8	16	7	16	0.2%	0.06 [-0.28, 0.41]	
Kamiya 2015	0	12	2	12	0.4%	-0.17 [-0.41, 0.07]	
Kanchi 2017	0	30	0	30	6.4%	0.00 [-0.06, 0.06]	+
Lassnigg 2000	0	21	1	40	3.5%	-0.03 [-0.11, 0.06]	
Lassnigg 2000a	0	21	4	41	2.0%	-0.10 [-0.21, 0.01]	
Liu 2010	12	25	8	25	0.3%	0.16 [-0.11, 0.43]	
Marik 1994	6	10	5	10	0.1%	0.10 [-0.33, 0.53]	
Martin 1993	10	16	7	16	0.2%	0.19 [-0.15, 0.53]	
Mathur 2007	19	25	14	25	0.4%	0.20 [-0.06, 0.46]	
Myles 1993	0	25	0	24	4.3%	0.00 [-0.08, 0.08]	+
Oppizzi 1997	3	13	0	13	0.4%	0.23 [-0.02, 0.48]	
Rosseel 1997	0	35	0	35	8.6%	0.00 [-0.05, 0.05]	+
Schmoelz 2006	2	10	7	20	0.2%	-0.15 [-0.47, 0.17]	
Schmoelz 2006a	2	11	5	20	0.3%	-0.07 [-0.36, 0.23]	
Schneider 1999	0	50	0	49	16.8%	0.00 [-0.04, 0.04]	+
Shah 2014	1	31	4	61	3.2%	-0.03 [-0.12, 0.05]	
Sharpe 1999	0	5	0	10	0.4%	0.00 [-0.25, 0.25]	
Sharpe 1999a	0	5	0	10	0.4%	0.00 [-0.25, 0.25]	
Sinclair 1997	0	16	0	14	1.7%	0.00 [-0.12, 0.12]	
Sindone 1998	0	8	3	8	0.2%	-0.38 [-0.73, -0.02]	
Sindone 1998a	1	8	2	26	0.4%	0.05 [-0.20, 0.30]	
Sindone 1998b	1	8	1	9	0.3%	0.01 [-0.29, 0.32]	
Soliman 2017	3	75	1	75	9.5%	0.03 [-0.02, 0.08]	
Sumeray 2001	Ō	19	0	19	2.7%	0.00 [-0.10, 0.10]	
Tarr 1993a	1	12	3	25	0.6%	-0.04 [-0.24, 0.17]	
Tarr 1993b	1	13	3	25	0.7%	-0.04 [-0.24, 0.15]	
Triposkiadis 2014	. 9	28	18	55	0.6%	-0.01 [-0.22, 0.21]	
Triposkiadis 2014a	10	28	19	50	0.5%	-0.02 [-0.25, 0.20]	
Varriale 1997	0	10	0	10	0.8%	0.00 [-0.17, 0.17]	
Woo 2002	2	25	0	25	1.6%	0.08 [-0.05, 0.21]	<u> </u>
Wu 2011	9	23	7	23	0.3%	0.09 [-0.19, 0.36]	
Zhuangyu 2011	9 14	45	13	23 45	0.3%	0.02 [-0.17, 0.21]	
Subtotal (95% CI)	14	40	13		100.0%	0.00 [-0.01, 0.02]	
Total events	640		614				ſ
Heterogeneity: Tau ² =		j² = 29 0		4 (P = 1),96); I² = ∩	1%	
Test for overall effect:							
		. 0.0	-/				
							-1 -0.5 0 0.5

Test for subgroup differences: Not applicable

Favours dopamine Favours control

E-Figure 2.5.2: worst-best case analysis

Study or Subgroup	Dopam Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
4.1.2 Worst-best cas						, , ,	
Arutiunov 2010	2	21	3	20	0.2%	0.63 [0.12, 3.41]	
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	3	40	4	40	0.3%	0.75 [0.18, 3.14]	
Carcoana 2003	9	34	Ó	33	0.1%	18.46 [1.12, 304.85]	
Carcoana 2003a	9	34	0	34	0.1%	19.00 [1.15, 314.00]	
Chen 2012	12	40	9	40	1.1%	1.33 [0.63, 2.81]	
Chen 2013	24	122	25	119	2.5%	0.94 [0.57, 1.54]	_ _ _
Cotter 1997	1	14	0	6	0.1%	1.40 [0.06, 30.23]	
De Backer 2010	472	858	427	821	78.0%	1.06 [0.97, 1.16]	
Gao 2008	2	21		23	1.2%	1.10 [0.54, 2.23]	_ _
Giamouzis 2010	3	30	3	30	0.3%	1.00 [0.22, 4.56]	
Hausen 1992	Ŭ	14	Ő	27	0.070	Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Hua 2013	8	16	7	16	1.1%	1.14 [0.54, 2.40]	
Kamiya 2015	0	12	2	12	0.1%	0.20 [0.01, 3.77]	
Kanchi 2017	0	0	0	0	0.170	Not estimable	
Lassnigg 2000	0	21	1	42	0.1%	0.65 [0.03, 15.34]	
Lassnigg 2000 Lassnigg 2000a	0	21	4	42	0.1%	0.22 [0.01, 3.85]	
	12	25	8	42 25		• • •	
Liu 2010 Morik 1994	6	25 10	5	10	1.3%	1.50 [0.74, 3.03]	
Marik 1994 Martin 1992			5		1.0%	1.20 [0.54, 2.67]	
Martin 1993 Mathur 2007	10	16		16	1.4%	1.43 [0.73, 2.80]	
Mathur 2007	19	25	14	25	3.7%	1.36 [0.90, 2.05]	
Myles 1993	1	26	0	26	0.1%	3.00 [0.13, 70.42]	
Oppizzi 1997 Decesel 1997	3	13	0	13	0.1%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35	0.50	Not estimable	
Schmoelz 2006	3	11	7	21	0.5%	0.82 [0.26, 2.56]	
Schmoelz 2006a	2	11	5	21	0.3%	0.76 [0.18, 3.32]	
Schneider 1999	0	50	0	50		Not estimable	
Shah 2014	1	31	4	62	0.1%	0.50 [0.06, 4.29]	· · · ·
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sindone 1998	0	8	3	8	0.1%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	0.1%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.1%	1.13 [0.08, 15.19]	
Soliman 2017	3	75	1	75	0.1%	3.00 [0.32, 28.19]	
Sumeray 2001	5	24	0	24	0.1%	11.00 [0.64, 188.55]	
Tarr 1993a	1	12	3	25	0.1%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	0.1%	0.64 [0.07, 5.57]	
Triposkiadis 2014	9	28	18	55	1.4%	0.98 [0.51, 1.90]	
Triposkiadis 2014a	10	28	19	50	1.7%	0.94 [0.51, 1.73]	-+-
Varriale 1997	0	10	0	10		Not estimable	
Woo 2002	2	25	0	25	0.1%	5.00 [0.25, 99.16]	
Wu 2011	9	23	7	23	1.0%	1.29 [0.58, 2.86]	- -
Zhuangyu 2011 Subtotal (95% CI)	14	45 1904	13	45 2063	1.6% 100.0%	1.08 [0.57, 2.03] 1.08 [1.00, 1.17]	
Total events	665		614				
Heterogeneity: Tau ² =	0.00; Chi	² = 25.3	3, df = 34	4 (P = 0	0.86); I^z = (0%	
Test for overall effect:	•		•	,			
			-				
							0.01 0.1 1 10 Eavours donamine Eavours control

Test for subgroup differences: Not applicable

Favours dopamine Favours control

E-Figure 2.5.3: best-worst case analysis

Study or Subgroup	Dopam Events		Contr		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
4.1.3 Best-worst case			Lycina	Total	Weight	m-n, Kandom, 55% Cr	wi-n, Kandoin, 55% Ci
Arutiunov 2010	2	21	3	20	0.2%	0.63 [0.12, 3.41]	
Birnbaum 1990	0	10	0	10	0.2 %	Not estimable	
Bove 2005	3	40	4	40	0.3%	0.75 [0.18, 3.14]	
Carcoana 2003	0	34	0	33	0.570	Not estimable	
Carcoana 2003 Carcoana 2003a	0	34	0	26		Not estimable	
Carcoaria 2003a Chen 2012	12	34 40	9	40	1.1%		
	24	40				1.33 [0.63, 2.81]	
Chen 2013			25	119	2.5%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.1%	1.40 [0.06, 30.23]	
De Backer 2010	472	858	427	821	78.2%	1.06 [0.97, 1.16]	
Gao 2008 Giana autria 2040	9	21	9	23	1.2%	1.10 [0.54, 2.23]	
Giamouzis 2010	3	30	3	30	0.3%	1.00 [0.22, 4.56]	
Hausen 1992 Hause 4999	0	14	0	27		Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Hua 2013	8	16	7	16	1.1%	1.14 [0.54, 2.40]	
Kamiya 2015 Kamabi 2017	0	12	2	12	0.1%	0.20 [0.01, 3.77]	
Kanchi 2017	0	30	0	30	o	Not estimable	
Lassnigg 2000	0	21	3	42	0.1%	0.28 [0.02, 5.17]	
Lassnigg 2000a	0	21	5	42	0.1%	0.18 [0.01, 3.07]	
Liu 2010	12	25	8	25	1.3%	1.50 [0.74, 3.03]	
Marik 1994	6	10	5	10	1.0%	1.20 [0.54, 2.67]	
Martin 1993	10	16	7	16	1.4%	1.43 [0.73, 2.80]	
Mathur 2007	19	25	14	25	3.7%	1.36 [0.90, 2.05]	+-
Myles 1993	0	26	2	26	0.1%	0.20 [0.01, 3.97]	
Oppizzi 1997	3	13	0	13	0.1%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
Schmoelz 2006	2	11	8	21	0.3%	0.48 [0.12, 1.87]	
Schmoelz 2006a	2	11	6	21	0.3%	0.64 [0.15, 2.64]	
Schneider 1999	0	50	1	50	0.1%	0.33 [0.01, 7.99]	
Shah 2014	1	31	5	62	0.1%	0.40 [0.05, 3.28]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sindone 1998	0	8	3	8	0.1%	0.14 [0.01, 2.39]	• · · · · · · · · · · · · · · · · · · ·
Sindone 1998a	1	8	2	26	0.1%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.1%	1.13 [0.08, 15.19]	
Soliman 2017	3	75	1	75	0.1%	3.00 [0.32, 28.19]	
Sumeray 2001	0	24	5	24	0.1%	0.09 [0.01, 1.56]	<
Tarr 1993a	1	12	3	25	0.1%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	0.1%	0.64 [0.07, 5.57]	
Triposkiadis 2014	9	28	18	55	1.4%	0.98 [0.51, 1.90]	_
Triposkiadis 2014a	10	28	19	50	1.7%	0.94 [0.51, 1.73]	_
Varriale 1997	0	10	0	10		Not estimable	
Woo 2002	2	25	0	25	0.1%	5.00 [0.25, 99.16]	
Wu 2011	9	23	7	23	1.0%	1.29 [0.58, 2.86]	_
Zhuangyu 2011	14	45	13	45	1.6%	1.08 [0.57, 2.03]	_
Subtotal (95% CI)		1934		2085	100.0%	1.06 [0.98, 1.15]	*
Total events Heterogeneity: Tau² = Test for overall effect: .				3 (P = 0).93); I² =	0%	
							Favours dopamine Favours control

Test for subgroup differences: Not applicable

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

Study or Subgroup	Dopan Events		Contr		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
4.1.4 Subgroup 1: Lo			LYCIILS	Total	Weight	m-n, Random, 55% Cr	m-n, Kandoin, 55% Ci
De Backer 2010	472	858	427	821	100.0%	1.06 [0.97, 1.16]	
Subtotal (95% CI)	472	858	427	821	100.0%	1.06 [0.97, 1.16]	T
Total events	472	000	427	021	1001070	100 [001, 110]	
Heterogeneity: Not ag			427				
Test for overall effect:	•	P-02	2)				
restion overall ellect.	Z = 1.23 (,r = 0.2	2)				
4.1.5 Subgroup 1: Un	clear or h	iah risl	k of bias				
Arutiunov 2010	2	21	3	20	1.0%	0.63 [0.12, 3.41]	
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	3	40	4	40	1.4%	0.75 [0.18, 3.14]	
Carcoana 2003	Ō	25	0 0	24		Not estimable	
Carcoana 2003a	Ō	25	Ō	26		Not estimable	
Chen 2012	12	40	9	40	5.2%	1.33 [0.63, 2.81]	_ _
Chen 2013	24	122	25	119	11.6%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.3%	1.40 [0.06, 30.23]	
Gao 2008	9	21	9	23	5.7%	1.10 [0.54, 2.23]	_ _
Giamouzis 2010	3	30	3	30	1.3%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27	1.570	Not estimable	
Hsueh 1998	0	10	0	10		Not estimable	
Hua 2013	8	16	7	16	5.3%	1.14 [0.54, 2.40]	_
Kamiya 2015	0	12	2	12	0.3%	0.20 [0.01, 3.77]	
Kanchi 2017	0	30	2 0	30	0.5 /0	Not estimable	
Lassnigg 2000	0	21	1	40	0.3%	0.62 [0.03, 14.62]	
Lassnigg 2000 Lassnigg 2000a	0	21	4	40	0.3%	0.21 [0.01, 3.76]	
Liu 2010	12	25	4	25	0.3% 5.9%		
	6	10	5	10	0.9% 4.5%	1.50 [0.74, 3.03] 1.20 [0.54, 2.67]	
Marik 1994 Martin 1993	10	16	7	16	4.0% 6.4%		
Mathur 2007	10	25	14	25	17.1%		
	19	25	14	20	17.170	1.36 [0.90, 2.05]	-
Myles 1993 Oppi ssi 1997	3	13	0	13	0.4%	Not estimable	
Oppizzi 1997 Recessel 1997	0	35	0	35	0.4 %	7.00 [0.40, 123.35] Not estimable	
Rosseel 1997	2	30 10	7	20	1.5%		
Schmoelz 2006	2	11	5	20		0.57 [0.14, 2.26]	
Schmoelz 2006a	0	50	5 0		1.3%	0.73 [0.17, 3.15]	
Schneider 1999 Chob 2014	1		4	49	0.60	Not estimable	
Shah 2014 Shama 4999		31		61	0.6%	0.49 [0.06, 4.22]	
Sharpe 1999 Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a Sinalain 1997	0	5	0	10		Not estimable	
Sinclair 1997 Sindana 4999	0	16	0	14	0.400	Not estimable	
Sindone 1998	0	8	3	8	0.4%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	0.6%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.4%	1.13 [0.08, 15.19]	
Soliman 2017	3	75	1	75	0.6%	3.00 [0.32, 28.19]	
Sumeray 2001	0	19	0	19		Not estimable	
Tarr 1993a	1	12	3	25	0.6%	0.69 [0.08, 6.00]	
Tarr 1993b	1	13	3	25	0.6%	0.64 [0.07, 5.57]	
Triposkiadis 2014	9	28	18	55	6.7%	0.98 [0.51, 1.90]	
Triposkiadis 2014a	10	28	19	50	7.8%	0.94 [0.51, 1.73]	_ _
Varriale 1997	0	10	0	10		Not estimable	
Woo 2002	2	25	0	25	0.3%	5.00 [0.25, 99.16]	
Wu 2011	9	23	7	23	4.5%	1.29 [0.58, 2.86]	
Zhuangyu 2011	14	45	13	45	7.2%	1.08 [0.57, 2.03]	
Subtotal (95% CI)		1051		1241	100.0%	1.12 [0.94, 1.32]	T
Total events	168		187				
Heterogeneity: Tau ² =				9 (P = 0	0.99); I ^z = 0	1%	
Test for overall effect:	Z=1.26 ((P = 0.2	1)				
							Favours dopamine Favours control
est for subaroup diff	ferences:	Chi² = ().30, df=	1 (P =	0.59), l² = l	0%	

E-Figures 2.5.4-2.5.5: risk differences

Study or Subgroup 4.1.4 Subgroup 1: Lo		Total	Contr Events		Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% Cl
2010 De Backer 2010 Subtotal (95% CI)	472	858 858	427	821 821	100.0% 100.0%	0.03 [-0.02, 0.08] 0.03 [-0.02, 0.08]	-
Fotal events	472		427				Ť
Heterogeneity: Not ap							
Fest for overall effect:	•	P = 0.2	2)				
4.1.5 Subgroup 1: Un	clear or h	igh ris	k of bias				
Arutiunov 2010	2	21	3	20	0.7%	-0.05 [-0.26, 0.15]	
3irnbaum 1990	0	10	0	10	0.9%	0.00 [-0.17, 0.17]	
3ove 2005	3	40	4	40	1.8%	-0.03 [-0.15, 0.10]	
Carcoana 2003	0	25	0	24	4.9%	0.00 [-0.08, 0.08]	-+-
Carcoana 2003a	0	25	0	26	5.2%	0.00 [-0.07, 0.07]	- + -
Chen 2012	12	40	9	40	0.8%	0.07 [-0.12, 0.27]	
Chen 2013	24	122	25	119	2.7%	-0.01 [-0.12, 0.09]	
otter 1997	1	14	0	6	0.5%	0.07 [-0.17, 0.32]	
)ao 2008	9	21	9	23	0.3%	0.04 [-0.25, 0.33]	
∂iamouzis 2010	3	30	3	30	1.2%	0.00 [-0.15, 0.15]	
lausen 1992	0	14	0	27	2.6%	0.00 [-0.10, 0.10]	
Isueh 1998	0	10	0	10	0.9%	0.00 [-0.17, 0.17]	
lua 2013	8	16	7	16	0.2%	0.06 [-0.28, 0.41]	
(amiya 2015	0	12	2	12	0.5%	-0.17 [-0.41, 0.07]	
(anchi 2017	0	30	0	30	7.2%	0.00 [-0.06, 0.06]	+
assnigg 2000.	0	21	1	40	3.9%	-0.03 [-0.11, 0.06]	-+
assnigg 2000a.	0	21	4	41	2.2%	-0.10 [-0.21, 0.01]	
.iu 2010	12	25	8	25	0.4%	0.16 [-0.11, 0.43]	
Aarik 1994	6	10	5	10	0.1%	0.10 [-0.33, 0.53]	
/lartin 1993	10	16	7	16	0.2%	0.19 [-0.15, 0.53]	
Aathur 2007	19	25	14	25	0.4%	0.20 [-0.06, 0.46]	
vlyles 1993	0	25	0	24	4.9%	0.00 [-0.08, 0.08]	
Oppizzi 1997	3	13	0	13	0.5%	0.23 [-0.02, 0.48]	
Rosseel 1997	0	35	0	35	9.6%	0.00 [-0.05, 0.05]	T
Schmoelz 2006	2	10	7	20	0.3%	-0.15 [-0.47, 0.17]	
Schmoelz 2006a	2	11	5	20	0.3%	-0.07 [-0.36, 0.23]	
Schneider 1999	0	50	0	49	18.9%	0.00 [-0.04, 0.04]	_ <u> </u>
Shah 2014 Shama 4888	1	31	4	61	3.6%	-0.03 [-0.12, 0.05]	
Sharpe 1999 Sharpa 1999	0 0	5 5	0 0	10 10	0.4% 0.4%	0.00 [-0.25, 0.25]	
Sharpe 1999a Sinclair 1997	0	16	0	14	1.9%	0.00 [-0.25, 0.25]	
Sindone 1998	0	8	3	8	0.2%	0.00 [-0.12, 0.12] -0.38 [-0.73, -0.02]	
Sindone 1998a	1	8	2	26	0.2%	0.05 [-0.20, 0.30]	
Sindone 1998b	1	8	1	20	0.3%	0.01 [-0.29, 0.32]	
Boliman 2017	3	75	1	75	10.7%	0.03 [-0.02, 0.08]	↓
Sumeray 2001	Ő	19	, O	19	3.0%	0.00 [-0.10, 0.10]	
arr 1993a	1	12	3	25	0.7%	-0.04 [-0.24, 0.17]	
arr 1993b	1	13	3	25	0.8%	-0.04 [-0.24, 0.15]	
Triposkiadis 2014	. 9	28	18	55	0.6%	-0.01 [-0.22, 0.21]	
riposkiadis 2014a	10	28	19	50	0.6%	-0.02 [-0.25, 0.20]	——— — ——
/arriale 1997	0	10	0	10	0.9%	0.00 [-0.17, 0.17]	-+
Voo 2002	2	25	0	25	1.8%	0.08 [-0.05, 0.21]	+
Vu 2011	9	23	7	23	0.4%	0.09 [-0.19, 0.36]	
Zhuangyu 2011 Subtotal (95% CI)	14	45 1051	13	45	0.8% 100.0%	0.02 [-0.17, 0.21] 0.00 [-0.02, 0.02]	
otal events leterogeneity: Tau² = est for overall effect:			•	3 (P = 0).98); I² = ()%	
							-1 -0.5 0 0.5

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

tai Events 25 0 25 0 22 25 30 0 21 1 25 0 21 1 25 0 31 4 5 0 31 4 5 0 31 4 5 0 31 4 5 0 31 4 5 0 34 58 3.79, df = 6 (P 0.53) 7 ve control 21 31 0 40 4 9 3 14 0 16 7 12 2 21 4	24 26 119 30 40 24 20 49 61 10 8 19 55 520 7 25 520 7 20 10 40 40 40 40 6 821 23 30 27 10 16 12	54.1% 1.4% 7.1% 2.9% 1.7% 31.2% 1.5% 100.0%	M-H, Random, 95% Cl Not estimable 0.94 [0.57, 1.54] Not estimable 0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 1.01 [0.54, 2.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable Not estimable Not estimable	M-H, Random, 95% Cl
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	26 119 30 40 24 20 49 61 10 8 19 55 10 25 520 * * * * * * * * * * * * * * * * * * *	1.4% 7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	Not estimable 0.94 [0.57, 1.54] Not estimable 0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	26 119 30 40 24 20 49 61 10 8 19 55 10 25 520 * * * * * * * * * * * * * * * * * * *	1.4% 7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	Not estimable 0.94 [0.57, 1.54] Not estimable 0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c} 119\\30\\40\\24\\20\\49\\61\\10\\8\\19\\55\\10\\25\\520\\\end{array} $	1.4% 7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	0.94 [0.57, 1.54] Not estimable 0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	30 40 24 20 49 61 10 8 19 55 10 25 520 7 20 10 40 40 40 6 821 23 30 27 10 16 12	1.4% 7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	Not estimable 0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c} 40\\ 24\\ 20\\ 49\\ 61\\ 10\\ 8\\ 19\\ 55\\ 10\\ 25\\ 520\\ -\\ -\\ 20\\ 10\\ 40\\ 40\\ 40\\ 40\\ 40\\ 40\\ 40\\ 40\\ 40\\ 4$	7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	0.62 [0.03, 14.62] Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	24 20 49 61 10 8 19 55 10 25 520	7.1% 2.9% 1.7% 31.2% 1.5% 100.0%); I ² = 0% 0.2% 0.3% 1.2% 0.3% 1.2%	Not estimable 0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.63, 2.12] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{ccccccc} 10 & 7 \\ 50 & 0 \\ 31 & 4 \\ 5 & 0 \\ 8 & 3 \\ 19 & 0 \\ 28 & 18 \\ 10 & 0 \\ 28 & 18 \\ 10 & 0 \\ 34 \\ & 58 \\ 3.79, df = 6 (P \\ 0.53) \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	$20 \\ 49 \\ 61 \\ 10 \\ 8 \\ 19 \\ 55 \\ 520 \\ 7 = 0.71)$ $20 \\ 10 \\ 40 \\ 40 \\ 6 \\ 821 \\ 23 \\ 30 \\ 27 \\ 10 \\ 16 \\ 12$	2.9% 1.7% 31.2% 1.5% 100.0%); ² = 0% 0.2% 0.3% 1.2% 0.1% 1.3% 0.3% 1.2%	0.57 [0.14, 2.26] Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 1.33 [0.63, 2.81] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	49 61 10 8 19 55 520 25 520 25 520 25 520 20 10 40 40 40 40 6 821 23 30 27 10 16 12	2.9% 1.7% 31.2% 1.5% 100.0%); ² = 0% 0.2% 0.3% 1.2% 0.1% 1.3% 0.3% 1.2%	Not estimable 0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	61 10 8 19 55 520 25 520 20 10 40 40 40 40 40 821 23 30 27 10 16 12	1.7% 31.2% 1.5% 100.0%); ² = 0% 0.2% 0.3% 1.2% 0.1% 82.1% 1.3% 0.3% 1.2%	0.49 [0.06, 4.22] Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 1.33 [0.63, 2.81] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
5 0 8 3 19 0 28 18 10 0 25 0 34 58 3.79, df = 6 (P 0.53) 7e control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 14 0 14 0 16 7 12 2	10 8 19 55 10 25 520 20 10 40 40 40 6 821 23 30 27 10 16 12	1.7% 31.2% 1.5% 100.0%); ² = 0% 0.2% 0.3% 1.2% 0.1% 82.1% 1.3% 0.3% 1.2%	Not estimable 0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] 1.33 [0.63, 2.81] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
8 3 19 0 28 18 10 0 25 0 34 58 3.79, df = 6 (P 0.53) 0 2e control 21 21 3 10 0 40 9 14 0 58 427 21 3 30 3 14 0 10 0 16 7 12 2	8 19 55 10 25 520 20 10 40 40 40 40 6 821 23 30 27 10 16 12	31.2% 1.5% 100.0%); F = 0% 0.2% 0.3% 1.2% 82.1% 1.3% 0.3% 1.2%	0.14 [0.01, 2.39] Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccc} 19 & 0 \\ 28 & 18 \\ 10 & 0 \\ 25 & 0 \\ 34 & 58 \\ 3.79, df = 6 (P \\ 0.53) \\ \hline \textbf{ve control} \\ 21 & 3 \\ 10 & 0 \\ 40 & 4 \\ 40 & 9 \\ 14 & 0 \\ 58 & 427 \\ 21 & 9 \\ 30 & 3 \\ 14 & 0 \\ 10 & 0 \\ 16 & 7 \\ 12 & 2 \end{array}$	$ \begin{array}{c} 19\\55\\10\\25\\520\\\end{array},\\ \begin{array}{c} 2\\520\\10\\40\\40\\6\\821\\23\\30\\27\\10\\16\\12\end{array} \end{array} $	31.2% 1.5% 100.0%); F = 0% 0.2% 0.3% 1.2% 82.1% 1.3% 0.3% 1.2%	Not estimable 0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.89 [0.62, 1.28] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccc} 28 & 18 \\ 10 & 0 \\ 25 & 0 \\ 34 & 58 \\ 3.79, df = 6 (P \\ 0.53) & \\ \hline \ensuremath{\textit{ve control}} \\ 21 & 3 \\ 10 & 0 \\ 40 & 4 \\ 40 & 9 \\ 14 & 0 \\ 58 & 427 \\ 21 & 9 \\ 30 & 3 \\ 14 & 0 \\ 10 & 0 \\ 16 & 7 \\ 12 & 2 \end{array}$	55 10 25 520 0 20 10 40 40 6 821 23 30 27 10 16 12	1.5% 100.0%); ₽ = 0% 0.2% 0.3% 1.2% 0.3% 1.3% 0.3%	0.98 [0.51, 1.90] Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
$\begin{array}{cccc} 10 & 0 \\ 25 & 0 \\ 34 \\ 58 \\ 3.79, df = 6 (P \\ 0.53) \\ \hline \mbox{ve control} \\ 21 & 3 \\ 10 & 0 \\ 40 & 4 \\ 40 & 9 \\ 14 & 0 \\ 58 & 427 \\ 21 & 9 \\ 30 & 3 \\ 14 & 0 \\ 10 & 0 \\ 16 & 7 \\ 12 & 2 \\ \end{array}$	$ \begin{array}{c} 10\\ 25\\ 520\\ \end{array} $ $ \begin{array}{c} 20\\ 10\\ 40\\ 6\\ 821\\ 23\\ 30\\ 27\\ 10\\ 16\\ 12\\ \end{array} $	1.5% 100.0%); ₽ = 0% 0.2% 0.3% 1.2% 0.3% 1.3% 0.3%	Not estimable 5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
25 0 34 58 3.79, df = 6 (P 0.53) 7e control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	25 520 20 10 40 6 821 23 30 27 10 16 12	100.0%); = 0% 0.2% 0.3% 1.2% 82.1% 1.3% 0.3% 1.2%	5.00 [0.25, 99.16] 0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
34 58 3.79, df = 6 (P 0.53) ve control 21 3 21 3 10 0 40 4 9 14 0 58 427 21 9 30 3 14 0 58 427 21 9 30 3 14 0 16 7 12 2 2	520 P = 0.71) 20 10 40 6 821 23 30 27 10 16 12	100.0%); = 0% 0.2% 0.3% 1.2% 82.1% 1.3% 0.3% 1.2%	0.89 [0.62, 1.28] 0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
58 3.79, df = 6 (P 0.53) e control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	P = 0.71) 20 10 40 6 821 23 30 27 10 16 12); ² = 0% 0.2% 0.3% 1.2% 82.1% 1.3% 0.3% 1.2%	0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
3.79, df = 6 (P 0.53) e control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	20 10 40 6 821 23 30 27 10 16 12	0.2% 0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
0.53) ve control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	20 10 40 6 821 23 30 27 10 16 12	0.2% 0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	0.63 [0.12, 3.41] Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable 1.14 [0.54, 2.40]	
ve control 21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	10 40 6 821 23 30 27 10 16 12	0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	10 40 6 821 23 30 27 10 16 12	0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
21 3 10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	10 40 6 821 23 30 27 10 16 12	0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
10 0 40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	10 40 6 821 23 30 27 10 16 12	0.3% 1.2% 0.1% 82.1% 1.3% 0.3%	Not estimable 0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
40 4 40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	40 6 821 23 30 27 10 16 12	1.2% 0.1% 82.1% 1.3% 0.3%	0.75 [0.18, 3.14] 1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
40 9 14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	40 6 821 23 30 27 10 16 12	1.2% 0.1% 82.1% 1.3% 0.3%	1.33 [0.63, 2.81] 1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
14 0 58 427 21 9 30 3 14 0 10 0 16 7 12 2	6 821 23 30 27 10 16 12	0.1% 82.1% 1.3% 0.3%	1.40 [0.06, 30.23] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
58 427 21 9 30 3 14 0 10 0 16 7 12 2	821 23 30 27 10 16 12	82.1% 1.3% 0.3% 1.2%	1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
21 9 30 3 14 0 10 0 16 7 12 2	23 30 27 10 16 12	1.3% 0.3% 1.2%	1.10 [0.54, 2.23] 1.00 [0.22, 4.56] Not estimable Not estimable 1.14 [0.54, 2.40]	
30 3 14 0 10 0 16 7 12 2	30 27 10 16 12	0.3% 1.2%	1.00 (0.22, 4.56) Not estimable Not estimable 1.14 (0.54, 2.40)	
14 0 10 0 16 7 12 2	27 10 16 12	1.2%	Not estimable Not estimable 1.14 [0.54, 2.40]	
14 0 10 0 16 7 12 2	27 10 16 12	1.2%	Not estimable Not estimable 1.14 [0.54, 2.40]	
16 7 12 2	16 12		Not estimable 1.14 [0.54, 2.40]	
16 7 12 2	12		1.14 [0.54, 2.40]	
12 2	12			
			0.2010.01.3.771	
	41	0.1%	0.21 [0.01, 3.76]	
25 8	25	1.3%	1.50 [0.74, 3.03]	
10 5	10	1.0%	1.20 [0.54, 2.67]	
16 7	16	1.4%	1.43 [0.73, 2.80]	
25 14	25	3.9%	1.36 [0.90, 2.05]	+ - -
13 0	13	0.1%	7.00 [0.40, 123.35]	
35 0	35		Not estimable	
11 5	20	0.3%	0.73 [0.17, 3.15]	
5 0	10	0.070	Not estimable	
16 0	14		Not estimable	
8 2	26	0.1%	1.63 [0.17, 15.66]	
8 1	20	0.1%	1.13 [0.08, 15.19]	
75 1	75	0.1%	3.00 [0.32, 28.19]	
12 3	25	0.1%	0.69 [0.08, 6.00]	
	1042		100 [100, 117]	ľ
000	2 (P - 0)	aa\- i z – c	196	
	v (r. – 0.)	.55/, F – C	, ,,,	
10.07, df = 23				
10.07, df = 23				0.01 0.1 1 10 100
14		28 19 50 23 7 23 45 13 45 75 1542 556 0.07, df = 23 (P = 0	28 19 50 1.8% 23 7 23 1.0% 45 13 45 1.6% 75 1542 100.0% 556 0.07, df = 23 (P = 0.99); I ^z = 0	28 19 50 1.8% 0.94 [0.51, 1.73] 23 7 23 1.0% 1.29 [0.58, 2.86] 45 13 45 1.6% 1.08 [0.57, 2.03] 75 1542 100.0% 1.08 [1.00, 1.17]

E-Figures 2.5.6-2.5.7: risk differences

Study or Subgroup	Dopam		Contr		Woight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
1.1.6 Subgroup 2: Ina			Events	TUtai	weight	M-n, Kalluolli, 55% Cl	M-n, Kaluolii, 95% Ci
arcoana 2003	0	25	0	24	8.3%	0.00 [-0.08, 0.08]	+
Carcoana 2003a	0	25	0	26	8.9%	0.00 [-0.07, 0.07]	+
hen 2013	24	122	25	119	4.7%	-0.01 [-0.12, 0.09]	
(anchi 2017	0	30	0	30	12.2%	0.00 [-0.06, 0.06]	+
assnigg 2000.	0	21	1	40	6.7%	-0.03 [-0.11, 0.06]	_
Ayles 1993	0	25	0	24	8.3%	0.00 [-0.08, 0.08]	+
Schmoelz 2006	2	10	7	20	0.5%	-0.15 [-0.47, 0.17]	
Schneider 1999	0	50	0	49	32.2%	0.00 [-0.04, 0.04]	+
3hah 2014	1	31	4	61	6.2%	-0.03 [-0.12, 0.05]	
Sharpe 1999	0	5	0	10	0.8%	0.00 [-0.25, 0.25]	
Sindone 1998	0	8	3	8	0.4%	-0.38 [-0.73, -0.02]	
Sumeray 2001	0	19	0	19	5.1%	0.00 [-0.10, 0.10]	
riposkiadis 2014	9	28	18	55	1.1%	-0.01 [-0.22, 0.21]	
, arriale 1997	0	10	0	10	1.6%	0.00 [-0.17, 0.17]	
Voo 2002	2	25	0	25	3.1%	0.08 [-0.05, 0.21]	
Subtotal (95% CI)		434		520	100.0%	-0.00 [-0.03, 0.02]	•
otal events	38		58				
leterogeneity: Tau ² =	0.00; Chi	² = 8.51	. df = 14	(P = 0.)	86); I² = 0	%	
est for overall effect:					.,,		
.1.7 Subgroup 2: Po	tentially a	ctive c	ontrol				
rutiunov 2010	2	21	3	20	1.3%	-0.05 [-0.26, 0.15]	
3irnbaum 1990	0	10	0	10	1.7%	0.00 [-0.17, 0.17]	
3ove 2005	3	40	4	40	3.4%	-0.03 [-0.15, 0.10]	_
Chen 2012	12	40	9	40	1.4%	0.07 [-0.12, 0.27]	
Cotter 1997	1	14	Ō	6	0.9%	0.07 [-0.17, 0.32]	
)e Backer 2010	472	858	427	821	23.0%	0.03 [-0.02, 0.08]	
€ 2008 €ao 2008	2	21	9	23	0.6%	0.04 [-0.25, 0.33]	
Fiamouzis 2010	3	30	3	30	2.3%	0.00 [-0.15, 0.15]	
lausen 1992	Ŭ	14	Ő	27	4.9%	0.00 [-0.10, 0.10]	
Isueh 1998	Ő	10	Ŭ	10	1.7%	0.00 [-0.17, 0.17]	
lua 2013	8	16	7	16	0.4%	0.06 [-0.28, 0.41]	
(amiya 2015	0	12	2	12	0.9%	-0.17 [-0.41, 0.07]	
assnigg 2000a	0	21	4	41	4.1%	-0.10 [-0.21, 0.01]	
iu 2010	12	25	8	25	0.7%	0.16 [-0.11, 0.43]	
1arik 1994	6	10	5	10	0.3%	0.10 [-0.33, 0.53]	
Aartin 1993	10	16	7	16	0.5%	0.19 [-0.15, 0.53]	
Aathur 2007	19	25	14	25	0.8%	0.20 [-0.06, 0.46]	
)ppizzi 1997	3	13	0	13	0.9%	0.23 [-0.02, 0.48]	
Rosseel 1997	0	35	0	35			↓
	2		5		17.9%		
Schmoelz 2006a		11		20	0.6%	-0.07 [-0.36, 0.23]	
Sharpe 1999a	0	10	0	10	0.8%	0.00 [-0.25, 0.25]	
Sinclair 1997	0	16	0	14	3.6%	0.00 [-0.12, 0.12]	
Sindone 1998a Sindone 1998b	1	8	2	26	0.8%	0.05 [-0.20, 0.30]	
	1	8	1	9	0.6%	0.01 [-0.29, 0.32]	
Soliman 2017	3	75	1	75	19.8%	0.03 [-0.02, 0.08]	
farr 1993a	1	12	3	25	1.3%	-0.04 [-0.24, 0.17]	
arr 1993b	1	13	3	25	1.4%	-0.04 [-0.24, 0.15]	
riposkiadis 2014a	10	28	19	50	1.1%	-0.02 [-0.25, 0.20]	
Vu 2011	9	23	7	23	0.7%	0.09 [-0.19, 0.36]	
Ihuangyu 2011 Subtotal (95% CI)	14	45 1475	13	45 1542	1.5% 100.0%	0.02 [-0.17, 0.21] 0.01 [-0.01, 0.04]	
otal events	602		556				[
leterogeneity: Tau² =		²= 19 0		9 (P = 1	.92); I ² = I	0%	
est for overall effect:					,,.		
							-1 -0.5 0 0.5

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

	Favours dopa		Contr		Moight	Risk Ratio	Risk Ratio
Study or Subgroup 4.1.8 Subgroup 3: Lo	Events	rotar	events	rotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Arutiunov 2010		24	2	20	1.204	0 6 3 70 4 3 3 4 4 1	
	2	21	3	20	4.2%	0.63 [0.12, 3.41]	-
Birnbaum 1990	0	10	0	10	C 700	Not estimable	
3ove 2005	3	40	4	40	5.7%	0.75 [0.18, 3.14]	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Chen 2012	12	40	9	40	21.2%	1.33 [0.63, 2.81]	_
Chen 2013	24	122	25	119	47.0%	0.94 [0.57, 1.54]	
Kamiya 2015	0	12	2	12	1.4%	0.20 [0.01, 3.77]	
Kanchi 2017	0	30	0	30		Not estimable	
Lassnigg 2000	0	21	1	40	1.2%	0.62 [0.03, 14.62]	
Lassnigg 2000a	0	21	4	41	1.4%	0.21 [0.01, 3.76]	
Myles 1993	0	25	Ó	24		Not estimable	
Rosseel 1997	ů	35	Ő	35		Not estimable	
	2		7		6.204		
Schmoelz 2006		10		20	6.2%	0.57 [0.14, 2.26]	
Schmoelz 2006a	2	11	5	20	5.5%	0.73 [0.17, 3.15]	
Schneider 1999	0	50	0	49		Not estimable	
Shah 2014	1	31	4	61	2.5%	0.49 [0.06, 4.22]	
Sinclair 1997	0	16	0	14		Not estimable	
Soliman 2017	3	75	1	75	2.3%	3.00 [0.32, 28.19]	
Sumeray 2001	0	19	0	19		Not estimable	
Varriale 1997	0	10	0	10		Not estimable	
Woo 2002	2	25	0	25	1.3%	5.00 [0.25, 99.16]	
Subtotal (95% CI)	-	674	·		100.0%	0.92 [0.66, 1.30]	•
Total events	51		65				1
		50 df_ 11		- 41 - 12 -	. 00		
Heterogeneity: Tau ² =			(P = 0.)	34); 17 =	0%0		
Test for overall effect:	Z = 0.45 (P = 0	.65)					
4.4.0 Subaroup 2: Ma	dorato dono						
4.1.9 Subgroup 3: Mo			-	-			
Cotter 1997	1	14	0	6	1.7%	1.40 [0.06, 30.23]	
Giamouzis 2010	3	30	3	30	7.1%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Llough 1000	0	10	0	10		Not estimable	
Hsueh 1998				4.0	2.0%	7.00 [0.40, 123.35]	
			0	13			
Oppizzi 1997	3	13	0 0	13 10	2.070		
Oppizzi 1997 Sharpe 1999	3 0	13 5	0	10	2.070	Not estimable	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a	3 0 0	13 5 5	0 0	10 10		Not estimable Not estimable	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a	3 0 0 1	13 5 5 12	0 0 3	10 10 25	3.5%	Not estimable Not estimable 0.69 (0.08, 6.00)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b	3 0 1 1	13 5 12 13	0 0 3 3	10 10 25 25	3.5% 3.5%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a	3 0 1 1 9	13 5 12 13 28	0 0 3 3 18	10 10 25 25 55	3.5% 3.5% 37.9%	Not estimable Not estimable 0.69 (0.08, 6.00)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a	3 0 1 1	13 5 12 13 28 28	0 0 3 3	10 10 25 25 55 50	3.5% 3.5% 37.9% 44.1%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014	3 0 1 1 9	13 5 12 13 28	0 0 3 3 18	10 10 25 25 55 50	3.5% 3.5% 37.9%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a	3 0 1 1 9	13 5 12 13 28 28	0 0 3 3 18	10 10 25 25 55 50	3.5% 3.5% 37.9% 44.1%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI)	3 0 1 1 9 10 28	13 5 12 13 28 28 172	0 3 3 18 19 46	10 25 25 55 50 261	3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events	3 0 1 1 9 10 28 0.00; Chi ² = 2.	13 5 12 13 28 28 172 17, df = 6	0 3 3 18 19 46	10 25 25 55 50 261	3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² =	3 0 1 1 9 10 28 0.00; Chi ² = 2.	13 5 12 13 28 28 172 17, df = 6	0 3 3 18 19 46	10 25 25 55 50 261	3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² =	3 0 1 1 9 10 28 0.00; Chi² = 2. Z = 0.09 (P = 0	13 5 12 13 28 28 172 17, df = 6	0 3 3 18 19 46	10 25 25 55 50 261	3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	3 0 1 1 9 10 28 0.00; Chi² = 2. Z = 0.09 (P = 0	13 5 12 13 28 28 172 17, df = 6	0 3 3 18 19 46	10 25 25 55 50 261	3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012	3 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12	13 5 12 13 28 172 17, df = 6 .93)	0 0 3 18 19 46 (P = 0.9)	10 10 25 55 50 261 0); I ² = (3.5% 3.5% 37.9% 44.1% 100.0%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73) 0.98 (0.65, 1.47)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472	13 5 12 13 28 172 17, df = 6 .93) 40 858	0 0 3 18 19 46 (P = 0.9) (P = 0.9) 9 427	10 10 25 55 50 261 0); I ² = (40 821	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.33 [0.63, 2.81] 1.06 [0.97, 1.16]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008	3 0 0 1 1 9 10 28 0.00; Chi ² = 2: Z = 0.09 (P = 0 igh dose 12 472 9	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21	0 0 3 18 19 46 (P = 0.9) (P = 0.9) 427 9	10 10 25 55 261 0); ² = 1 40 821 23	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.4%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.33 [0.63, 2.81] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 472 9 8	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7	10 10 25 55 50 261 0); ² = 1 40 821 23 16	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.4% 1.2%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.33 [0.63, 2.81] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8	10 10 25 55 261 0); ² = 1 40 821 23 16 25	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.4% 1.2% 1.4%	Not estimable Not estimable 0.69 (0.08, 6.00) 0.64 (0.07, 5.57) 0.98 (0.51, 1.90) 0.94 (0.51, 1.73) 0.98 (0.65, 1.47) 1.08 (0.65, 1.47) 1.06 (0.97, 1.16) 1.10 (0.54, 2.23) 1.14 (0.54, 2.40) 1.50 (0.74, 3.03)	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994	30011910280.00; Chi2 = 2.Z = 0.09 (P = 0igh dose1247298126	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5	10 10 25 55 50 261 0); ² = 1 40 821 23 16 25 10	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.4% 1.2% 1.4% 1.1%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993	30011910280.00; Chi2 = 2.Z = 0.09 (P = 0igh dose124729812610	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7	10 10 25 55 50 261 0); ² = 1 40 821 23 16 25 10 16	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.2% 1.4% 1.4% 1.4% 1.1%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994	30011910280.00; Chi2 = 2.Z = 0.09 (P = 0igh dose1247298126	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5	10 10 25 55 50 261 0); ² = 1 40 821 23 16 25 10	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.4% 1.2% 1.4% 1.1%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993	30011910280.00; Chi2 = 2.Z = 0.09 (P = 0igh dose124729812610	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7	10 10 25 55 50 261 0); ² = 1 40 821 23 16 25 10 16	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 85.4% 1.2% 1.4% 1.4% 1.4% 1.1%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007	30011910280.00; Chi2 = 2:Z = 0.09 (P = 0124729812472981261019	13 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7 14	10 10 25 55 50 261 0); ² = (0); ² = (40 821 23 16 25 10 16 25	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.4% 1.4% 1.4% 1.4% 1.4% 1.5% 4.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.33 [0.63, 2.81] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011	3 0 0 1 1 9 10 28 0.00; Chi² = 2. Z = 0.09 (P = 0 12 472 9 8 12 6 10 19 9 9	13 5 12 13 28 17 17 , df = 6 .93) 40 858 21 16 25 10 16 25 23	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 427 9 7 7 8 5 7 14 7	10 10 25 55 50 261 30); r = 1 40 821 23 16 25 10 10 25 23 45	3.5% 3.5% 37.9% 44.1% 100.0% 3% 1.2% 1.4% 1.2% 1.4% 1.1% 4.0% 1.1%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Martin 1993 Mathur 2007 Wu 2011 Zhuangyu 2011 Subtotal (95% CI)	3 0 0 1 1 9 10 28 0.00; Chi ² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 23 45	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 427 8 5 7 8 5 7 4 7 13	10 10 25 55 50 261 30); r = 1 40 821 23 16 25 10 10 25 23 45	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.4% 1.4% 1.4% 1.1% 1.1% 4.0% 1.1% 1.7%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011 Zhuangyu 2011 Subtotal (95% CI) Total events	30011910280.00; Chi2 = 2:Z = 0.09 (P = 0igh dose12472981261019914571	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 16 25	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7 14 7 13 506	10 10 25 55 55 261 261)); ² = 1 40 821 23 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 10 261 261 265 10 261 261 261 261 261 261 261 261	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.2% 1.4% 1.4% 1.1% 1.5% 4.0% 1.7% 100.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011 Zhuangyu 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi² = 3.	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 10 16 25 10 46, df = 9	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7 14 7 13 506	10 10 25 55 55 261 261)); ² = 1 40 821 23 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 10 261 261 265 10 261 261 261 261 261 261 261 261	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.2% 1.4% 1.4% 1.1% 1.5% 4.0% 1.7% 100.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Farr 1993a Farr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Martin 1993 Mathin 1993 Mathin 2007 X/u 2011 Subtotal (95% CI) Total events	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi² = 3.	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 10 16 25 10 46, df = 9	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7 14 7 13 506	10 10 25 55 55 261 261)); ² = 1 40 821 23 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 10 261 261 265 10 261 261 261 261 261 261 261 261	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.2% 1.4% 1.4% 1.1% 1.5% 4.0% 1.7% 100.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Farr 1993a Farr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Martin 1993 Mathin 1993 Mathin 2007 X/u 2011 Subtotal (95% CI) Total events	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi² = 3.	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 10 16 25 10 46, df = 9	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 7 8 5 7 14 7 13 506	10 10 25 55 55 261 261)); ² = 1 40 821 23 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 10 261 261 265 10 261 261 261 261 261 261 261 261	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.2% 1.4% 1.4% 1.1% 1.5% 4.0% 1.7% 100.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03] 1.09 [1.00, 1.18]	
Oppizzi 1997 Sharpe 1999 Sharpe 1999a Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011 Zhuangyu 2011 Subtotal (95% CI) Total events	3 0 0 1 1 9 10 28 0.00; Chi² = 2: Z = 0.09 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi² = 3.	13 5 5 12 13 28 172 17, df = 6 .93) 40 858 21 16 25 10 16 25 10 16 25 10 16 25 10 46, df = 9	0 0 3 18 19 46 (P = 0.9) 427 9 427 9 427 8 5 7 14 7 13 506	10 10 25 55 55 261 261)); ² = 1 40 821 23 16 25 10 16 25 10 16 25 10 16 25 10 16 25 10 10 261 261 265 10 261 261 261 261 261 261 261 261	3.5% 3.5% 37.9% 44.1% 100.0% 0% 1.2% 1.2% 1.4% 1.4% 1.1% 1.5% 4.0% 1.7% 100.0%	Not estimable Not estimable 0.69 [0.08, 6.00] 0.64 [0.07, 5.57] 0.98 [0.51, 1.90] 0.94 [0.51, 1.73] 0.98 [0.65, 1.47] 1.06 [0.97, 1.16] 1.10 [0.54, 2.23] 1.14 [0.54, 2.40] 1.50 [0.74, 3.03] 1.20 [0.54, 2.67] 1.43 [0.73, 2.80] 1.36 [0.90, 2.05] 1.29 [0.58, 2.86] 1.08 [0.57, 2.03] 1.09 [1.00, 1.18]	

E-Figures 2.5.8-2.5.10: risk differences

Study or Subgroup	Events	amine Total	Contre		Woight	Risk Difference	Risk Difference
4.1.8 Subgroup 3: Lo		TOTAL	events	rotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
		24	2	20	0.00	0.05 (0.06 0.45)	
Arutiunov 2010	2	21	3	20	0.8%	-0.05 [-0.26, 0.15]	
Birnbaum 1990	0	10	0	10	1.1%	0.00 [-0.17, 0.17]	
Bove 2005	3	40	4	40	2.1%	-0.03 [-0.15, 0.10]	
Carcoana 2003	0	25	0	24	5.6%	0.00 [-0.08, 0.08]	
Carcoana 2003a	0	25	0	26	6.0%	0.00 [-0.07, 0.07]	Ť
Chen 2012	12	40	9	40	0.9%	0.07 [-0.12, 0.27]	
Chen 2013	24	122	25	119	3.1%	-0.01 [-0.12, 0.09]	
Kamiya 2015	0	12	2	12	0.6%	-0.17 [-0.41, 0.07]	
Kanchi 2017	0	30	0	30	8.3%	0.00 [-0.06, 0.06]	+
Lassnigg 2000	0	21	1	40	4.5%	-0.03 [-0.11, 0.06]	
Lassnigg 2000a	0	21	4	41	2.6%	-0.10 [-0.21, 0.01]	
Myles 1993	0	25	0	24	5.6%	0.00 [-0.08, 0.08]	+
Rosseel 1997	0	35	0	35	11.1%	0.00 [-0.05, 0.05]	+
Schmoelz 2006	2	10	7	20	0.3%	-0.15 [-0.47, 0.17]	
Schmoelz 2006a	2	11	5	20	0.4%	-0.07 [-0.36, 0.23]	
Schneider 1999	0	50	0	49	21.8%	0.00 [-0.04, 0.04]	+
Shah 2014	1	31	4	61	4.2%	-0.03 [-0.12, 0.05]	
Sinclair 1997	0	16	0	14	2.2%	0.00 [-0.12, 0.12]	_
Soliman 2017	3	75	1	75	12.3%	0.03 [-0.02, 0.08]	+- -
Sumeray 2001	0	19	Ó	19	3.5%	0.00 [-0.10, 0.10]	_ + _
Varriale 1997	0	10	0	10	1.1%	0.00 [-0.17, 0.17]	
Woo 2002	2	25	ŏ	25	2.1%	0.08 [-0.05, 0.21]	+
Subtotal (95% CI)	-	674	·		100.0%	-0.00 [-0.02, 0.02]	4
Total events Heterogeneity: Tau² = Test for overall effect:		•	65 21 (P = 0	.97); I²	= 0%		
4.1.9 Subgroup 3: Mo	derate dose						
Cotter 1997	1	14	0	6	5.1%	0.07 [-0.17, 0.32]	
Giamouzis 2010	3	30	3	30	13.2%	0.00 [-0.15, 0.15]	_
Hausen 1992	0	14	0	27	28.6%	0.00 [-0.10, 0.10]	_ + _
Hsueh 1998	0	10	0	10	10.0%	0.00 [-0.17, 0.17]	_
Oppizzi 1997	3	13	0	13	5.0%	0.23 [-0.02, 0.48]	
Sharpe 1999	0	5	0	10	4.8%	0.00 [-0.25, 0.25]	
		5	0	10	4.8%	0.00 [-0.25, 0.25]	
Sharpe 1999a					7.5%		
Sharpe 1999a Tarr 1993a	0		3			-111141-1174 11171	
Tarr 1993a	0 1	12	3	25 25		-0.04 [-0.24, 0.17] -0.04 [-0.24, 0.15]	
Tarr 1993a Tarr 1993b	0 1 1	12 13	3	25	8.2%	-0.04 [-0.24, 0.15]	
Tarr 1993a Tarr 1993b Triposkiadis 2014	0 1 1 9	12 13 28	3 18	25 55	8.2% 6.7%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a	0 1 1	12 13 28 28	3	25 55 50	8.2% 6.7% 6.1%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI)	0 1 9 10	12 13 28	3 18 19	25 55 50	8.2% 6.7%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0	12 13 28 28 172 99, df = 10	3 18 19 46	25 55 50 261	8.2% 6.7% 6.1% 100.0%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0 igh dose	12 13 28 28 172 99, df = 10 .80)	3 18 19 46) (P = 0.9	25 55 50 261 95); I ² =	8.2% 6.7% 6.1% 100.0%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06]	•
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0 igh dose 12	12 13 28 28 172 99, df = 10 .80) 40	3 18 19 46) (P = 0.9 9	25 55 50 261 35); I ² = 40	8.2% 6.7% 6.1% 100.0% :0% 4.7%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtoal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472	12 13 28 172 99, df = 10 .80) 40 858	3 18 19 46) (P = 0.9 9 427	25 55 50 261 35); I ² = 40 821	8.2% 6.7% 6.1% 100.0% :0% 4.7% 77.0%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27] 0.03 [-0.02, 0.08]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9	12 13 28 172 99, df = 10 .80) 40 858 21	3 18 19 46) (P = 0.9 427 9	25 55 261 95); I ² = 40 821 23	8.2% 6.7% 6.1% 100.0% :0% 4.7% 77.0% 2.1%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8	12 13 28 172 99, df = 10 .80) 40 858 21 16	3 18 19 46) (P = 0.9 427 9 7	25 55 50 261 95); I ² = 40 821 23 16	8.2% 6.7% 6.1% 100.0% * 0% 4.7% 77.0% 2.1% 1.5%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8 12	12 13 28 172 99, df = 10 .80) 40 858 21	3 18 19 46 0 (P = 0.9 9 427 9 7 8	25 55 261 95); I ² = 40 821 23	8.2% 6.7% 6.1% 100.0% 0% 4.7% 77.0% 2.1% 1.5% 2.4%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8	12 13 28 172 99, df = 10 .80) 40 858 21 16	3 18 19 46) (P = 0.9 427 9 7	25 55 50 261 95); I ² = 40 821 23 16	8.2% 6.7% 6.1% 100.0% * 0% 4.7% 77.0% 2.1% 1.5%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.07 [-0.12, 0.27] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8 12	12 13 28 172 99, df = 10 .80) 40 858 21 16 25	3 18 19 46 0 (P = 0.9 9 427 9 7 8	25 55 50 261 95); I ² = 40 821 23 16 25	8.2% 6.7% 6.1% 100.0% 0% 4.7% 77.0% 2.1% 1.5% 2.4%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 12 472 9 8 12 6	12 13 28 172 99, df = 10 .80) 40 858 21 16 25 10	3 18 19 46) (P = 0.9 427 9 427 7 8 5	25 55 261 95); I ² = 40 821 23 16 25 10	8.2% 6.7% 6.1% 100.0% 0% 4.7% 77.0% 2.1% 1.5% 2.4% 0.9%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0 12 472 9 8 12 6 10	12 13 28 172 99, df = 10 .80) 40 858 21 16 25 10 16	3 18 19 46 0 (P = 0.9 427 9 427 7 8 5 7	25 55 2 61 95); I ² = 40 821 23 16 25 10 16	8.2% 6.7% 6.1% 100.0% 0% 4.7% 77.0% 2.1% 1.5% 2.4% 0.9% 1.5%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0 12 472 9 8 12 6 10 19	12 13 28 172 99, df = 10 80) 40 858 21 16 25 10 16 25	3 18 19 46 0 (P = 0.9 427 9 427 9 7 7 8 5 7 14	25 55 50 261 35); I ² = 40 821 23 16 25 10 16 25	8.2% 6.7% 6.1% 100.0% * 0% * 0% * 4.7% 77.0% 2.1% 1.5% 2.4% 0.9% 1.5% 2.7%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007	0 1 1 9 10 28 0.00; Chi² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 9	12 13 28 172 99, df = 10 80 40 858 21 16 25 10 16 25 23	3 18 19 46) (P = 0.9 9 427 9 427 9 7 8 5 7 14 5 7	25 55 50 261 35); I ² = 40 821 23 16 25 10 16 25 23 45	8.2% 6.7% 6.1% 100.0% * 0% * 0% * 2.1% 1.5% 2.4% 0.1.5% 2.7% 2.3%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] 0.09 [-0.19, 0.36]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtoal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Wu 2011 Zhuangyu 2011	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi ² = 3.	12 13 28 28 172 99, df = 10 809 40 858 21 16 25 10 16 25 23 45 1079 48, df = 9	3 18 19 46 0 (P = 0.9 9 427 9 427 9 7 8 5 7 14 7 13 506	25 55 50 261 35); ² = 40 821 23 16 25 10 16 25 23 45 23 45 104	8.2% 6.7% 6.1% 100.0% * 0% 4.7% 77.0% 2.1% 1.5% 2.4% 0.9% 1.5% 2.7% 2.3% 4.9% 4.9%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	
Tarr 1993a Tarr 1993b Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 4.1.10 Subgroup 3: H Chen 2012 De Backer 2010 Gao 2008 Hua 2013 Liu 2010 Marik 1994 Mathur 1993 Mathur 2007 Wu 2011 Zhuangyu 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	0 1 1 9 10 28 0.00; Chi ² = 3. Z = 0.25 (P = 0 igh dose 12 472 9 8 12 6 10 19 9 14 571 0.00; Chi ² = 3.	12 13 28 28 172 99, df = 10 809 40 858 21 16 25 10 16 25 23 45 1079 48, df = 9	3 18 19 46 0 (P = 0.9 9 427 9 427 9 7 8 5 7 14 7 13 506	25 55 50 261 35); ² = 40 821 23 16 25 10 16 25 23 45 23 45 104	8.2% 6.7% 6.1% 100.0% * 0% 4.7% 77.0% 2.1% 1.5% 2.4% 0.9% 1.5% 2.7% 2.3% 4.9% 4.9%	-0.04 [-0.24, 0.15] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.01 [-0.05, 0.06] 0.03 [-0.02, 0.08] 0.04 [-0.25, 0.33] 0.06 [-0.28, 0.41] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	

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

Ctudu or Cubarrow	Favours dopar		Contr		Mainht	Risk Ratio	Risk Ratio
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.1.11 Subgroup 4: (_				
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	3	40	4	40	31.1%	0.75 [0.18, 3.14]	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Hausen 1992	0	14	0	27		Not estimable	
Kanchi 2017	0	30	0	30		Not estimable	
Lassnigg 2000	0	21	1	40	6.4%	0.62 [0.03, 14.62]	
Lassnigg 2000a	0	21	4	41	7.7%	0.21 [0.01, 3.76]	
Myles 1993	0	25	0	24		Not estimable	
Oppizzi 1997	3	13	0	13	7.7%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35		Not estimable	
Schneider 1999	0	50	0	49		Not estimable	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Soliman 2017	3	75	1	75	12.7%	3.00 [0.32, 28.19]	
Sumeray 2001	Ő	19	O	19		Not estimable	
Tarr 1993a	1	12	3	25	13.7%	0.69 [0.08, 6.00]	_
Tarr 1993b	1	13	3	25	13.6%	0.64 [0.07, 5.57]	_
Woo 2002	2	25	0	25	7.1%	5.00 [0.25, 99.16]	
Subtotal (95% CI)	-	479			100.0%	1.06 [0.48, 2.35]	
Total events	13		16				
4.1.12 Subgroup 4: N	-	-	-				
Arutiunov 2010	2	21	3	20	0.2%	0.63 [0.12, 3.41]	
Chen 2012	12	40	9	40	1.2%	1.33 [0.63, 2.81]	
Chen 2013	24	122	25	119	2.6%	0.94 [0.57, 1.54]	
Cotter 1997	1	14	0	6	0.1%	1.40 [0.06, 30.23]	
De Backer 2010	349	529	319	507	78.6%	1.05 [0.96, 1.15]	
Gao 2008	9	21	9	23	1.3%	1.10 [0.54, 2.23]	
Giamouzis 2010	3	30	3	30	0.3%	1.00 [0.22, 4.56]	
Hsueh 1998	0	10	0	10		Not estimable	
Hua 2013	8	16	7	16	1.2%	1.14 [0.54, 2.40]	
Kamiya 2015	0	12	2	12	0.1%	0.20 [0.01, 3.77]	
Liu 2010	12	25	8	25	1.3%	1.50 [0.74, 3.03]	
Marik 1994	6	10	5	10	1.0%	1.20 [0.54, 2.67]	_
Martin 1993	10	16	7	16	1.4%	1.43 [0.73, 2.80]	+
Mathur 2007	19	25	14	25	3.8%	1.36 [0.90, 2.05]	+
Schmoelz 2006	2	10	7	20	0.3%	0.57 [0.14, 2.26]	
Schmoelz 2006a	2	11	5	20	0.3%	0.73 [0.17, 3.15]	
Shah 2014	1	31	4	61	0.1%	0.49 [0.06, 4.22]	
Sindone 1998	0	8	3	8	0.1%	0.14 [0.01, 2.39]	• · · · · · · · · · · · · · · · · · · ·
Sindone 1998a	1	8	2	26	0.1%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.1%	1.13 [0.08, 15.19]	
Triposkiadis 2014	9	28	18	55	1.5%	0.98 [0.51, 1.90]	
Triposkiadis 2014a	10	28	19	50	1.7%	0.94 [0.51, 1.73]	-+-
Varriale 1997	0	10	0	10		Not estimable	
Wu 2011	9	23	7	23	1.0%	1.29 [0.58, 2.86]	-+
Zhuangyu 2011 Subtotal (95% CI)	14	45 1101	13	45 1186	1.6% 100.0%	1.08 [0.57, 2.03] 1.06 [0.98, 1.15]	
	504		490	1100	100.070	1.00 [0.30, 1.13]	ľ
Total events Hotorogonoity: Tou?-		1 df = 2		00\·IZ	. 00%		
Heterogeneity: Tau² = Test for everall effect			2 (F = 0.)	aa), r=	070		
Test for overall effect	. Z = 1.49 (P = 0.1	4)					
							0.01 0.1 1 10 1
							Favours dopamine Favours control

0.01 0.1 1 10 Favours dopamine Favours control

Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $l^2 = 0\%$

E-Figures 2.5.11-2.5.12: risk differences

Study or Subgroup	Favours dopa		Contr			Risk Difference	Risk Difference
	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.1.11 Subgroup 4: C			_				
Birnbaum 1990	0	10	0	10	1.1%	0.00 [-0.17, 0.17]	
Bove 2005	3	40	4	40	2.2%	-0.03 [-0.15, 0.10]	
Carcoana 2003	0	25	0	24	5.9%	0.00 [-0.08, 0.08]	+
Carcoana 2003a	0	25	0	26	6.4%	0.00 [-0.07, 0.07]	+
Hausen 1992	0	14	0	27	3.2%	0.00 [-0.10, 0.10]	
Kanchi 2017	0	30	0	30	8.7%	0.00 [-0.06, 0.06]	
Lassnigg 2000	0	21	1	40	4.8%	-0.03 [-0.11, 0.06]	
Lassnigg 2000a	0	21	4	41	2.7%	-0.10 [-0.21, 0.01]	
Myles 1993	0	25	0	24	5.9%	0.00 [-0.08, 0.08]	+
Oppizzi 1997	3	13	0	13	0.6%	0.23 [-0.02, 0.48]	
Rosseel 1997	0	35	0	35	11.7%	0.00 [-0.05, 0.05]	T
Schneider 1999	0	50	0	49	22.9%	0.00 [-0.04, 0.04]	T
Sharpe 1999	0	5	0	10	0.5%	0.00 [-0.25, 0.25]	
Sharpe 1999a	0	5	0	10	0.5%	0.00 [-0.25, 0.25]	
Sinclair 1997	0	16	0	14	2.3%	0.00 [-0.12, 0.12]	
Soliman 2017	3	75	1	75	12.9%	0.03 [-0.02, 0.08]	† −
Sumeray 2001	0	19	0	19	3.7%	0.00 [-0.10, 0.10]	+
Tarr 1993a	1	12	3	25	0.8%	-0.04 [-0.24, 0.17]	
Tarr 1993b	1	13	3	25	0.9%	-0.04 [-0.24, 0.15]	
Woo 2002	2	25	0	25	2.2%	0.08 [-0.05, 0.21]	1
Subtotal (95% CI)		479		562	100.0%	0.00 [-0.02, 0.02]	
Total events	13		16				
Heterogeneity: Tau ² =		•	3 (P = 0.9	96); I² =	:0%		
Test for overall effect:	Z = 0.15 (P = 0.	88)					
4.1.12 Subgroup 4: N	lot having cardi						
	-	-	-	0	0.70	0.0510.00.045	
Arutiunov 2010	2	21	3	20	2.7%	-0.05 [-0.26, 0.15]	
Chen 2012	12	40	9	40	2.9%	0.07 [-0.12, 0.27]	
Chen 2013	24	122	25	119	10.5%	-0.01 [-0.12, 0.09]	
	1	14	0	6	1.8% 32.0%	0.07 [-0.17, 0.32]	
Cotter 1997		600	24.0				
De Backer 2010	349	529	319	507		0.03 [-0.03, 0.09]	
De Backer 2010 Gao 2008	349 9	21	9	23	1.3%	0.04 [-0.25, 0.33]	
De Backer 2010 Gao 2008 Giamouzis 2010	349 9 3	21 30	9 3	23 30	1.3% 4.7%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998	349 9 3 0	21 30 10	9 3 0	23 30 10	1.3% 4.7% 3.6%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013	349 9 3 0 8	21 30 10 16	9 3 0 7	23 30 10 16	1.3% 4.7% 3.6% 0.9%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015	349 9 3 0 8 0	21 30 10 16 12	9 3 0 7 2	23 30 10 16 12	1.3% 4.7% 3.6% 0.9% 1.9%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010	349 9 3 0 8 0 12	21 30 10 16 12 25	9 3 0 7 2 8	23 30 10 16 12 25	1.3% 4.7% 3.6% 0.9% 1.9% 1.5%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994	349 9 3 0 8 0 12 6	21 30 10 16 12 25 10	9 3 7 2 8 5	23 30 10 16 12 25 10	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993	349 9 3 0 8 0 12 6 10	21 30 10 16 12 25 10 16	9 3 7 2 8 5 7	23 30 10 16 12 25 10 16	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6% 0.9%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007	349 9 3 0 8 12 6 10 19	21 30 10 16 12 25 10 16 25	9 3 7 2 8 5 7 14	23 30 10 12 25 10 16 25	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6% 0.9% 1.7%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Maritin 1993 Mathur 2007 Schmoelz 2006	349 9 3 0 12 6 10 19 2	21 30 10 16 12 25 10 16 25 10	9 3 7 2 8 5 7 14 7	23 30 10 16 12 25 10 16 25 20	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6% 0.9% 1.7% 1.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a	349 9 3 0 12 6 10 19 2 2	21 30 16 12 25 10 16 25 10 11	9 3 7 2 8 5 7 14 7 5	23 30 10 16 12 25 10 16 25 20 20	1.3% 4.7% 3.6% 0.9% 1.9% 0.6% 0.9% 1.7% 1.0% 1.2%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a Shah 2014	349 9 3 0 12 6 10 19 2 2 1	21 30 10 16 25 10 16 25 10 11 31	9 3 7 2 8 5 7 14 7 5 4	23 30 10 16 25 10 16 25 20 20 61	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.0% 1.2% 14.1%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.03 [-0.12, 0.05]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a Shah 2014 Sindone 1998	349 9 3 0 12 6 10 19 2 2 1 0	21 30 10 12 25 10 16 25 10 11 31 8	9 3 7 2 8 5 7 14 7 5 4 3	23 30 10 16 12 25 10 16 25 20 20 61 8	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.0% 1.2% 14.1% 0.9%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a Shah 2014 Sindone 1998	349 9 3 0 12 6 10 19 2 2 1 0 1	21 30 10 12 25 10 16 25 10 11 31 8 8	9 3 7 2 8 5 7 14 7 5 4 3 2	23 30 10 16 12 25 10 16 25 20 20 61 8 26	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 1.5% 1.0% 1.2% 1.2% 14.1% 0.9% 1.7%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.38, 0.23] -0.03 [-0.73, -0.02] 0.05 [-0.20, 0.30]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a Shah 2014 Sindone 1998 Sindone 1998a Sindone 1998b	349 9 3 0 12 6 10 19 2 2 2 1 0 1 1	21 30 10 12 25 10 16 25 10 11 31 8 8 8	9 3 7 2 8 5 7 4 7 4 3 2 1	23 30 10 16 25 20 61 8 26 9	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 1.0% 1.0% 1.2% 14.1% 0.9% 1.2%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.03 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.29, 0.32]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006a Shah 2014 Sindone 1998 Sindone 1998a Sindone 1998b Triposkiadis 2014	349 9 3 0 12 6 10 19 2 2 1 0 1 1 9	21 30 10 12 25 10 11 31 31 8 8 8 8	9 3 7 2 8 5 7 14 7 5 4 3 2 1 8	23 30 10 16 25 20 61 8 26 9 55	1.3% 4.7% 3.6% 0.9% 1.9% 0.6% 0.9% 1.7% 1.2% 14.1% 0.9% 1.7% 1.2% 2.4%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.03 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.29, 0.32] -0.01 [-0.22, 0.21]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Schmoel 2006 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014	349 9 3 0 12 6 10 19 2 2 1 0 1 1 9 10	21 30 10 12 25 10 16 25 10 11 31 8 8 8 8 28 28	9 3 7 2 8 5 7 14 7 5 4 3 2 1 18 19	23 30 10 12 25 10 16 25 20 61 8 26 9 55 50	1.3% 4.7% 3.6% 0.9% 1.9% 0.6% 0.9% 1.2% 1.2% 1.2% 1.2% 1.2% 2.4% 2.2%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.03 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014a Varriale 1997	349 9 3 0 12 6 10 19 2 2 1 0 1 1 9 10 0	21 30 10 12 25 10 16 25 10 11 31 8 8 8 8 28 28 28 10	9 3 7 2 8 5 7 14 7 5 4 3 2 1 18 19 0	23 30 10 12 25 10 16 25 20 61 8 26 9 55 50 10	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6% 1.2% 1.0% 1.2% 1.2% 1.2% 1.2% 2.2% 3.6%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.29, 0.32] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Marik 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014a Varriale 1997 Wu 2011	349 9 3 0 12 6 10 19 2 2 1 0 1 9 10 9 9	21 30 10 12 25 10 16 25 10 11 31 8 8 8 8 28 28 28 10 23	9 3 7 2 8 5 7 14 7 5 4 3 2 1 18 19 0 7	23 30 10 12 25 10 16 25 20 20 61 8 26 9 55 50 10 23	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.8% 1.2% 1.2% 1.2% 1.2% 2.4% 2.2% 3.6% 1.4%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.29, 0.32] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014a Varriale 1997	349 9 3 0 12 6 10 19 2 2 1 0 1 1 9 10 0	21 30 10 12 25 10 16 25 10 11 31 8 8 8 8 28 28 28 10	9 3 7 2 8 5 7 14 7 5 4 3 2 1 18 19 0	23 30 10 16 25 10 16 25 20 20 61 8 26 9 9 55 50 10 23 45	1.3% 4.7% 3.6% 0.9% 1.9% 1.5% 0.6% 1.2% 1.0% 1.2% 1.2% 1.2% 1.2% 2.2% 3.6%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.29, 0.32] -0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Sindone 1998 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014a Varriale 1997 Wu 2011 Zhuangyu 2011	349 9 3 0 12 6 10 19 2 2 1 0 1 9 10 0 9 14	21 30 10 12 25 10 16 25 10 11 31 31 8 8 8 8 28 28 28 10 23 45	9 3 7 2 8 5 7 14 7 5 4 3 2 1 18 19 0 7	23 30 10 16 25 10 16 25 20 20 61 8 26 9 9 55 50 10 23 45	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.6% 1.7% 1.0% 1.2% 1.2% 2.4% 2.2% 2.2% 3.6% 1.4% 3.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Toposkiadis 2014 Subtotal (95% CI) Total events	349 9 3 0 8 0 12 6 10 19 2 2 2 1 0 19 2 2 1 0 1 1 9 10 0 9 14 504 504 504	21 30 10 16 25 10 11 31 8 8 28 28 28 28 10 23 45 101 48, df = 2	9 3 0 7 2 8 5 7 14 7 5 4 3 2 1 1 8 9 0 7 13 490	23 30 10 16 12 25 10 16 25 20 20 61 8 26 9 55 50 10 23 45 51 1186	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.2% 1.2% 2.4% 2.2% 3.6% 1.4% 3.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014a Varriale 1997 Wu 2011 Zhuangyu 2011 Subtotal (95% CI) Total events	349 9 3 0 8 0 12 6 10 19 2 2 2 1 0 19 2 2 1 0 1 1 9 10 0 9 14 504 504 504	21 30 10 16 25 10 11 31 8 8 28 28 28 28 10 23 45 101 48, df = 2	9 3 0 7 2 8 5 7 14 7 5 4 3 2 1 1 8 9 0 7 13 490	23 30 10 16 12 25 10 16 25 20 20 61 8 26 9 55 50 10 23 45 51 1186	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.2% 1.2% 2.4% 2.2% 3.6% 1.4% 3.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Shah 2014 Sindone 1998 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Toposkiadis 2014 Subtotal (95% CI) Total events	349 9 3 0 8 0 12 6 10 19 2 2 2 1 0 19 2 2 1 0 1 1 9 10 0 9 14 504 504 504	21 30 10 16 25 10 11 31 8 8 28 28 28 28 10 23 45 101 48, df = 2	9 3 0 7 2 8 5 7 14 7 5 4 3 2 1 1 8 9 0 7 13 490	23 30 10 16 12 25 10 16 25 20 20 61 8 26 9 55 50 10 23 45 51 1186	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.2% 1.2% 2.4% 2.2% 3.6% 1.4% 3.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.03 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21] 0.01 [-0.02, 0.04]	
De Backer 2010 Gao 2008 Giamouzis 2010 Hsueh 1998 Hua 2013 Kamiya 2015 Liu 2010 Marik 1994 Martin 1993 Mathur 2007 Schmoelz 2006 Schmoelz 2006 Schmoelz 2006 Sindone 1998 Sindone 1998 Sindone 1998 Sindone 1998b Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Triposkiadis 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	349 9 3 0 8 0 12 6 10 19 2 2 2 1 0 19 2 2 1 0 1 9 10 0 9 14 504 504 504	21 30 10 16 25 10 11 31 8 8 28 28 28 28 10 23 45 101 48, df = 2	9 3 0 7 2 8 5 7 14 7 5 4 3 2 1 1 8 9 0 7 13 490	23 30 10 16 12 25 10 16 25 20 20 61 8 26 9 55 50 10 23 45 51 1186	1.3% 4.7% 3.6% 0.9% 1.5% 0.6% 0.9% 1.7% 1.2% 1.2% 2.4% 2.2% 3.6% 1.4% 3.0%	0.04 [-0.25, 0.33] 0.00 [-0.15, 0.15] 0.00 [-0.17, 0.17] 0.06 [-0.28, 0.41] -0.17 [-0.41, 0.07] 0.16 [-0.11, 0.43] 0.10 [-0.33, 0.53] 0.19 [-0.15, 0.53] 0.20 [-0.06, 0.46] -0.15 [-0.47, 0.17] -0.07 [-0.36, 0.23] -0.38 [-0.73, -0.02] 0.05 [-0.20, 0.30] 0.01 [-0.22, 0.21] -0.02 [-0.25, 0.20] 0.00 [-0.17, 0.17] 0.09 [-0.19, 0.36] 0.02 [-0.17, 0.21]	

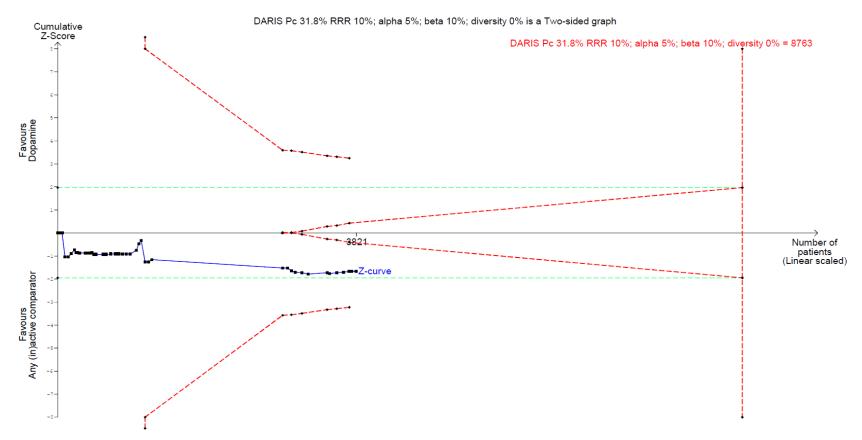
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E-Figures 2.5.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

Chudu on Cubanau	Favours dopa		Contr		Mainh	Risk Ratio	Risk Ratio
Study or Subgroup 4.1.1 All included stu	Events	rotal	Events	rotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
			-				
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	3	40	4	40	0.3%	0.75 [0.18, 3.14]	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Chen 2012	12	40	9	40	1.1%	1.33 [0.63, 2.81]	
Chen 2013	24	122	25	119	2.5%	0.94 [0.57, 1.54]	
De Backer 2010	472	858	427	821	78.8%	1.06 [0.97, 1.16]	
∋ao 2008	9	21	9	23	1.2%	1.10 [0.54, 2.23]	
∂iamouzis 2010	3	30	3	30	0.3%	1.00 [0.22, 4.56]	
Hausen 1992	0	14	0	27		Not estimable	
Hua 2013	8	16	7	16	1.1%	1.14 [0.54, 2.40]	
Kamiya 2015	0	12	2	12	0.1%	0.20 [0.01, 3.77]	
Kanchi 2017	0	30	0	30		Not estimable	
_assnigg 2000	0	21	1	40	0.1%	0.62 [0.03, 14.62]	
_assnigg 2000a	0	21	4	41	0.1%	0.21 [0.01, 3.76]	
_iu 2010	12	25	8	25	1.3%	1.50 [0.74, 3.03]	+
⁄larik 1994	6	10	5	10	1.0%	1.20 [0.54, 2.67]	
Martin 1993	10	16	7	16	1.4%	1.43 [0.73, 2.80]	+
Mathur 2007	19	25	14	25	3.7%	1.36 [0.90, 2.05]	+
vlyles 1993	0	25	0	24		Not estimable	
Schmoelz 2006	2	10	7	20	0.3%	0.57 [0.14, 2.26]	
Schmoelz 2006a	2	11	5	20	0.3%	0.73 [0.17, 3.15]	
Schneider 1999	0	50	0	49		Not estimable	
Shah 2014	1	31	4	61	0.1%	0.49 [0.06, 4.22]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sindone 1998	0	8	3	8	0.1%	0.14 [0.01, 2.39]	•
Sindone 1998a	1	8	2	26	0.1%	1.63 [0.17, 15.66]	
Sindone 1998b	1	8	1	9	0.1%	1.13 [0.08, 15.19]	
Soliman 2017	3	75	1	75	0.1%	3.00 [0.32, 28.19]	
Sumeray 2001	0	19	Ó	19		Not estimable	
Triposkiadis 2014	9	28	18	55	1.5%	0.98 [0.51, 1.90]	
Triposkiadis 2014a	10	28	19	50	1.7%	0.94 [0.51, 1.73]	
Woo 2002	2	25	0	25	0.1%	5.00 [0.25, 99.16]	<u> </u>
Wu 2011	9	23	7	23	1.0%	1.29 [0.58, 2.86]	
Zhuangyu 2011	14	45	13	45	1.6%	1.08 [0.57, 2.03]	
Subtotal (95% CI)	14	1781	10		100.0%	1.07 [0.99, 1.16]	
Total events	632		605				
Heterogeneity: Tau ² = Test for overall effect:	0.00; Chi² = 12			.98); I²	= 0%		
4.1.13 Pure cardiac o	dysfunction stu	dies					
Arutiunov 2010	2	21	3	20	35.0%	0.63 [0.12, 3.41]	
Cotter 1997	1	14	0	20	10.5%	1.40 [0.06, 30.23]	
Hsueh 1998	, O	10	0	10	. 0.0 10	Not estimable	
Oppizzi 1997	3	13	0	13	12.0%	7.00 [0.40, 123.35]	
Rosseel 1997	0	35	0	35	. 2.0 %	Not estimable	
Tarr 1993a	2	25	6	50	42.5%	0.67 [0.14, 3.07]	
Varriale 1997	2	10	0	10	72.370	Not estimable	-
Subtotal (95% CI)	0	128	U		100.0%	0.94 [0.35, 2.54]	
Total events	8	120	9		1001070	010 1 [0100] 2104]	
Heterogeneity: Tau ² = Test for overall effect:	0.00; Chi ² = 2.4		-	9); I² = ()%		
							0.01 0.1 1 10 1
					= 0%		Favours dopamine Favours control

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 $\alpha = 0.05$ (two-sided), $\beta = 0.10$ (power 90%), D² = 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

	Favours dopa		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
.2.1 All included studi	es						
3irnbaum 1990	0	10	0	10		Not estimable	
Chen 2012	13	40	4	40	9.3%	3.25 [1.16, 9.12]	
Chen 2013	19	122	12	119	16.0%	1.54 [0.78, 3.04]	+
Giamouzis 2010	6	30	2	30	5.0%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	2.9%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	28.1%	1.04 [0.77, 1.42]	+
Schneider 1999	20	50	10	49	16.7%	1.96 [1.02, 3.75]	_ _ _
Binclair 1997	20	16	0	14	10.1.0	Not estimable	
Triposkiadis 2014	4	28	6	55	7.6%	1.31 [0.40, 4.26]	
•	4	28	6	50		• • •	
Friposkiadis 2014a					7.6%	1.19 [0.37, 3.86]	
Noo 2002 Subtotol (05%, CD	3	25	6	25	6.7%	0.50 [0.14, 1.78]	
Subtotal (95% CI)		409		4 3 Z	100.0%	1.47 [1.02, 2.12]	-
Fotal events	98		71				
Heterogeneity: Tau² = 0			B (P = 0.1	12); l²=	37%		
Fest for overall effect: Z	= 2.06 (P = 0	.04)					
3.2.2 Worst-best case	-		_				
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2012	13	40	4	40	9.4%	3.25 [1.16, 9.12]	
Chen 2013	19	122	12	119	16.0%	1.54 [0.78, 3.04]	+
Giamouzis 2010	6	30	2	30	5.1%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	3.0%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	27.8%	1.04 [0.77, 1.42]	+
Schneider 1999	20	50	10	50	16.7%	2.00 [1.04, 3.83]	
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014	4	28	6	55	7.7%	1.31 [0.40, 4.26]	.
Triposkiadis 2014	4	28	6	50	7.7%	1.19 [0.37, 3.86]	
Woo 2002	3	20	6	25	6.8%	0.50 [0.14, 1.78]	
Subtotal (95% CI)	3	409	0		100.0%	1.48 [1.02, 2.14]	
	00	405	74	455	100.0%	1.40 [1.02, 2.14]	•
Total events	98 40: 05:2-40	07 46-0	71	0.01	2000		
Heterogeneity: Tau² = 0	•	•	B(P = 0.1)	12); 1*=	38%		
Test for overall effect: Z	= 2.07 (P = 0	.04)					
3.2.3 Best-worst case	analveie						
		40		4.0			
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2012	13	40	4	40	9.0%	3.25 [1.16, 9.12]	
Chen 2013	19	122	12	119	15.8%	1.54 [0.78, 3.04]	
Giamouzis 2010	6	30	2	30	4.8%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	2.8%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	29.2%	1.04 [0.77, 1.42]	+
Schneider 1999	20	50	11	50	17.4%	1.82 [0.98, 3.39]	⊢ ∎—
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014	4	28	6	55	7.3%	1.31 [0.40, 4.26]	+-
Triposkiadis 2014a	4	28	6	50	7.3%	1.19 [0.37, 3.86]	_
Noo 2002	3	25	6	25	6.5%	0.50 [0.14, 1.78]	
Subtotal (95% CI)	5	409	0		100.0%	1.45 [1.01, 2.06]	
	00	405	72	455	100.070	1.45 [1.01, 2.00]	•
Total events Hotorogonoity: Tou 3 – 0	98 100: Chi z - 1 2	17 -46- 4		1.41.12	2400		
Heterogeneity: Tau² = 0			5 (H = 0.1	14), 11=	3470		
Test for overall effect: Z	= 2.04 (P = 0	.04)					
							0.01 0.1 1 10 1
							Favours dopamine Favours control
est for subgroup differ	ences: Chi ^z =	= 0.01, df=	= 2 (P = 1	1.00), l ^a	= 0%		Favours dopamine Favours control

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

	Favours dopa		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.2.4 Subgroup 1: Lo	w risk of bias			_			
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap							
Test for overall effect:	Not applicable						
3.2.5 Subgroup 1: Un	clear or high ris	k of bia	s				
Birnbaum 1990	0	10	0	10		Not estimable	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Chen 2012	13	40	4	40	8.1%	3.25 [1.16, 9.12]	_
Chen 2013	30	122	24	119	21.7%	1.22 [0.76, 1.96]	
Giamouzis 2010	6	30	2	30	4.2%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Myles 1993	0	25	0	24		Not estimable	
Oppizzi 1997	4	13	1	13	2.4%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	29.4%	1.04 [0.77, 1.42]	+
Schneider 1999	20	50	10	49	15.5%	1.96 [1.02, 3.75]	
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014	4	28	6	55	6.5%	1.31 [0.40, 4.26]	-
Triposkiadis 2014a	4	28	6	50	6.5%	1.19 [0.37, 3.86]	
Woo 2002	3	25	6	25	5.7%	0.50 [0.14, 1.78]	
Subtotal (95% CI)		484		526	100.0%	1.38 [0.99, 1.92]	◆
Total events	109		83				
Heterogeneity: Tau ² =	: 0.07; Chi ² = 11.	94, df=	8 (P = 0.1	15); I ^z =	: 33%		
Test for overall effect:	Z = 1.93 (P = 0.0	05)					
							Favours dopamine Favours control

Test for subgroup differences: Not applicable

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

	Favours dopa	mine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.2.6 Subgroup 2: Ina	ctive control						
Chen 2013	19	122	12	119	35.7%	1.54 [0.78, 3.04]	+ -
Schneider 1999	20	50	10	49	38.0%	1.96 [1.02, 3.75]	⊢∎
Triposkiadis 2014	4	28	6	55	14.0%	1.31 [0.40, 4.26]	
Woo 2002 Subtotal (95% Cl)	3	25 225	6	25 248	12.3% 100.0%	0.50 [0.14, 1.78] 1.44 [0.90, 2.29]	
Total events	46		34				
Heterogeneity: Tau ² =	0.04; Chi ² = 3.5	9, df = 3	3 (P = 0.3 ⁻	1); I ^z = 1	16%		
Test for overall effect:	Z = 1.53 (P = 0.1	13)	`				
3.2.7 Subgroup 2: Po	tentially active	control					
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2012	13	40	4	40	21.5%	3.25 [1.16, 9.12]	
Giamouzis 2010	6	30	2	30	14.2%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Oppizzi 1997	4	13	1	13	9.3%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	36.1%	1.04 [0.77, 1.42]	+
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014a Subtotal (95% CI)	4	28 184	6	50 204	18.9% 100.0%	1.19 [0.37, 3.86] 1.80 [0.88, 3.68]	
Total events	52	104	37	204	100.070	1.00 [0.00, 0.00]	
Heterogeneity: Tau ² =		7 df = 4		5): I 2 = 5	58%		
Test for overall effect:			• 0.0.	-/1			
	2	,					

Test for subgroup differences: $Chi^2 = 0.26$, df = 1 (P = 0.61), $I^2 = 0\%$

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

	Favours dopa	amine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.2.8 Subgroup 3: Lo	wdose						
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	19	122	12	119	23.3%	1.54 [0.78, 3.04]	
Kamiya 2015	0	12	0	12		Not estimable	
Rosseel 1997	25	35	24	35	42.7%	1.04 [0.77, 1.42]	+
Schneider 1999	20	50	10	49	24.4%	1.96 [1.02, 3.75]	
Sinclair 1997	0	16	0	14		Not estimable	
Woo 2002	3	25	6	25	9.6%	0.50 [0.14, 1.78]	
Subtotal (95% CI)		270		264	100.0%	1.24 [0.81, 1.91]	◆
Total events	67		52				
Heterogeneity: Tau ² =	: 0.09; Chi ^z = 5.;	74, df = 3	8 (P = 0.1	3); I ² = 4	18%		
Test for overall effect:	Z = 0.98 (P = 0.	.33)					
3.2.9 Subgroup 3: Mo	oderate dose						
Giamouzis 2010	6	30	2	30	20.6%	3.00 [0.66, 13.69]	
Oppizzi 1997	4	13	1	13	11.3%	4.00 [0.51, 31.13]	
Triposkiadis 2014	4	28	6	55	34.0%	1.31 [0.40, 4.26]	
Triposkiadis 2014a	4	28	6	50	34.2%	1.19 [0.37, 3.86]	
Subtotal (95% CI)		99		148	100.0%	1.70 [0.86, 3.39]	◆
Total events	18		15				
Heterogeneity: Tau ² =	: 0.00; Chi ² = 1.3	77, df = 3	8 (P = 0.6	2); I 2 = 0)%		
Test for overall effect:	Z = 1.52 (P = 0.	.13)					
3.2.10 Subgroup 3: H	iah doso						
Chen 2012	13	40	4	40	100.0%	3.25 [1.16, 9.12]	
Subtotal (95% CI)	13	40 40	4		100.0%	3.25 [1.16, 9.12] 3.25 [1.16, 9.12]	
Total events	13	40	4	40	100.070	5.25 [1.10, 5.12]	
Heterogeneity: Not ap			4				
Test for overall effect:		03)					
resciul overall ellect.	Z = 2.24 (F = 0.	.03)					
							0.01 0.1 1 10 100
Test for subaroup dif	foroncos: Chiž –	3 0 2 df	= 2 (P -	0.221 18	- 33.8%		Favours dopamine Favours control
reación subgroup un	erences. Chr =	· 5.02, ui	- 2 (F =	0.22), 1	- 33.070		

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

	Favours dopa		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.2.11 Subgroup 4: C	ardiac surgery						
Birnbaum 1990	0	10	0	10		Not estimable	
Oppizzi 1997	4	13	1	13	7.1%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	45.7%	1.04 [0.77, 1.42]	
Schneider 1999	20	50	10	49	32.0%	1.96 [1.02, 3.75]	
Sinclair 1997	0	16	0	14		Not estimable	
Woo 2002	3	25	6	25	15.2%	0.50 [0.14, 1.78]	
Subtotal (95% CI)		149		146	100.0%	1.25 [0.70, 2.26]	•
Total events	52		41				
Test for overall effect:	Z = 0.75 (P = 0.	45)					
2 2 4 2 Subaroup A: N	ot having cardi						
3.2.12 Subgroup 4: N			-	40	40.00	2.25 14 46 0.421	
Chen 2012	13	40	4	40	18.8%	3.25 [1.16, 9.12]	
Chen 2012 Chen 2013	13 19	40 122	4 12	119	43.7%	1.54 [0.78, 3.04]	
Chen 2012 Chen 2013 Giamouzis 2010	13 19 6	40 122 30	4 12 2	119 30		1.54 [0.78, 3.04] 3.00 [0.66, 13.69]	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015	13 19	40 122 30 12	4 12 2 0	119 30 12	43.7% 8.7%	1.54 [0.78, 3.04] 3.00 [0.66, 13.69] Not estimable	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014	13 19 6 0 4	40 122 30 12 28	4 12 2 0 6	119 30 12 55	43.7% 8.7% 14.4%	1.54 [0.78, 3.04] 3.00 [0.66, 13.69] Not estimable 1.31 [0.40, 4.26]	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015	13 19 6	40 122 30 12	4 12 2 0	119 30 12	43.7% 8.7% 14.4% 14.4%	1.54 [0.78, 3.04] 3.00 [0.66, 13.69] Not estimable	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a	13 19 6 0 4	40 122 30 12 28 28	4 12 2 0 6	119 30 12 55 50	43.7% 8.7% 14.4% 14.4%	1.54 (0.78, 3.04) 3.00 (0.66, 13.69) Not estimable 1.31 (0.40, 4.26) 1.19 (0.37, 3.86)	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI)	13 19 6 0 4 4 46	40 122 30 12 28 28 28 260	4 12 2 0 6 6 30	119 30 12 55 50 306	43.7% 8.7% 14.4% 14.4% 100.0%	1.54 (0.78, 3.04) 3.00 (0.66, 13.69) Not estimable 1.31 (0.40, 4.26) 1.19 (0.37, 3.86)	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events	13 19 6 0 4 4 4 6 0.00; Chi ² = 2.6	40 122 30 12 28 28 28 260 i5, df = 4	4 12 2 0 6 6 30	119 30 12 55 50 306	43.7% 8.7% 14.4% 14.4% 100.0%	1.54 (0.78, 3.04) 3.00 (0.66, 13.69) Not estimable 1.31 (0.40, 4.26) 1.19 (0.37, 3.86)	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² =	13 19 6 0 4 4 4 6 0.00; Chi ² = 2.6	40 122 30 12 28 28 28 260 i5, df = 4	4 12 2 0 6 6 30	119 30 12 55 50 306	43.7% 8.7% 14.4% 14.4% 100.0%	1.54 (0.78, 3.04) 3.00 (0.66, 13.69) Not estimable 1.31 (0.40, 4.26) 1.19 (0.37, 3.86)	
Chen 2012 Chen 2013 Giamouzis 2010 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Subtotal (95% CI) Total events Heterogeneity: Tau ² =	13 19 6 0 4 4 4 6 0.00; Chi ² = 2.6	40 122 30 12 28 28 28 260 i5, df = 4	4 12 2 0 6 6 30	119 30 12 55 50 306	43.7% 8.7% 14.4% 14.4% 100.0%	1.54 (0.78, 3.04) 3.00 (0.66, 13.69) Not estimable 1.31 (0.40, 4.26) 1.19 (0.37, 3.86)	

Test for subgroup differences: $Chi^2 = 0.83$, df = 1 (P = 0.36), $l^2 = 0\%$

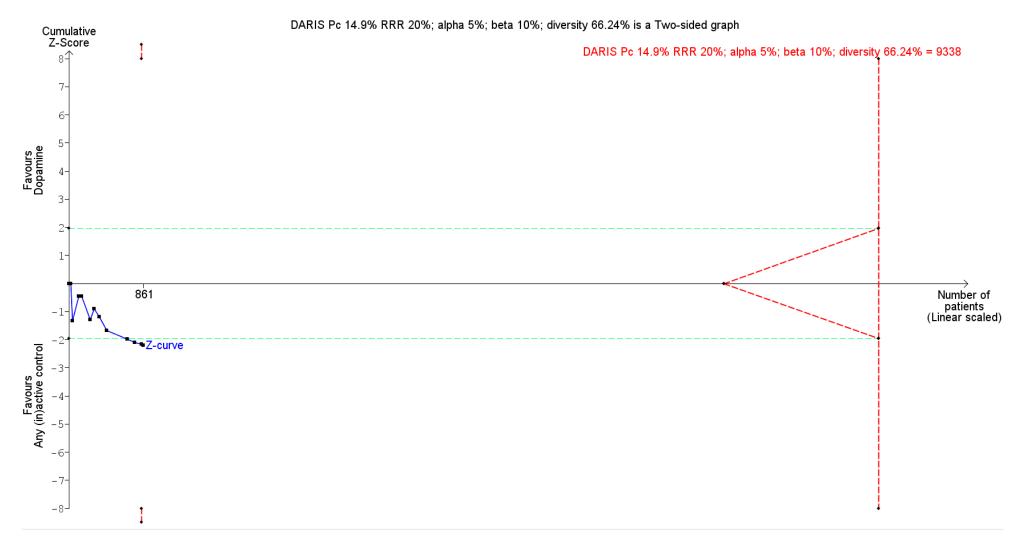
E-Figures 2.7.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

	Dopam	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.2.1 All included stu	dies						
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2012	13	40	4	40	12.2%	3.25 [1.16, 9.12]	
Chen 2013	19	122	12	119	26.4%	1.54 [0.78, 3.04]	+
Giamouzis 2010	6	30	2	30	5.8%	3.00 [0.66, 13.69]	
Kamiya 2015	0	12	0	12		Not estimable	
Schneider 1999	20	50	10	49	28.4%	1.96 [1.02, 3.75]	⊢ ∎−-
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014	4	28	6	55	9.4%	1.31 [0.40, 4.26]	
Triposkiadis 2014a	4	28	6	50	9.5%	1.19 [0.37, 3.86]	
Woo 2002	3	25	6	25	8.2%	0.50 [0.14, 1.78]	
Subtotal (95% CI)		361		404	100.0%	1.65 [1.14, 2.39]	◆
Total events	69		46				
Heterogeneity: Tau ² =	0.02; Chi	² = 6.40	D, df = 6 (P = 0.3	8); I ^z = 6%)	
Test for overall effect:	Z=2.64 (P = 0.0	08)				
3.2.3 Pure cardiac dy	sfunctior	n studie	es				
Oppizzi 1997	4	13	1	13	24.4%	4.00 [0.51, 31.13]	
Rosseel 1997	25	35	24	35	75.6%	1.04 [0.77, 1.42]	
Subtotal (95% CI)		48		48	100.0%	1.45 [0.43, 4.90]	
Total events	29		25				
Heterogeneity: Tau ² =	0.49; Chi	² = 1.87	7, df = 1 (i	P = 0.1	7); l² = 47'	%	
Test for overall effect:	Z = 0.59 (P = 0.5	5)				
			-				
							0.01 0.1 1 10 100

Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $l^2 = 0\%$

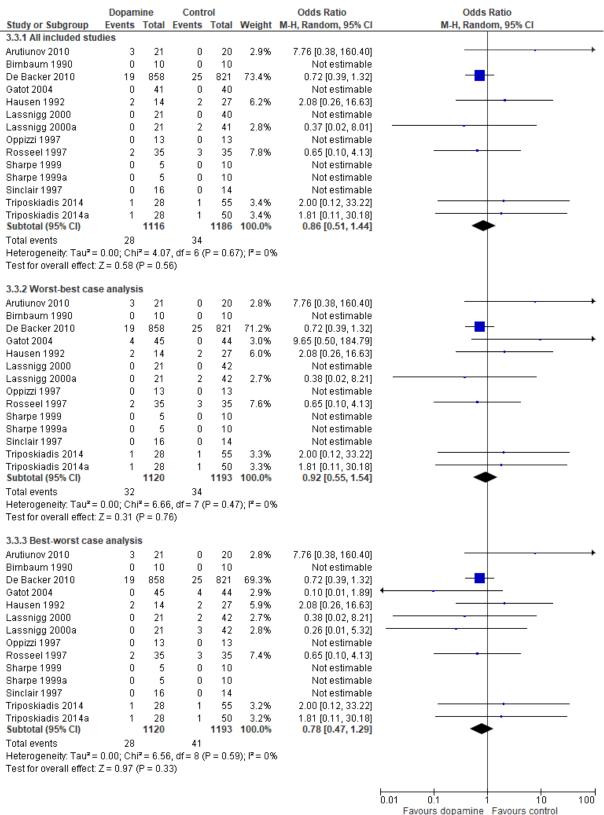
2.8. Trial sequential analysis of serious adverse events

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.



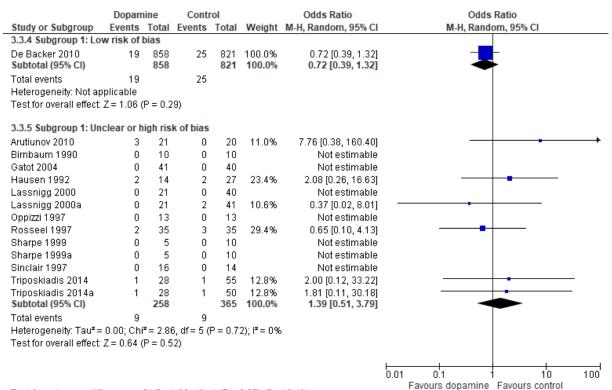
2.9. Forest plots of myocardial infarction

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



Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), $I^2 = 0\%$

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



Test for subgroup differences: Chi² = 1.20, df = 1 (P = 0.27), l² = 16.4%

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

	Dopan		Cont			Odds Ratio	Odds Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
3.3.6 Subgroup 2: Ina	active con	trol					
Gatot 2004	0	41	0	40		Not estimable	
Lassnigg 2000	0	21	0	40		Not estimable	
Sharpe 1999	0	10	0	10		Not estimable	
Triposkiadis 2014	1	28	1	55	100.0%	2.00 [0.12, 33.22]	
Subtotal (95% CI)		100		145	100.0%	2.00 [0.12, 33.22]	
Total events	1		1				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z=0.48 ((P = 0.6	3)				
3.3.7 Subgroup 2: Po	tentially a	ictive c	ontrol				
Arutiunov 2010	3	21	0	20	3.0%	7.76 [0.38, 160.40]	
Birnbaum 1990	0	10	0	10		Not estimable	
De Backer 2010	19	858	25	821	76.0%	0.72 [0.39, 1.32]	
Hausen 1992	2	14	2	27	6.4%	2.08 [0.26, 16.63]	•
Lassnigg 2000a	0	21	2	41	2.9%	0.37 [0.02, 8.01]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	8.1%	0.65 [0.10, 4.13]	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014a	1	28	1	50	3.5%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		1021		1041	100.0%	0.83 [0.49, 1.41]	•
Total events	27		33				
Heterogeneity: Tau ² =	: 0.00; Chi	z = 3.7 ⁻	1, df = 5 (P = 0.5	9); I² = 0%)	
Test for overall effect:							
							0.01 0.1 1 10 10

Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), l² = 0%

Favours dopamine Favours control

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

	Dopam		Cont			Odds Ratio	Odds Ratio
		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.3.8 Subgroup 3: Low	dose						
Arutiunov 2010	3	21	0	20	24.2%	7.76 [0.38, 160.40]	
Birnbaum 1990	0	10	0	10		Not estimable	
Lassnigg 2000	0	21	0	40		Not estimable	
Lassnigg 2000a	0	21	2	41	23.5%	0.37 [0.02, 8.01]	
Rosseel 1997	2	35	3	35	52.3%	0.65 [0.10, 4.13]	
Sinclair 1997	0	16	0	14		Not estimable	
Subtotal (95% CI)		124		160	100.0%	1.03 [0.21, 5.14]	
Total events	5		5				
Heterogeneity: Tau ² = 0.	.39; Chi	z = 2.43	3, df = 2 (P = 0.3	0); I ^z = 189	%	
Test for overall effect: Z	= 0.04 (P = 0.9	7)				
3.3.9 Subgroup 3: Mode	erate do	ose					
Gatot 2004	0	41	0	40		Not estimable	
Hausen 1992	2	14	2	27	47.8%	2.08 [0.26, 16.63]	
Oppizzi 1997	0	13	0	13		Not estimable	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Triposkiadis 2014	1	28	1	55	26.1%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	26.1%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		134		205	100.0%	1.99 [0.47, 8.36]	
Total events	4		4				
Heterogeneity: Tau ² = 0.	.00: Chi	² = 0.01	l.df=2(P = 1.0)); ² = 0%	1	
Test for overall effect: Z	•		•				
3.3.10 Subgroup 3: Higl	h dose						
De Backer 2010	19	858	25	821	100.0%	0.72 [0.39, 1.32]	
Subtotal (95% CI)		858	20		100.0%	0.72 [0.39, 1.32]	
Total events	19		25			. ,	-
Heterogeneity: Not appl							
Test for overall effect: Z		P=02	9)				
			-,				
Test for subaroup differ	oncos: i	∩hi≅ – 1	- 16 9 df	2 (P - 1	1 / 3) IZ -	n%	Favours dopamine Favours control

Test for subgroup differences: $Chi^2 = 1.68$, df = 2 (P = 0.43), $I^2 = 0\%$

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

	Dopan	nine	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.3.11 Subgroup 4: C	ardiac su	rgery					
Birnbaum 1990	0	10	0	10		Not estimable	
Gatot 2004	0	41	0	40		Not estimable	
Hausen 1992	2	14	2	27	36.9%	2.08 [0.26, 16.63]	
Lassnigg 2000	0	21	0	40		Not estimable	
Lassnigg 2000a	0	21	2	41	16.8%	0.37 [0.02, 8.01]	
Oppizzi 1997	0	13	0	13		Not estimable	
Rosseel 1997	2	35	3	35	46.3%	0.65 [0.10, 4.13]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Subtotal (95% CI)		181		240	100.0%	0.91 [0.26, 3.20]	
Total events	4		7				
Heterogeneity: Tau ² = Test for overall effect:	•			P = 0.5	8); I² = 0%	6	
3.3.12 Subgroup 4: N	lot having	cardia	c surger	у			
Arutiunov 2010	3	21	0	20	3.5%	7.76 [0.38, 160.40]	
De Backer 2010	19	858	25	821	88.3%	0.72 [0.39, 1.32]	
Triposkiadis 2014	1	28	1	55	4.1%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	4.1%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		935		946	100.0%	0.85 [0.48, 1.50]	•
Total events	24		27				
Heterogeneity: Tau ² =	= 0.00; Chi	i ^z = 3.00), df = 3 (P = 0.3	9); I² = 0%	6	
Test for overall effect:	Z= 0.57 ((P = 0.5	7)				
							0.01 0.1 1 10 100 Favours dopamine Favours control
Test for subgroup diff	ferences [.]	Chi² = (-101 df=	1 (P =	0.93) E=	0%	Favours dopartime Favours control

Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.93), $l^2 = 0\%$

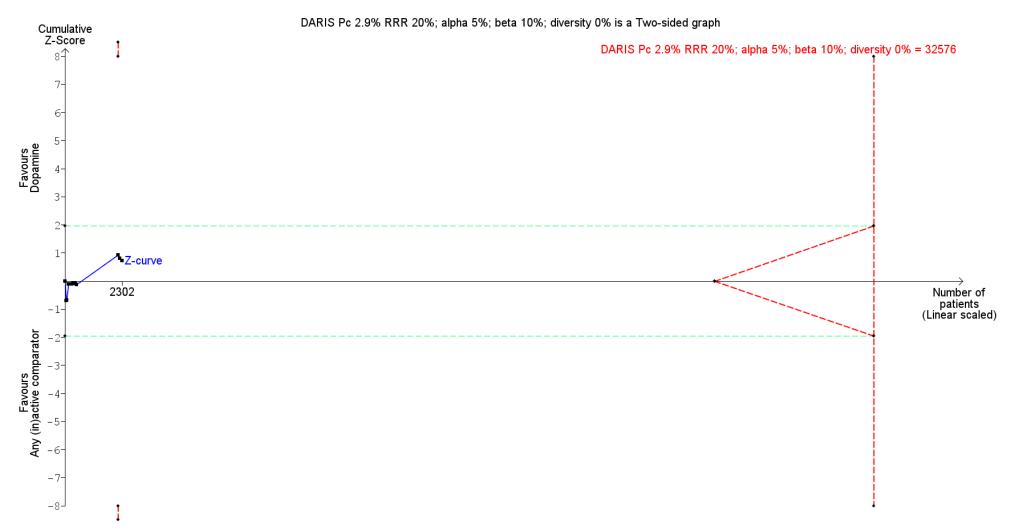
E-Figures 2.9.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

	Dopam	nine	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.3.1 All included stu	dies						
Birnbaum 1990	0	10	0	10		Not estimable	
De Backer 2010	19	858	25	821	82.3%	0.72 [0.39, 1.32]	
Gatot 2004	0	41	0	40		Not estimable	
Hausen 1992	2	14	2	27	7.0%	2.08 [0.26, 16.63]	
Lassnigg 2000	0	21	0	40		Not estimable	
Lassnigg 2000a	0	21	2	41	3.2%	0.37 [0.02, 8.01]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Binclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014	1	28	1	55	3.8%	2.00 [0.12, 33.22]	
Triposkiadis 2014a	1	28	1	50	3.8%	1.81 [0.11, 30.18]	
Subtotal (95% CI)		1047		1118	100.0%	0.82 [0.47, 1.42]	◆
Total events	23		31				
Heterogeneity: Tau ² =	: 0.00; Chi	r = 1.90	0, df = 4 (P = 0.7	5); I ^z = 0%		
Test for overall effect:	Z=0.72 ((P = 0.4	-7)				
3.3.2 Pure cardiac dy	ysfunctior	ı studie	es				
3.3.2 Pure cardiac dy Arutiunov 2010	ysfunctior 3	n <mark>studi</mark> e 21	es O	20	38.4%	7.76 [0.38, 160.40]	
	-			20 13	38.4%	7.76 (0.38, 160.40) Not estimable	
Arutiunov 2010	3	21	0		38.4% 61.6%	• • •	
Arutiunov 2010 Oppizzi 1997	- 3 0	21 13	0 0	13 35		Not estimable	
Arutiunov 2010 Oppizzi 1997 Rosseel 1997	- 3 0	21 13 35	0 0	13 35	61.6%	Not estimable 0.65 [0.10, 4.13]	
Arutiunov 2010 Oppizzi 1997 Rosseel 1997 Subtotal (95% CI)	3 0 2 5	21 13 35 <mark>69</mark>	0 0 3 3	13 35 <mark>68</mark>	61.6% 100.0%	Not estimable 0.65 [0.10, 4.13] 1.68 [0.15, 18.75]	
Arutiunov 2010 Oppizzi 1997 Rosseel 1997 Subtotal (95% CI) Total events	3 0 2 5 = 1.57; Chi	21 13 35 69 i ² = 1.98	0 0 3 5, df = 1 (1	13 35 <mark>68</mark>	61.6% 100.0%	Not estimable 0.65 [0.10, 4.13] 1.68 [0.15, 18.75]	
Arutiunov 2010 Oppizzi 1997 Rosseel 1997 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	3 0 2 5 = 1.57; Chi	21 13 35 69 i ² = 1.98	0 0 3 5, df = 1 (1	13 35 <mark>68</mark>	61.6% 100.0%	Not estimable 0.65 [0.10, 4.13] 1.68 [0.15, 18.75]	
Arutiunov 2010 Oppizzi 1997 Rosseel 1997 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	3 0 2 5 = 1.57; Chi	21 13 35 69 i ² = 1.98	0 0 3 5, df = 1 (1	13 35 <mark>68</mark>	61.6% 100.0%	Not estimable 0.65 [0.10, 4.13] 1.68 [0.15, 18.75]	

Test for subgroup differences: $Chi^2 = 0.32$, df = 1 (P = 0.57), $l^2 = 0\%$

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.

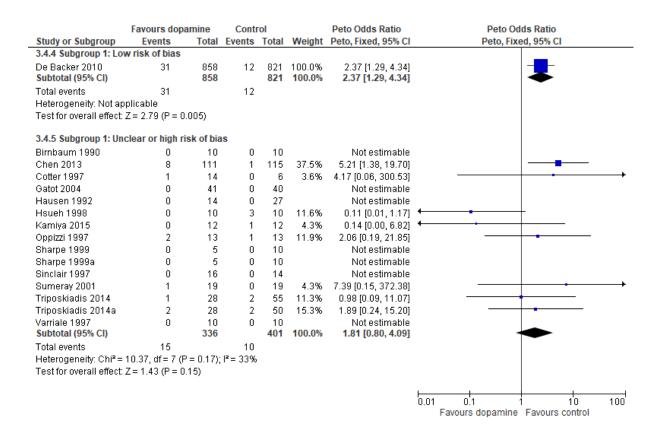


2.11. Forest plots of ventricular tachyarrhythmias

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

Study or Subarous	Favours dopa Events		Contr		Woight	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup 3.4.1 All included stud		rotal	events	Total	weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	8	111	1	115	13.3%	5.21 [1.38, 19.70]	
Cotter 1997	1	14	0	6	1.3%	4.17 [0.06, 300.53]	
De Backer 2010	31	858	12	821	64.4%	2.37 [1.29, 4.34]	
Gatot 2004	0	41	0	40	•	Not estimable	
			-				
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	3	10	4.1%	0.11 [0.01, 1.17]	
Kamiya 2015	0	12	1	12	1.5%	0.14 [0.00, 6.82]	←
Oppizzi 1997	2	13	1	13	4.2%	2.06 [0.19, 21.85]	
Sharpe 1999	0	5	Ó	10		Not estimable	
Sharpe 1999a	Ő	5	0	10			
						Not estimable	
Binclair 1997	0	16	0	14		Not estimable	
Sumeray 2001	1	19	0	19	1.5%	7.39 [0.15, 372.38]	
Friposkiadis 2014	1	28	2	55	4.0%	0.98 [0.09, 11.07]	
Friposkiadis 2014a	2	28	2	50	5.4%	1.89 [0.24, 15.20]	
•					0.470		
/arriale 1997 Subtotal (05% CI)	0	10	0	10	100.0%	Not estimable	
Subtotal (95% CI)		1194		1222	100.0%	2.15 [1.32, 3.50]	-
Fotal events	46		22				
Heterogeneity: Chi ² = 1	10.64, df = 8 (P	= 0.22);	I ^z = 25%				
est for overall effect: 2							
.4.2 Worst-best case	e analysis						
	-	4.0	0	4.0		Not cotimable	
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	8	111	1	115	11.8%	5.21 [1.38, 19.70]	
Cotter 1997	1	14	0	6	1.1%	4.17 [0.06, 300.53]	
De Backer 2010	31	858	12	821	57.2%	2.37 [1.29, 4.34]	∎
Gatot 2004	4	45	0	44	5.3%	7.75 [1.05, 56.94]	
Hausen 1992	ů,	14	Ő	27	0.070		
					0.70	Not estimable	
Hsueh 1998	0	10	3	10	3.7%	0.11 [0.01, 1.17]	
Kamiya 2015	0	12	1	12	1.4%	0.14 [0.00, 6.82]	• • • • • • • • • • • • • • • • • • • •
Oppizzi 1997	2	13	1	13	3.8%	2.06 [0.19, 21.85]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	Ő	5	Ŭ	10		Not estimable	
		-					
Binclair 1997	0	16	0	14		Not estimable	
Sumeray 2001	6	24	0	24	7.3%	9.38 [1.72, 50.96]	
Triposkiadis 2014	1	28	2	55	3.6%	0.98 [0.09, 11.07]	
Triposkiadis 2014a	2	28	2	50	4.8%	1.89 [0.24, 15.20]	
Varriale 1997	õ	10	Õ	10	4.070		
	U		U		400.0%	Not estimable	
Subtotal (95% CI)		1203		1231	100.0%	2.52 [1.59, 3.99]	
Total events	55		22				
Heterogeneity: Chi ² = 1			I ² = 37%				
Test for overall effect: 2	2 = 3.96 (P < 0.	.0001)					
3.4.3 Best-worst case	-						
3irnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	8	111	1	115	11.8%	5.21 [1.38, 19.70]	
Cotter 1997	1	14	O	6	1.1%	4.17 [0.06, 300.53]	
							_
De Backer 2010	31	858	12	821	57.2%	2.37 [1.29, 4.34]	
∋atot 2004	0	45	4	44	5.3%	0.12 [0.02, 0.91]	
Hausen 1992	0	14	0	27		Not estimable	
	0	10	3	10	3.7%	0.11 [0.01, 1.17]	← → →
HSUEN 1998		12	1	12	1.4%	0.14 [0.00, 6.82]	·
Kamiya 2015	0			13	3.8%	2.06 [0.19, 21.85]	
<amiya 2015<br="">Oppizzi 1997</amiya>	0 2	13	1				
<amiya 2015<br="">Oppizzi 1997</amiya>	0 2 0	13 5	0	10		Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999	0 2	13				Not estimable Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a	0 2 0 0	13 5 5	0 0	10 10		Not estimable	
<amiya 2015<br="">Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997</amiya>	0 2 0 0	13 5 5 16	0 0 0	10 10 14	7 204	Not estimable Not estimable	
<amiya 2015<br="">Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001</amiya>	0 2 0 0 1	13 5 16 24	0 0 0 5	10 10 14 24	7.3%	Not estimable Not estimable 0.22 [0.04, 1.22]	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Friposkiadis 2014	0 2 0 0 1 1	13 5 16 24 28	0 0 5 2	10 10 14 24 55	3.6%	Not estimable Not estimable 0.22 (0.04, 1.22) 0.98 (0.09, 11.07)	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Friposkiadis 2014	0 2 0 0 1	13 5 16 24	0 0 0 5	10 10 14 24		Not estimable Not estimable 0.22 [0.04, 1.22]	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Friposkiadis 2014 Friposkiadis 2014a	0 2 0 0 1 1	13 5 16 24 28 28	0 0 5 2	10 10 14 24 55	3.6%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20]	
Hsueh 1998 Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Varriale 1997 Subtotal (95% CI)	0 2 0 0 1 1 2	13 5 16 24 28	0 0 5 2 2	10 10 14 24 55 50 10	3.6%	Not estimable Not estimable 0.22 (0.04, 1.22) 0.98 (0.09, 11.07)	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Varriale 1997	0 2 0 0 1 1 2	13 5 16 24 28 28 10	0 0 5 2 2	10 10 14 24 55 50 10	3.6% 4.8%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sinclair 1997 Sumeray 2001 Triposkiadis 2014 Friposkiadis 2014a Kariale 1997 Subtotal (95% CI)	0 2 0 1 1 2 0 46	13 5 16 24 28 28 10 1203	0 0 5 2 0 31	10 10 14 24 55 50 10 1231	3.6% 4.8%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Friposkiadis 2014 /arriale 1997 Subtotal (95% CI) Fotal events	0 2 0 1 1 2 0 46 22.97, df = 9 (P	13 5 16 24 28 28 10 1203	0 0 5 2 0 31	10 10 14 24 55 50 10 1231	3.6% 4.8%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Karriale 1997 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2	0 2 0 1 1 2 0 46 22.97, df = 9 (P	13 5 16 24 28 28 10 1203	0 0 5 2 0 31	10 10 14 24 55 50 10 1231	3.6% 4.8%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
Kamiya 2015 Oppizzi 1997 Sharpe 1999 Sharpe 1999a Sinclair 1997 Sumeray 2001 Friposkiadis 2014 Friposkiadis 2014a Varriale 1997 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 2	0 2 0 1 1 2 0 46 22.97, df = 9 (P	13 5 16 24 28 28 10 1203	0 0 5 2 0 31	10 10 14 24 55 50 10 1231	3.6% 4.8%	Not estimable Not estimable 0.22 [0.04, 1.22] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	

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

	Favours dopa		Cont			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
3.4.6 Subgroup 2: Ina	active control						
Chen 2013	8	111	1	115	70.6%	5.21 [1.38, 19.70]	
Gatot 2004	0	41	0	40		Not estimable	
Sharpe 1999	0	5	0	10		Not estimable	
Sumeray 2001	1	19	0	19	8.1%	7.39 [0.15, 372.38]	
Triposkiadis 2014	1	28	2	55	21.3%	0.98 [0.09, 11.07]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		214		249	100.0%	3.76 [1.23, 11.49]	
Total events	10		3				
Heterogeneity: Chi ² =	1.52, df = 2 (P =	= 0.47);1	²=0%				
Test for overall effect:	Z = 2.32 (P = 0	02)					
3.4.7 Subgroup 2: Po	tentially active	control					
Birnbaum 1990	0	10	0	10		Not estimable	
Cotter 1997	1	14	0	6	1.6%	4.17 [0.06, 300.53]	
De Backer 2010	31	858	12	821	79.5%	2.37 [1.29, 4.34]	-∎-
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	3	10	5.1%	0.11 [0.01, 1.17]	•
Kamiya 2015	0	12	1	12	1.9%	0.14 [0.00, 6.82]	•
Oppizzi 1997	2	13	1	13	5.2%	2.06 [0.19, 21.85]	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Triposkiadis 2014a	2	28	2	50	6.7%	1.89 [0.24, 15.20]	
Subtotal (95% CI)		980		973	100.0%	1.89 [1.10, 3.24]	●
Total events	36		19				
Heterogeneity: Chi ² =			² = 37%				
Test for overall effect:	Z = 2.31 (P = 0	02)					
							0.01 0.1 1 10 1

Favours dopamine Favours control

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

	Favours dopa	mine	Contr	ol		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.4.8 Subgroup 3: Lov	vdose						
Birnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	8	111	1	115	81.3%	5.21 [1.38, 19.70]	
Kamiya 2015	0	12	1	12	9.4%	0.14 [0.00, 6.82]	•
Sinclair 1997	0	16	0	14		Not estimable	
Sumeray 2001	1	19	0	19	9.4%	7.39 [0.15, 372.38]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		178		180	100.0%	3.82 [1.15, 12.69]	
Total events	9		2				
Heterogeneity: Chi ² = 3			²= 36%				
Test for overall effect: 2	Z = 2.19 (P = 0.	03)					
3.4.9 Subgroup 3: Mod	derate dose						
Cotter 1997	1	14	0	6	6.8%	4.17 [0.06, 300.53]	
Gatot 2004	0	41	0	40		Not estimable	
Hausen 1992	0	14	0	27		Not estimable	
Hsueh 1998	0	10	3	10	21.6%	0.11 [0.01, 1.17]	← ■
Oppizzi 1997	2	13	1	13	22.2%	2.06 [0.19, 21.85]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Triposkiadis 2014	1	28	2	55	21.0%	0.98 [0.09, 11.07]	
Triposkiadis 2014a	2	28	2	50	28.4%	1.89 [0.24, 15.20]	
Subtotal (95% CI)		158		221	100.0%	0.95 [0.31, 2.90]	
Total events	6		8				
Heterogeneity: Chi ² = 4			²=11%				
Test for overall effect: 2	Z = 0.08 (P = 0.	93)					
3.4.10 Subgroup 3: Hig	gh dose						
De Backer 2010	31	858	12	821	100.0%	2.37 [1.29, 4.34]	
Subtotal (95% CI)		858		821	100.0%	2.37 [1.29, 4.34]	
Total events	31		12				
Heterogeneity: Not app	plicable						
Test for overall effect: 2	Z = 2.79 (P = 0.	005)					
							0.01 0.1 1 10 100
							Favours dopamine Favours control

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

	Favours dopa		Contr			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Subgroup Events Total Events Total Weight Peto bgroup 4: Cardiac surgery		Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl			
• •	ardiac surgery						
3irnbaum 1990	0	10	0	10		Not estimable	
∋atot 2004	0	41	0	40		Not estimable	
lausen 1992	0	14	0	27		Not estimable	
Oppizzi 1997	2	13	1	13	73.4%	2.06 [0.19, 21.85]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sumeray 2001 Subtotal (95% CI)	1	19 123	0	19 143	26.6% 100.0%	7.39 [0.15, 372.38] 2.90 [0.38, 21.88]	
otal events	3		1				
est for overall effect:	2 = 1.00 (i = 0	50)					
3.4.12 Subgroup 4: N		ŕ	егу				
		ŕ	ery 1	115	14.2%	5.21 [1.38, 19.70]	
3.4.12 Subgroup 4: N	lot having cardi	ac surge	ery 1 0	115 6	14.2% 1.4%	5.21 [1.38, 19.70] 4.17 [0.06, 300,53]	
3 .4.12 Subgroup 4: N Chen 2013	lot having cardi	ac surge	1			5.21 [1.38, 19.70] 4.17 [0.06, 300.53] 2.37 [1.29, 4.34]	
3.4.12 Subgroup 4: N Chen 2013 Cotter 1997	lot having cardi 8 1	ac surge 111 14	1 0	6	1.4%	4.17 [0.06, 300.53]	
3.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010	lot having cardi 8 1 31	ac surge 111 14 858	1 0 12	6 821	1.4% 68.4%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34]	
6.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998	lot having cardi 8 1 31 0	ac surge 111 14 858 10	1 0 12 3	6 821 10	1.4% 68.4% 4.4%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17]	
3.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015	lot having cardi 8 1 31 0	ac surge 111 14 858 10 12	1 0 12 3 1	6 821 10 12	1.4% 68.4% 4.4% 1.6%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82]	
3.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015 Triposkiadis 2014	lot having cardi 8 1 31 0 0 1	ac surge 111 14 858 10 12 28	1 0 12 3 1 2	6 821 10 12 55	1.4% 68.4% 4.4% 1.6% 4.3%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07]	
5.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a	lot having cardi 8 1 31 0 0 1 2	ac surge 111 14 858 10 12 28 28	1 0 12 3 1 2 2	6 821 10 12 55 50 10	1.4% 68.4% 4.4% 1.6% 4.3%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20]	
6.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Kariale 1997	lot having cardi 8 1 31 0 0 1 2	ac surge 111 14 858 10 12 28 28 28 10	1 0 12 3 1 2 2	6 821 10 12 55 50 10	1.4% 68.4% 4.4% 1.6% 4.3% 5.8%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
6.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014a Yarriale 1997 Subtotal (95% CI)	lot having cardi 8 1 31 0 0 1 2 0 43	ac surge 111 14 858 10 12 28 28 28 28 10 1071	1 0 12 3 1 2 2 0 21	6 821 10 12 55 50 10	1.4% 68.4% 4.4% 1.6% 4.3% 5.8%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
6.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Camiya 2015 Triposkiadis 2014 Triposkiadis 2014a Yarriale 1997 Subtotal (95% CI) Total events	lot having cardi 8 1 31 0 1 2 0 43 10.25, df = 6 (F	ac surge 111 14 858 10 12 28 28 10 1071 '= 0.11);	1 0 12 3 1 2 2 0 21	6 821 10 12 55 50 10	1.4% 68.4% 4.4% 1.6% 4.3% 5.8%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	
6.4.12 Subgroup 4: N Chen 2013 Cotter 1997 De Backer 2010 Hsueh 1998 Kamiya 2015 Triposkiadis 2014 Triposkiadis 2014 Arriale 1997 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	lot having cardi 8 1 31 0 1 2 0 43 10.25, df = 6 (F	ac surge 111 14 858 10 12 28 28 10 1071 '= 0.11);	1 0 12 3 1 2 2 0 21	6 821 10 12 55 50 10	1.4% 68.4% 4.4% 1.6% 4.3% 5.8%	4.17 [0.06, 300.53] 2.37 [1.29, 4.34] 0.11 [0.01, 1.17] 0.14 [0.00, 6.82] 0.98 [0.09, 11.07] 1.89 [0.24, 15.20] Not estimable	

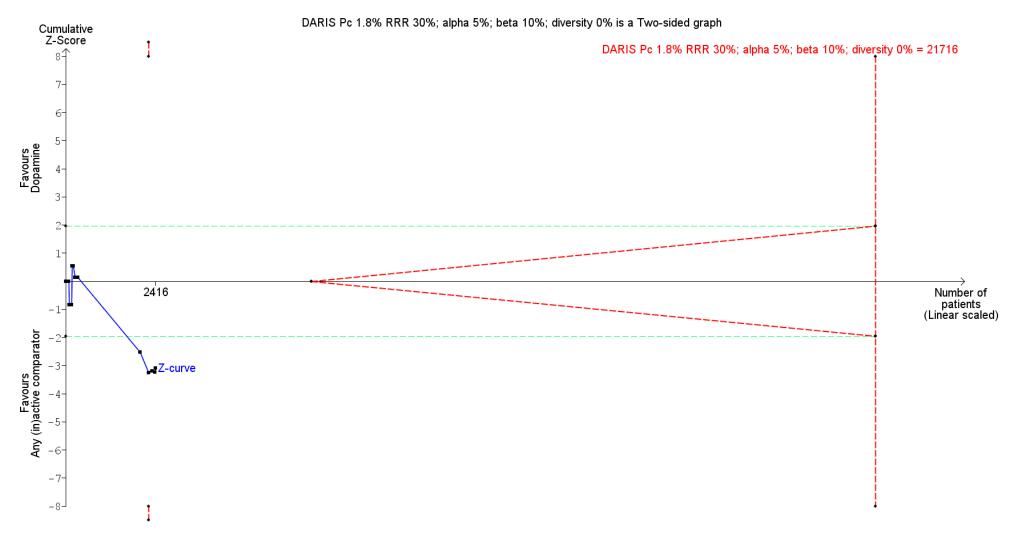
0.01 0.1 1 10 Favours dopamine Favours control

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

	Dopam		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.4.1 All included stu	dies						
3irnbaum 1990	0	10	0	10		Not estimable	
Chen 2013	8	111	1	115	7.5%	8.85 [1.09, 72.01]	
De Backer 2010	31	858	12	821	72.7%	2.53 [1.29, 4.96]	
∋atot 2004	0	41	0	40		Not estimable	
lausen 1992	0	14	0	27		Not estimable	
(amiya 2015	0	12	1	12	3.0%	0.31 [0.01, 8.31]	
harpe 1999	0	5	0	10		Not estimable	
harpe 1999a	0	5	0	10		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sumeray 2001	1	19	0	19	3.1%	3.16 [0.12, 82.64]	
riposkiadis 2014	1	28	2	55	5.5%	0.98 [0.09, 11.31]	
riposkiadis 2014a	2	28	2	50	8.1%	1.85 [0.25, 13.88]	
Subtotal (95% CI)		1147		1183	100.0%	2.43 [1.37, 4.31]	◆
Total events	43		18				
Heterogeneity: Tau² =	0.00; Chi	² = 3.60	3, df = 5 (P = 0.6	0); I ² = 0%		
est for overall effect:	Z = 3.03 ((P = 0.0)	102)				
3.4.2 Pure cardiac dy	sfunctior	n studie	es				
otter 1997	1	14	0	6	27.2%	1.44 [0.05, 40.54]	
Isueh 1998	0	10	3	10	30.6%	0.10 [0.00, 2.28]	← ■
)ppizzi 1997	2	13	1	13	42.2%	2.18 [0.17, 27.56]	
/arriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		47		39	100.0%	0.76 [0.11, 5.08]	
otal events	3		4				
Heterogeneity: Tau ² =	0.54; Chi	² = 2.43	7, df = 2 (P = 0.2	9); I ² = 19	%	
est for overall effect:	Z = 0.28 ((P = 0.7	8)				
estitut üverall ellett.							
estilor overall ellect.							
estion overall ellect.							0.01 0.1 1 10 100

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.

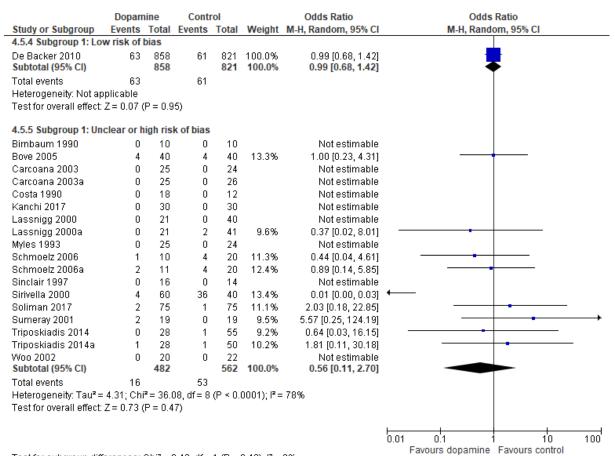


2.13. Forest plots of renal replacement therapy

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

Study or Subgroup	Dopan Events		Conti Events		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
.5.1 All included stu							
3imbaum 1990	0	10	0	10		Not estimable	
30ve 2005	4	40	4	40	12.2%	1.00 [0.23, 4.31]	
arcoana 2003	Ö	25	, O	24	12.270	Not estimable	
arcoana 2003a	0	25	0	26		Not estimable	
costa 1990	0	18	0	12		Not estimable	
) e Backer 2010	63	858	61	821	14.6%		
			0		14.0%	0.99 [0.68, 1.42]	Ī
(anchi 2017	0	30		30		Not estimable	
assnigg 2000	0	21	0	40	7.00	Not estimable	
assnigg 2000a	0	21	2	41	7.6%	0.37 [0.02, 8.01]	
fyles 1993	0	25	0	24		Not estimable	
Schmoelz 2006	1	10	4	20	9.6%	0.44 [0.04, 4.61]	
Schmoelz 2006a	2	11	4	20	11.0%	0.89 [0.14, 5.85]	
Sinclair 1997	0	16	0	14		Not estimable	
Sirivella 2000	4	60	36	40	12.3%	0.01 [0.00, 0.03]	←
Soliman 2017	2	75	1	75	9.4%	2.03 [0.18, 22.85]	
Sumeray 2001	2	19	0	19	7.6%	5.57 [0.25, 124.19]	
riposkiadis 2014	0	28	1	55	7.3%	0.64 [0.03, 16.15]	
riposkiadis 2014a	1	28	1	50	8.3%	1.81 [0.11, 30.18]	
Voo 2002	O	20	0	22		Not estimable	
ubtotal (95% CI)	Ŭ	1340	Ŭ		100.0%	0.58 [0.17, 1.96]	
otal events	79		114				
leterogeneity: Tau² =		i² = 44.7		(P ≤ 0.	00001); I ^z	= 80%	
est for overall effect:	Z = 0.88 ((P = 0.3	8)				
.5.2 Worst-best cas	-						
3imbaum 1990	0	10	0	10		Not estimable	
3ove 2005	4	40	4	40	8.6%	1.00 [0.23, 4.31]	
arcoana 2003	9	34	0	33	5.8%	24.96 [1.39, 449.17]	
arcoana 2003a	9	34	0	34	5.8%	25.71 [1.43, 462.31]	
osta 1990	6	24	0	12	5.7%	8.78 [0.45, 170.29]	
)e Backer 2010	63	858	61	821	10.2%	0.99 [0.68, 1.42]	
anchi 2017	0	30	0	30	10.270	Not estimable	
assnigg 2000	Ő	21	0	42		Not estimable	
	0	21	2	42	E E 04		
assnigg 2000a					5.5%	0.38 [0.02, 8.21]	
fyles 1993	1	26	0	26	5.2%	3.12 [0.12, 80.12]	
chmoelz 2006	2	11	4	21	7.8%	0.94 [0.14, 6.19]	
ichmoelz 2006a	2	11	4	21	7.8%	0.94 [0.14, 6.19]	
linclair 1997	0	16	0	14		Not estimable	
irivella 2000	4	60	36	40	8.6%	0.01 [0.00, 0.03]	←
oliman 2017	2	75	1	75	6.7%	2.03 [0.18, 22.85]	
Sumeray 2001	7	24	0	24	5.7%	21.00 [1.12, 392.38]	
riposkiadis 2014	0	28	1	55	5.2%	0.64 [0.03, 16.15]	
riposkiadis 2014a	1	28	1	50	5.9%	1.81 [0.11, 30.18]	
Voo 2002	5	25	Ó	25	5.7%	13.68 [0.71, 262.17]	
Subtotal (95% CI)	Ŭ	1376	Ŭ		100.0%	1.58 [0.55, 4.51]	
otal events	115		114			1000 [0100, 1101]	
		8-620		4 /D - 0	000043	IZ - 700/	
leterogeneity: Tau² = 'est for overall effect:				4 (P < l	.00001);	17 = 78%	
. 5.3 Best-worst cas Birnbaum 1990	e analysi O	s 10	0	10		Not estimable	
ove 2005	4	40	4	40	8.7%	1.00 [0.23, 4.31]	_
arcoana 2003	Ū,	34	8	33	5.5%	0.04 [0.00, 0.79]	← - − − − − −
arcoana 2003 arcoana 2003a	0	34	9	34	5.5%	0.04 [0.00, 0.70]	
osta 1990	0	24	9	12	5.5 %	Not estimable	
			-		10.8%		<u> </u>
e Backer 2010	63	858	61	821	10.8%	0.99 [0.68, 1.42]	Ţ
anchi 2017	0	30	0	30		Not estimable	
assnigg 2000	0	21	2	42	5.2%	0.38 [0.02, 8.21]	
assnigg 2000a	0	21	3	42	5.3%	0.26 [0.01, 5.32]	
lyles 1993	0	26	2	26	5.2%	0.18 [0.01, 4.05]	• • • • • • • • • • • • • • • • • • • •
chmoelz 2006	1	11	5	21	6.8%	0.32 [0.03, 3.15]	
chmoelz 2006a	2	11	5	21	7.8%	0.71 [0.11, 4.44]	
	0	16	0	14		Not estimable	
inclair 1997	4	60	36	40	8.8%	0.01 [0.00, 0.03]	←
		75	1	75	6.5%	2.03 [0.18, 22.85]	
irivella 2000			5	24	8.0%	0.35 [0.06, 1.99]	.
Sirivella 2000 Soliman 2017	2	24		24		0.64 [0.03, 16.15]	
Sinclair 1997 Sirivella 2000 Soliman 2017 Sumeray 2001 Sincekiadie 2014	2 2	24		66			
irivella 2000 Soliman 2017 Sumeray 2001 Tiposkiadis 2014	2 2 0	28	1	55	4.9%		
Sirivella 2000 Soliman 2017 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a	2 2 0 1	28 28	1 1	50	5.7%	1.81 [0.11, 30.18]	
Sirivella 2000 Soliman 2017 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Voo 2002	2 2 0	28 28 25	1	50 25	5.7% 5.3%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58]	·
Sirivella 2000 Soliman 2017 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a	2 2 0 1 0	28 28	1 1	50 25	5.7%	1.81 [0.11, 30.18]	
Sirivella 2000 Soliman 2017 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Voo 2002	2 2 0 1	28 28 25	1 1	50 25	5.7% 5.3%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58]	
Sirivella 2000 Soliman 2017 Sumeray 2001 Triposkiadis 2014 Triposkiadis 2014a Voo 2002 Subtotal (95% CI)	2 2 0 1 0 79	28 28 25 1376	1 1 3 146	50 25 1415	5.7% 5.3% 100.0%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58] 0.29 [0.11, 0.77]	
irivella 2000 coliman 2017 rumeray 2001 riposkiadis 2014 riposkiadis 2014a voo 2002 ubtotal (95% CI) iotal events	2 2 0 1 0 79 2.23; Chi	28 28 25 1376 i ² = 55.0	1 1 3 146)4, df= 1	50 25 1415	5.7% 5.3% 100.0%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58] 0.29 [0.11, 0.77]	
irivella 2000 oliman 2017 umeray 2001 riposkiadis 2014 riposkiadis 2014a (oo 2002 ubtotal (95% CI) otal events leterogeneity: Tau ² =	2 2 0 1 0 79 2.23; Chi	28 28 25 1376 i ² = 55.0	1 1 3 146)4, df= 1	50 25 1415	5.7% 5.3% 100.0%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58] 0.29 [0.11, 0.77]	
irivella 2000 oliman 2017 umeray 2001 riposkiadis 2014 riposkiadis 2014a /oo 2002 ubtotal (95% CI) otal events leterogeneity: Tau ² =	2 2 0 1 0 79 2.23; Chi	28 28 25 1376 i ² = 55.0	1 1 3 146)4, df= 1	50 25 1415	5.7% 5.3% 100.0%	1.81 [0.11, 30.18] 0.13 [0.01, 2.58] 0.29 [0.11, 0.77]	

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



Test for subgroup differences: $Chi^2 = 0.48$, df = 1 (P = 0.49), $I^2 = 0\%$

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

	Dopam		Contr			Odds Ratio	Odds Ratio
Study or Subgroup			Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.5.6 Subgroup 2: In	active con	trol					
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Costa 1990	0	18	0	12		Not estimable	
Kanchi 2017	0	30	0	30		Not estimable	
assnigg 2000_	0	21	0	40		Not estimable	
vlyles 1993	0	25	0	24		Not estimable	
3chmoelz 2006	1	10	4	20	47.8%	0.44 [0.04, 4.61]	
Sumeray 2001	2	19	0	19	27.1%	5.57 [0.25, 124.19]	
Friposkiadis 2014	0	28	1	55	25.0%	0.64 [0.03, 16.15]	
Noo 2002	0	20	0	22		Not estimable	
Subtotal (95% CI)		221		272	100.0%	0.97 [0.19, 4.87]	
Fotal events	3		5				
Heterogeneity: Tau ² :	= 0.00; Chi	² = 1.73), df = 2 (P = 0.4	2); I ² = 0%		
Fest for overall effect	: Z = 0.04 (P = 0.9	7)				
4.5.7 Subgroup 2: Po	-						
3irnbaum 1990	Ō	10	0	10		Not estimable	
3irnbaum 1990 3ove 2005	0 4	10 40	0 4	40	16.0%	1.00 [0.23, 4.31]	
Birnbaum 1990 Bove 2005 De Backer 2010	0 4 63	10 40 858	0 4 61	40 821	18.4%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a	0 4 63 0	10 40 858 21	0 4 61 2	40 821 41	18.4% 10.7%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Bchmoelz 2006a	0 4 63 0 2	10 40 858 21 11	0 4 61 2 4	40 821 41 20	18.4%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Bchmoelz 2006a Binclair 1997	0 4 63 0 2 0	10 40 858 21 11 16	0 4 61 2 4 0	40 821 41 20 14	18.4% 10.7% 14.6%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000	0 4 63 0 2 0 4	10 40 858 21 11 16 60	0 4 61 2 4 0 36	40 821 41 20 14 40	18.4% 10.7% 14.6% 16.0%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000 Boliman 2017	0 4 63 0 2 0 4 2	10 40 858 21 11 16 60 75	0 4 61 2 4 0 36 1	40 821 41 20 14 40 75	18.4% 10.7% 14.6% 16.0% 12.8%	1.00 (0.23, 4.31) 0.99 (0.68, 1.42) 0.37 (0.02, 8.01) 0.89 (0.14, 5.85) Not estimable 0.01 (0.00, 0.03) 2.03 (0.18, 22.85)	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000 Boliman 2017 Friposkiadis 2014a	0 4 63 0 2 0 4	10 40 858 21 11 16 60 75 28	0 4 61 2 4 0 36	40 821 41 20 14 40 75 50	18.4% 10.7% 14.6% 16.0% 12.8% 11.5%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03] 2.03 [0.18, 22.85] 1.81 [0.11, 30.18]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000 Boliman 2017 Friposkiadis 2014a Subtotal (95% CI)	0 4 63 0 2 0 4 2 1	10 40 858 21 11 16 60 75	0 4 61 2 4 0 36 1 1	40 821 41 20 14 40 75 50	18.4% 10.7% 14.6% 16.0% 12.8%	1.00 (0.23, 4.31) 0.99 (0.68, 1.42) 0.37 (0.02, 8.01) 0.89 (0.14, 5.85) Not estimable 0.01 (0.00, 0.03) 2.03 (0.18, 22.85)	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000 Soliman 2017 Friposkiadis 2014a Subtotal (95% CI) Fotal events	0 4 63 0 2 0 4 2 1 76	10 40 858 21 11 16 60 75 28 1119	0 4 61 2 4 0 36 1 1 109	40 821 41 20 14 40 75 50 1111	18.4% 10.7% 14.6% 16.0% 12.8% 11.5% 100.0%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03] 2.03 [0.18, 22.85] 1.81 [0.11, 30.18] 0.48 [0.10, 2.23]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Bohmoelz 2006a Binclair 1997 Birivella 2000 Soliman 2017 Friposkiadis 2014a Subtotal (95% CI) Fotal events Heterogeneity: Tau ² :	0 4 63 0 2 0 4 2 1 1 76 = 3.33; Chi	10 40 858 21 11 16 60 75 28 1119 ² = 43.1	0 4 61 2 4 0 36 1 1 1 9 0, df = 6	40 821 41 20 14 40 75 50 1111	18.4% 10.7% 14.6% 16.0% 12.8% 11.5% 100.0%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03] 2.03 [0.18, 22.85] 1.81 [0.11, 30.18] 0.48 [0.10, 2.23]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Binclair 1997 Birivella 2000 Soliman 2017 Friposkiadis 2014a Subtotal (95% CI) Fotal events	0 4 63 0 2 0 4 2 1 1 76 = 3.33; Chi	10 40 858 21 11 16 60 75 28 1119 ² = 43.1	0 4 61 2 4 0 36 1 1 1 9 0, df = 6	40 821 41 20 14 40 75 50 1111	18.4% 10.7% 14.6% 16.0% 12.8% 11.5% 100.0%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03] 2.03 [0.18, 22.85] 1.81 [0.11, 30.18] 0.48 [0.10, 2.23]	
Birnbaum 1990 Bove 2005 De Backer 2010 Lassnigg 2000a Bohmoelz 2006a Binclair 1997 Birivella 2000 Soliman 2017 Friposkiadis 2014a Subtotal (95% CI) Fotal events Heterogeneity: Tau ² :	0 4 63 0 2 0 4 2 1 1 76 = 3.33; Chi	10 40 858 21 11 16 60 75 28 1119 ² = 43.1	0 4 61 2 4 0 36 1 1 1 9 0, df = 6	40 821 41 20 14 40 75 50 1111	18.4% 10.7% 14.6% 16.0% 12.8% 11.5% 100.0%	1.00 [0.23, 4.31] 0.99 [0.68, 1.42] 0.37 [0.02, 8.01] 0.89 [0.14, 5.85] Not estimable 0.01 [0.00, 0.03] 2.03 [0.18, 22.85] 1.81 [0.11, 30.18] 0.48 [0.10, 2.23]	

Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), l² = 0%

Favours dopamine Favours control

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

	Dopam		Cont			Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events Total Weight M-H, Random, 95% Cl		M-H, Random, 95% Cl	M-H, Random, 95% Cl	
4.5.8 Subgroup 3: Lov			_				
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	4	40	4	40	18.5%	1.00 [0.23, 4.31]	
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Costa 1990	0	18	0	12		Not estimable	
Kanchi 2017	0	30	0	30		Not estimable	
Lassnigg 2000	0	21	0	40		Not estimable	
Lassnigg 2000a	0	21	2	41	13.8%	0.37 [0.02, 8.01]	
Myles 1993	0	25	0	24		Not estimable	
Schmoelz 2006	1	10	4	20	16.0%	0.44 [0.04, 4.61]	
Schmoelz 2006a	2	11	4	20	17.4%	0.89 [0.14, 5.85]	
Sinclair 1997	0	16	0	14		Not estimable	
Sirivella 2000	0	0	0	0		Not estimable	
Soliman 2017	2	75	1	75	15.8%	2.03 [0.18, 22.85]	
Sumeray 2001	4	60	36	40	18.6%	0.01 [0.00, 0.03]	<u>←</u>
Woo 2002	0	20	0	22		Not estimable	
Subtotal (95% CI)		407		438	100.0%	0.34 [0.05, 2.48]	
Total events	13		51				
Heterogeneity: Tau ² = Test for overall effect: .				(P < 0.)	0001); I² =	: 84%	
4.5.9 Subgroup 3: Mo	derate do	se					
Triposkiadis 2014	0	28	1	55	43.1%	0.64 [0.03, 16.15]	_
Triposkiadis 2014a	1	28	1	50	56.9%	1.81 [0.11, 30,18]	
Subtotal (95% CI)	'	56		105	100.0%	1.16 [0.14, 9.65]	
Total events	1		2				
Heterogeneity: Tau ² =	•	² = 0.2°	_	P = 0.6	3): I≊ = 0.%		
Test for overall effect:			•	, = 0.0	0,,, = 0,,	,	
4.5.10 Subgroup 3: Hi	iah doso						
	-	050	64	0.04	400.00	0.00.00.00.4.403	_
De Backer 2010 Subtotal (95% CI)	63	858 <mark>858</mark>	61	821 <mark>821</mark>	100.0% 100.0%	0.99 [0.68, 1.42] 0.99 [0.68, 1.42]	—
Total events Heterogeneity: Not ap	63 nlicable		61				
Test for overall effect:	•	P = 0.9	5)				
Test for subgroup diff	erences: (Chi ^z = 1	l.10. df=	2 (P = 1	0.58), I ² =	0%	Favours dopamine Favours control

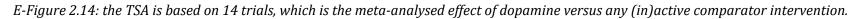
E-Figures 2.13.11-2.13.12: subgroup analysis 4 – trials subdivided by clinical setting

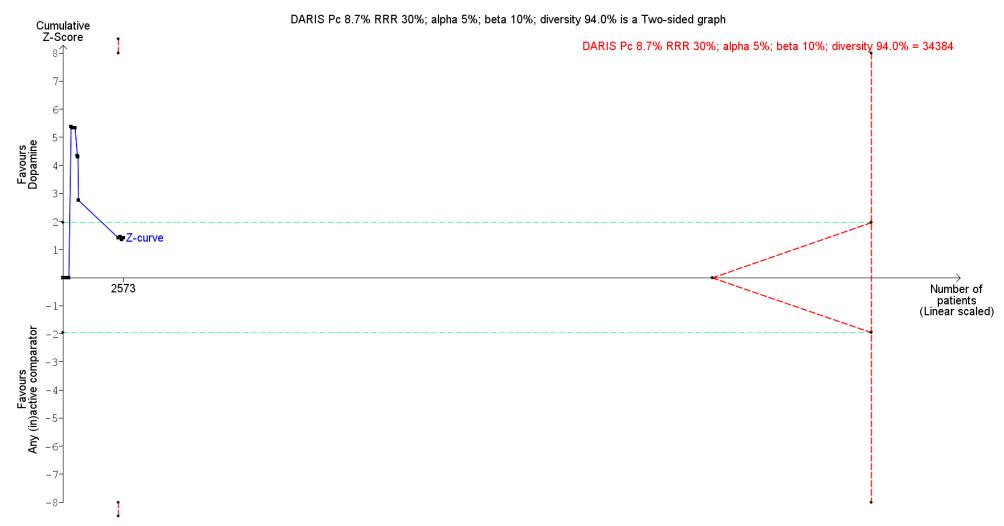
	Doparr	nine	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
4.5.11 Subgroup 4: C	ardiac su	rgery					
Birnbaum 1990	0	10	0	10		Not estimable	
Bove 2005	4	40	4	40	22.2%	1.00 [0.23, 4.31]	_
Carcoana 2003	0	25	0	24		Not estimable	
Carcoana 2003a	0	25	0	26		Not estimable	
Costa 1990	0	18	0	12		Not estimable	
Kanchi 2017	0	30	0	30		Not estimable	
Lassnigg 2000	0	21	0	40		Not estimable	
Lassnigg 2000a	0	21	2	41	18.0%	0.37 [0.02, 8.01]	
Myles 1993	0	25	0	24		Not estimable	
Sinclair 1997	0	16	0	14		Not estimable	
Sirivella 2000	4	60	36	40	22.2%	0.01 [0.00, 0.03]	<u>←</u>
Soliman 2017	2	75	1	75	19.8%	2.03 [0.18, 22.85]	
Sumeray 2001	2	19	0	19	17.9%	5.57 [0.25, 124.19]	
Noo 2002	0	20	0	22		Not estimable	
Subtotal (95% CI)		405		417	100.0%	0.45 [0.03, 6.26]	
Total events	12		43				
Heterogeneity: Tau ² =	= 7.63; Chi	² = 31.0	84, df = 4	(P ≤ 0.	00001); P	²= 87%	
Test for overall effect:	Z = 0.60 (P = 0.5	5)				
4.5.12 Subgroup 4: N	lot having	cardia	c surgor	v			
4.3.12 Subgroup 4. N De Backer 2010	63	858	61	9 821	91.6%	0.00.00.00.4.401	_
Schmoelz 2006	03 1	858 10	4	20	2.2%	0.99 [0.68, 1.42]	
Schmoelz 2006 Schmoelz 2006a	2	10	4	20	2.2%	0.44 [0.04, 4.61] 0.89 [0.14, 5.85]	
Triposkiadis 2014	2	28	4	55	1.2%	0.64 [0.03, 16.15]	
Triposkiadis 2014 Triposkiadis 2014a	1	20	1	50	1.2%	1.81 [0.11, 30.18]	
Subtotal (95% CI)	I	935	I		100.0%	0.97 [0.68, 1.38]	•
Total events	67		71				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 0.71	D, df = 4 (P = 0.9	5); I ^z = 09	6	
Test for overall effect:	Z=0.17 (P = 0.8	(7)				
							0.01 0.1 1 10 10
							Favours dopamine Favours control
Fest for subgroup dif	ferences:	Chi ^z = I	0.33, df =	1 (P =	0.57), I ^z =	:0%	

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



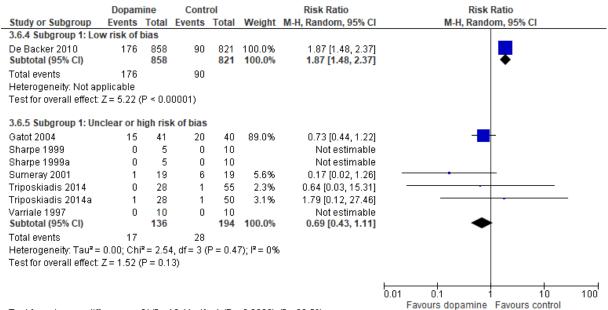


2.15. Forest plots of atrial tachyarrhythmias

	Dopan		Cont			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.6.1 All included stu							
De Backer 2010	176	858	90	821	39.6%	1.87 [1.48, 2.37]	_ =
Gatot 2004	15	41	20	40	35.4%	0.73 [0.44, 1.22]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sumeray 2001	1	19	6	19	11.8%	0.17 [0.02, 1.26]	
Triposkiadis 2014	0	28	1	55	5.8%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	7.4%	1.79 [0.12, 27.46]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		994		1015	100.0%	0.94 [0.42, 2.15]	-
Total events	193		118				
Heterogeneity: Tau² =	0.43; Chi	i ^z = 15.8	38, df = 4	(P = 0.1)	003); I ² =	75%	
Test for overall effect:	Z = 0.13 ((P = 0.8	9)				
3.6.2 Worst-best cas	e analysi	s					
De Backer 2010	176	858	90	821	44.9%	1.87 [1.48, 2.37]	■
Gatot 2004	19	45	20	44	33.9%	0.93 [0.58, 1.49]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	Ō	5	Ō	10		Not estimable	
Sumeray 2001	6	24	6	24	16.2%	1.00 [0.38, 2.66]	_
Triposkiadis 2014	0	28	1	55	2.2%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	2.9%	1.79 [0.12, 27.46]	
Varriale 1997	O	10	O	10	2.070	Not estimable	
Subtotal (95% CI)	Ŭ	1003	Ŭ		100.0%	1.30 [0.81, 2.10]	★
Total events	202		118				-
Heterogeneity: Tau ² =		i ² = 8.20		P = 0.0	8): F = 51	%	
Test for overall effect:					-,,. 01		
3.6.3 Best-worst cas	e analysi	s					
De Backer 2010	176	858	90	821	35.2%	1.87 [1.48, 2.37]	
Gatot 2004	15	45	24	44	33.0%	0.61 [0.37, 1.00]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	Ő	5	Ő	10		Not estimable	
Sumeray 2001	1	24	11	24	14.7%	0.09 [0.01, 0.65]	
Triposkiadis 2014	O	28	1	55	7.6%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	9.5%	1.79 [0.12, 27.46]	_
Varriale 1997		10	n	10	0.070	Not estimable	
		1003			100.0%	0.76 [0.29, 2.03]	
Subiolai (95% CI)	193		127				-
Subtotal (95% CI) Total events		i ^z = 24.1		(P < 0.	0001): I P =	= 83%	
Total events	0.70.000						
		(P = 0.5	9)				
Total events Heterogeneity: Tau² =		(P = 0.5	9)				
Total events Heterogeneity: Tau² =		(P = 0.5	9)				

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



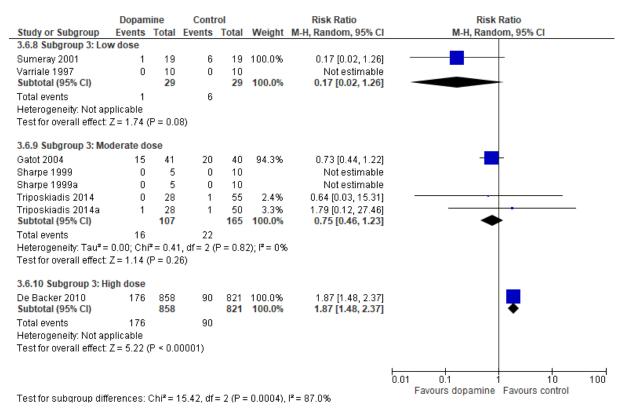
Test for subgroup differences: Chi² = 13.41, df = 1 (P = 0.0003), l² = 92.5%

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

	Dopam	ine	Cont	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
3.6.6 Subgroup 2: Ina	active con	trol					
Gatot 2004	15	41	20	40	87.5%	0.73 [0.44, 1.22]	
Sharpe 1999	0	5	0	10		Not estimable	
Sumeray 2001	1	19	6	19	8.8%	0.17 [0.02, 1.26]	
Triposkiadis 2014	0	28	1	55	3.7%	0.64 [0.03, 15.31]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		103		134	100.0%	0.64 [0.35, 1.18]	
Total events	16		27				
Heterogeneity: Tau ² =	= 0.04; Chi	² = 2.1 ⁴	1, df = 2 (P = 0.3	5); I² = 5%	6	
Test for overall effect:	Z=1.43 (P = 0.1	5)				
3.6.7 Subgroup 2: Po	-						
De Backer 2010	176	858	90	821	99.3%	1.87 [1.48, 2.37]	
Sharpe 1999a	0	5	0	10		Not estimable	
Triposkiadis 2014a	1	28	1	50	0.7%	1.79 [0.12, 27.46]	
Subtotal (95% CI)		891		881	100.0%	1.87 [1.48, 2.36]	•
Total events	177		91				
Heterogeneity: Tau² =	= 0.00; Chi	² = 0.01	D, df = 1 (P = 0.9	7); I² = 0%	6	
Test for overall effect:	Z= 5.24 (P < 0.0	0001)				
							0.01 0.1 1 10 10
							Favours dopamine Favours control

Test for subgroup differences: $Chi^2 = 10.30$, df = 1 (P = 0.001), l² = 90.3%

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

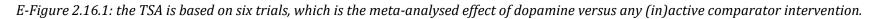
	Dopam	ine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.6.11 Subgroup 4: Ca	ardiac su	rgery					
Gatot 2004	15	41	20	40	70.8%	0.73 [0.44, 1.22]	
Sharpe 1999	0	5	0	10		Not estimable	
Sharpe 1999a	0	5	0	10		Not estimable	
Sumeray 2001	1	19	6	19	29.2%	0.17 [0.02, 1.26]	
Subtotal (95% CI)		70		79	100.0%	0.48 [0.12, 1.88]	
Total events	16		26				
Heterogeneity: Tau² =	0.63; Chi ^a	²= 2.12	2, df = 1 (P = 0.1	5); I² = 53	%	
Test for overall effect:	Z = 1.06 (ł	P = 0.2	9)				
2.0.42.0.0							
3.6.12 Subgroup 4: No	-			-			
De Backer 2010	176	858	90	821	98.7%	1.87 [1.48, 2.37]	
Triposkiadis 2014	0	28	1	55	0.5%	0.64 [0.03, 15.31]	
Triposkiadis 2014a	1	28	1	50	0.7%	1.79 [0.12, 27.46]	
Varriale 1997	0	10	0	10		Not estimable	
Subtotal (95% CI)		924		936	100.0%	1.86 [1.47, 2.35]	▲
Total events	177		92				
Heterogeneity: Tau ² =	0.00; Chi ^a	² = 0.40	3, df = 2 (P = 0.8	0); I ² = 0%	6	
Test for overall effect:	Z = 5.20 (ł	P < 0.0	0001)				
							0.01 0.1 1 10 100
To at fair and success diff			0.07.46		0.000 17	70.70	Favours dopamine Favours control

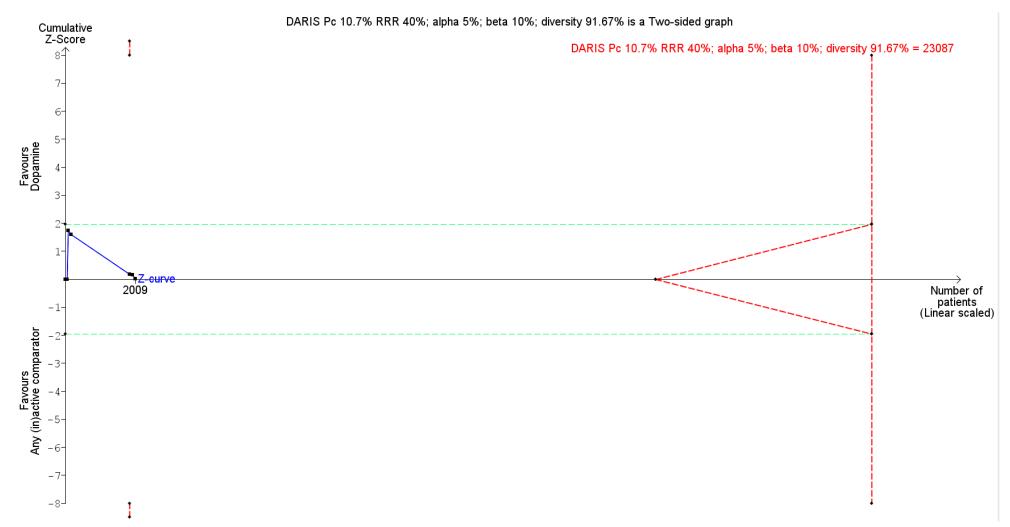
Test for subgroup differences: $Chi^2 = 3.67$, df = 1 (P = 0.06), $l^2 = 72.7\%$

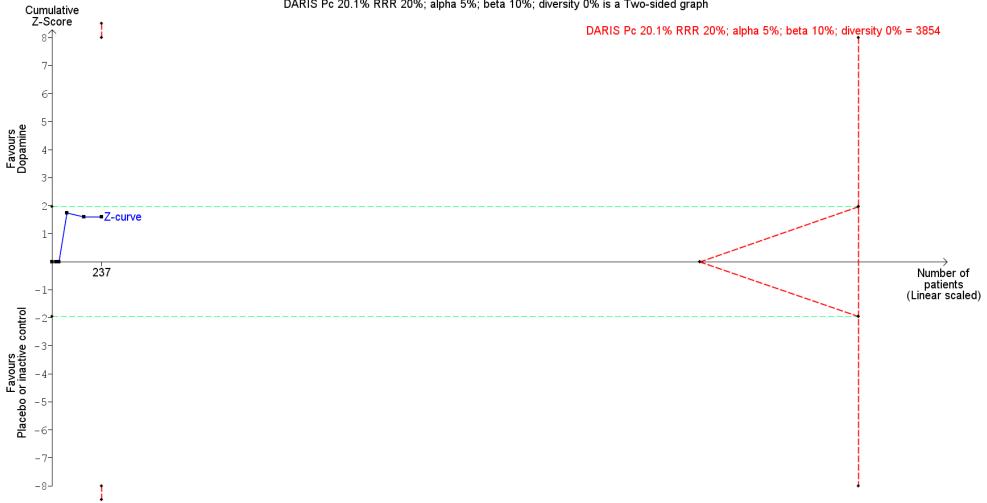
E-Figures 2.15.13: sensitivity analysis – patients with cardiac dysfunction versus a majority/large proportion of patients with cardiac dysfunction

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

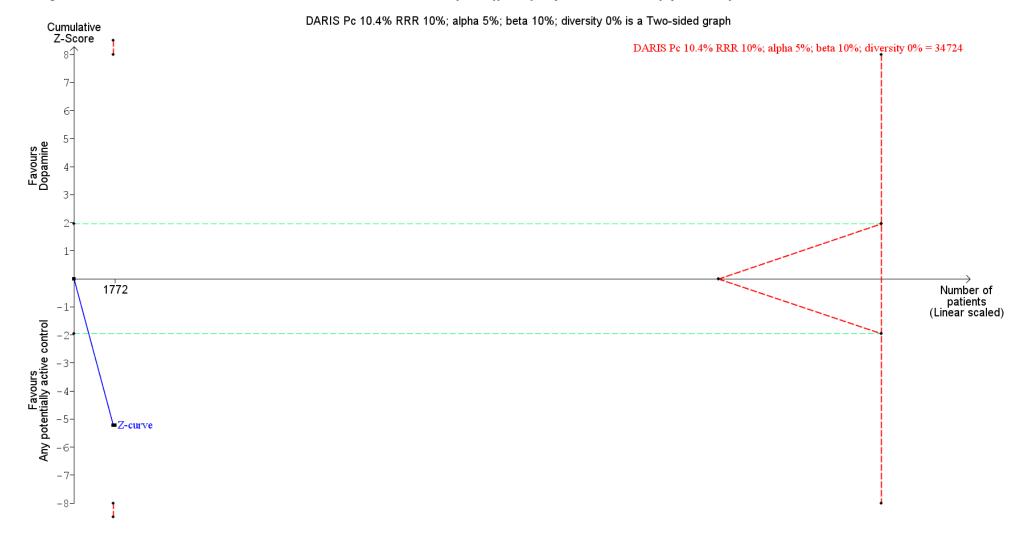
2.16. Trial sequential analyses of atrial tachyarryhythmias







E-Figure 2.16.2: the TSA is based on five trials, which is the meta-analysed effect of dopamine versus placebo or inactive control. DARIS Pc 20.1% RRR 20%; alpha 5%; beta 10%; diversity 0% is a Two-sided graph



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 a	assessment						Nº of patien	ts	Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dopamine	Any (in)active comparator	Relative (95% Cl)	Absolute (95% CI)	Quality	Importance
Mortalit	y at maximum	follow-up	- All included stud	ies						·		
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)		CRITICAL
Serious a	adverse events	- All includ	ded 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)		CRITICAL
Myocard	lial infarction -	All include	ed 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
Ventricu	lar tachyarrhy	thmias - Al	l 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 re	placement the	rapy - All ii	ncluded 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 ta	chyarrhythmia	s - All inclu	ded 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".

Allocation concealment (selection bias)	Low risk	Comment: probably low risk, because a meta-analysis of the same research group describes the use of "Computer- generated random numbers" in this trial. 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	Low risk	Quote: "use of computer-generated random-number tables".
(selection bias)		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	Low risk	Quote: "supplied by the Department of Investigational
personnel (performance bias)		Pharmacy in a blinded manner".
		Comment: probably done.
Blinding of outcome	Low risk	Quote: "supplied by the Department of Investigational
assessment (detection bias)		Pharmacy in a blinded manner".
		Comment: probably done.
Incomplete outcome data	High risk	Quote: "Of the 135 patients enrolled, 35 patients were
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	High risk -	Quote: "randomly assigned to one of two groups according to
(selection bias)	REMOVED	odd or even unit registry numbers".
		Comment: high risk, as randomization on patient number is
		'quasi-random'. QUASI RANDOMISED TRIAL
Allocation concealment	High risk	Not described. Probably not performed properly as the
(selection bias)		method of randomization was 'quasi-random'.
Blinding of participants and	High risk	Quote: "blinded prospective randomized study".
personnel (performance bias)		Comment: Probably not done, because control group did not
		receive a placebo and therefore the personnel was probably
		not blinded.
Blinding of outcome	High risk	Not stated. Probably not.
assessment (detection bias)		Comment: low risk for mortality (not reported), high risk for
		other outcomes.
Incomplete outcome data	High risk	"Two patients were excluded from the study because of unse-
(attrition bias)		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	High risk	The authors did not register the trial or prepublished the trial
bias)		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	Unclear risk	Quote: "randomly divided into two groups"
(selection bias)		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	Unclear risk	Not stated, probably not.
assessment (detection bias)		Low risk for mortality, high risk for other outcomes.
Incomplete outcome data (attrition bias)	Unclear risk	Not specified.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "'Randomly divided into three groups".
(selection bias)		Comment: no description of randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated.
Blinding of outcome	Unclear risk	Not stated.
assessment (detection bias)		Not stateu.
Incomplete outcome data	High risk	Quote: "Because six patients were disqualified from the study,
(attrition bias)		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	High risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	High risk –	Quote: "divided by simple randomization into 2 groups." (even
(selection bias)	REMOVED	numbers 1st group, uneven 2nd group).
		Comment: not random and predice-Table allocation. QUASI
		RANDOMISED TRIAL
Allocation concealment	High risk	Quote: "divided by simple randomization into 2 groups." (even
(selection bias)		numbers 1st group, uneven 2nd group).
		Comment: not random and predice-Table allocation.
Blinding of participants and	High risk	Quote: "A pilot prospective one-center open-ended
personnel (performance bias)		randomized trial".
		Comment: not blinded.
Blinding of outcome	High risk	Not described. Probably not blinded because it was an open-
assessment (detection bias)		label trial.
Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence	Unclear	Quote: "The patients were randomly and blindly assigned".
generation (selection bias)	risk	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	Unclear	Not described.
(selection bias)	risk	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
	Lauradal.	opacity and numbering.
Blinding of participants and	Low risk	Quote: "Dopamine and saline were provided in code uniformly
personnel (performance bias)		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	Low risk	Quote: "Dopamine and saline were provided in code uniformly
assessment (detection bias)	LOW HISK	appearing 10 mL syringes. The content of the syringes was
discission (detection sids)		unknown to the caring staff and to the investigators."
		Comment: probably done.
Incomplete outcome data	Low risk	Quote: ""A total of 89 patients were initially enrolled in the
(attrition bias)		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	High risk	The authors did not register the trial or prepublished the trial
bias)		design. The primary outcome of this meta-analysis (mortality) is
		not reported.
Other bias	Unclear	The manuscript does not contain a statement on conflicts of
	risk	interest or financial disclosures.

Giamouzis et al. 2010 [5]

Bias	Authors'	Support for judgement
	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] [,
Allocation concealment (selection bias)	Unclear risk	count by (groupvars)])". 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'	Support for judgement
	judgement	
Random sequence generation	Low risk	Quote: "Patients were allocated to either group according to
(selection bias)		randomization tables provided by the Statistical Program for
		the Social Sciences (SPSS)."
		Comment: probably done.
Allocation concealment	High risk	Quote: "Patients were allocated to either group according to
(selection bias)		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	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	Unclear risk	Not stated. probably not done.
assessment (detection bias)		Comment: low risk for mortality, high risk for other outcomes.
Incomplete outcome data	Low risk	Quote: "There are no reports regarding late death in any
(attrition bias)		case".
		Comment: probably none lost to follow-up.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "randomized to either".
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Allocation concealment	Unclear risk	Not described.
(selection bias)		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	Low risk	Quote: "The ECGs were further edited and analyzed by an
assessment (detection bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Low risk	Quote: "Patients were randomized to one of two study groups
(selection bias)		using
		a computer-generated random number table".
		Comment: probably done.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		Comment: Low risk for mortality outcomes, high risk for other
		outcomes.
Incomplete outcome data	Low risk	Quote: "None of the enrolled patients died during the study
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "patients were randomized to".
(selection bias)		Comment:No further details described and previous trials
		from the same researchers also do not elaborate on allocation concealment.
Allocation concealment	Unclear risk	No details on allocation method described and previous trials
(selection bias)		from the same researchers also do not elaborate on allocation concealment.
Blinding of participants and	High risk	Quote: "This study was a prospective, open-labeled".
personnel (performance bias)		Comment: personnel was not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "patients were randomized to".
(selection bias)		Comment: No further details described and previous trials
		from the same researchers also do not elaborate on allocation
		concealment.
Allocation concealment	Unclear risk	No details on allocation method described and previous trials
(selection bias)		from the same researchers also do not elaborate on allocation
		concealment.
Blinding of participants and	High risk	Quote: "This study was a prospective, open-labeled".
personnel (performance bias)		Comment: personnel was not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	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'	Support for judgement
Random sequence generation (selection bias)	judgement 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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "Patients were randomized to 2 groups".
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not elaborate on their method of randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably high risk.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data	Low risk	Probably all patients had complete follow-up until hospital
(attrition bias)		discharge.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	Low risk	Quote: "Group assignment was performed using a computer-
(selection bias)		generated randomization table".
		Comment: probably done.
Allocation concealment	Unclear risk	Quote: "the drug infusions were prepared by a study nurse
(selection bias)		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	Low risk	Quote: "the drug infusions were prepared by a study nurse
personnel (performance bias)		who was not involved in the care of the patients".
		Comment: probably blinded.
Blinding of outcome	Unclear risk	Not described.
assessment (detection bias)		Comment: unclear. Low risk for mortality and renal
		replacement therapy.
Incomplete outcome data	Low risk	Quote: "One patient from each group was excluded from the
(attrition bias)		trial because of a protocol violation".
		Comment: only 3/61 excluded and reason for exclusion is
		described.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	Unclear risk	Quote: "were randomly allocated".
(selection bias)		Comment: unclear information, as a previous trial of the same
		group also did not describe their method of randomization.
Allocation concealment	Unclear risk	Quote: "contents of a sealed envelope in a 2 x 2 factorial
(selection bias)		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	Low risk	Quote: "Clinicians involved with the case were blinded to the
personnel (performance bias)		study drug".
		Comment: probably done.
Blinding of outcome	Unclear risk	Not described.
assessment (detection bias)		Comment: unclear. Low risk for mortality, high risk for SEAs.
Incomplete outcome data	Low risk	Quote: "One patient (group 2) had to be withdrawn from the
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	Low risk	Quote: "they were randomized into three groups".
(selection bias)		Comment: Probably done properly, as a similar trial by these
		investigators state that they used a "simple random method"
		for randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data	Low risk	Quote: "One patient each expired in the infusion b dopamine
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	Unclear risk	Quote: "were prospectively randomized".
(selection bias)		Comment: unclear, as a similar trial by these investigators also
		did not elaborate on their method of randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	Low risk	Quote: "An unmarked syringe of the study agent was then
personnel (performance bias)		infused at a predetermined rate."
		Comment: probably done.
Blinding of outcome	Low risk	Quote: "All observations were made by a single blinded
assessment (detection bias)		observer".
		Comment: probably done.
Incomplete outcome data	Unclear risk	Quote: "All patients left intensive care on the first
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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	Unclear risk	Quote: "were randomly allocated".
(selection bias)		Comment: unclear, as a similar trial by these investigators also
		did not elaborate on their method of randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	High risk	Quote: "allocated to receive an infusion of either dopexamine
personnel (performance bias)		2.0 mg/kg per min, or dopamine 2.5 mg/kg per min"
		Comment: probably not blinded.
Blinding of outcome	High risk	Quote: "Urinary analysis was blinded to which
assessment (detection bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)	Officieal fisk	design. The outcome measures are mentioned in methods and
51357		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	Unclear risk	Quote: "Patients were randomized either to receive".
(selection bias)		Comment: unclear, as a similar trial by these investigators also did not elaborate on their method of randomization.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	High risk	Quote: "Criteria for dialysis were the same in both groups, and
assessment (detection bias)		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	Unclear risk	No patients seemed to be lost to follow-up. However one
(attrition bias)		might argue that the follow-up period is too short to assess
		the true number of mortality and SAEs.
Selective reporting (reporting	High risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Low risk	Quote: "randomised patients according to a e-Table of
(selection bias)		random numbers".
		Comment: probably done.
Allocation concealment	Low risk	Quote: "The Pharmacy Department (UCLH) randomised
(selection bias)		patients".
		Comment: probably done properly as allocation was
		performed centrally.
Blinding of participants and	Low risk	Quote: "Participating physicians and nursing staff were
personnel (performance bias)		blinded to the syringe contents until the conclusion of the
		trial".
Blinding of outcome	Unclear risk	Not stated. Probably not done.
assessment (detection bias)		Comment: Low risk for mortality, high risk for other outcomes.
Incomplete outcome data	Low risk	Quote: "2 patients were excluded due to technical error with
(attrition bias)		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	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "were randomly allocated".
(selection bias)		Comment: unclear, as a similar trial by these investigators also
		did not elaborate on their method of randomization

·		
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: unclear, as one similar trial by these investigators
		also did not include a statement on their allocation
		concealment.
Blinding of participants and	Low risk	Quote: "ideal values and accepe-Table ranges were
personnel (performance bias)		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	Low risk	Not stated. Probably not done.
assessment (detection bias)		Comment: Low risk for mortality.
Incomplete outcome data (attrition bias)	High risk	This trial excluded patients who not responded to therapy.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "randomized consecutively to one of two treatment
(selection bias)		strategies".
		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Allocation concealment	Unclear risk	Quote: "randomized consecutively to one of two treatment
(selection bias)		strategies".
		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	Unclear risk	Not stated.
assessment (detection bias)		
Incomplete outcome data	Low risk	All included patients completed the study and none seemed to
(attrition bias)		be lost to follow-up.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "Subjects were randomized into two groups".
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Allocation concealment	Unclear risk	Quote: "Subjects were randomized into two groups".
(selection bias)		Comment: no details on allocation method described and no
		previous trials from the same researchers are available for
		additional information.
Blinding of participants and	High risk	No statement on blinding.
personnel (performance bias)		Comment: probably not blinded.
Blinding of outcome	High risk	No statement on blinding.
assessment (detection bias)		Comment: probably not blinded
Incomplete outcome data	Low risk	Quote: "Forty-two of the 50 patients enrolled completed the
(attrition bias)		study".
		Comment: Reasons for exclusion of the 8 patients (< 10%) are
		well described.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "received dopamine or noradrenaline randomly".
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		
Incomplete outcome data	Low risk	All included patients completed the study and none seemed to
(attrition bias)		be lost to follow-up.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Quote: "randomly divided into two groups".
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Allocation concealment	Unclear risk	Not described.
(selection bias)		Comment: insufficient information and no previous trials from
		the same researchers are available for additional information.
Blinding of participants and	High risk	Blinding not described, however dosing schemes of both
personnel (performance bias)		interventions differed.
		Comment: probably not blinded.
Blinding of outcome	High risk	Not stated. Probably not done.
assessment (detection bias)		Not stated. I robably not done.
Incomplete outcome data	Low risk	All included patients completed the study and none seemed to
(attrition bias)		be lost to follow-up.
Selective reporting (reporting	Unclear risk	The authors did not register the trial or prepublished the trial
bias)		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.

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