APPENDICES

APPENDIX A- SEARCH

INFORMATION SOURCES

The following databases were systematically searched from their receptive inception to the stated date: Embase (1974 to November 2021, via OVID), MEDLINE(R) (1946 to November 2021, via OVID), PsycInfo (1806 to November 2021, via OVID), CINAHL (1981 to November 2021, via EBSCOhost), Cochrane Central Register of Controlled Trials (up to November 2021). This selection of databases was able to cast a wide and comprehensive net. As well as the electronic database searches, other information sources were also searched in order to reduce publication bias. This included hand-searching the references of included studies and other pertinent publications to identify studies which met the inclusion criteria that had not already been identified. Citation searches of the studies to be included was also performed, along with a grey literature search on OpenGrey.

SEARCH

The search strategy was developed using the PICOS framework as a guide to identify search terms and categories. The process of creating the final search strategies began with a preliminary search in Embase and MEDLINE to ascertain suitable search terms and combinations. The search strategy was adjusted to account for the individual electronic databases being searched, and the full search strategy for each database with the total number of results generated can be found below.

Embase Search 1974 to 2021 November 10 via OVID

	Search Terms	Number of Results
1	exp Heart Failure/	552920
2	chronic heart failure.mp.	29910
3	(advanced adj6 heart failure).mp.	9447
4	NYHA III.mp.	2910
5	NYHA IV.mp.	793
6	end-stage heart failure.mp.	5435
7	congestive heart failure.mp.	97604
8	1 or 2 or 3 or 4 or 5 or 6 or 7	568929
9	exp Diuretics/	403790
10	diuretic*.mp.	129012
11	exp Furosemide/	60448
12	furosemide.mp	62622
13	frusemide.mp.	1807
14	9 or 10 or 11 or 12 or 13	420519
15	exp Infusions, Intravenous/	360975
16	infusion*.mp.	421295
17	exp Administration, Intravenous/	360975
18	exp Injections, Intravenous/	360975
19	intravenous.mp.	1145930
20	exp Infusions, Subcutaneous/	92831
21	exp Injections, Subcutaneous/	92831
22	subcutaneous.mp.	419294
23	exp Infusions, Parenteral/	740302
24	parenteral.mp.	111969
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	2076510
26	exp Palliative Care/	122522
27	palliat*.mp.	174702
28	End of life.mp	40058
29	exp Dyspnea/	199982
30	exp Dyspnea, Paroxysmal/	1143
31	dyspn?ea.mp.	219170
32	(short* adj2 breath).mp.	23390
33	breathless*.mp.	10009
34	exp Edema/	314586
35	edema.mp.	352469
36	oedema.mp.	40854
37	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	765895
38	8 and 14 and 25 and 37	4460

MEDLINE(R) ALL 1946 to November 10, 2021 via OVID

	Search Terms	Number of Results
1	exp Heart Failure/	132913
2	chronic heart failure.mp.	17299
3	(advanced adj6 heart failure).mp.	5069
4	NYHA III.mp.	803
5	NYHA IV.mp.	291
6	end-stage heart failure.mp.	3128
7	congestive heart failure.mp.	41814
8	1 or 2 or 3 or 4 or 5 or 6 or 7	160898
9	exp Diuretics/	81445
10	diuretic*.mp.	56085
11	exp Furosemide/	12059
12	furosemide.mp	17190
13	frusemide.mp.	1377
14	9 or 10 or 11 or 12 or 13	106801
15	exp Infusions, Intravenous/	56261
16	infusion*.mp.	306961
17	exp Administration, Intravenous/	146808
18	exp Injections, Intravenous/	82247
19	intravenous.mp.	411209
20	exp Infusions, Subcutaneous/	1307
21	exp Injections, Subcutaneous/	41567
22	subcutaneous.mp.	162972
23	exp Infusions, Parenteral/	94225
24	parenteral.mp.	86213
25	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	803096
26	exp Palliative Care/	58602
27	palliat*.mp.	105747
28	End of life.mp	27269
29	exp Dyspnea/	23195
30	exp Dyspnea, Paroxysmal/	354
31	dyspn?ea.mp.	63390
32	(short* adj2 breath).mp.	10583
33	breathless*.mp.	5786
34	exp Edema/	44534
35	edema.mp.	162329
36	oedema.mp.	28218
37	exp Weight Loss/	45541
38	weight loss.mp.	108491
39	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	480379
40	8 and 14 and 25 and 39	308

PsycInfo 1806 to November Week 2 2021 via OVID

	Search Terms	Number of Results
1	exp Heart Disorders/	15173
2	chronic heart failure.mp.	482
3	(advanced adj6 heart failure).mp.	145
4	NYHA III.mp.	14
5	NYHA IV.mp.	4
6	end-stage heart failure.mp.	52
7	congestive heart failure.mp.	951
8	1 or 2 or 3 or 4 or 5 or 6 or 7	15825
9	exp Diuretics/	3396
10	diuretic*.mp.	1092
11	furosemide.mp	318
12	frusemide.mp.	6
13	9 or 10 or 11 or 12	4451
14	exp Intravenous Drug Usage/	4355
15	exp Intravenous Injections/	1377
16	intravenous.mp.	14659
17	infusion*.mp.	15397
18	exp Subcutaneous Injections/	234
19	subcutaneous.mp.	5066
20	parenteral.mp.	1038
21	14 or 15 or 16 or 17 or 18 or 19 or 20	32898
22	exp Palliative Care/	15252
23	palliat*.mp.	18007
24	End of life.mp	10774
25	exp Dyspnea/	5295
26	dyspn?ea.mp.	1914
27	(short* adj2 breath).mp.	653
28	breathless*.mp.	480
29	exp Edema/	510
30	edema.mp.	3259
31	oedema.mp.	511
32	exp Weight Loss/	4140
33	weight loss.mp.	13511
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	46962
35	8 and 13 and 21 and 34	5

CINAHL November 10, 2021 via EBSCOhost

	Search Terms	Number of Results
S1	(MH "Heart Failure")	45,201
S2	“chronic heart failure"	36,403
S3	“advanced heart failure"	1,402
S4	“NYHA III"	139
S5	“NYHA IV"	22
S6	“end-stage heart failure"	666
S7	“congestive heart failure"	40,550
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	51,598
S9	(MH "Diuretics")	4,410
S10	(MH "Diuretics, Potassium Sparing")	37
S11	(MH "Diuretics, Thiazide")	672
S12	“diuretic*"	9,204
S13	(MH "Furosemide")	1,118
S14	“furosemide"	1,752
S15	“frusemide"	542
S16	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	10,267
S17	(MH "Administration, Intravenous")	9,486
S18	(MH "Home Intravenous Therapy")	1,578
S19	“Intravenous"	79,797
S20	(MH "Infusions, Intravenous")	11,388
S21	“Infusion*"	50,359
S22	(MH "Injections, Subcutaneous")	4,717
S23	(MH "Infusions, Subcutaneous")	906
S24	“subcutaneous"	22,633
S25	(MH "Infusions, Parenteral")	1,584
S26	“parenteral"	16,333
S27	17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	138,991
S28	(MH "Palliative Care")	38,901
S29	(MH "Palliative Medicine")	46
S30	“palliat*"	57,939
S31	“End of life"	30,827
S32	“MH "Dyspnea")	10,154
S33	(MH "Dyspnea, Paroxysmal")	53
S34	“Dyspn?ea"	2,326
S35	“shortness of breath"	7,054
S36	“breathless*"	2,027
S37	(MH "Edema")	8,688
S38	“edema"	26,881
S39	“oedema”	7,584
S40	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	121,256
S41	S8 AND S16 AND S27 AND S40	61

Cochrane Central Register of Controlled Trials (CENTRAL) November 10, 2021

	Search Terms	Number of Results
#1	MeSH descriptor: [Heart Failure] explode all trees	10029
#2	chronic heart failure	12194
#3	(advanced adj6 heart failure)	47
#4	NYHA III	2516
#5	NYHA IV	1757
#6	end-stage heart failure	1060
#7	congestive heart failure	7185
#8	1 or 2 or 3 or 4 or 5 or 6 or 7	24146
#9	MeSH descriptor: [Diuretics] explode all trees	3187
#10	diuretic*	9828
#11	MeSH descriptor: [Furosemide] explode all trees	1200
#12	furosemide	2807
#13	frusemide	381
#14	#9 OR #10 OR #11 OR #12 OR #13	11740
#15	MeSH descriptor: [Infusions, Intravenous] explode all trees	10459
#16	infusion*	72859
#17	MeSH descriptor: [Administration, Intravenous] explode all	19002
#18	MeSH descriptor: [Injections, Intravenous] explode all trees	7725
#19	intravenous	94458
#20	MeSH descriptor: [Infusions, Subcutaneous] explode all trees	156
#21	MeSH descriptor: [Injections, Subcutaneous] explode all trees	4649
#22	subcutaneous	30064
#23	MeSH descriptor: [Infusions, Parenteral] explode all trees	12620
#24	parenteral	11948
#25	#15 OR #16 OR #17 OR #18 OR #19 #20 OR #21 OR #22 OR #23 OR #24	114659
#26	MeSH descriptor: [Palliative Care] explode all trees	1709
#27	palliat*	10429
#28	End of life	42149
#29	MeSH descriptor: [Dyspnea] explode all trees	1377
#30	MeSH descriptor: [Dyspnea, Paroxysmal] explode all trees	3
#31	dyspn?ea	13228
#32	(short* adj2 breath)	128
#33	breathless*	2113
#34	MeSH descriptor: [Edema] explode all trees	1892
#35	edema	21077
#36	oedema	20988
#37	MeSH descriptor: [Weight Loss] explode all trees	6824
#38	weight loss	30532
#39	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	108213
#40	8 and 14 and 25 and 39	128

STUDY SELECTION

Citations were imported into Covidence and deduplicated both electronically and manually. Titles and abstracts were then screened for eligibility by two reviewers (AH and NB). Full text articles were then assessed against the inclusion and exclusion criteria by two independent reviewers (AH and SB) to identify eligible studies. Any disagreements regarding study inclusion were settled through discussion by reviewers.

APPENDIX B – DATA EXTRACTION

DATA COLLECTION PROCESS

A data extraction form was developed for this systematic review based on the Cochrane Handbook for Systematic Reviews of Interventions. This was then piloted on two of the studies and modified as necessary to ensure appropriate coverage. Data extraction was undertaken by the review author independently (AH). Data items included study summary, study characteristics, sample population, intervention, comparator, outcomes and results. The data extraction form was inputted into an excel spreadsheet and used to extract the following data items from included studies:

- Study Summary
    - Author
    - Title
    - Year
    - Country and Journal Published
- Study Characteristics
    - Aims and Objectives
    - Design
    - Inclusion and exclusion Criteria

    - Recruitment and randomisation
    - Sample size
    - Setting
- Sample Population
    - Gender
    - Age
    - NYHA classification
    - LVEF
    - Comorbidities
- Intervention
    - Intervention type, dose and route
    - Number of participants enrolled
    - Number of participants included in analysis
- Comparator
    - Intervention type, dose and route if present
    - Number of participants enrolled
    - Number of participants included in analysis
- Outcomes and Results
    - Outcome and measurement tool
    - Follow up time
    - Statistical analysis method
    - Result

APPENDIX C- STUDY CHARACTERISTICS AND RESULTS

Author, Year, Country	Study Design	Study Location	Intervention & Comparator: Type, Dose, Route	Sample: Size (n), Sex. Age (years), NYHA Class, LVEF		Reported Outcomes and measurement tool if used	Results
				Continuous	Bolus		
Frea et al.[22] 2020 Germany	Single-centre, double-blind, double-dummy, RCT	Cardiac Care Unit	<u>Continuous</u> Administration of furosemide by continuous intravenous infusion. The dose of furosemide (low dose 120 mg/day vs. high dose 240 mg/day) was defined before randomisation according to criteria. <u>Bolus</u> Administration of furosemide by intravenous bolus every 12 hours. The dose of furosemide (low dose 120 mg/day vs. high dose 240 mg/day) was defined before randomization according to criteria.	n= 40 Sex: F 3 (7%), M 37 (93%) Mean age (years)= 63.0±13 NYHA class IV 40 (100%) Mean LVEF=19.4% ±9.0	n= 40 Sex: F 5 (12%), M 35 (88%) Mean age (years)= 58.7±10 NYHA class IV 40 (100%) Mean LVEF=19.2% ±6.4	1) Freedom from congestion (defined as jugular venous pressure of < 8 cm, with no orthopnoea and with trace peripheral oedema or no oedema) at 72h 2) Total urinary output (ml) at 72 h 3) Treatment failure (defined as persistent congestion with wet score ≥ 12/18) at 72 h 4) Worsening renal function (defined as an absolute increase in serum creatinine > 0.3 mg/dl or > 1.5-fold from baseline) at 72 h 5) Diuretic response (defined as Δ weight/40 mg furosemide) at 72h 6) Worsening or persistent heart failure at 72h 7) Rate of single events or composite of death	1) Statistically significant. Occurred in 10 patients (25%) in the bolus arm and in 19 (48%) in the continuous infusion arm: OR 2.71, 95% CI 1.05–7.00, (p=0.04) 2) Statistically significant. Urinary output 8612±2984 ml in the bolus arm vs 10,020±3032 ml in the continuous arm (p=0.04) 3) Statistically significant. Higher incidence in the bolus arm compared to continuous 38% vs 15%, (p=0.02) 4) No significant difference 5) Statistically significant. Higher in the continuous arm −1±0.7 kg/40 mg furosemide /72 h vs bolus arm −0.6±0.6 kg/40 mg furosemide /72 h (p<0.01) 6) No significant difference 7) No significant difference
Shree et al.[23] 2021	Single-centre, open-	Intensive care department	<u>Continuous</u> Intravenous furosemide infusion at a dose of 2-3mg/h. Subsequent dose titration of furosemide was allowed only after 24 h of enrolment based on the patient's response.	n=28 Sex: F 14 (50%), M 14 (50%) Mean age (years)= 69 ± 9	n=28 Sex: F 10 (36%), M 18 (64%) Mean age (years)= 63 ± 13	1) Daily urine output (ml/24h) at 24, 48 and 72 h 2) Change in renal function at ICU discharge (creatinine and eGFR) 3) Change in serum electrolytes at ICU discharge	1) No significant difference 2) Creatinine on discharge is statistically significant with 1.73±0.52 mg/dl in continuous arm vs 1.18±0.68 mg/dl in bolus arm, (P= 0.002). Change in eGFR at discharge not statistically significant 3) No significant difference

Author, Year, Country	Study Design	Study Location	Intervention & Comparator: Type, Dose, Route	Sample: Size (n), Sex. Age (years), NYHA Class, LVEF		Reported Outcomes and measurement tool if used	Results
				Continuous	Bolus		
India	label, RCT		Bolus Intravenous furosemide at a dose of 40mg every 8hours. Subsequent dose titration of furosemide was allowed only after 24 h of enrolment based on the patient's response.	NYHA class III 11 (39.2%) NYHA class IV 17 (60.7%) Mean LVEF= 33%	NYHA class III 16 (57.1%) NYHA class IV 12 (42.8%) Mean LVEF= 36%	4) Average ICU length of stay (days) 5) NYHA improvement after treatment completion	4) Statistically significant. The mean length of stay in the continuous arm was 7 ± 2 days vs bolus arm 4 ± 1days, (P =0.032) 5) No significant difference
Palazzuoli et al.[19] 2015 Italy	Single-centre, open label pilot RCT	Tertiary-care Cardiology Section Centre	Continuous Furosemide administered in a continuous infusion (mixed as a 1:1 ratio in 5 % dextrose in water) for a time period ranging from 72 to120 h. The dose escalation and subsequent titration of furosemide was guided by clinical response. The mean dosage of furosemide was188±70 mg/day. Bolus Furosemide divided into a twice-daily bolus injection for a time period ranging from 72 to120 h. The dose escalation and subsequent titration of furosemide was guided by clinical response. The mean dosage of furosemide was 170±80 mg/day.	n= 30 Sex: F 14 (46%), M 16 (53%) Mean age (years)= 71 ± 7 NYHA class III 4 (13%) NYHA class IV 27 (90%) Mean LVEF= 34.3%± 10	n=28 Sex: F 13 (46%), M 15 (53%) Mean age (years)= 73 ± 8 NYHA class III 5 (18%) NYHA class IV 22 (79%) Mean LVEF= 33%±8	1) Evaluation of renal function (Change in creatinine and eGFR levels) after treatment 2) Evaluation of mean urine output volume (mL/24h) 3) Evaluation of BNP levels after treatment 4) Weight loss (kg) after infusion period 5) Electrolyte balance measurement after treatment 6) Length of hospitalization (days) 7) Need for additional treatment during treatment period 8) Rehospitalisation and mortality at 6 months	1) Statistically significant. Impairment demonstrated by creatinine changes in continuous arm 1.78±0.5 mg/dl vs bolus arm 1.51±0.3 mg/dl, (p<0.01) eGFR reduction of 44.8±6.1 ml/min/1.73 m^2 in continuous arm vs bolus arm 46.7±6.1 ml/min/1.73 m^2 (p<0.05) 2) Statistically significant. Greater in continuous arm 2,505±796 ml vs bolus arm 2,140±468 ml, (p<0.04) 3) Statistically significant. Reduced in continuous arm 679.6±397 pg/ml vs bolus arm 949±548 pg/ml, (p<0.04) 4) No significant difference 5) No significant difference 6) Statistically significant. Increased in continuous arm 14.3±5 vs bolus arm 11.5±4.3, (p<0.03) 7) Statistically significant. Continuous arm required hypertonic saline solutions at a higher frequency (40 vs 19 %, p<0.01). Dobutamine infusions administered more frequently in continuous arm (50 vs 26 %, p<0.01). 8) Increased in the continuous arm 43% vs bolus arm 34 %, (p<0.03)

Author, Year, Country	Study Design	Study Location	Intervention & Comparator: Type, Dose, Route	Sample: Size (n), Sex. Age (years), NYHA Class, LVEF		Reported Outcomes and measurement tool if used	Results
				Continuous	Bolus		
Ragab et al.[20] 2018 Egypt	Single-centre, pilot RCT	Critical care department	<u>Continuous</u> Furosemide infusion at a dose of 5 mg/h. Subsequent dose titration of furosemide was allowed only after 24 h of enrolment based on the patient's response. The use of additional agents to manage ADHF were decided based upon current guidelines of management of ADHF but no other types of diuretic agents were allowed during the study period. <u>Bolus</u> Furosemide at a dose of 40 mg every 8 h. Subsequent dose titration of furosemide was allowed only after 24 h of enrolment based on the patient's response. The use of additional agents to manage ADHF were decided based upon current guidelines of management of ADHF but no other types of diuretic agents were allowed during the study period.	n= 20 Sex: F 7 (35%), M 13 (65%) Mean age (years)= 53.5 NYHA class III 5 (25%) NYHA class IV 15 (75%) Mean LVEF= 38% (27.3–41.8)	n= 20 Sex: F 9 (45%), M 11 (55%) Mean age (years)= 57 NYHA class III 8 (40%) NYHA class IV 12 (60%) Mean LVEF= 37% (30–40)	1) Change in TFC ($k\Omega^{-1}$) at 24 and 48h 2) Hourly urine output for every kg of body weight (mL/kg/h) at 24, 48 and 72h 3) Weight reduction at 24 and 48h (kg/day) 4) Change in serum electrolytes at 24 and 48h 5) Worsening renal function (serum creatinine mg% and CrCl ml/min) at 24 and 48h 6) Occurrence of acute kidney injury (elevation of serum creatinine >0.3 mg/dl within 48 h) 7) Occurrence of hypokalaemia (serum K^+ level <3.5 meq/L) at 48h 8) Average ICU length of stay 9) In-hospital mortality 10) NYHA improvement at 24 and 48h	1) Statistically Significant. Change in TFC after 24h was higher in continuous arm 10 (6.3–14.5) $k\Omega^{-1}$ vs bolus arm 7(3.3–9.8) $k\Omega^{-1}$, (P = .02) Statistically Significant. Change in TFC from 24-48h was 8 (6–11) $k\Omega^{-1}$ f in continuous arm vs bolus arm 6 (3.3–8.5) $k\Omega^{-1}$, (P = .02) 2) No significant difference 3) Statistically significant. Reduced during the first 24 h in continuous arm 2 (1.5–2.5) kg vs bolus arm 1.5 (1–2) kg, (P = .03). 4) No significant difference 5) Statistically significant. Serum creatinine level elevated after 48 h in continuous arm 0.2 (0.1–0.5) mg % vs bolus arm 0 (0.1to 0.2) mg %, (P = .009). Statistically significant. The decline in CrCl was also greater at 48h in continuous arm 7.4(4.5–12.3) ml/min vs bolus arm. 3.1 (0.2–8.8) ml/min, (P = .02) 6) No significant difference 7) Statistically significant. After 48h occurred more frequently in the continuous arm 8 patients vs bolus arm 1 patient, (P = .02). 8) No significant difference 9) No significant difference 10) No significant difference
			<u>Continuous</u> Continuous infusion of furosemide. The mean daily dose of furosemide was	n=26 Sex: F 10 (38%), M 15 (62%)	n=30 Sex: F 4 (19%), M 17 (81%)	1) Net daily urine output (defined as urine output minus oral plus IV intake	1) No significant difference 2) No significant difference 3) Statistically significant. Greater diuresis in the continuous arm 3726

Author, Year, Country	Study Design	Study Location	Intervention & Comparator: Type, Dose, Route	Sample: Size (n), Sex. Age (years), NYHA Class, LVEF		Reported Outcomes and measurement tool if used	Results
				Continuous	Bolus		
Thomson et al.[21] 2010 United States	Multi-centre, pilot RCT	Tertiary-care medical centre	197±48 mg. The mean duration of administration was 86.4± 50.5 h <u>Bolus</u> Intermittent infusion of furosemide. The mean daily dose of furosemide was 172 ±97mg. The mean duration of administration was 12.5 ± 73 h	Mean age(years) = 56.4 NYHA class III 10 (38%) NYHA class IV 9 (35%) Not reported 7 (27) Mean LVEF= 29%	Mean age(years) = 54.6 NYHA class III 11 (37%) NYHA class IV 11 (37%) Not reported 7 (23) Mean LVEF= 24%	normalized per 24 hours.) 2) Net daily urine output normalized for amount of furosemide received (nUOP/mg furosemide) 3) Total daily urine output (ml/24h) 4) Total daily urine output normalized for amount of furosemide received (tUOP/mg furosemide) 5) Weight loss during the study (kg) 6) Need for additional therapy during study 7) Duration of furosemide administration (days) 8) Length of hospitalization in (days) 9) Daily amount of potassium and magnesium supplementation required 10) Increase in serum creatinine (defined as 0.5 mg/dL or greater) 11) Significant hypotension	+/-1121 mL/24 h vs bolus arm 2955 +/- 1267 mL/24 h (P=.019) 4) Statistically significant. Greater diuresis in continuous arm 38 ml/mg of furosemide versus bolus arm 22 mL/mg of furosemide (P=.021) 5) No significant difference 6) No significant difference 7) No significant difference 8) Statistically significant. Continuous arm associated with a shorter length of hospital stay, 6.9 +/- 3.7 days, vs bolus arm 10.9 +/- 8.3 days (P=.006). 9) No significant difference 10) No significant difference 11) No significant difference
			<u>Continuous</u> Received a fixed total dose of furosemide as a 6 h intravenous continuous infusion according to eGFR. The fixed dose of furosemide was 160 mg per day for group A and 200 mg per day for group B	n=47 Sex: F 14 (33.33%), M 28 (66.67%) Mean age(years) = 65.53 ± 7.84	n=47 Sex: F 14 (35.9%), M 25 (64.1%) Mean age(years) = 67.38 ± 8.57	1) Freedom from congestion at 72 h (defined as jugular venous pressure of <8 cm without orthopnoea and with trace peripheral oedema or no oedema)	1) Statistically significant. Higher in continuous arm 69.05% vs bolus arm 43.59%, (P= 0.02) 2) Statistically significant. Lower dyspnoea score in continuous arm 1.15 ± 0.35 vs bolus arm 2.66 ± 0.83, (P= 0.003) 3) Statistically significant. Higher in continuous arm 5145.98ml ± 621.37

Author, Year, Country	Study Design	Study Location	Intervention & Comparator: Type, Dose, Route	Sample: Size (n), Sex. Age (years), NYHA Class, LVEF		Reported Outcomes and measurement tool if used	Results
				Continuous	Bolus		
Zheng et al.[24] 2021 China	Single-centre, RCT	Tertiary-care medical centre	according to the ceiling dose for the respective eGFR. <u>Bolus</u> Received a fixed total dose of furosemide as an intravenous bolus injection within 5 minutes every day according to eGFR. The fixed dose of furosemide was 160 mg per day for group A and 200 mg per day for group B according to the ceiling dose for the respective eGFR.	NYHA class III 32 (76.19%) NYHA class IV 10 (23.81%) Mean LVEF= 56.12% ± 10.92	NYHA class III 33 (84.62%) NYHA class IV 6 (15.38%) Mean LVEF= 58.80% ± 11.24	2) The degree of dyspnoea at 72 h (Borg's category ratio scale) 3) Total net urinary output (defined as urine output minus oral plus IV intake normalized per 72 hours) 4) Weight loss (kg) at 72 h 5) Total urinary sodium excretion at 72h 6) Length of hospital stay (days) 7) Adverse events at 72 h	vs bolus arm 3755.95ml ± 456.93, (P=0.01) 4) Statistically significant. Greater reductions observed in continuous arm -4.72kg ± 1.01 vs bolus arm.-3.53kg ± 0.73, (P= 0.02) 5) Statistically significant. Higher in continuous arm 385.05 ± 38.15 vs bolus arm 320.33 ± 37.67, (p=0.02) 6) Statistically significant. Shorter in the continuous arm 10.36 ± 4.20 days vs bolus arm 15.68 ± 6.15 days, (P= 0.02) 7) No significant difference

Abbreviations: NYHA= New York Heart Association, LVEF= Left ventricular ejection fraction, RCT= Randomized controlled trial, OR= Odds ratio, CI= Confidence interval, ICU= Intensive care unit, ADHF= Acute decompensated heart failure, TFC= Thoracic fluid content , CrCl= Creatinine clearance*, GFR= Estimated glomerular filtration rate*

Appendix D: Overview of the risk of bias assessment undertaken using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2)

Legend: ✓ Low risk of bias, x High risk of bias, ~ Some concerns

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Frea et al.[22]	✓	✓	✓	✓	✓	✓
Shree et al.[23]	x	~	x	✓	~	x
Palazzuoli et al.[19]	✓	✓	✓	✓	✓	✓
Ragab et al.[20]	x	✓	✓	✓	~	x
Thomson et al.[21]	✓	~	✓	✓	~	~
Zheng et al.[24]	✓	~	~	✓	~	~

APPENDIX E - RISK OF BIAS ASSESSMENT USING ROB2

Frea et al. Risk of bias assessment
Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.
Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Randomization was carried out by the use of sequentially numbered cases prepared before starting the study by a computerized sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant differences in baseline characteristics	N
Risk-of-bias judgement		Low

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	A double-blind, double- dummy design was used.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	A nurse unassigned to patients' care prepared a syringe pump for continuous infusion and syringes for boluses. According to the assigned treatment arm, syringes contained the assigned dose of furosemide or a 5% glucose solution placebo.	PN
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Intention to treat analysis	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

DOMAIN 3: MISSING OUTCOME DATA

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	0 excluded from analysis	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

DOMAIN 4: RISK OF BIAS IN MEASUREMENT OF THE OUTCOME

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	A double-blind, double- dummy design was used.	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The researchers' pre-specified intentions are available in sufficient detail, with planned outcomes ,measurements and analyses which be compared with those presented in the published report.	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	There is clear evidence that all eligible reported results for the outcome domain correspond to all intended outcome measurements.	N
5.3 ... multiple eligible analyses of the data?		N
Risk-of-bias judgement		Low

OVERALL RISK OF BIAS

Risk-of-bias judgement	The study is judged to be at low risk of bias for all domains for this result.	Low

Shree et al. Risk of bias assessment
Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.
Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	No random element was used in generating the allocation sequence	N
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	There is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation.	N
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	There are imbalances that indicate problems with the randomization process,	Y
Risk-of-bias judgement		High

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS (EFFECT OF ASSIGNMENT TO INTERVENTION)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open label study	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No evidence that the result was not biased by missing outcome data	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NI
Risk-of-bias judgement		High

DOMAIN 4: RISK OF BIAS IN MEASUREMENT OF THE OUTCOME

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The method of measuring the outcome is appropriate	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement involving the same methods and thresholds were used at comparable time points.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely to influence observer-reported outcomes which are used in the study as they do not involve judgement,	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No protocol available	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Analysis intentions are not available,	NI
5.3 ... multiple eligible analyses of the data?	Analysis intentions are not available,	NI
Risk-of-bias judgement		Some concerns

OVERALL RISK OF BIAS

Risk-of-bias judgement		High

Palazzuoli Risk of bias assessment
Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.
Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Patients were randomized using a 1:1 ratio using a computer-generated scheme	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	The randomization was casual, and the physicians did not previously know the assigned arm.	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant Baseline Differences	N
Risk-of-bias judgement		Low

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS (EFFECT OF ASSIGNMENT TO INTERVENTION)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open label study	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No blinding of carers and people delivering the interventions	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All data were analyzed with intention-to-treat.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

DOMAIN 3: MISSING OUTCOME DATA

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	One patient was excluded from the analysis because of missing data regarding various laboratory measurements. The number of participants with missing outcome data is sufficiently small and should have made no important difference to the estimated effect of intervention.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

DOMAIN 4: RISK OF BIAS IN MEASUREMENT OF THE OUTCOME

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Methods of outcome measurement are suitable for the outcome intended to evaluate. Outcome measurement likely to be sensitive to plausible intervention effects.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement involve the same measurement methods and thresholds, used at comparable time points.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Outcome assessors were not blinded to intervention status.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely to influence as observer-reported outcomes do not involve judgement which is the case in this study	N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The researcher's pre-specified intentions are available in sufficient detail and planned outcome measurements and analyses can be compared with those presented in the published report	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
5.3 ... multiple eligible analyses of the data?	Particular outcome measurement were not analysed in multiple ways.	N
Risk-of-bias judgement		Low

OVERALL RISK OF BIAS

Risk-of-bias judgement		Low

Ragab et al Risk of bias assessment
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Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	The only information about randomization methods is a statement that the study is randomized.	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PN
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No imbalances are apparent	N
Risk-of-bias judgement		High

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS (EFFECT OF ASSIGNMENT TO INTERVENTION)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Appears to be intention to treat analysis but does not specify this.	PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

DOMAIN 3: MISSING OUTCOME DATA

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Outcome measurements are unsuitable for the outcome they are intended to evaluate.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement used the same measurement methods and thresholds at comparable time points.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely to influence as outcomes used in study are observer-reported outcomes that do not involve judgement.	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No protocol available	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Analysis intentions are not available	NI
5.3 ... multiple eligible analyses of the data?	Analysis intentions are not available,	NI
Risk-of-bias judgement		Some concerns

OVERALL RISK OF BIAS

Risk-of-bias judgement		High

Thomson et al Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Randomization occurred separately at each institution and in each stratum in blocks of 10. Group assignments were contained in individual sealed envelopes located at each institution.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Any observed imbalances are compatible with chance.	N
Risk-of-bias judgement		Low

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS (EFFECT OF ASSIGNMENT TO INTERVENTION)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All data were analyzed by intention-to-treat.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns

DOMAIN 3: MISSING OUTCOME DATA

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	The number of participants with missing outcome data is sufficiently small so which means there is no important difference to the estimated effect of intervention. One patient was excluded from final data analysis because of an incomplete consent form. Two patients in the iIV group were crossed over into the continuous infusion group and 1 patient in the cIV group received intermittent dosing. Removal of these patients in an as-treated analysis did not affect the overall results.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Methods of outcome measurement were suitable for the outcome they were intended to evaluate.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement were used as the same measurement methods and thresholds are comparable.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely to influence as observer-reported outcomes do not involve judgement which is the case in this study	N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No protocol available	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Analysis intentions are not available.	NI
5.3 ... multiple eligible analyses of the data?	Analysis intentions are not available.	NI
Risk-of-bias judgement		Some concerns

OVERALL RISK OF BIAS

Risk-of-bias judgement		Some concerns

Zheng et al Risk of bias assessment
Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.
Where questions relate only to sign posts to other questions, no formatting is used.

DOMAIN 1: RISK OF BIAS ARISING FROM THE RANDOMIZATION PROCESS

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Randomization was performed using the sequentially numbered cases by computer-generated scheme.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No imbalances are apparent	N
Risk-of-bias judgement		Low

DOMAIN 2: RISK OF BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTIONS (EFFECT OF ASSIGNMENT TO INTERVENTION)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All analyses were conducted on an intention-to-treat basis.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Some concerns

DOMAIN 3: MISSING OUTCOME DATA

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Less than 95% of data was available from participants that had been randomised.	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No evidence provided	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	All missing outcome data occurred for documented reasons that are related to the outcome. Reported reasons for missing outcome data were similar between the intervention groups.	PY
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		PN
Risk-of-bias judgement		Some concerns

DOMAIN 4: RISK OF BIAS IN MEASUREMENT OF THE OUTCOME

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Methods of outcome measurement are suitable for the outcome intended to evaluate. Outcome measurement likely to be sensitive to plausible intervention effects.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement involve the same measurement methods and thresholds, used at comparable time points.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Unlikely to influence as observer-reported outcomes do not involve judgement which is the case in this study	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low

DOMAIN 5: RISK OF BIAS IN SELECTION OF THE REPORTED RESULT

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No protocol available	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Analysis intentions are not available	NI
5.3 ... multiple eligible analyses of the data?	Analysis intentions are not available	NI
Risk-of-bias judgement		Some concerns

OVERALL RISK OF BIAS

Risk-of-bias judgement		Some concerns