

SUPPLEMENTARY

The efficacy and safety of sarcomeric contractile activators in patients with reduced ejection fraction in heart failure: a network meta-analysis

Beibei Xu¹, Jikai Zhao¹, Zhi Li¹, Liming Yu^{1,*}, and Huishan Wang^{1,*}

¹Department of Cardiovascular Surgery, General Hospital of Northern Theatre Command, 83 Wenhua Road, Shenyang, Liaoning 110016, China

***Correspondence:**

Huishan Wang, M.D. and Liming Yu M.D.

Department of Cardiovascular Surgery

General Hospital of Northern Theatre Command

83 Wenhua Road

Shenyang City 110016, China

E-mail: huishanw@126.com (Huishan Wang) and lmyu2012@163.com (Liming Yu)

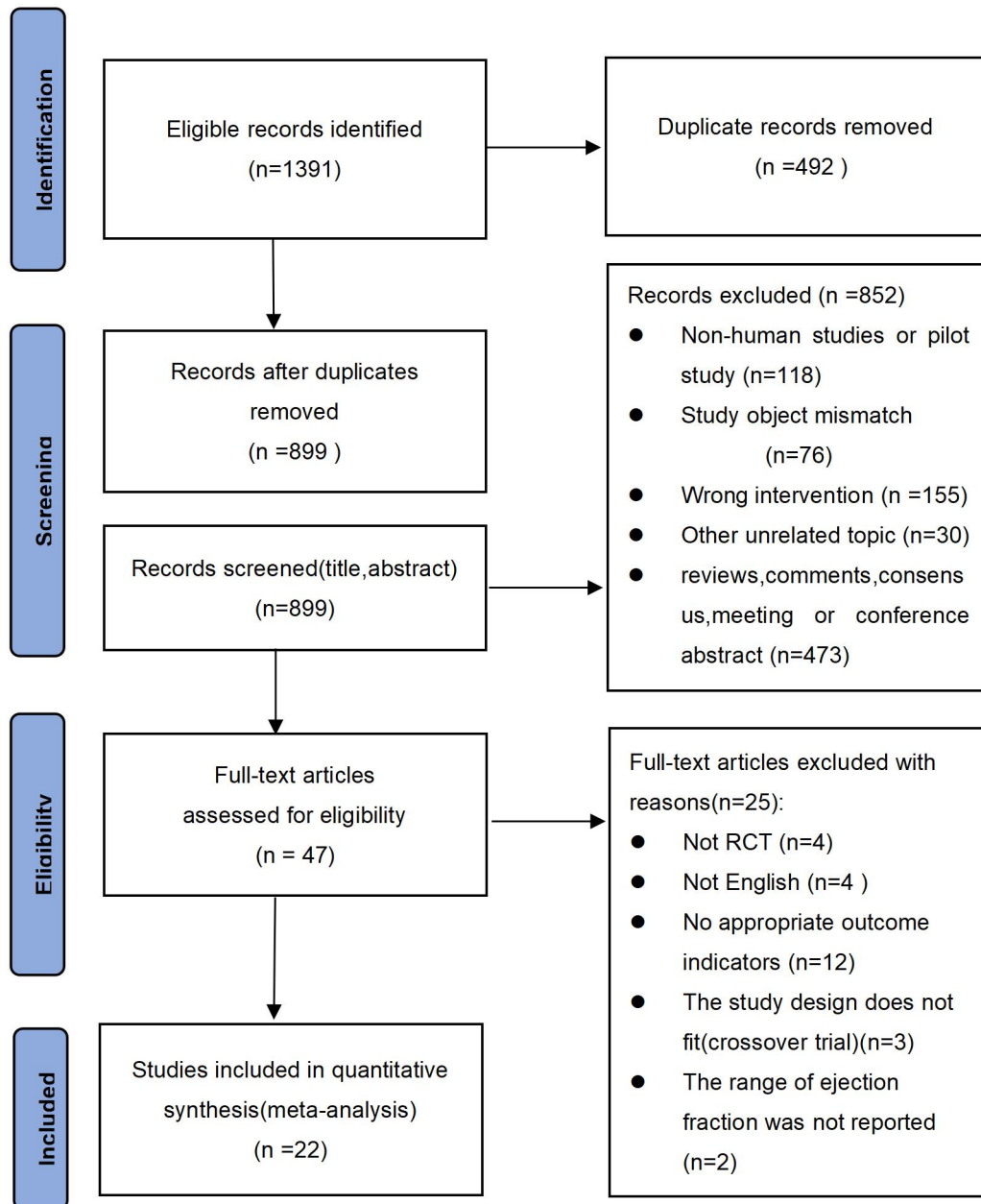
Tel: +86 24 28897382

Fax: +86 24 23912376

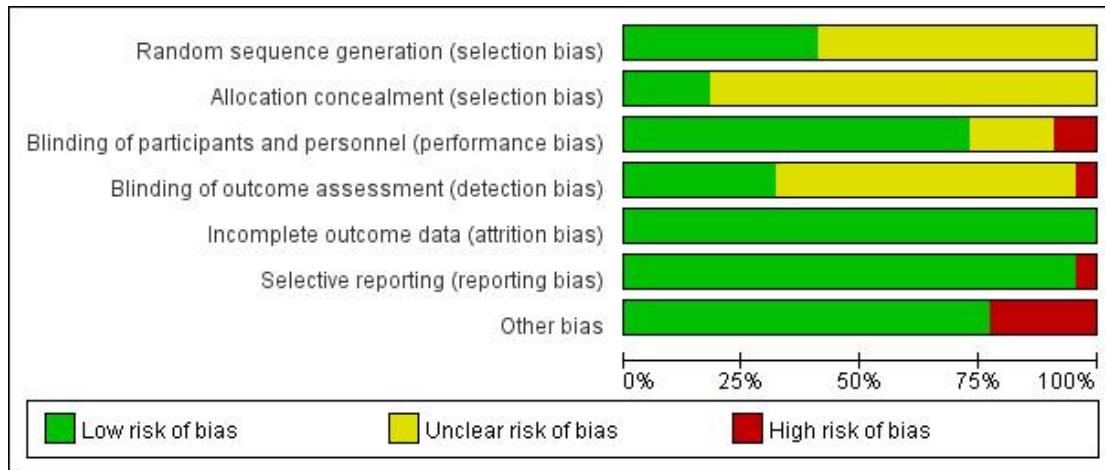
Database	Search string
PubMed (n=205)	((((("Simendan"[Mesh]) OR (((((((4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl)hydrazono)propanedinitrile[Title/Abstract]) OR (Simadax[Title/Abstract])) OR (Dextrosimendan[Title/Abstract])) OR (OR-1259[Title/Abstract])) OR (Levosimendan[Title/Abstract])) OR (OR-1855[Title/Abstract])) OR ((omecamtiv mecarbil[Title/Abstract]) OR (AMG-423[Title/Abstract]) OR (CK 1827452[Title/Abstract]) OR (CK-1827452[Title/Abstract])) OR ((((Danicamtiv[Title/Abstract]) OR ((MYK-491[Title/Abstract])) OR (C16H20F3N5O4S[Title/Abstract])) OR (CB44844686[Title/Abstract])) OR (((((((Cardiac Myosin[Title/Abstract]) OR (Myosin, Cardiac[Title/Abstract])) OR (Myosins, Cardiac[Title/Abstract])) OR (Cardiac Muscle Myosins[Title/Abstract])) OR (Muscle Myosins, Cardiac[Title/Abstract])) OR (Myosins, Cardiac Muscle[Title/Abstract])) OR ("Cardiac Myosins"[Mesh])) AND (("Heart Failure"[Mesh]) OR (Cardiac Failure[Title/Abstract]) OR (Heart Decompensation[Title/Abstract]) OR (Decompensation, Heart[Title/Abstract]) OR (Heart Failure, Right-Sided[Title/Abstract]) OR (Heart Failure, Right Sided[Title/Abstract]) OR (Right-Sided Heart Failure[Title/Abstract]) OR (Right Sided Heart Failure[Title/Abstract]) OR (Myocardial Failure[Title/Abstract]) OR (Congestive Heart Failure[Title/Abstract]) OR (Heart Failure, Congestive[Title/Abstract]) OR (Heart Failure, Left-Sided[Title/Abstract]) OR (Heart Failure, Left Sided[Title/Abstract]) OR (Left-Sided Heart Failure[Title/Abstract]) OR (Left Sided Heart Failure[Title/Abstract])) AND ((Randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract]) OR (placebo[Title/Abstract]))
Web of Science (n=631)	1. TS=(Cardiac Failure OR Heart Decompensation OR Decompensation, Heart OR Heart Failure, Right-Sided OR Heart Failure, Right Sided OR Right-Sided Heart Failure OR Right Sided Heart Failure OR Myocardial Failure OR Congestive Heart Failure OR Heart Failure, Congestive OR Heart Failure, Left-Sided OR Heart Failure, Left Sided OR Left-Sided Heart Failure OR Left Sided Heart Failure OR Heart Failure) 2. TS=(Cardiac Myosin OR Myosin, Cardiac OR Myosins, Cardiac OR Cardiac Muscle Myosins OR Muscle Myosins, Cardiac OR Myosins, Cardiac Muscle OR Cardiac Myosins) 3. TS=(Danicamtiv OR MYK-491 OR C16H20F3N5O4S OR CB44844686) 4. TS=(omecamtiv mecarbil OR AMG-423 OR CK 1827452 OR CK-1827452) 5. TS=(((4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl)hydrazono)propanedinitrile) 6. TS=(Simadax) 7. TS=(Dextrosimendan) 8. TS=(OR-1259) 9. TS=(Levosimendan) 10. TS=(OR-1855) 11. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 12. #1 AND #11 13. TS=(Randomized controlled trial OR randomized OR placebo)

	14. #12 AND #13
Embase (n=555)	1. 'heart failure'/exp 2. 'cardiac failure':ti,ab OR 'heart decompensation':ti,ab OR 'decompensation, heart':ti,ab OR 'heart failure, right-sided':ti,ab OR 'heart failure, right sided':ti,ab OR 'right-sided heart failure':ti,ab OR 'right sided heart failure':ti,ab OR 'myocardial failure':ti,ab OR 'congestive heart failure':ti,ab OR 'heart failure, congestive':ti,ab OR 'heart failure, left-sided':ti,ab OR 'heart failure, left sided':ti,ab OR 'left-sided heart failure':ti,ab OR 'left sided heart failure':ti,ab 3. #1 OR #2 4. 'cardiac myosin'/exp 5. 'myosin, cardiac':ti,ab OR 'myosins, cardiac':ti,ab OR 'cardiac muscle myosins':ti,ab OR 'muscle myosins, cardiac':ti,ab OR 'myosins, cardiac muscle':ti,ab OR 'cardiac myosins':ti,ab 6. #4 OR #5 7. 'danicamtiv'/exp 8. 'myk-491':ti,ab OR 'c16h20f3n5o4s':ti,ab OR 'cb44844686':ti,ab 9. #7 OR #8 10. 'omecamtiv mecarbil'/exp 11. 'amg-423':ti,ab OR 'ck 1827452':ti,ab OR 'ck-1827452':ti,ab 12. #10 OR #11 13. 'levosimendan'/exp 14. '((4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl)hydrazono)propanedinitrile':ti,ab OR 'simadax':ti,ab OR 'dextrosimendan':ti,ab OR 'or 1259':ti,ab OR 'or-1259':ti,ab OR 'or 1855':ti,ab OR 'or-1855':ti,ab 15. #13 OR #14 16. #6 OR #9 OR #12 OR #15 17. #3 AND #16 18. 'randomized controlled trial'/exp 19. 'randomized':ti,ab OR 'placebo':ti,ab 20. #18 OR #19 21. #17 AND #20

Supplementary Table S1. Search strings and databases used for the systematic review.



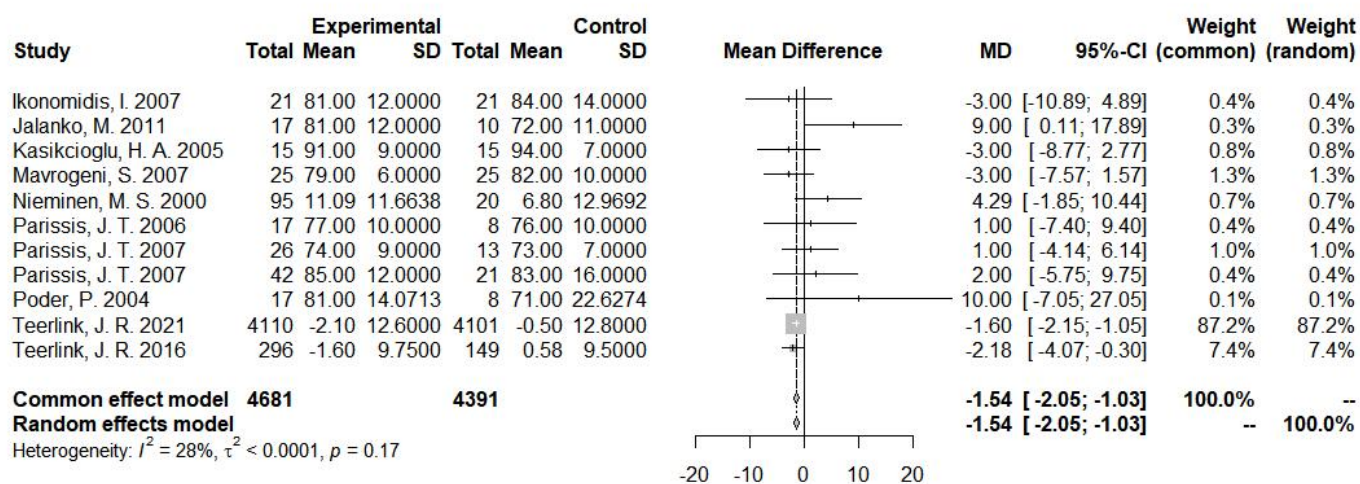
Supplementary Figure S1. Research screening flow chart.



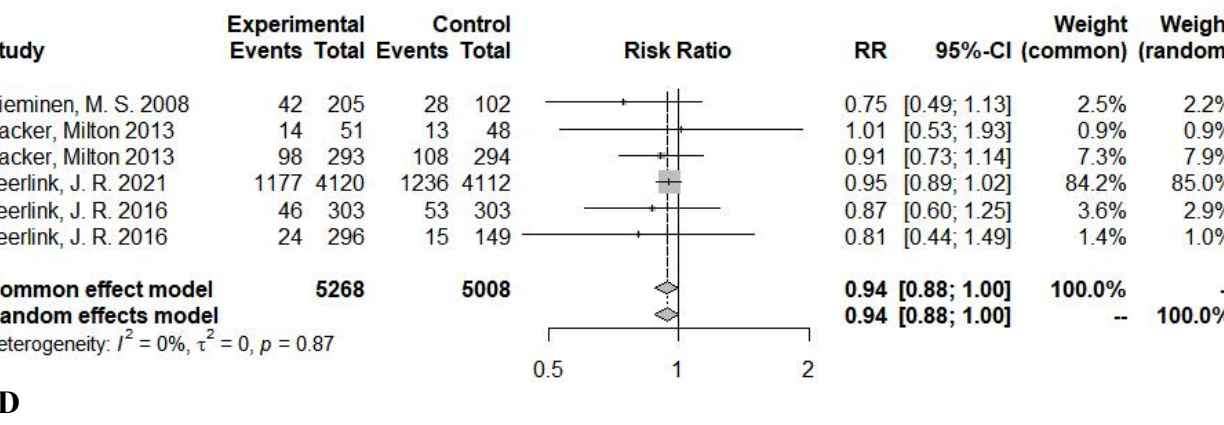
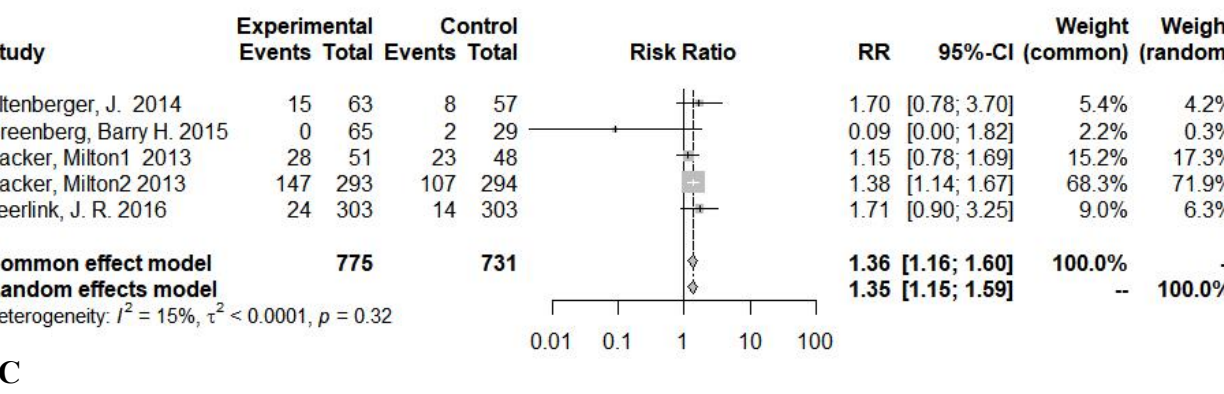
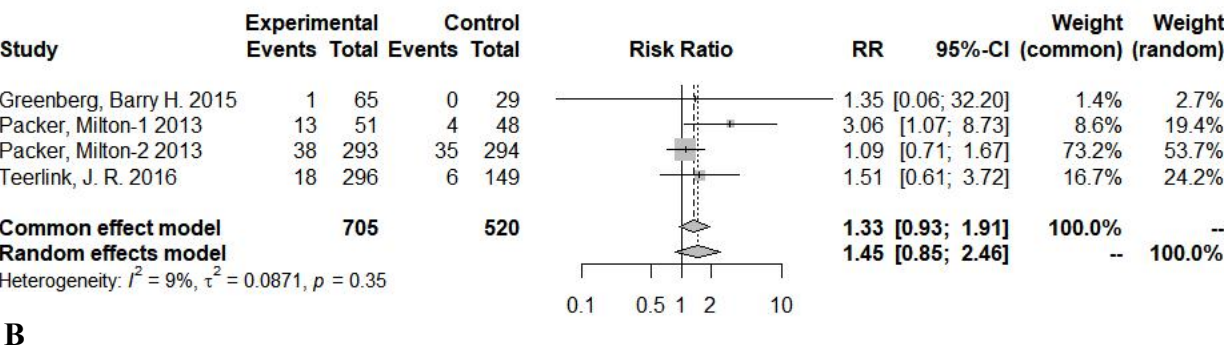
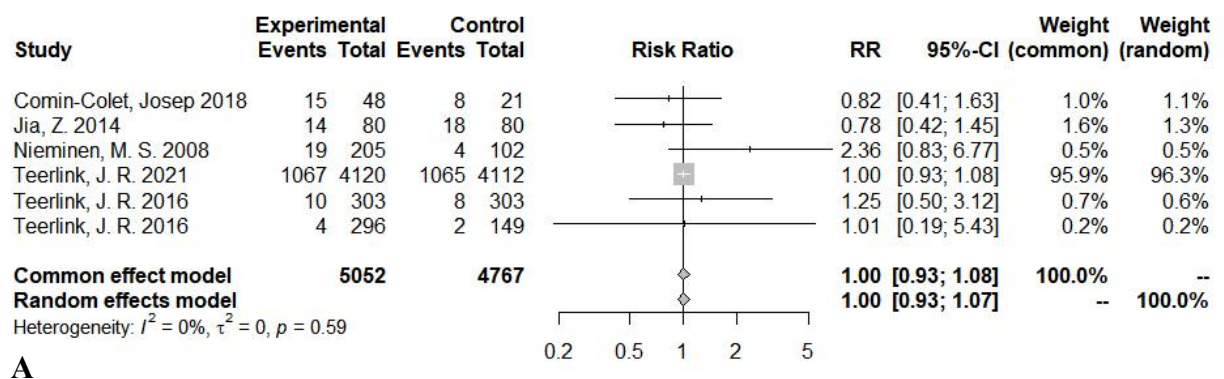
Supplementary Figure S2A. Quality assessment of the included studies.

	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
Altenberger, J. 2014	+	+	+	?	+	+	+
Comin-Colet, Josep 2018	+	+	+	+	+	+	+
Cui, X. R. 2020	?	?	?	?	+	+	+
Greenberg, Barry H. 2015	+	+	+	?	+	+	+
Ikonomidis, I. 2007	?	?	+	+	+	+	+
Jalanko, M. 2011	?	?	+	?	+	+	+
Jia, Z. 2014	+	?	+	?	+	+	+
Kasikcioglu, H. A. 2005	?	?	?	+	+	+	+
Lilleberg, J. 2007	?	?	+	+	+	+	+
Mavrogeni, S. 2007	+	?	+	+	+	+	+
Nieminen, M. S. 2000	?	?	+	?	+	+	+
Nieminen, M. S. 2008	?	?	+	?	+	+	+
Packer, Milton 2013	?	?	+	?	+	+	+
Parissis, J. T. 2006	?	?	+	?	+	+	+
Parissis, J. T. 2007.7	?	?	?	?	+	+	+
Parissis, J. T. 2007.8	?	?	?	+	+	+	+
Poder, P. 2004	?	?	+	?	+	+	+
Slawsky, M. T. 2000	?	?	+	?	+	+	+
Teerlink, J. R. 2016ATOMIC	+	?	+	?	+	+	+
Teerlink, J. R. 2016COSMIC	+	+	+	+	+	+	+
Teerlink, J. R. 2021	+	?	+	+	+	+	+
Zhang, D. 2015	+	?	+	?	+	+	+

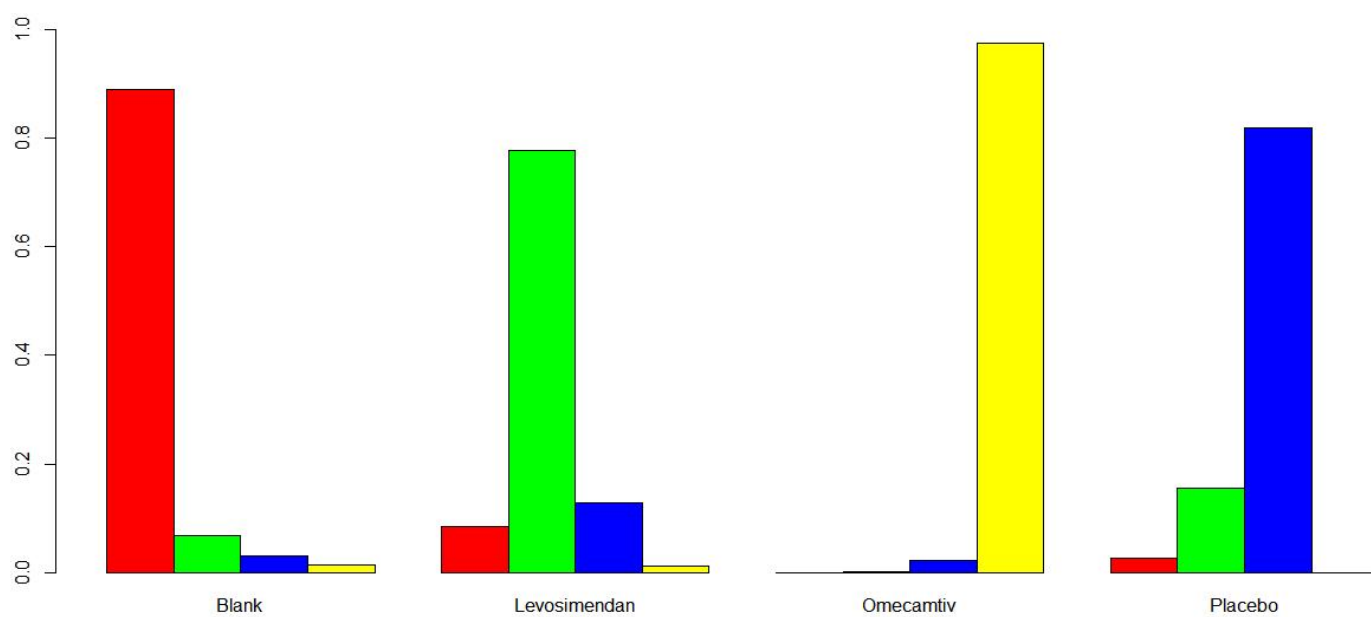
Supplementary Figure S2B. Quality assessment of the included studies.



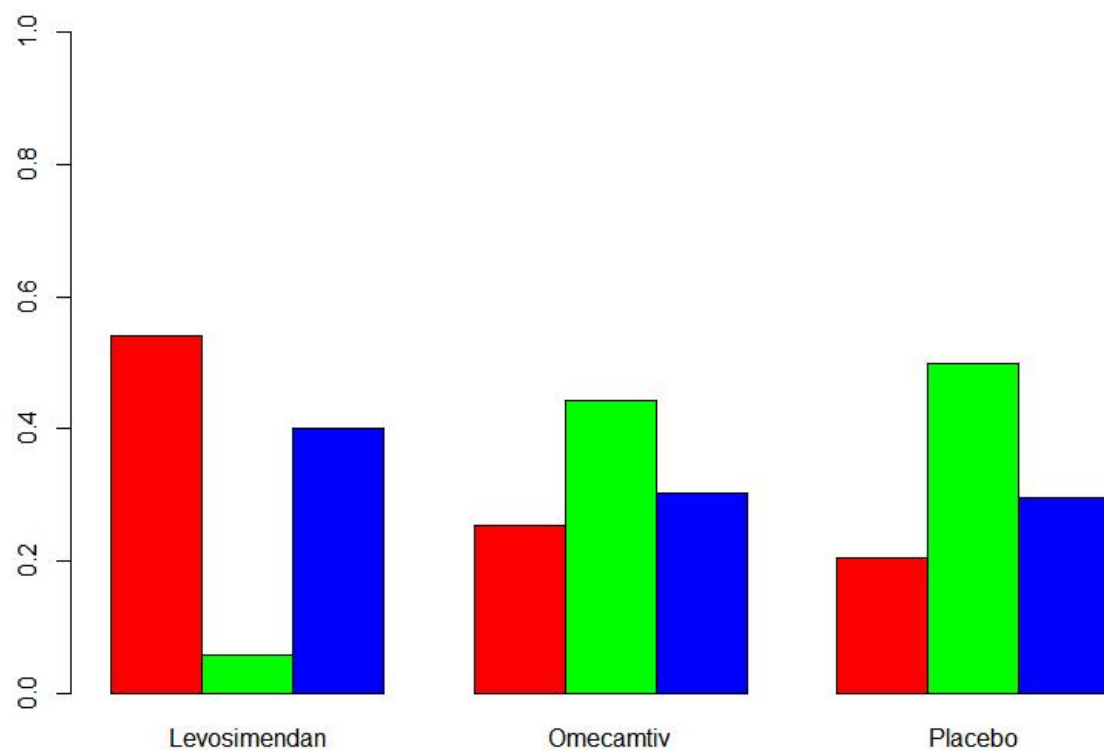
Supplementary Figure S3. Forest plot summarizing data from individual studies for heart rate.



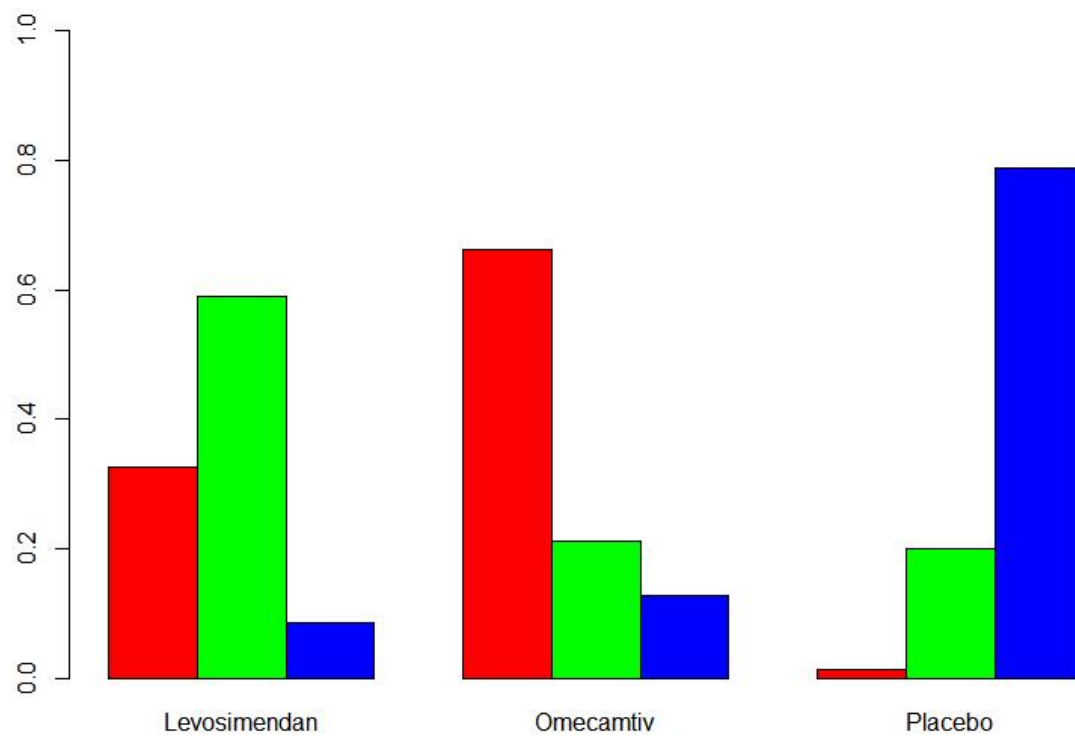
Supplementary Figure S4. Forest plots of secondary outcomes.



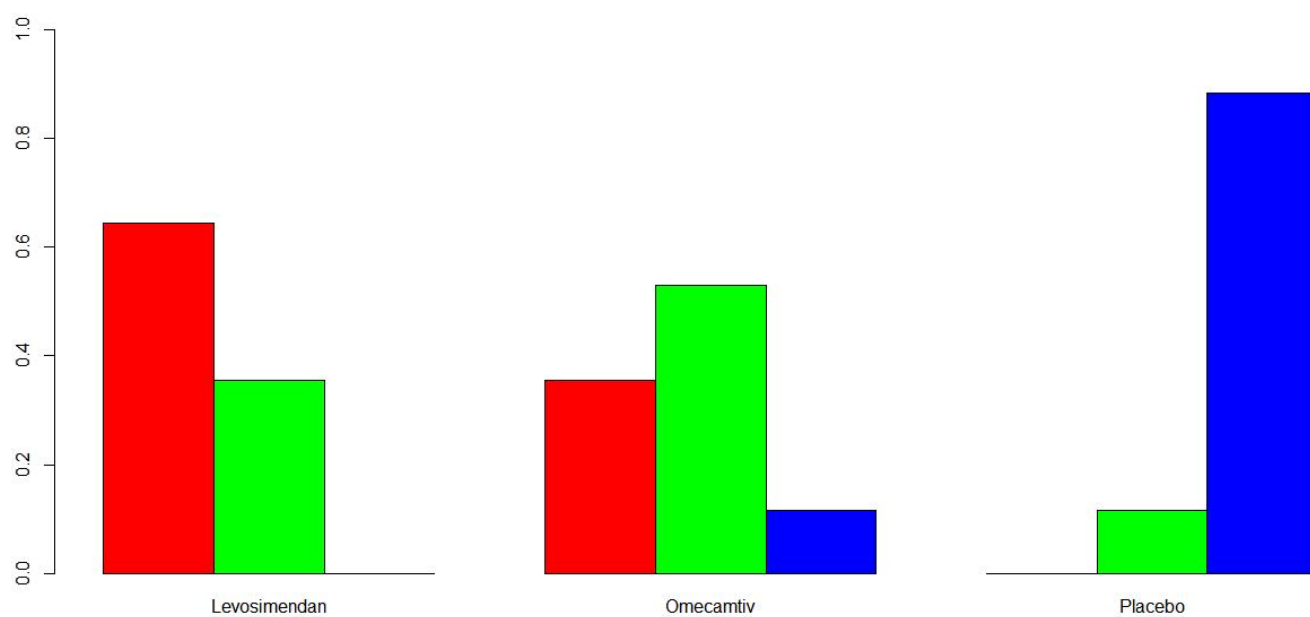
Supplementary Figure S5. Rank probability of heart rate in pharmacological treatments. Omecamtiv = Omecamtiv mecarbil



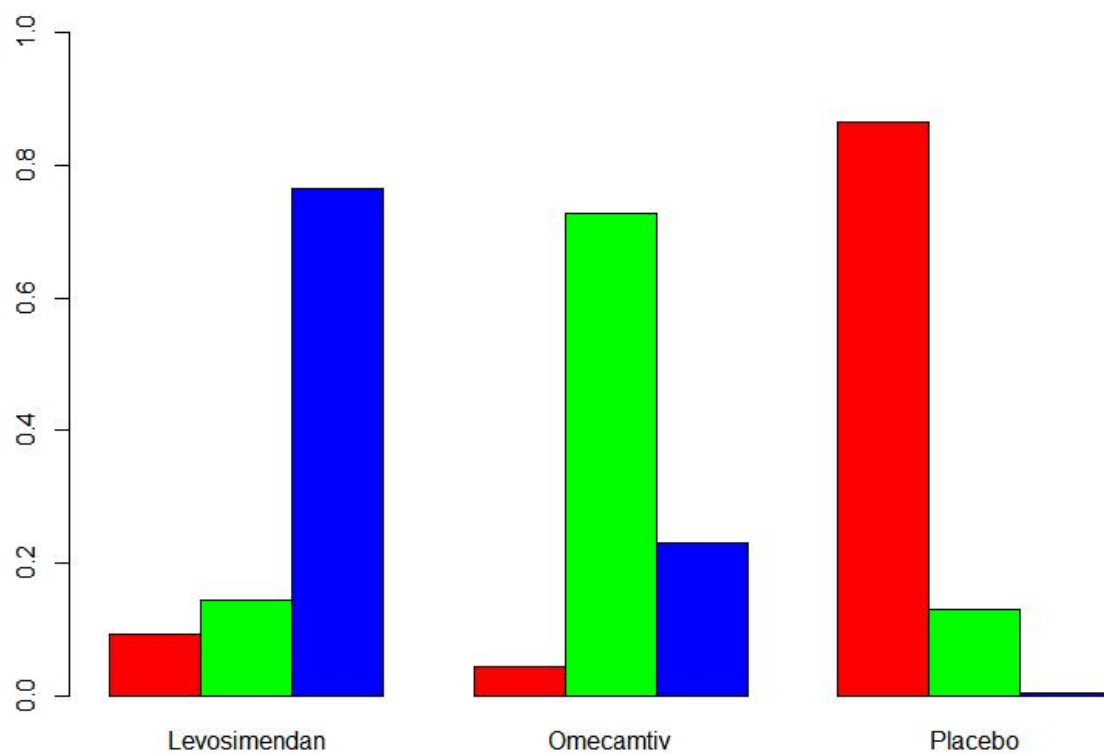
Supplementary Figure S6. Rank probability of all cause death in pharmacological treatments. Omecamtiv = Omecamtiv mecarbil



Supplementary Figure S7. Rank probability of dizziness in pharmacological treatments. Omecamtiv = Omecamtiv mecarbil



Supplementary Figure S8. Rank probability of hypotension in pharmacological treatments. Omecamtiv = Omecamtiv mecarbil



Supplementary Figure S9. Rank probability of cardiac failure events in pharmacological treatments. Omecamtiv = Omecamtiv mecarbil

Secondary endpoints (Rank 1 is worst , rank N is best)				
Drug	Rank 1	Rank 2	Rank 3	Rank 4
Heart rate				
Blank	0.888	0.068	0.031	0.013
Levosimendan	0.086	0.776	0.127	0.011
Omecamtiv mecarbil	0.000	0.002	0.022	0.976
Placebo	0.026	0.154	0.819	0.000
All-cause death				
Levosimendan	0.542	0.058	0.401	
Omecamtiv mecarbil	0.254	0.443	0.303	
Placebo	0.204	0.500	0.296	
Dizziness				
Levosimendan	0.327	0.589	0.084	
Omecamtiv mecarbil	0.661	0.212	0.127	
Placebo	0.012	0.199	0.789	
Hypotension				
Levosimendan	0.645	0.355	0.000	
Omecamtiv mecarbil	0.355	0.530	0.116	
Placebo	0.000	0.116	0.884	
Cardiac failure events				
Levosimendan	0.091	0.144	0.765	
Omecamtiv mecarbil	0.043	0.727	0.231	
Placebo	0.866	0.130	0.004	

Supplementary Table S2. Rank probability of endpoints in pharmacological treatments.

First author	Year	Treatment	nPatients	Principle health problem	Age (Years)	Male Sex(%)	EF (%)	NYHA	Follow-up
Altenberger	2014	Levosimendan vs Placebo	120	Ischaemic cardiomyopathy	Lev 69.5±11.5 P 69.5±10.5	79	≤35	III/IV	6 months
Comín-Colet	2018	Levosimendan vs Placebo	69	advanced chronic HF	Lev 68±10 P 63±9	83	<35	III/IV	6 months
Cui, X. R.	2020	Levosimendan vs Blank	49	chronic systolic HF	Lev 50.15 ±13.42 P 54.43 ±13.22	84	≤40	III/IV	one month
Greenberg,Barry H.	2015	Omecamtiv mecarbil vs. Placebo	94	ischemic cardiomyopathy and angina	63.4±9.3	79.8	≤35	II/III	6-14 days
Ikonomidis, I.	2007	Levosimendan vs Placebo	42	Advanced HF Ischemic/dilated	Lev 63 ± 8 P 63 ± 12	90.5	<35	III/IV	24h
Jalanko, M.	2011	Levosimendan vs Placebo	29	Congestive CHF	Lev 63±13 P 63 ±12	93.1	≤30	IIIB/IV	6 months
Jia, Z.	2014	Levosimendan vs Placebo	160	heart failure complicated by AMI	Lev 63.7±11.4 P 62.6±11.3	60	<40	Killip grade III/IV	6 months
Kasikcioglu, H. A.	2005	Levosimendan vs Placebo	30	decompensated heart failure	Lev 59 ± 10 P 60 ± 6	NA	≤35	III	6 – 9 months
Lilleberg, J.	2007	Levosimendan vs Placebo	22	congestive heart failure	Lev 55±9 P 55±8	81.8	< 35	II -IV	2 weeks
Mavrogeni	2007	Levosimendan vs Blank	50	Advanced HF ischemic/dilated/ valvular	45-65	80	<30	III/IV	6 months
Nieminen, M. S.	2000	Levosimendan vs Placebo	115	acute decompensated heart failure	63 ± 2.5	82	<40	II-IV	24h
Nieminen, M. S.	2008	Levosimendan vs Placebo	307	chronic heart failure	Lev 63.49±11.13 Placebo 63±10	78.5	≤30	IIIB/IV	6 months
Packer, Milton (REVIVEI and II trials)	2013	Levosimendan vs Placebo	I-100 II-600	acute decompensated heart failure	I Lev 59±15 Placebo 58±15 II Lev 64±15 Placebo:63±15 (mean±SEM)	I-77 II-NA	≤35	NA	5 days
Parissis, J. T.	2006	Levosimendan vs Placebo	25	Decompensated CHF ischemic/ dilated	67.0 ± 6.0	92	≤30	III/IV	114 days
Parissis, J. T.	2007	Levosimendan vs Placebo	39	Advanced HF	Lev 65 ± 8 Placebo 61±14	84.6	<35	NA	48h

Parissis, J. T.	2007	Levosimendan vs Placebo	63	Advanced chronic HF	65 ± 8	82.5	<30	III/IV	NA
Poder, P.	2004	Levosimendan vs Placebo	25	severe congestive heart failure	Lev 58.59±9.94 Placebo 55±14.14	NA	≤ 35	III/IV	28 days
Slawsky, M. T.	2000	Levosimendan vs Placebo	146	decompensated heart failure	Lev 58±1 Placebo 56±2	81.5	≤ 30	III/IV	6h
Teerlink, J. R.	2021	Omecamtiv mecarbil vs. Placebo	8232	chronic heart failure	65	79	≤35	II-IV	21.8 months (median)
Teerlink, J. R.	2016	Omecamtiv mecarbil vs. Placebo	606	acute heart failure	66 ± 11	76.9	≤40	I-IV	6 months
Teerlink, J. R.	2016	Omecamtiv mecarbil vs. Placebo	445	chronic heart failure	63	82	≤40	II/III	24 weeks
Zhang, D.	2015	Levosimendan vs Blank	42	elderly patients with refractory HF	75.3±4.8	46	≤40	III/IV	1 week

Supplementary Table S3. The characteristics of the 22 eligible randomized controlled trials.