SUPPLEMENTARY MATERIAL

Levosimendan in patients with cardiogenic shock complicating myocardial infarction: a meta-analysis

Fang Mingxing, MD; Cao Hui, MD; Wang Zhiyong.

SUMMARY:

- Full PubMed search strategy
- Major exclusions and reasons for exclusions; Supplemental references
- Study quality and risk of bias
- Study flow diagram
- Funnel plot of mortality
- Forest plot of mortality
- Forest plot of mortality in randomized rontrolled trial
- Forest plot of mortality in non-randomized control trial
- Forest plot of Sequential Organ Failure Assessment score (SOFA)
- Forest plot of Cardiac Index (CI)
- Forest plot of Heart Rate (HR)
- Forest plot of Cardiac Powder Index (CPI)
- Forest plot of Ejection Fraction (EF)
- Forest plot of End-Systolic Volume (ESV)
- Funnel plot of Mean Blood Pressure (MBP)
- Forest plot of Pulmonary Atrial Pressure (PAP)
- Funnel plot of mixed venous oxygen saturation ($ScVO_2$)
- Forest plot of Pulmonary artery occlusion Pressure (PAOP)
- Forest plot of ICU days
- Forest plot of glomerular filtration rate (GFR)

Full PubMed, Embase, search strategy

(Levosimendan [Mesh]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR controlled trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR “case control”[tw] OR match*[tw] OR “case series”[tw] OR OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]))) NOT (animal[mh] NOT human[mh])

Major exclusions and reasons for exclusions

Thirty trials were excluded because of:

- 18 Not Randomized Controlled Trials [1–18]
- 6 Case report [19-24]
- 3 Study design problems [25-27]
- 3 duplicate publication [28-30]

Supplemental references: all excluded trials

1. Summaria F, Mustilli M, Sette A, etc. Early ‘ in-lab’ use of levosimendan in patients with cariogenic shock unsuitable for intra-aortic balloon pump couterpulsation. Ther Adv Cardiovasc 2014 Feb;8(1):28-31
2. Taccone FS, Brasseur A, Vincent JL,etc. Levosimendan for the treatment of subarachnoid hemorrhage-related cardiogenic shock. Intenisve Care Med 2013 Aug;39(8):1497-8
3. Liu Y, Liu B, Zhou H, etc. Continuous levosimendan infusion for refractory cardiogenic shock complicating severe acute dichlorvos poisioning. Am J Med Sci 2012 Aug;344(2):166-70
4. Rass MA, Prondzinsky R, Carter JM, etc. Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. Crit Care Med 2009 Dec;37(12):3017-23
5. Grief M, Zwermann L, Reithmann C, etc. Levosimendan as rescue therapy in severe cardiogenic shock after ST-elevation myocardial infarction. Acute Card Care 2008;10(3):185-90
6. Russ MA, Prondzinsky R, Christoph A, etc. Hemodynamic improvement following levosimendan treatment in patients with acute myocardial infarction and cardiogenic shock. Crit Care Med 2007; 35(12):2732-9
7. Dominguez-Rodriguez A, Samimi-Fard S, Garica-Gonzalez MJ, etc. Effects of levosimendan versus dobutamine on left ventricular diastolic function in patients with cardiogenic shock after primary angioplasty. Int J Cardiol 2008;128(2):214-7
8. Rokyta R Jr, Pechman V. The effects of Levosimendan on global haemodynamics in patients with cardiogenic shock. Neuro Endocrinol Lett 2006;27(1-2):121-7
9. Delle Karth G, Buberl A, Geppert A, etc. Hemodynamic effects of a continuous infusion of levosimendan in critically ill patients with cardiogenic shock requiring catecholamines. Acta Anaesthesiol Scand 2003;47(10):1251-6
10. Antonini M, Stazi GV, Cirasa MT, etc. Efficacy of levosimendan in Takotsubo-related cardiogenic shock. Acta Anaesthesiol Scand 2010;54(1): 119-20
11. Lehmann A, Lang J, Boldt J, etc. Levosimendan in patients with cardiogenic shock undergoing surgical revascularization: a case series. Med Sci Monit 2004; 10(8):MT 89-93
12. Alhashemi JA. Treatment of cardiogenic shock with levosimendan in combination with beta-adrenergic antagonists. Br J Anaesth 2005; 95(5):648-50
13. Tsagalou EP, Kanakakis J, Anastasiou-Nana MI, etc. Hemodynamic effects of levosimendan in acute myocardial infarction complicated by cardiogenic shock and high systemic vascular resistance. Acute Card Care 2009; 11(2): 99-106

14. Carcia-Gonzalez MJ, Dominguez-Rodriguez A, Ferrer-Hita JJ, etc. Cardiogenic shock after primary percutaneous coronary intervention: Effects of levosimendan compared with dobutamine on haemodynaics. Eur J Heart Fail 2006; 8(7): 723-8
15. Zobel C, Reuter H, Schwinger RH. Treatment of cardiogenic shock with the Ca^{2+} sensitizer levosimendan. Med Klin(Munich) 2004; 99(12): 742-6
16. Marco Grazi, Gianfranco Lauri, Corrado Carbucicchio, etc. Use of Levosimendan for Treatment of Cardiogenic Shock Associated with Electrical Storm. Ann Intern Med 2009; 150(10): 738-740
17. Vincenzo De Santis, Domenico Vitale, Luigi Tritapepe, etc. Use of Levosimendan for Cardiogenic Shock in a Patient with the Apical Ballooning Syndrome. Ann Intern Med 2008; 149(5): 365-367
18. Garcia-Gonzalez MJ, Dominguez-Rodriguez A, Ferrer-Hita JJ. Utility of levosimendan, a new calcium sensitizing agent, in the treatment of cardiogenic shock due to myocardial stunning in patients with ST-elevation myocardial infarction: a series of cases. J Clin Pharmacol 2005; 45(6): 704-8
19. Taha A, Shafie A, Mostafa M,etc. Assessment of levosimendan as a therapeutic option to recruit the microcirculation in cardiogenic shock-initial experience in cardiac ICU. Critical Care 2016 20 SUPPL.2
20. Poli M, Trambaiolo P, Basso V, etc. Dobutamine versus levosimendan in weaning of difficult-to-wean ventilator dependent patients with cardiogenic shock complicated by respiratory failure after stemi. Giornale Italiano di Cardiologia 201415:4 SUPPLE.2
21. Marzorati C, Erba L, Cortinovis B, etc. Levosimendan infusion during ECMO weaning: Effect on endothelial function and haemodynamics. Applied Cardiopulmonary Pathophysiology 2013 17:2(170-171)
22. Husebye T, Eritsland J, Arnesen H, etc. Levosimendan improves regional contractility in patients with acutely revasvularised infarction complicated by decompensated heart failure. European Journal Heart Failure, Supplement 2012 11 SUPPL.1(S238-)
23. Russ M.A, Prondzinsky R, Carter J.M,etc. Right ventricular function in myocardial infaction complicated by cardiogenic shock: Improvement with levosimendan. Critical Care Medicine 2009 37; 12(3017-3023)
24. JA Alhashemi, Q Alotaibi. Effects of levosimendan in acute heart failure and cariogenic and septic shock. Crit Care 2008;12(Suppl 2): P267
25. Lehmann A, Kiessling A.H, Isgro F, etc. Levosimendan in patients with acute myocardial ischaemia undergoing emergency surgical revascularization. European Journal of Anaesthesiology 2008 25:3(224-229)
26. Garcia-Gonzalez M.J., Dominguez-Rodriguez A, Ferrer-Hita J.J, etc. Cardiogenic shock after primary percutaneous coronary intervention: Effects of levosimendan compared with dobutamine on haemodynamics. European Journal of Heart Failure 2006 8:7(723-728)
27. Mclean AS, Nalos M, Huang S.J, etc. The use of levosimendan in shocked patients with compromised left ventricular function and requiring catecholamine support- A case series. Critical Care and Shock 2005 8:1(6-13)
28. I Labbene, M Bel hadj Amor, S Dhahri, etc. Hemodynamic and echographic effects of levosimendan in patients with cardiogenic shock refractory to catecholamines. Critical Care 2006 10（Suppl 1）:P358
29. Grant CA, Price J, Jeanrenaud P, etc. A randomized controlled trial of levosimendan versus enoximone in cardiogenic shock-a pilot study Intensive care medicine 2008; 34(Suppl 1), S252
30. Buerke M, Prondzinsky R. Levosimendan in cardiogenic shock: better than enoximone. Crit Care Med 2008; 36(8):2450-1

1. Affronti A, di Bella I, Carino D, etc. Levosimendan may improve weaning outcomes in venoarterial ECMO patients. ASAIO J 2013 Nov-Dec;59(6):554-7
2. Omerovic E, Ramunddal T, Albertsson P, etc. Levosimendan neither improves nor worsens mortality in patients with cardiogenic shock due to ST-elevation myocardial infarction. Vasc Health Risk Manag 2010 Sep;7(6):657-63
3. Husebye T, Eritsland J, Muller C, etc. Levosimendan in acute heart failure following primary percutaneous coronary intervention treated acute ST-elevation myocardial infarction. Results from the LEAF trial: a randomized,placebo-controlled study. European Journal of Heart Failure 2013;15:565-572
4. Fuhrmann JT, Schmeisser A, Schulze MR, etc. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. Crit Care Med 2008; 36(8):2257-66
5. Christoph A, Prondzinsky R, Russ M, etc. Early and sustained haemodynamic improvement with levosimendan compared to intraaortic balloon counterpulsation (IABP) in cardiogenic shock complicating acute myocardial infarction. Acute Cardiac Care 2008;10:49-57
6. Samimi-Fard S, Garcia-Gonzalez MJ, Dominguez-Rodriguez A, etc. Effects of levsimendan versus dobutamine on long-term survival of patients with cardiogenic shock after primary coronary angioplasty. Int J Cardiol 2008; 127(2): 284-7
7. P Soos, D Becker, G Barczi, etc. Levosimendan therapy does not improve survival of post-resuscitation cardiogenic shock patients. Critical Care 2009 13(Suppl 1):P172
8. Poli M, Trambaiolo P, Mustili M, etc. Mixed venous oxygen saturation. its role in the assessment of patients developing after ST-elevation myocardial infarction (STEMI). Giornale Italiano di Cardiologia 2011 12:5 SUPPL.1(39S-40S)
9. Caetano F, Almeida I, Silva J,etc. Cardiogenic shock in acute myocardial infarction: Still looking for the best inotrope. European Heart Journal: Acute Cardiovascular Care 2012 1 SUPPL.1(28-29)
10. Igor Katsytadze, Ekaterina Amosova, Igor Prudkyi, etc. Long term effects of levosimendan therapy in patients with cardiogenic shock. Resuscitation 84S(2013)S11
11. Massimo Mancone, Mauro Pennachhi, Luigi Lucisano, etc. Hemodynamic improvement following levosimendan treatment in acute myocardial infraction complicated by cardiogenic shock patients treated with primary PCI and IABP. JACC 2013; Volume 61, Issue 10
12. Li Peng, Li Rui, Zhou Yongguang, etc. Levosimendan for Treating Acute Myocardial Infarction Complicated by Cardiogenic Shock in 54 Cases. Drug Rearch 2015;9(5):46-47
13. 罗毅， 刘路培，杨振宇等。左西孟旦对急性心肌梗死并发心源性休克患者的疗效。实用医学杂志 2013；第 29 卷 19 期：3229-3230

Study quality and risk of bias

Assess of risk of bias for RCT

Study	Bias	Author's judgement	Support for judgement
2008 Fuhrmann	Random sequence generation	Low	Randomised controlled trial
High risk of bias	Allocation concealment	Unclear	Not stated
	Blinding of participants and personnel	High	Open-label trial
	Blinding of outcome assessment	High	Open-label trial
	Incomplete outcome data	Low	Trial data is completed
	Selective reporting	Low	Apparently free of selecting reporting
	Other bias	High	Sample size not stated
2008Samimi-Fard	Random sequence generation	Low	Randomised controlled trial
High risk of bias	Allocation concealment	Unclear	Not stated
	Blinding of participants and personnel	High	Open-label trial
	Blinding of outcome assessment	High	Open-Label trial
	Incomplete outcome data	Low	Trial data is completed
	Selective reporting	Low	Apparently free of selecting reporting
	Other bias	Unclear	Insufficient information to assess whether a important risk of bias exists.
2013 Husebye	Random sequence generation	Low	randomised controlled trial
Low risk of bias	Allocation concealment	Low	randomised controlled trial
	Blinding of participants and personnel	Low	Double Blind
	Blinding of outcome assessment	Low	Double Blind
	Incomplete outcome data	Low	Data is completed
	Selective reporting	Low	Apparently free of selecting reporting
	Other bias	Low	Sample size not stated.
2013 Luo	Random sequence generation	Low	Randomized controlled trialtated
Unclear risk of bias	Allocation concealment	Unclear	Not stated
	Blinding of participants and personnel	Unclear	Not stated
	Blinding of outcome assessment	Unclear	Not stated
	Incomplete outcome data	Low	Data is completed
	Selective reporting	Unclear	Not stated
	Other bias	Unclear	Insufficient information to assess whether an important risk of bias
2015 Li	Random sequence generation	Low	Randomized controlled trialtated
Unclear risk of	Allocation concealment	Unclear	Not stated

bias

Blinding of participants and personnel	Unclear	Not stated
Blinding of outcome assessment	Unclear	Not stated
Incomplete outcome data	Low	Data is completed
Selective reporting	Low	Apparently free of selecting reporting
Other bias	Unclear	Insufficient information to assess whether an important risk of bias

Assess of risk of bias for nRCT

Study	Selection	Star Number
2008 Christoph 6 □	Is the Case Definition Adequate?	*
	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the Design or Analysis	* *
	EXPOSURE	
	Ascertainment of exposure	*
	Same method of ascertainment for cases and controls	*
	Non-Response rate	
Study	Selection	Star number
2008 Soos 5□	Is the Case Definition Adequate?	*
	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the Design or Analysis	* *

	EXPOSURE	
	Ascertainment of exposure	
	Same method of ascertainment for cases and controls	*
	Non-Response rate	
Study	Seleciton	Star number
2010	Is the Case Definition Adequate?	
Omerovic		
5□	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	* *
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	
	Same method of ascertainment for cases and controls	*
	Non-Response rate	
Study	Selection	Star number
2011 Poli	Is the Case Definition Adequate?	*
5□	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	*

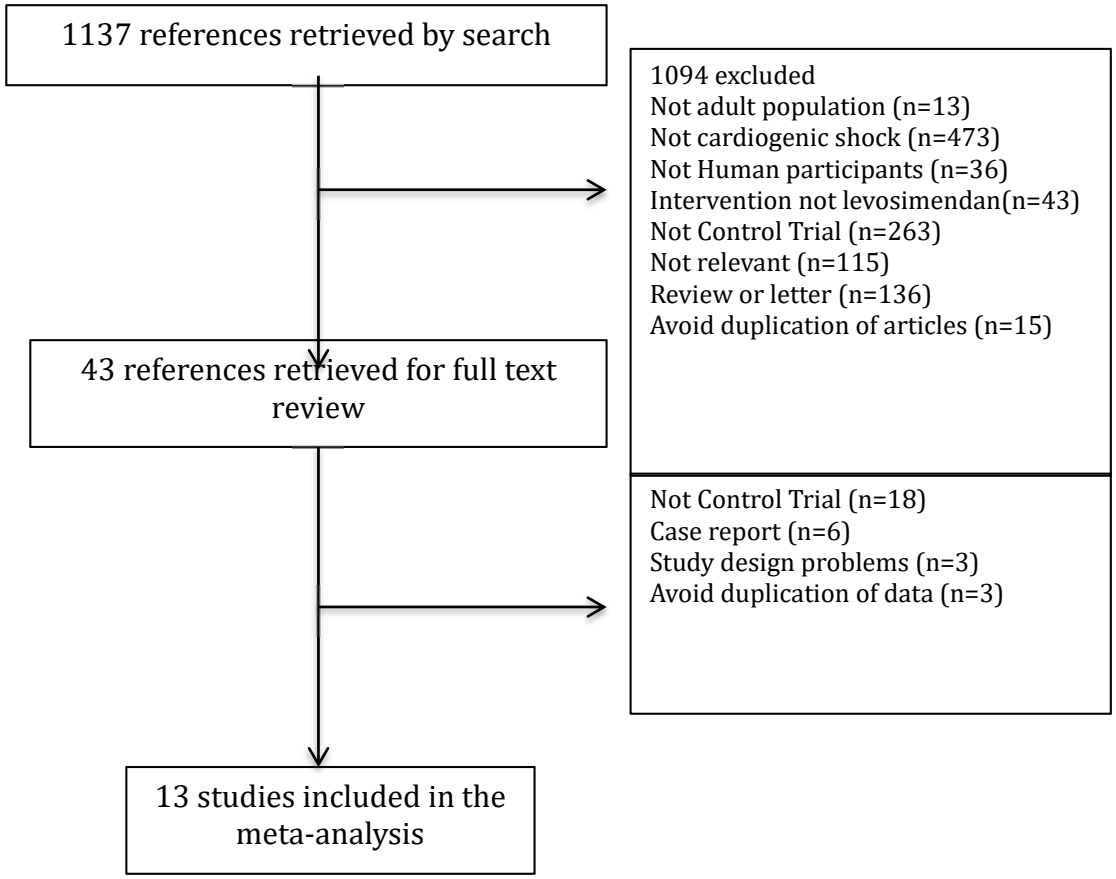
	Same method of ascertainment for cases and controls	*
	Non-Response rate	
Study	Selection	Star number
2012	Is the Case Definition Adequate?	
Caetano		
4□	Representativeness of the Case	*
	Selection of Controls	*
	Definition of Controls	
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	*
	Same method of ascertainment for cases and controls	*
	Non-Response rate	
Study	Selection	Star number
2013	Is the Case Definition Adequate?	*
Affronti		
7□	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	* *
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	*
	Same method of ascertainment for cases and controls	*

	Non-Response rate	
Study	Selection	Star number
2013	Is the Case Definition Adequate?	*
Katstadze		
6□	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	* *
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	*
	Same method of ascertainment for cases and controls	
	Non-Response rate	
Study	Selection	Star number
2013	Is the Case Definition Adequate?	*
Mancone		
5□	Representativeness of the Case	*
	Selection of Controls	
	Definition of Controls	*
	COMPARABILITY	
	Comparability of Cases and Controls on the Basis of the	
	Design or Analysis	
	EXPOSURE	
	Ascertainment of exposure	*
	Same method of ascertainment for cases and controls	*
	Non-Response rate	

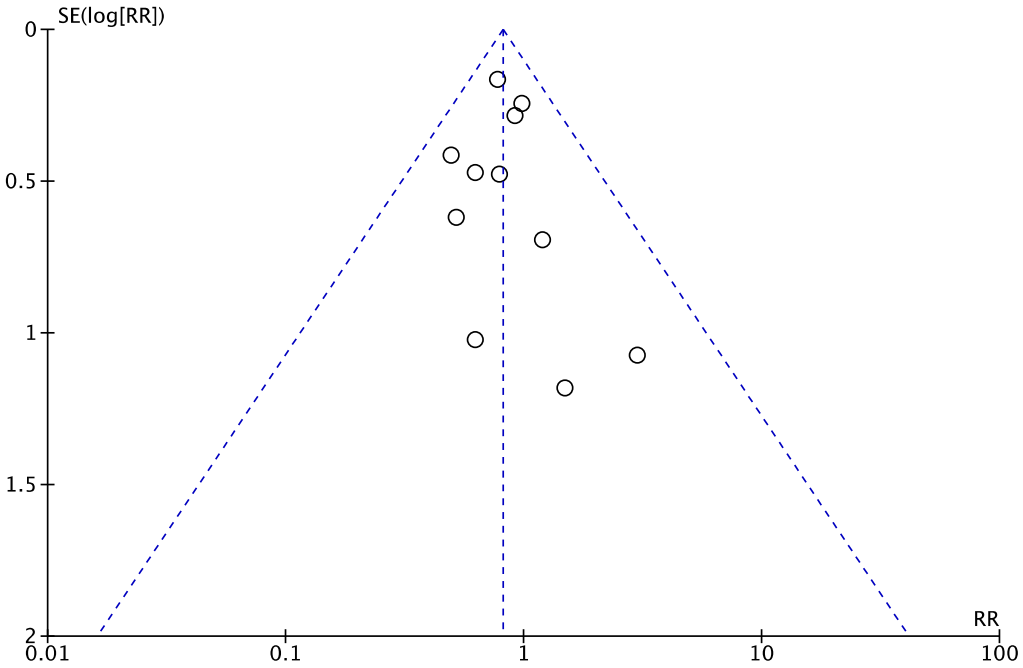
Follow-up for the mortality

Study	Follow-up
2008 Christoph	Hospital stay
2008 Joerg T	30d all-cause mortality
2008 Samimi-Fard	12-months cardiac death
2009 Soos	200-day mortality
2010 Omerovic	30-day mortality
2011 Poli	In-hospital mortality
2012 Caetano	In-hospital mortality
2013 Husebye	6-month mortality
2013 Affronti	In-hospital mortality
2013 Katsytadze	1-year mortality
2013 Mancone	1-month Cardiovascular mortality
2013 Luo	No metality
2015 Li	No metality

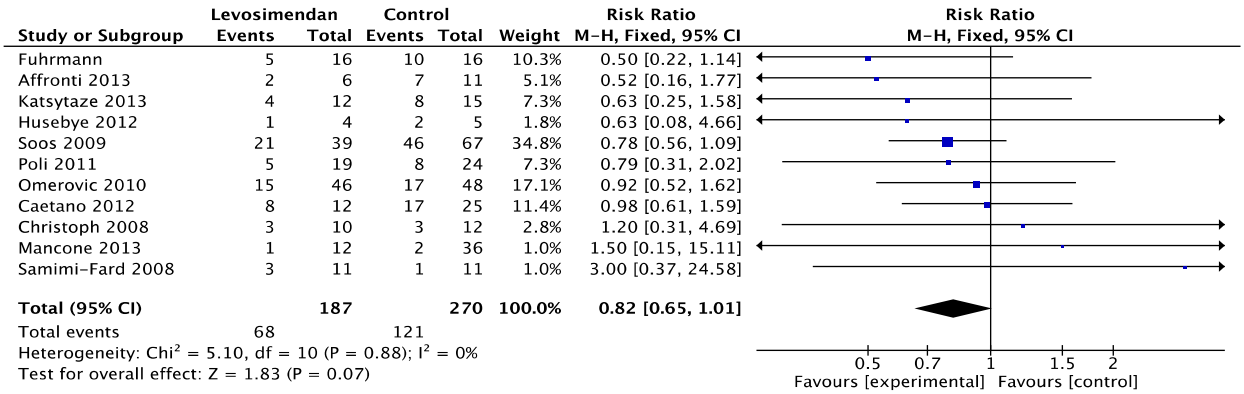
Study flow diagram



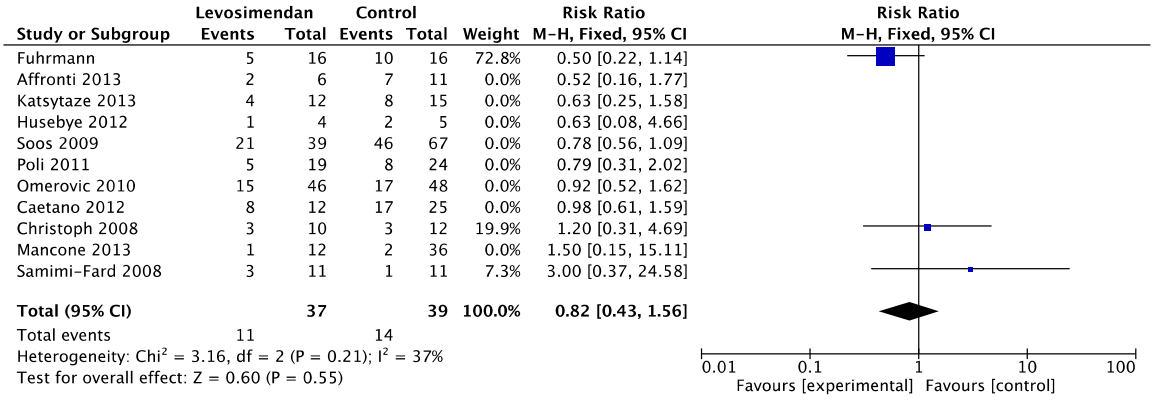
Funnel plot of mortality



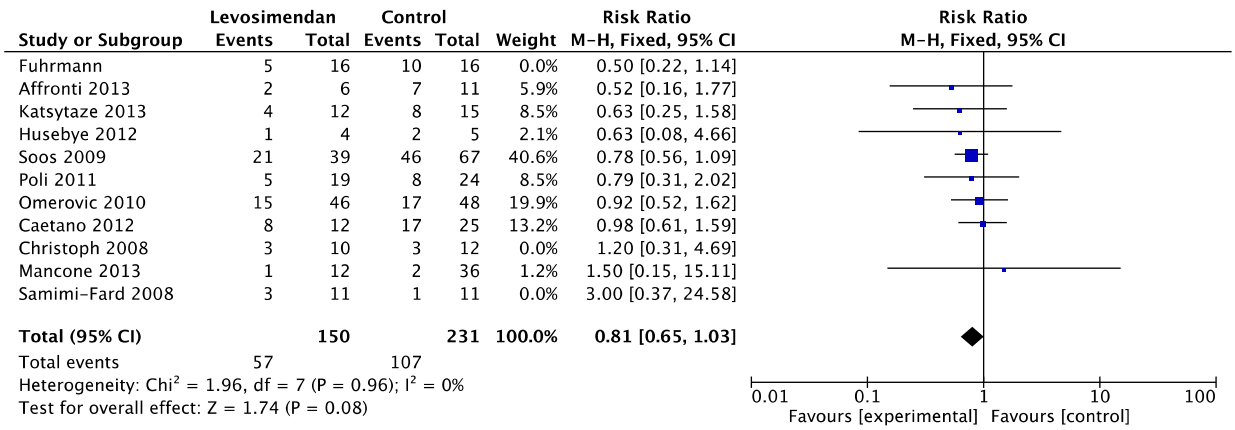
Forest Plot of Mortality



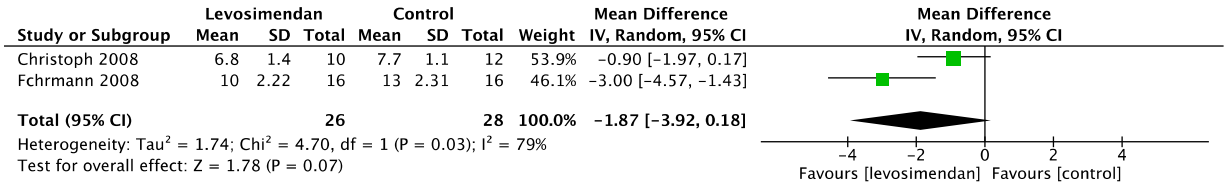
Forest plot of mortality in RCTs



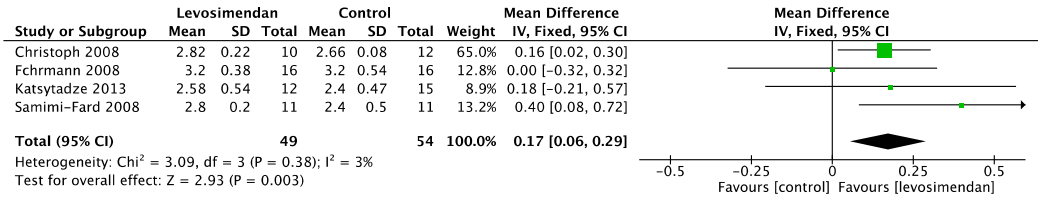
Forest plot of mortality in nRCTs



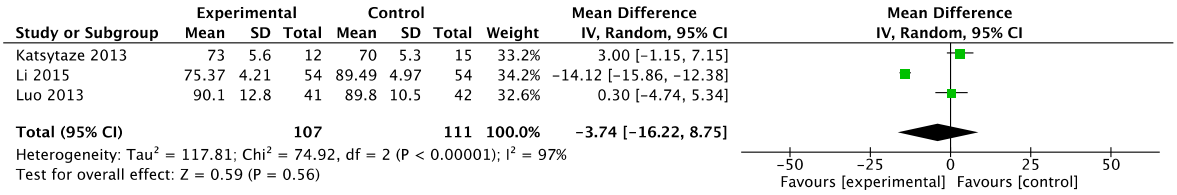
Forest plot of Sequential Organ Failure Assessment (SOFA) score



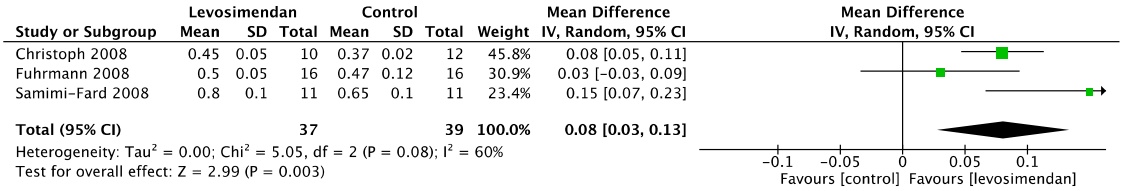
Forest plot of Cardiac Index (CI)



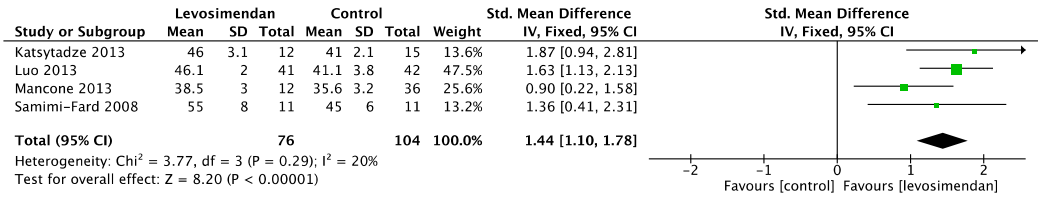
Forest plot of Heart Rate (HR)



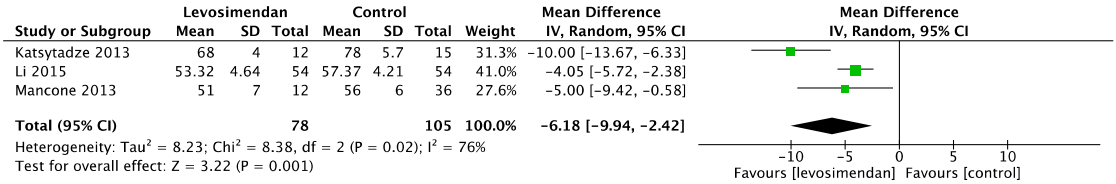
Forest plot of Cardiac Powder Index (CPI)



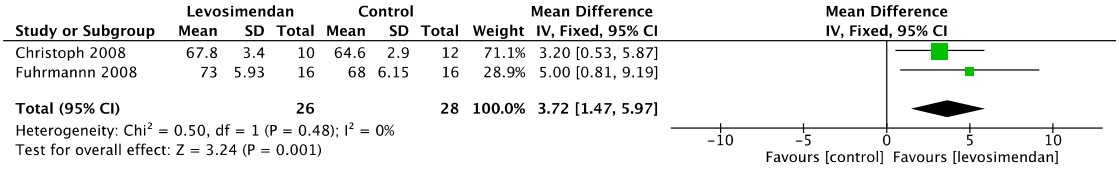
Forest plot of Ejection Fraction (EF)



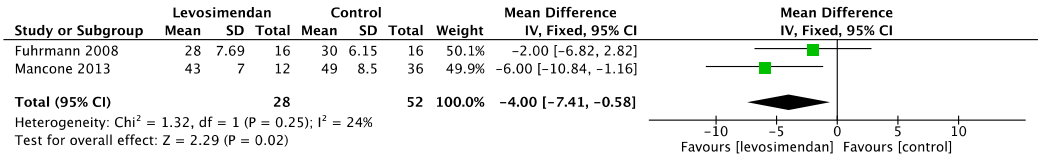
Forest plot of End-Systolic Volume (ESV)



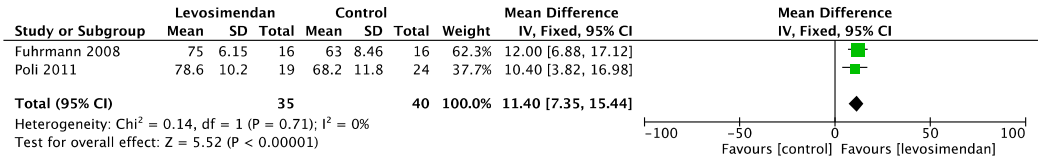
Forest plot of Mean Blood Pressure (MBP)



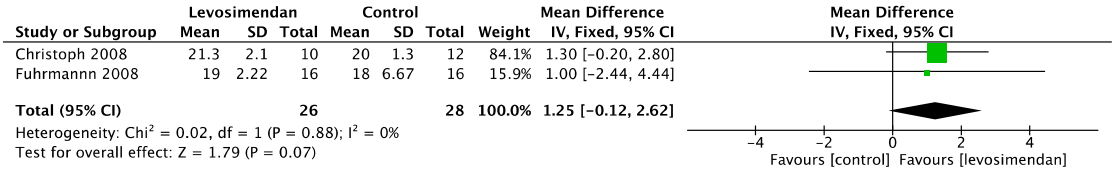
Forest plot of Pulmonary Atrial Pressure (PAP)



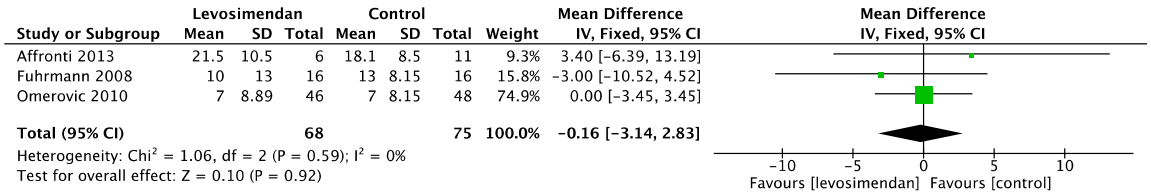
Forest plot of mixed venous oxygen saturation (ScvO2)



Forest plot of Pulmonary artery occlusion Pressure (PAOP)



Forest plot of ICU days



Forest plot of glomerular filtration rate(GFR)