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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)

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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])

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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

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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

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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	* *

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	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	*

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	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	*

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	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	

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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

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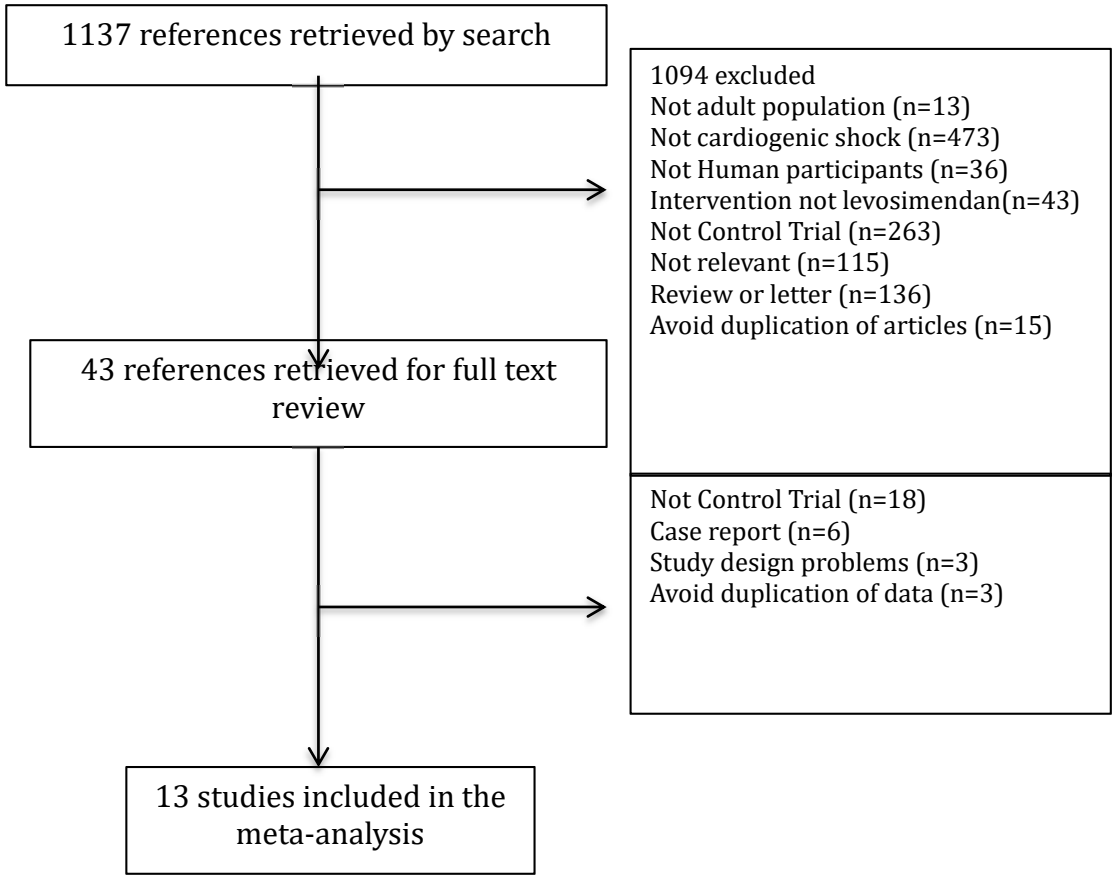
Study flow diagram



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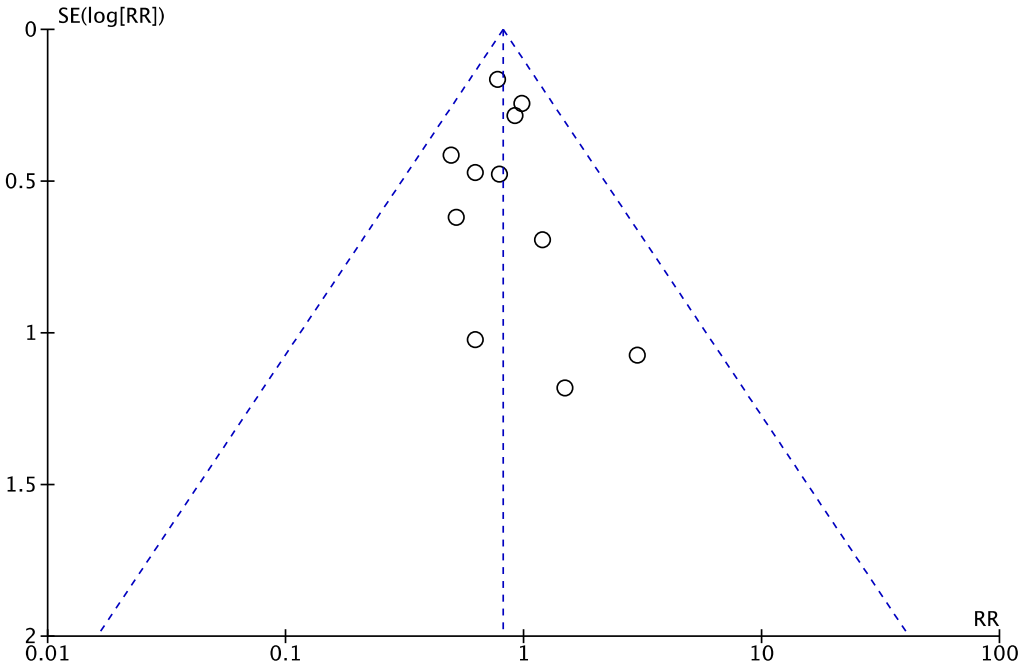
Funnel plot of mortality



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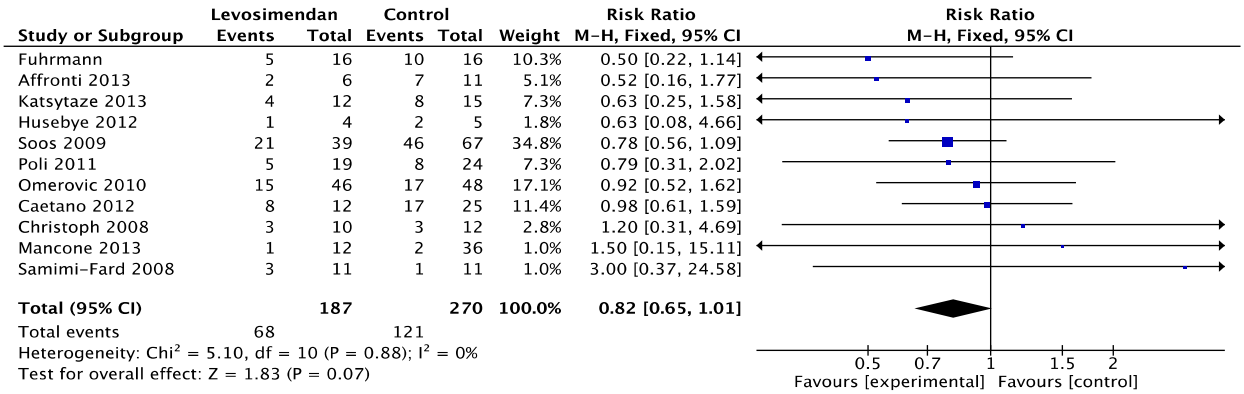
Forest Plot of Mortality



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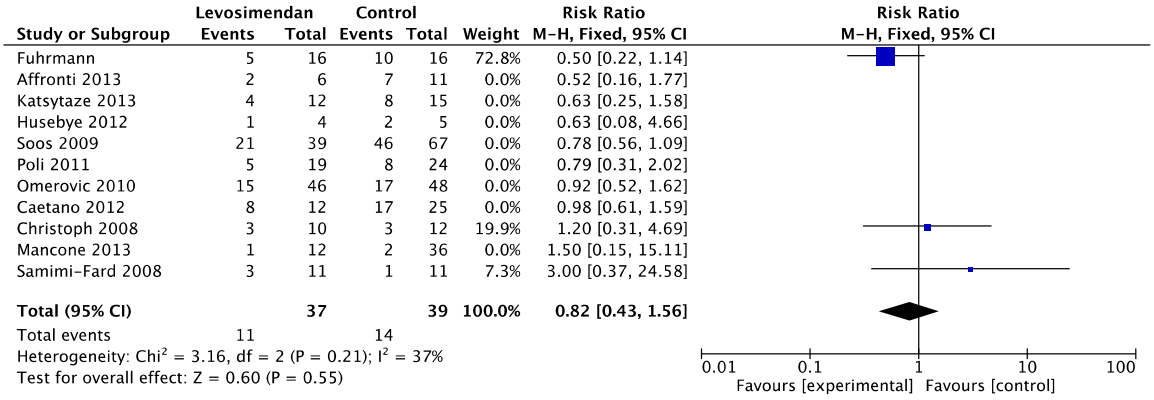
Forest plot of mortality in RCTs



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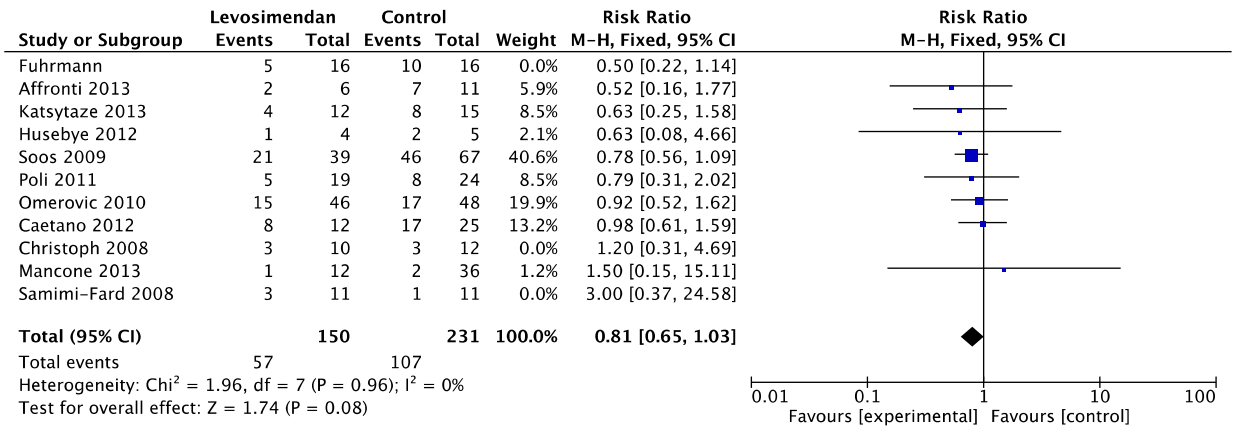
Forest plot of mortality in nRCTs



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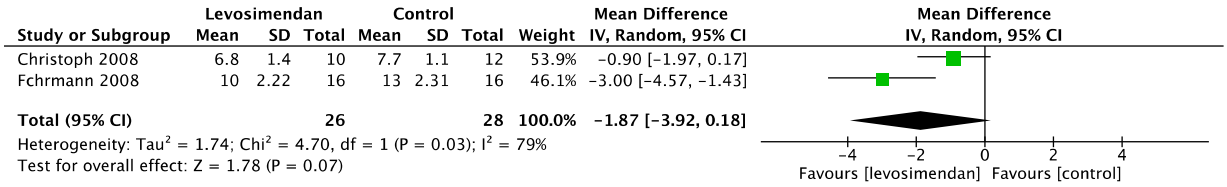
Forest plot of Sequential Organ Failure Assessment (SOFA) score



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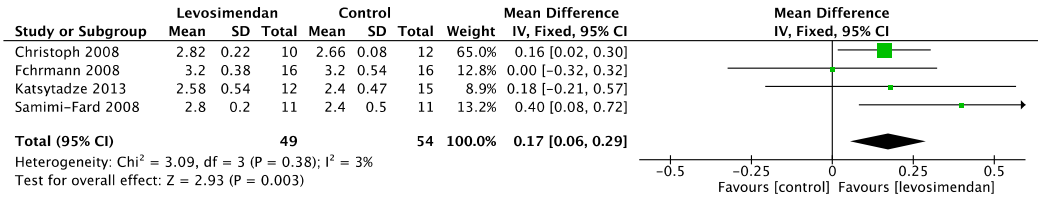
Forest plot of Cardiac Index (CI)



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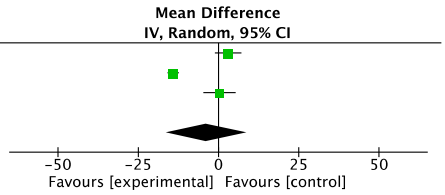
Forest plot of Heart Rate (HR)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Katsytaze 2013	73	5.6	12	70	5.3	15	33.2%	3.00 [-1.15, 7.15]
Li 2015	75.37	4.21	54	89.49	4.97	54	34.2%	-14.12 [-15.86, -12.38]
Luo 2013	90.1	12.8	41	89.8	10.5	42	32.6%	0.30 [-4.74, 5.34]
Total (95% CI)			**107**			**111**	**100.0%**	**-3.74 [-16.22, 8.75]**

Heterogeneity: $Tau^2 = 117.81$; $Chi^2 = 74.92$, df = 2 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 0.59 (P = 0.56)



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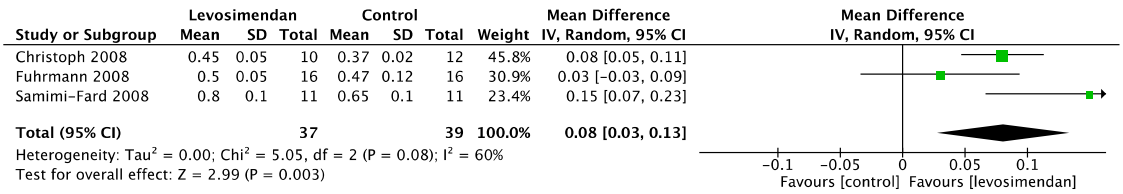
Forest plot of Cardiac Powder Index (CPI)



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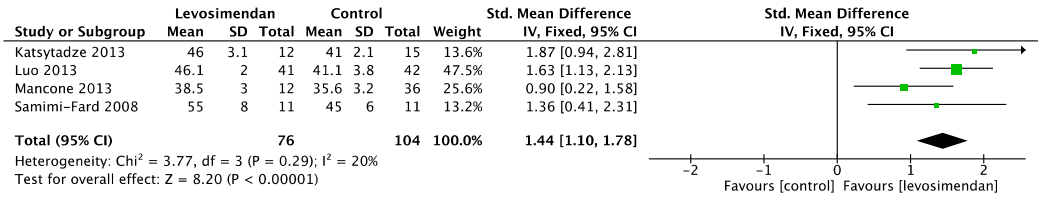
Forest plot of Ejection Fraction (EF)



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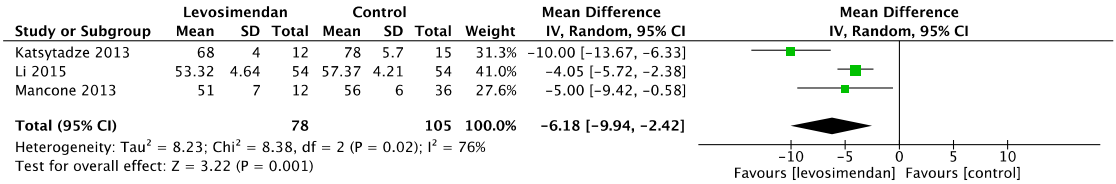
Forest plot of End-Systolic Volume (ESV)



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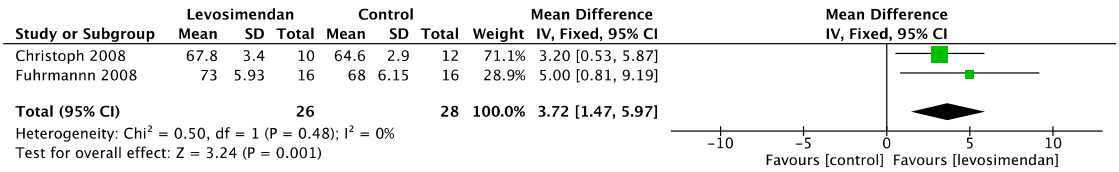
Forest plot of Mean Blood Pressure (MBP)



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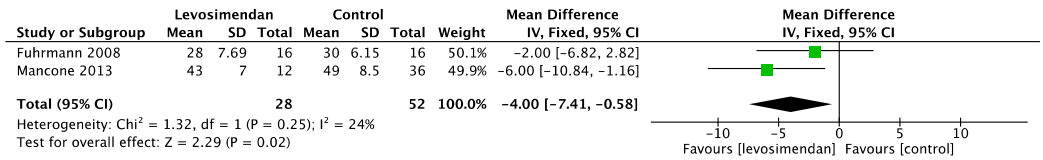
Forest plot of Pulmonary Atrial Pressure (PAP)



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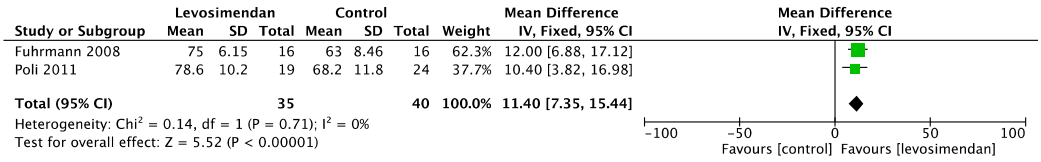
Forest plot of mixed venous oxygen saturation (ScvO2)



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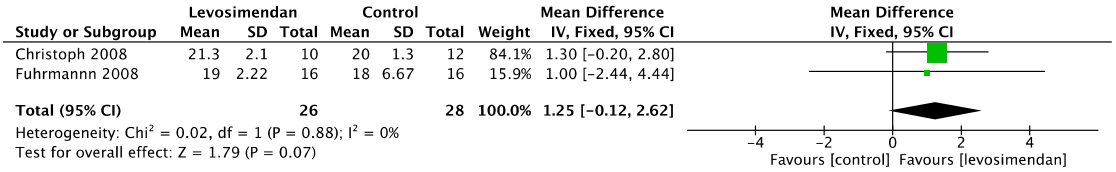
Forest plot of Pulmonary artery occlusion Pressure (PAOP)



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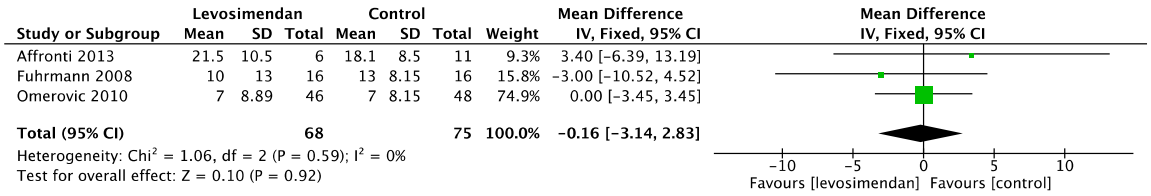
Forest plot of ICU days



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Forest plot of glomerular filtration rate(GFR)