SUPPLEMENTS 1: search strategy and additional tables and figures

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

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Table of contents

Search strategy

Last search conducted at: 19 April 2018

PubMed (3007 hits)

("Dopamine"[Mesh] OR dopamine[tiab] OR dopamina[tiab] OR dopaminum[tiab] OR dophamine[tiab] OR dopastat[tiab] OR deoxyepinephrine [tiab] OR dynatra[tiab] OR intropin[tiab] OR hydroxytyramin[tiab] OR oxytyramin*[tiab] OR revivan[tiab] OR 3,4-dihydroxyphenyl*[tiab])*
AND
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AND
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Embase (4653 hits)
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AND
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OR
('intensive care' OR ICU OR 'critical care' OR 'critically ill' OR hospital* OR 'cardiac surgery' OR shock OR hemodynamic* OR haemodynamic* OR 'kidney injury' OR 'renal failure' OR 'renal insufficiency' OR mortality):ab,ti OR surg*:ti)*
AND
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comparison'/exp OR 'drug dose comparison'/exp OR (randomi OR randomly OR trial OR controls OR 'control group' OR 'clinical study' OR 'controlled study' OR cohort OR prospective OR observational):ab,ti OR (patients AND (compared OR comparison OR versus)):ab,ti OR (efficacy AND safety):ab,ti)*

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<u>*Cochrane central (1846 hits with filter: trials)*</u>

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AND

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NOT

(([mh animals] not [mh human]) OR (([mh Child] OR [mh Infant]) not [mh Adult]) OR (animal OR rat* OR mouse OR mice OR child* OR infant* OR pediatr* OR paediatr* OR neonat* OR newborn OR parkinson* OR schizo*):ti)*

<u>*ISI web of science (389 hits without PubMed database) (4652 with PubMed database)*</u>

TS=(dopamine OR dopamina OR dopaminum OR dophamine OR dopastat OR deoxyepinephrine OR dynatra OR intropin OR hydroxytyramin OR oxytyramin* OR revivan OR 3,4-dihydroxyphenyl*)*

AND

(TS=("critical care" OR "critical illness" OR "critically ill*" OR "intensive care" OR ICU OR "coronary care" OR surger* OR surgic*) OR TS=((coronary OR thoracic OR heart OR cardiac OR renal OR kidney) NEAR/10 acute) OR TS=(mortality OR shock OR h$emodynamic*) OR TS=((kidney OR renal) NEAR/10 (injur* OR failure OR function* OR dysfunction*)) OR TS=("heart failure" OR hospital*) OR TI=(surg*))*

AND

(TS=(random OR "clinical study" OR "controlled study" OR "clinical trial" OR "controlled trial" OR "control group*" OR "comparative study" OR cohort OR prospective OR observational OR "treatment outcome") OR TS=(patients AND (compared OR comparison OR versus)) OR TS=(efficacy AND safety) OR TI=trial*)*

NOT

TI=(child OR infant* OR p$ediatr* OR neonat* OR newborn* OR parkinson* OR schizo* OR animal* OR rat OR rats OR mouse OR mice)*

<u>*CINAHL (EBSCO) (907 hits)*</u>

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AND

((MH "Critical Care+" OR MH "Emergency Care+" OR MH "Acute Disease" OR MH "Critical Illness" OR MH "Emergency Patients" OR MH "Critically Ill Patients" OR MH "Surgical Patients" OR MH "Mortality" OR MH "Heart Diseases+/SU" OR MH "Intensive Care Units+" OR MH "Critical Care Nursing+" OR MH "Shock+" OR MH "Hemodynamics+" OR MH "Kidney Failure, Acute+" OR "critical care " OR "critical illness " OR "critically ill " OR "coronary care " OR "heart surg OR "thoracic surg* " OR "cardiac surg* " OR mortality OR shock OR hemodynamic* OR haemodynamic* OR "kidney injury " OR "renal failure " OR "renal dysfunction" OR "renal funcion* OR "OR hospital*) OR TI surg*)*

AND

((MH "Clinical Trials+") OR (random N3 trial*) OR (random* N3 stud*) OR "randomized controlled " OR "randomised controlled" OR "treatment outcome" OR "drug evaluation" OR "drug therapy" OR "clinical study" OR "comparative study" OR cohort OR prospective OR observational OR (patients AND (compared OR comparison OR versus)) OR (efficacy AND safety)) OR TI trial*)*

NOT

(TI (child OR infant* OR pediatr* OR paediatr* OR neonat* OR newborn* OR parkinson* OR schizo* OR animal* OR rat OR rats Or mouse OR mice))*

Table S1: In- and exclusion criteria of trials included in the meta-analysis

Trial, year	Inclusion criteria	Exclusion criteria
Acute heart failure		
Kamiya [1] 2015	▪ NYHA class III–IV	▪ Age <20 years or >85 years ▪ Systolic blood pressure <90 mmHg ▪ Severe liver injury (ASAT/ALAT >100 IU/L) ▪ Severe renal failure (creatinine >2.0 mg/dL) ▪ Acute myocardial infarction within 3 months
Chen [4] 2013	▪ Age ≥18 years ▪ Prior clinical diagnosis of HF ▪ Enrolled <24 hours of hospital admission ▪ Anticipated hospitalization of ≥72 hours ▪ At least one symptom (dyspnoea, orthopnoea, or oedema) and one sign (rales on auscultation, peripheral oedema, ascites, pulmonary vascular congestion on chest radiography ▪ Estimated GFR >15 but <60 mL/min/1.73 m^2 ▪ Ability to have a PICC or central line placed <12 hours of randomization and study drug infusion started	▪ Received or anticipated need for IV vasoactive treatment or ultrafiltration therapy for HF ▪ Systolic blood pressure <90 mmHg ▪ Haemoglobin <9 g/dL (<5.6 mmol/L) ▪ Renal replacement therapy ▪ History of renal artery stenosis >50% ▪ Haemodynamically significant arrhythmias <4 weeks ▪ Acute coronary syndrome <4 weeks ▪ HF secondary to: active myocarditis, hypertrophic obstructive cardiomyopathy, greater than moderate stenotic valvular disease, restrictive or constrictive cardiomyopathy, complex congenital heart disease, constrictive pericarditis ▪ Non-cardiac pulmonary oedema ▪ Clinical evidence of digoxin toxicity ▪ Need for mechanical hemodynamic support ▪ Sepsis ▪ Terminal illness with expected survival of <1 year ▪ Pregnancy or nursing mothers ▪ Anticipated need for IV contrast use
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 ▪ Chemical markers of renal impairment: urea nitrogen ≥25 mg/dL and creatinine ≥1.5 mg/dL.	▪ Systolic blood pressure <100 mmHg ▪ Oliguria ▪ Serum creatinine >2.9 mg/dL ▪ Serum potassium <3.0 mmol/dL ▪ Haematocrit <30%
Shah [2] 2014	▪ Age ≥18 years ▪ HF and on daily use of oral loop diuretic > 1 month ▪ Enrolled <24h of hospital admission ▪ At least one symptom (dyspnoea, orthopnoea, or oedema) and one sign (rales on auscultation, peripheral oedema, ascites) or pulmonary vascular congestion on chest radiography ▪ Anticipated need for IV loop diuretics for ≥48 h	▪ Systolic blood pressure <90 mmHg ▪ Serum creatinine >3.0 mg/dL or renal replacement therapy ▪ Anticipated need for IV contrast use
Arutiunov [6] 2010	▪ Age >18 years ▪ Decompensated congestive HF with an ischemic origin ▪ Sinus rhythm or persistent tachycardia at rest ▪ Pulmonary artery wedge pressure >20 mmHg ▪ Cardiac index <2.6 L/min/m^2 ▪ *LVEF <35%* ▪ Systolic blood pressure >85 mmHg ▪ Serum creatinine <200 µmol/L	▪ Systolic blood pressure <85 mmHg) ▪ Creatinine >200 µmol/L, GFR <30 ml/min ▪ Acute coronary syndrome <2 months ▪ Rheumatic valvular heart disease ▪ Chronic obstructive pulmonary disease ▪ Obstructive or restrictive cardiomyopathy ▪ Mobitz II or III atrioventricular blockade without pacemaker ▪ Arrhythmia or atrial flutter ▪ Heart rate <40 beats/minute ▪ Pregnancy or period of breastfeeding ▪ Acute cerebrovascular accident <6 months ▪ Regular intake of β-blockers
Hsueh [7] 1998	▪ HF of NYHA class III or IV; ▪ Previously untreated HF or had stopped medications by personal decision for >2 weeks ▪ *LVEF ≤45%*	▪ Active myocarditis ▪ Thyroid disease ▪ Severe hypertension ▪ Atrial flutter-fibrillation ▪ High-degree atrioventricular block ▪ Pacemaker therapy ▪ Chronic obstructive lung disease ▪ Severe hepatic or renal disease

		▪ Diabetes mellitus
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%
Giamouzis [5] 2010	▪ Age >18 years ▪ History of HF ▪ Oxygen saturation <90% on admission ▪ Deterioration of HF symptoms <6 hours: dyspnoea at rest, orthopnoea, and paroxysmal nocturnal dyspnoea, accompanied by signs of congestion (3rd heart sound, jugular venous distension, pulmonary rales) ▪ B-type natriuretic peptide >400 pg/mL or NT-proBNP >1500 pg/mL	▪ Acute de novo HF ▪ Systolic blood pressure <90 mmHg ▪ Severe renal failure (admission creatinine >215 mmol/L or estimated GFR >30 mL/min/1.73 m^2 ▪ Severe valvular disease ▪ HF secondary to congenital heart disease ▪ Scheduled cardiac surgery <2 months ▪ Anticipated need for IV contrast use
Triposkiadis [3] 2014	▪ Age >18 years ▪ History of HF ▪ Dyspnoea on minimal exertion or rest dyspnoea and oxygen saturation <90% on admission ▪ At least one or more: signs of congestion (3rd heart sound or pulmonary rales >⅓ or lower extremity/ sacral oedema >1+), interstitial congestion or pleural effusion on chest radiography, and B-type natriuretic peptide >400 pg/mL or NT-proBNP >1500 pg/mL	▪ Creatinine >200 µmol/L or GFR >30 mL/min/1.73 m^2 ▪ Systolic blood pressure <90 mmHg ▪ Severe valvular disease ▪ HF secondary to complex congenital heart disease ▪ Suspected or confirmed acute coronary syndrome ▪ Scheduled cardiac surgery <6 months ▪ Anticipated need for IV contrast use
Sindone [8] 1998	▪ HF of NYHA class IV	▪ Not described (abstract only)
Cardiac surgery		
Sirivella [14] 2000	▪ Manifested with either acute oliguric or anuric renal failure in the postoperative period ▪ Adequate cardiac output and tissue perfusion	▪ Acute renal failure associated with inadequate cardiac output and tissue perfusion ▪ Preoperative renal replacement therapy
Costa [12] 1990	▪ Cardiac surgery requiring cardiopulmonary bypass ▪ Preoperative renal dysfunction: creatinine clearance ≤50 mL/min	▪ Usage of enflurane ▪ Usage of diuretics
Bove [13] 2005	▪ Age >18 years ▪ Continuous Improvement in Cardiac Surgery Program (CICSP) score >10	▪ Emergent procedure ▪ Pre-operative renal replacement therapy ▪ Glaucoma
Rosseel [15] 1997	▪ Elective CABG ▪ *Low cardiac output syndrome*, defined as a CI <2.2 L/min/m^2 in the absence of hypovolaemia (central venous pressure ≥8 mmHg and/or pulmonary capillary wedge pressure ≥12 mmHg and/or diastolic pulmonary artery pressure ≥12 mm Hg)	▪ Age >75 years ▪ Preoperative renal dysfunction (serum creatinine > 200 mmol/L) ▪ Liver dysfunction (g-GT >20% above normal) ▪ Pheochromocytoma ▪ With monoamine oxidase inhibitors ▪ Pregnancy
Hausen [17] 1992	▪ Age >18 years ▪ Mitral valve operation ▪ Mitral valve disease ▪ CI <2.5 L/min/m^2 pre-operatively at rest	▪ Revascularization procedures ▪ Aortic valve operations
Oppizzi [11] 1997	▪ Severe left ventricular dysfunction (*LVEF <35%*) ▪ Requiring CABG	▪ The need for an associated intervention during cardiac surgery
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

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.

Table S2: Risk and odds ratios with TSA-adjusted confidence intervals (CI) for all outcomes, stratified by intervention

	Main meta-analysis: **>50% patients had cardiac dysfunction**			**Sensitivity analysis:** **Only patients with cardiac dysfunction**			**Post-hoc meta-analysis:** **>25% patients had cardiac dysfunction**		
	Trials	*Patients*	*RR or OR (95% CI)**	*Trials*	*Patients*	*RR or OR (95% CI)**	*Trials*	*Patients*	*RR or OR (95% & TSA-adjusted CI)**
Mortality									
Placebo or control	5	452	0.93 (0.63 to 1.38)	1	20	-	15	954	0.89 (0.62 to 1.28)
Potentially active control	12	586	0.90 (0.14 to 5.84)	6	252	0.94 (0.35 to 2.54)	28	3017	1.08 (1.00 to 1.17) ; (0.95 to 1.23)
Any comparator	15	1038	0.92 (0.68 to 1.23)	7	272	0.94 (0.35 to 2.54)	36	3971	1.07 (0.99 to 1.16) ; (0.95 to 1.20)
Serious adverse events									
Placebo or control	2	324	1.48 (0.82 to 2.67)	0	0	-	4	473	1.44 (0.90 to 2.29)
Potentially active control	5	258	1.12 (0.84 to 1.50)	2	96	1.45 (0.43 to 4.90)	8	388	1.55 (0.94 to 2.54)
Any comparator	6	582	1.18 (0.91 to 1.53)	2	96	1.45 (0.43 to 4.90)	11	861	1.44 (1.03 to 2.00)
Myocardial infarction									
Placebo or control	1	83	2.00 (0.06 to 62.15)	0	0	-	4	240	2.01 (0.12 to 32.78)
Potentially active control	5	256	1.21 (0.35 to 4.20)	3	137	1.68 (0.15 to 18.75)	10	2062	0.80 (0.46 to 1.37)
Any comparator	5	339	1.32 (0.42 to 4.09)	3	137	1.68 (0.15 to 18.75)	11	2302	0.82 (0.48 to 1.40)
Ventricular tachyarrhythmias									
Placebo or control	3	329	3.49 (0.71 to 17.11)	1	20	-	6	463	3.52 (0.72 to 17.20)
Potentially active control	6	209	1.94 (0.40 to 9.32)	3	66	0.76 (0.11 to 5.08)	10	1953	1.89 (1.10 to 3.24)
Any comparator	8	538	2.59 (0.85 to 7.91)	4	86	0.76 (0.11 to 5.08)	14	2416	2.15 (1.32 to 3.50)
Renal replacement therapy									
Placebo or control	2	113	1.00 (0.03 to 29.03)	0	0	-	9	493	0.46 (0.05 to 4.61)
Potentially active control	3	258	0.42 (0.05 to 3.58)	0	0	-	9	2230	0.56 (0.17 to 1.87)
Any comparator	4	371	0.40 (0.06 to 2.85)	0	0	-	15	2723	0.54 (0.23 to 1.27)
Atrial tachyarrhythmias									
Placebo or control	2	103	1.00 (0.03 to 29.04)	1	20	-	5	237	0.67 (0.41 to 1.10)[#]
Potentially active control	1	78	1.81 (0.06 to 50.77)	0	0	-	3	1757	1.87 (1.48 to 2.36)[#] ; (0.72 to 4.87)
Any comparator	2	181	1.68 (0.10 to 27.22)	1	20	-	6	2009	1.00 (0.47 to 2.13)

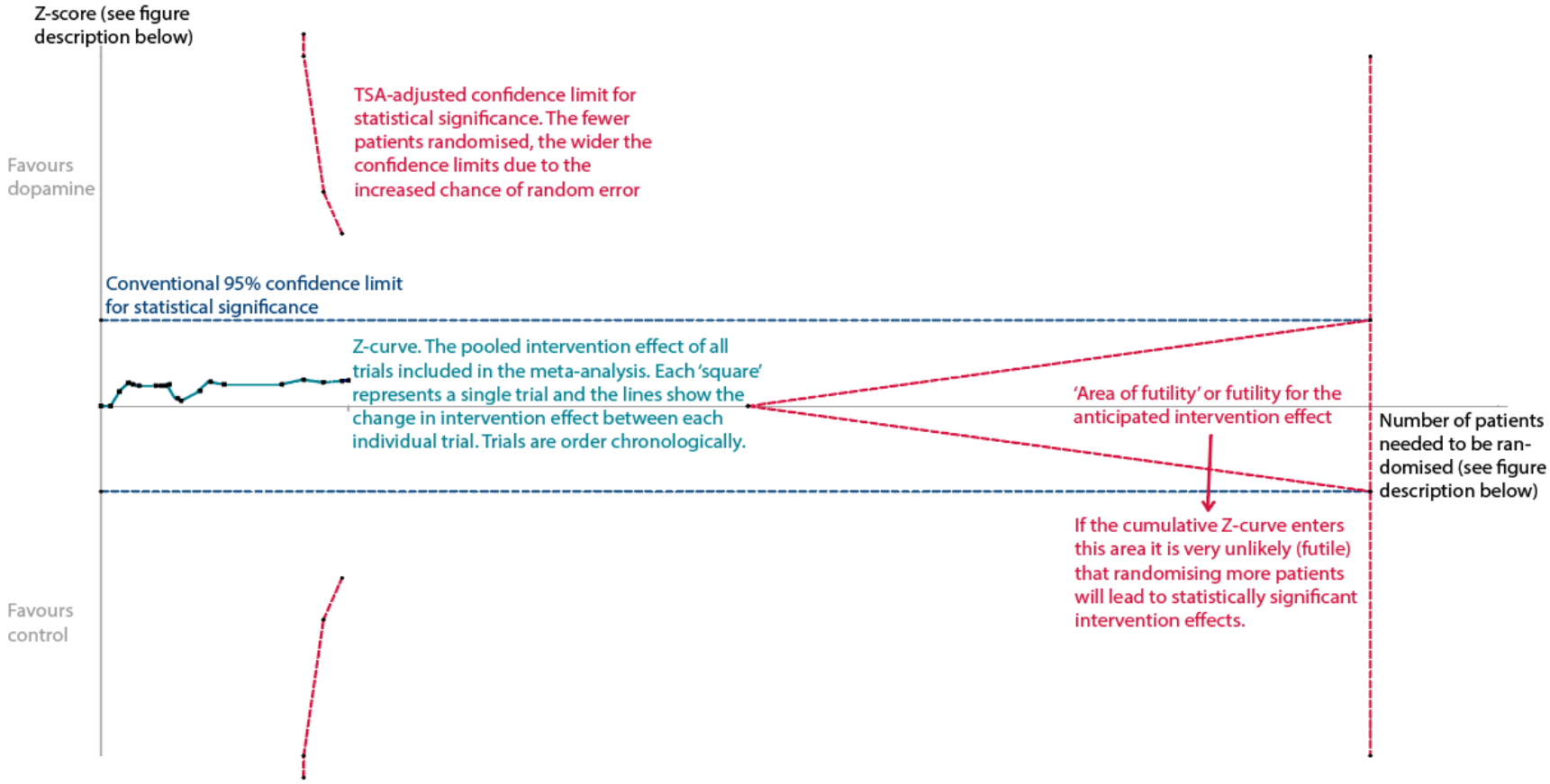
*We only displayed TSA-adjusted CIs if the diversity adjusted required information size was more than 5% with a relative risk reduction of 10%, α of 5%, and β of 10%. [#]There was a significant test of interaction between placebo or inactive control and potentially active control (P = 0.001). Abbreviations: RR, relative risk; OR, odds ratio; CI, confidence interval; TSA, trial-sequential analysis.

Table S3. Reported harms in observational studies

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

Abbreviations: CI, confidence interval.

Figure S1: Explanation on how to interpret the Trial Sequential Analysis



The y-axis displays the cumulative Z-score, which indicates the number of standard deviations the Z-curve is from the mean (in this case: relative risk of 1.0). A standard deviation or Z-score of 1.96 from the mean corresponds to an α of 0.05. The x-axis displays the number of patients that need to be randomised before a definite conclusion can be made. The calculation of this number is comparable to a sample size calculation for a randomised clinical trial. The TSA graph displays whether there is sufficient evidence to reach a conclusion: this occurs when the cumulative Z-score crosses the TSA-adjusted confidence limits or enters the futility area (i.e. one of the red-dashed lines).

Figure S2: Trial Sequential Analysis of serious adverse events

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

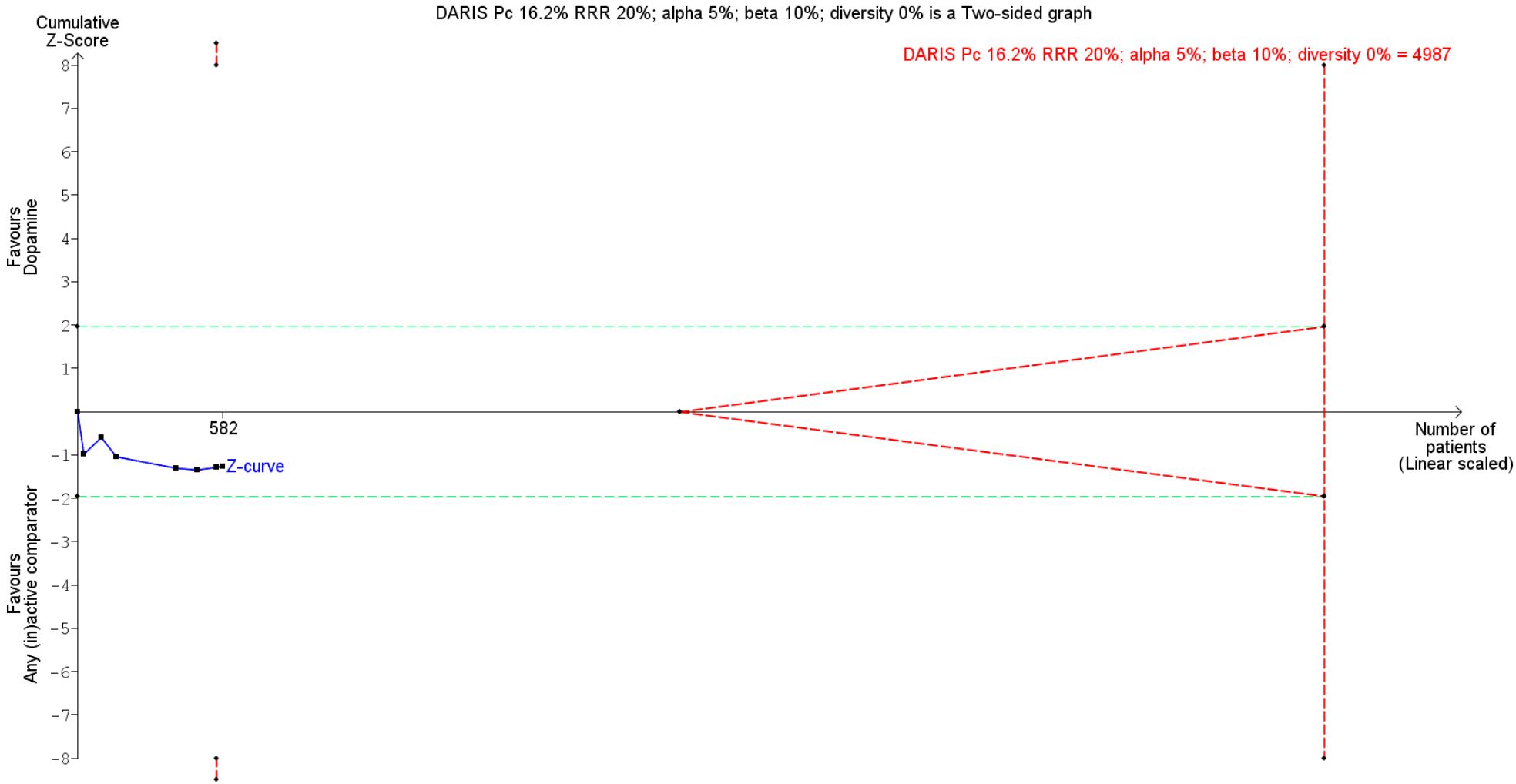


Figure S3: Forest plot of all-cause mortality in the post-hoc meta-analysis

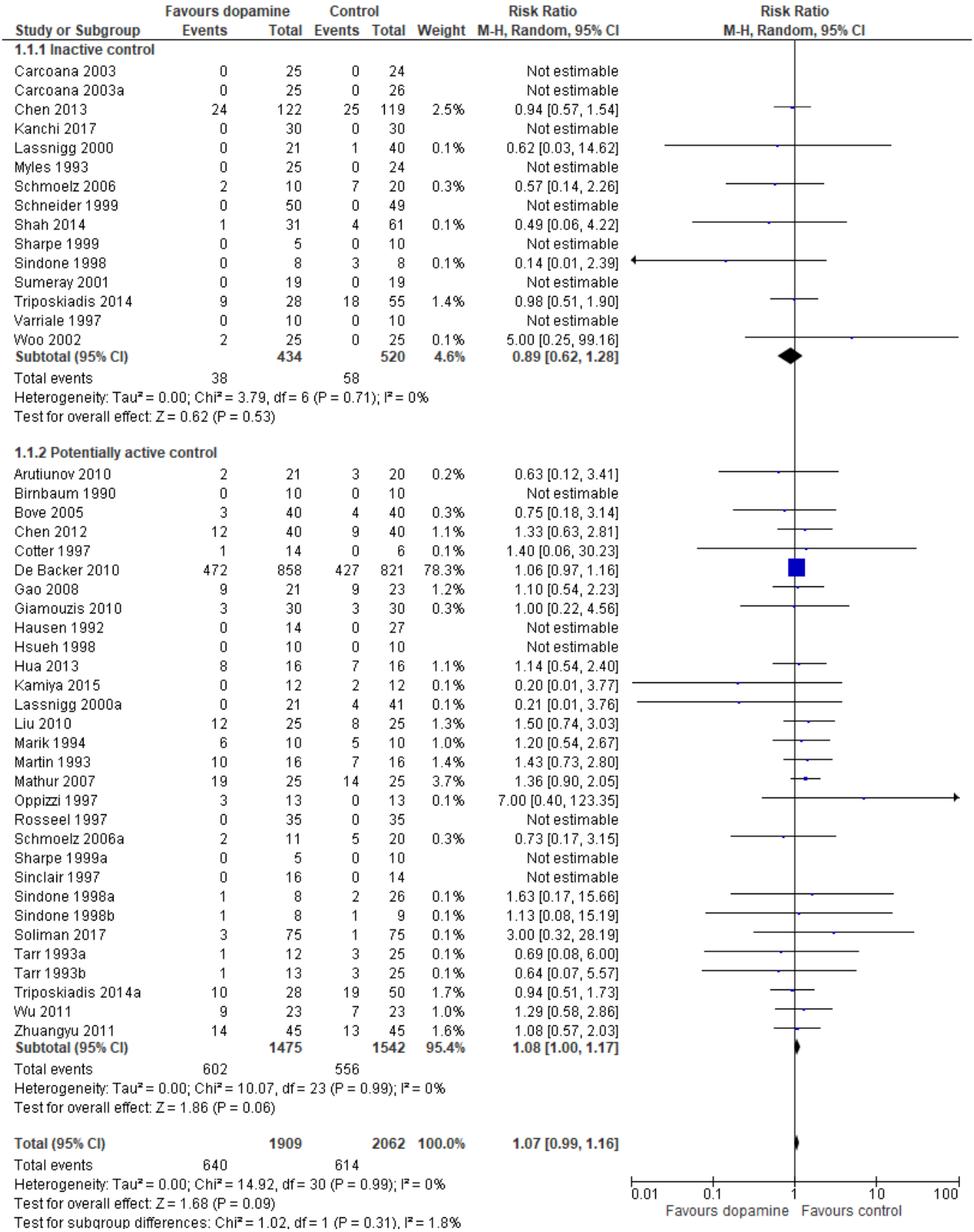


Figure S4: Trial Sequential Analysis for all-cause mortality in the post-hoc meta-analysis

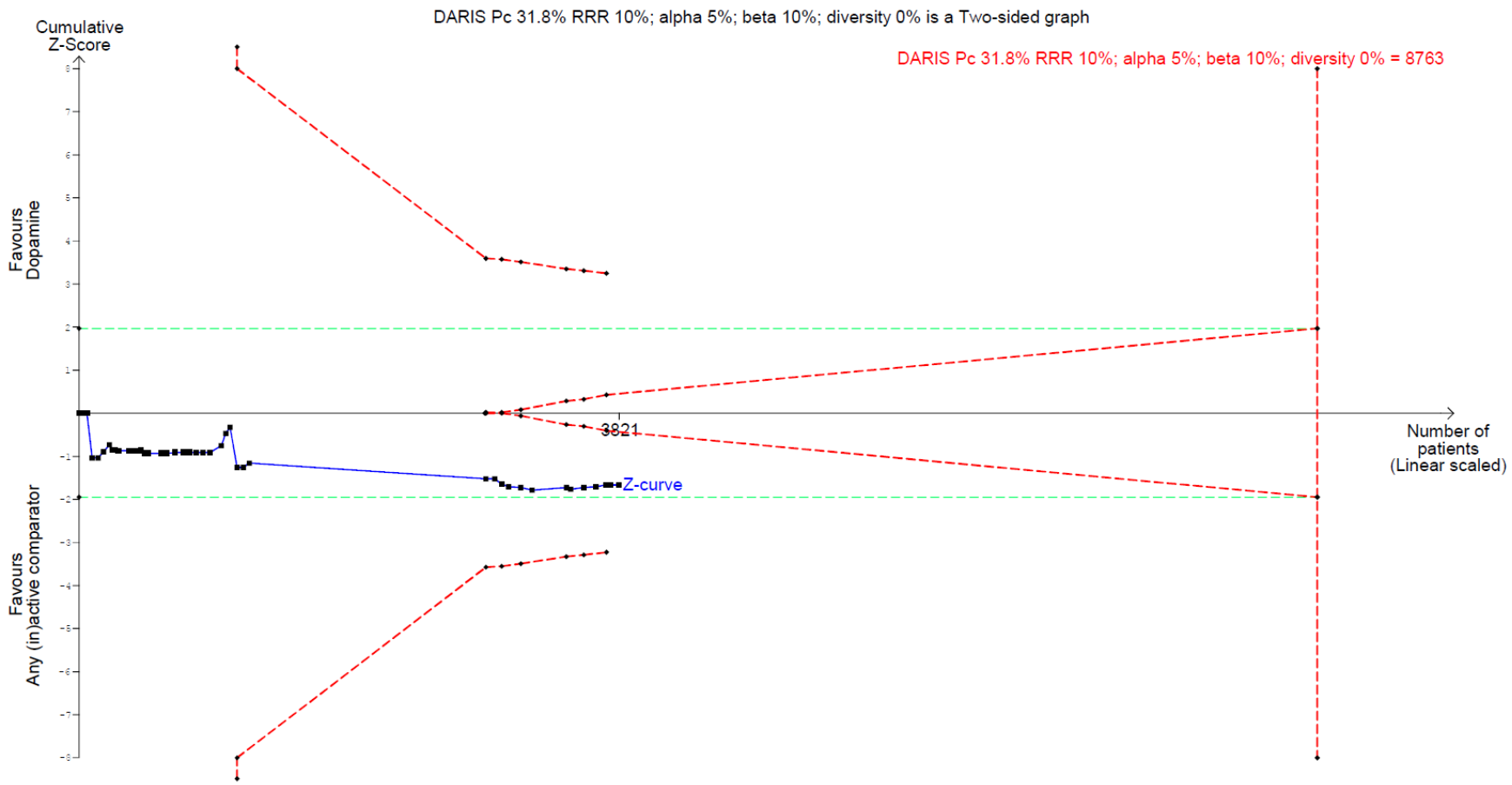


Figure legend. A diversity-adjusted required information size (RIS) of 8,763 patients was calculated using the predefined α = 0.05 (two-sided), β = 0.10 (power 90%), D^2 = 0%, an anticipated relative risk reduction of 10% and an event proportion of 31.8% in the control arm. The *blue cumulative z-curve*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

Figure S5a: Manhattan matrix plot with beneficial outcomes

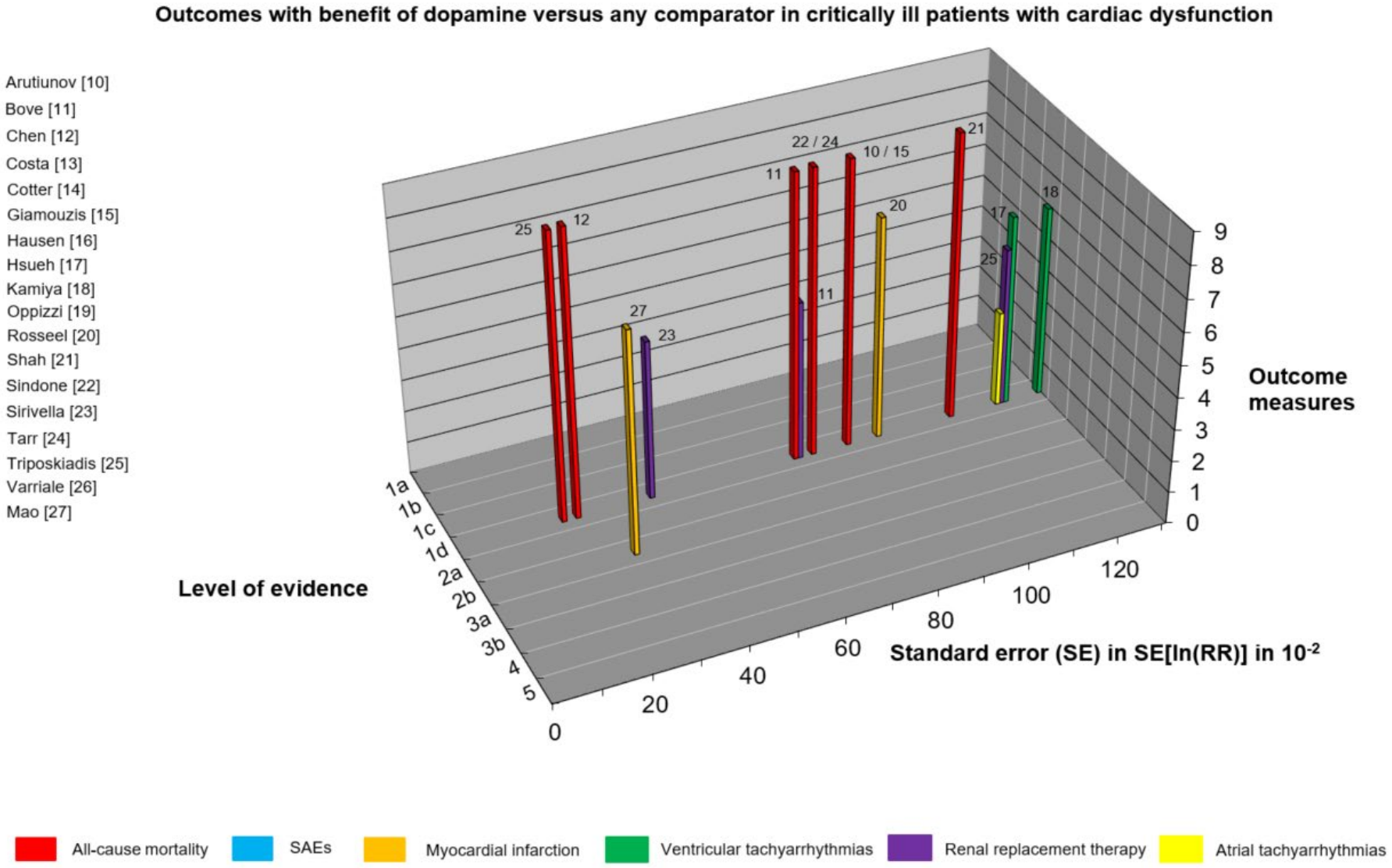


Figure S5b: Manhattan matrix plot with harmful outcomes

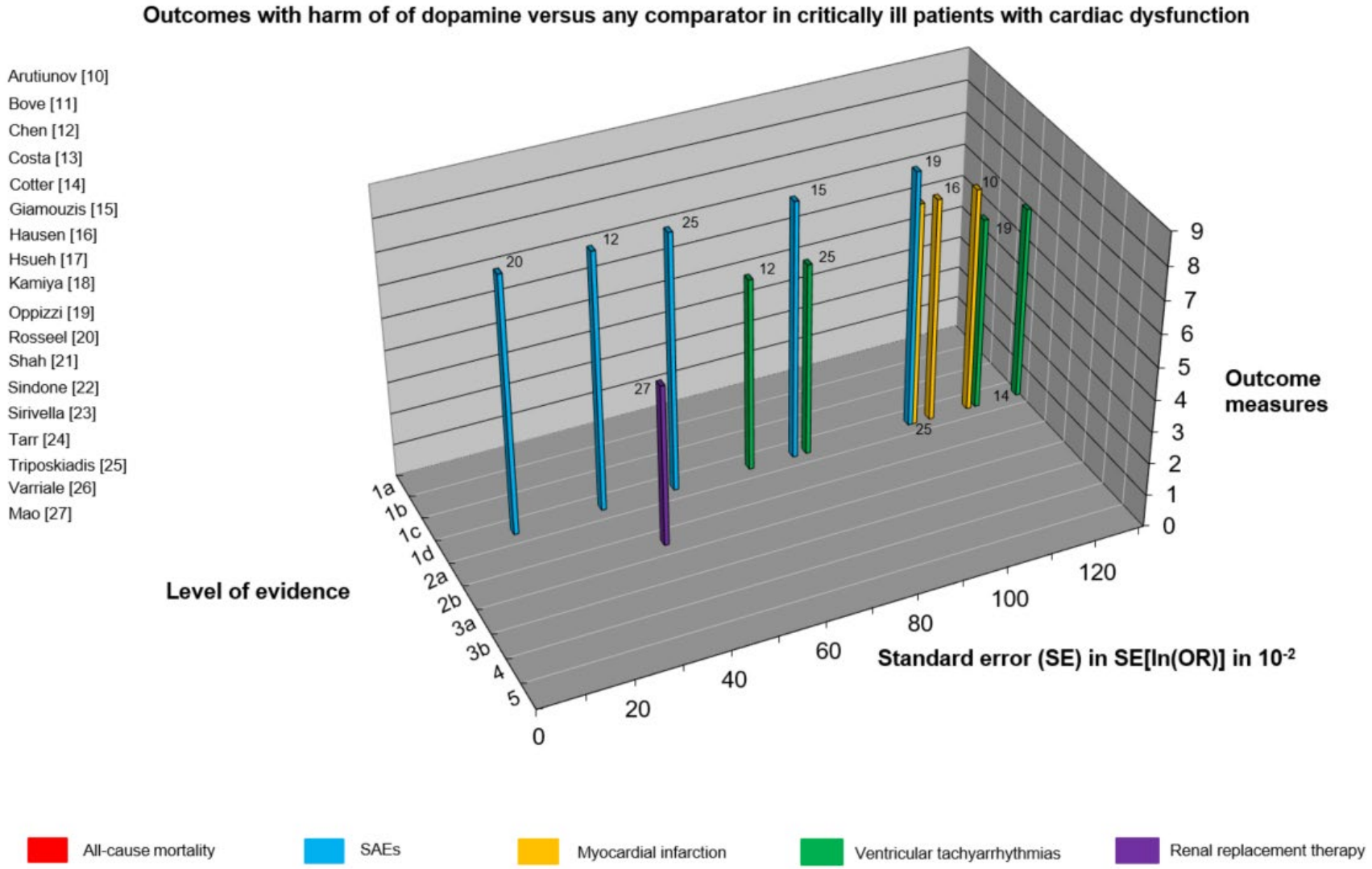


Figure S6: Funnel plots for small trial bias including publication bias

Figure S6a: Mortality at maximum follow-up

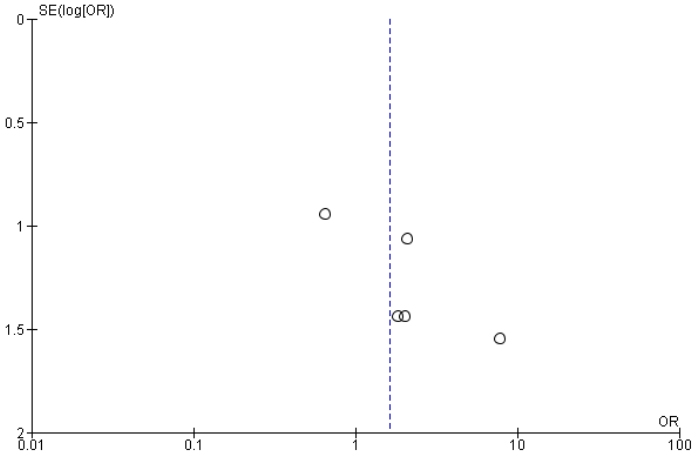


Figure S6b: Serious adverse events

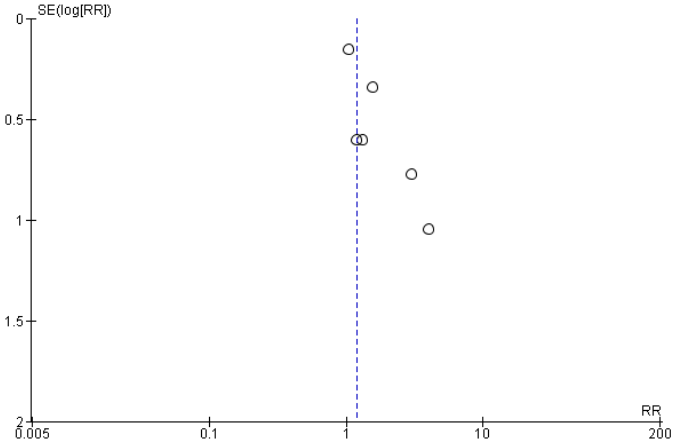


Figure S6c: Myocardial infarction

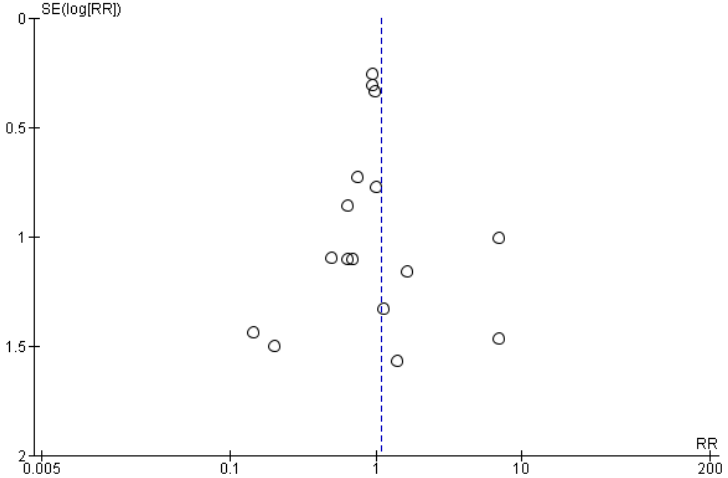


Figure S6d: ventricular tachyarrhythmias

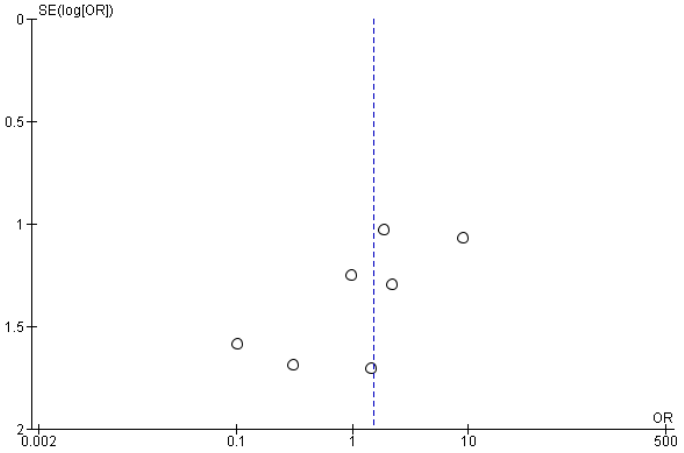


Figure S6e: Renal replacement therapy

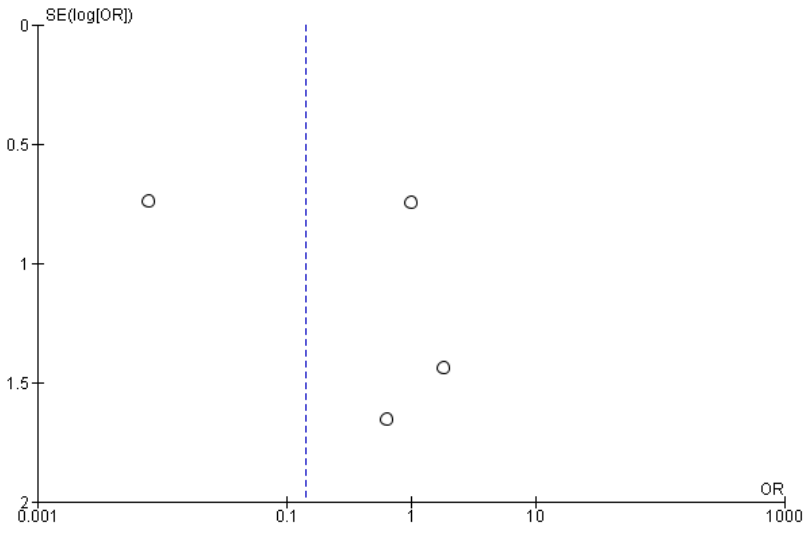
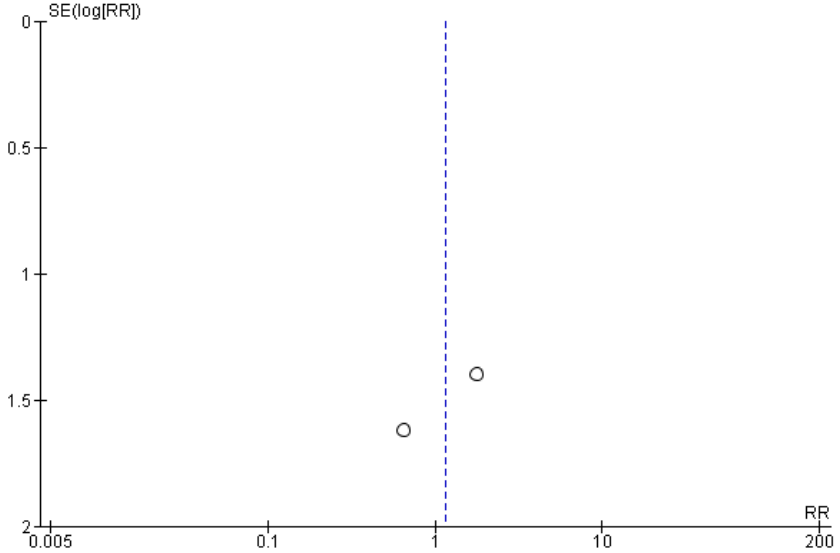


Figure S6f: atrial tachyarrhythmias



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