Trial			Study design, Arms, and Objectives	Outcomes	Results	Conclusion
Vasodilatory Therapies						
Vasopressin Receptor Antagonists						
Tolvaptan (N= 6)						
1	AQUAMARINE	Matsue et al., 2016[23] Japan	RCT (n=217 AHF and renal dysfunction) compared the efficacy of adding tolvaptan 15 (mg/day) to loop diuretics	Primary endpoint: UOP within 48h of hospitalisation. Secondary endpoints: - Improvement of dyspnea from baseline measured on patient-reported 7-point Likert scale up to 48 h after enrollment. - Change in B-type natriuretic peptide (BNP) - Change in body weight	- The tolvaptan enhanced diuresis more than the conventional treatment (6464.4 vs 4999.2 mL; P < .001) - At all time points within 48 hours, except 6 hours after randomisation, dyspnea improved significantly in the tolvaptan group than in the placebo group. - Significantly more significant weight loss in the tolvaptan group - No significant difference in absolute BNP reduction.	In AHF patients with renal dysfunction, adding tolvaptan to conventional therapy increased diuresis and alleviated dyspnea symptoms.
2	TACTICS-HF	Felker et al., 2017[30] USA	RCT (n=257 patients with AHF) received either 30 mg of oral tolvaptan or a placebo	Primary endpoint: The proportion of patients who improved at least moderately in dyspnea on a 7-point Likert scale after 8 and 24 hours. Secondary endpoints: - Dyspnea relief - Fluid loss - Change in body weight - The proportion of patients free from clinical congestion at 48 and 72 h	- Proportion of patients experienced dyspnea relief did not differ significantly between tolvaptan and placebo groups at 8 h (p = 0.59) and at 24 h (p = 0.80). - For the 48-hour treatment period, Tolvaptan was linked to significantly greater weight and fluid loss.	Tolvaptan did not improve the proportion of AHF patients classified as responders.

3	EVEREST	Gheorghiade, et al.,2007[31] Multinational	RCT (n=4133 patients with AHF) assessed the effects of tolvaptan 30 mg/day versus placebo.	Primary endpoints: - Composite score of changes from baseline in patient-assessed global clinical status and body weight.	- Tolvaptan showed superiority about the composite endpoint at day 7, P<0.001 and the bodyweight reduction at day one and day 7: P<0.001. - Global clinical status improvements were comparable between groups.	Tolvaptan improved symptoms in AHF patients.
4	SECRET	Konstam et al., 2017[24] USA	RCT (n=250 patients with AHF) assessed the effects of tolvaptan 30 mg/day versus placebo.	Primary endpoint: - Change in dyspnea score (Likert scale). Secondary endpoints: - Change in body weight. Other endpoints: - Change in BNP	- At day 3, tolvaptan was associated with significant dyspnea reduction (81.2% vs. 66.3%; p = 0.02) and greater weight loss (p < 0.01), than the placebo group. - There were no reported differences in BNP levels between study groups.	Tolvaptan showed improvement in dyspnea and weight loss.
5	K STAR	Inomata et al., 2017[32] Japan	RCT in 81 patients with fluid retention (despite taking ⩾40 mg/day furosemide, with an eGFR <45 mL/min/1.73m2 administered either ⩽15 mg/day tolvaptan or ⩽40 mg/day increased furosemide.	Primary endpoint: - The average change in UOP compared with its baseline values. Secondary endpoints: - Changes in body weight - Congestive signs and symptoms	- Urine volumes were significantly higher in the tolvaptan than the furosemide group. - There was a modest difference in body weight or improved congestion between the two groups	Tolvaptan increased diuresis without further renal impairment.
6	ACTIV	Gheorghiade et al., 2004 [25] USA	RCT (n=250 patients) compared different doses (30, 60, or 90 mg/d) of tolvaptan versus placebo in addition to standard therapy	Primary endpoints: - Change in body weight at 24 h - worsening heart failure Secondary endpoints: - Changes in dyspnea, oedema, urine output, diuretics use, patient- and physician-assessed symptom scales.	- At 24 h, body weight decreased in tolvaptan groups 30, 60, and 90 mg/d compared to placebo (P< or =.008). - No significant difference in worsening heart failure was reported between tolvaptan and placebo groups. - Differences in secondary endpoints were not significant except for dyspnea.	Tolvaptan decreased bodyweight more effectively than standard therapy.
Conivaptan						

7		Goldsmith et al., 2008[33] USA	RCT (n=170 patients) dose-finding study; examined different escalating doses of conivaptan or placebo.	Did not specify a primary endpoint - Change in patient-assessed severity of dyspnea - Change in global status (VAS score) - Urinary output	- Both groups were comparable in both patient or clinician global and respiratory status assessments at 48 h. - At 24 hours, conivaptan increased UOP significantly more than placebo (P=0.02).	Conivaptan safely improves UOP but does not relieve dyspnea.
Tezosentan						
8	VERITAS I, II	McMurray et al., 2007[34] Multi	RCT (n=1435 patients with AHF) evaluated the effect of adjuvant tezosentan use.	The primary endpoint of the individual studies: - changes in dyspnea using a VAS over 24 h.	- Tezosentan did not improve dyspnea more than placebo	Tezosentan did not improve symptoms in AHF patients.
Serelaxin (N= 2)						
9	Pre-RELAX AHF	Teerlink et al., 2009 [26] Multinational	RCT (n= 234) dose-finding study compared different relaxin doses 10, 30, 100, or 250 µg/kg vs placebo	Primary endpoints (not prespecified) :the overall effect of relaxin across several clinical domains: - Relief of dyspnea (Likert scale and VAS). - In-hospital worsening heart failure	- Absolute increase in early and sustained dyspnea relief was found in 17·5%, vs 76% in placebo and relaxin (30 µg/kg), respectively. - The VAS changes proposed a positive effect on dyspnea relief.	Relaxin (30µg/kg) use relieving dyspnea.
10	RELAX-AHF	Teerlink et al., 2013 [27] Multinational	RCT (n=1161 patients with AHF) receive either 30 µg/kg/day serelaxin or placebo	Primary endpoints: - Relief of dyspnea (Likert scale), and by VAS.	- Serelaxin improved the VAS AUC dyspnea endpoint (448 mm × h; p=0·007) compared with placebo but had no significant effect on the other primary outcomes	Treatment with serelaxin was associated with dyspnea relief.
Neseritide (N= 3)						

11	VMAC	Publication Committee for the VMAC Investigators, 2002 [35]	RCT (n= 489 patients) compared the efficacy of nesiritide, nitroglycerin, and placebo.	Primary endpoints: - The absolute changes in PCWP - The patient's self-evaluation of dyspnea	- Nesiritide decreased PCWP from baseline more than placebo (P<0.001) and improved early dyspnea compared with placebo (P=.03).	Nesiritide improves hemodynamic function and dyspnea more effectively than placebo.
12	ASCEND-HF	O'Connor et al., 2011 [36] Multinational	RCT (n= 7141 patients with AHF compared nesiritide or placebo	Primary endpoint: Coprimary endpoints of dyspnea change after six and 24hr (Likert scale).	- Nesiritide showed non-significant improvements in dyspnea at 6 h (44.5% vs. 42.1%) and 24 h (68.2% vs. 66.1%), compared to placebo.	Nesiritide has a nonsignificant effect on dyspnea.
13		Shihui Fu et al., 2012 [37] China	RCT (n= 140 geriatric patients) compared conventional treatment vs nesiritide.	Primary endpoints not specified - Dyspnea using the medical research council (MRC) scales. - Assessment of oedema - Assessment of water loss volume	- The nesiritide group had significantly lower MRC scales (p<0.05) and more net body fluid losses (p<0.05) compared to the control group - Sores of oedema had no significant difference on day four between the two groups (p>0.05) but were significantly lower in the nesiritide group on days 8 and 14 (all p<0.05).	Nesiritide was associated with better symptoms relief, such as dyspnea and oedema.
Rolofylline (N=2)						

14	PROTECT pilot study	Cotter et al., 2008 [38] Multinational	RCT (n=301 patients with AHF and renal impairment) dose-finding study compared placebo or rolofylline 10, 20, or 30 mg.	Composite primary trichotomous endpoint: - Patient-reported dyspnea (7-point Likert scale), worsening heart failure and worsening renal insufficiency. - Patients were classified as improved, worse, or unchanged).	- Patient-reported dyspnea: rolofylline significantly improved dyspnea compared to placebo (52.7% vs 37.2%). - Comparing rolofylline 30 mg (the dose selected for the pivotal study) with placebo, the estimated odds ratio was 0.51 (95% CI 0.28-0.94) for the Composite primary trichotomous endpoint.	Rolofylline improved dyspnea relief and decreased worsening heart failure or renal function.
15	PROTECT	Massie et al., 2011 [39] Multinational	RCT (n=2,033) patients with dyspnea at rest or minimal activity, estimated CrCl 20–80 mL/ min, BNP ≥500 pg/mL to rolofylline 30 mg/day or placebo for up to 3 days).	The primary endpoint (clinical composite) - Treatment success, i.e., moderate /marked improvement in dyspnea. - Treatment failure, death or readmission for heart failure (HF) or worsening heart failure (WHF) - No change in the patient's condition.	- Rolofylline was not found to be superior to placebo in terms of the primary endpoint (odds ratio, 0.92; P=0.35).	Rolofylline does not show promise in treating patients AHF with renal dysfunction.
Calcitrope trials						
Levosimendan						
16	REVIVE I and II	Packer et al., 2013 [40] USA	Revive I) n =100), II) n=600)patients with ADHF) evaluated the effect of adjuvant levosimendan use.	Composite endpoint of clinically Patient-reported measures: - Improved: moderate / markedly improvement - Worse: Persistent /unresponsive symptoms - Unchanged	- More patients were improved in the levosimendan group compared to placebo (58 vs 44). - Clinical worsening occurred in fewer levosimendan patients (58 vs 82, p = 0.015).	levosimendan can produce significant symptomatic benefits.
Istaroxime						

17		Carubelli et al., 2020 [41] Multinational	RCT (n=120 AHF patients with reduced LVEF and low SBP) evaluated the efficacy of two different doses of istaroxime (0.5 and 1.0 µg/kg/min) compared to placebo.	Secondary endpoints - Changes in dyspnea by VAS - Changes in NT-proBNP - Worsening heart failure	- There were no significant differences between istaroxime and placebo on any secondary endpoints. - Overall diuresis was numerically more significant in istaroxime-treated patients during a 24-hour infusion.	Istaroxime use did not add benefit to the diuretic response.
Cimlanod						
18	STAND-UP AHF	Felker et al., 2021[42] Multinational	RCT (n=322 patients) done in 2 sequential cohorts - Cohort I: escalate cimlanod doses or placebo. - Cohorts II: use the highest tolerated doses of cimlanod (6 and 12 mg/kg/min) or placebo.	Secondary endpoints: - Change in plasma concentration of NT-proBNP. - Change in patient-reported resting dyspnea using the AUC of the numeric rating scale.	- The reduction in NT-proBNP was more significant with cimlanod than with placebo. - Dyspnea symptoms were generally comparable between patients assigned to cimlanod and placebo.	Cimlanod marginally improved some parameters related to congestion.
Myotrope trials						
Omecamtiv mecarbil						
19	ATOMIC-AHF	Teerlink et al., 2016[43] Multinational	RCT (n=606 patients), a dose-finding study, evaluated the effect of omecamtiv mecarbil on dyspnea relief. Patients were randomised in three sequential cohorts to escalate doses (low, medium or high) versus placebo.	Primary endpoint - Dyspnea relief (Likert scale) Secondary endpoints - Dyspnea numerical response AUC - Patient global assessment response - NT-proBNP change from baseline.	- Dyspnea relief with omecamtiv mecarbil marginally differed from pooled placebo of the three doses cohorts (p=0.33). - There were no statistically significant differences in secondary endpoints between treatment cohorts and the pooled placebo. - The high dose cohort had more remarkable dyspnea improvement than its matching placebo group (p = 0.038).	In patients with AHF, omecamtiv mecarbil had no significant effect on dyspnea.
SGLT2 Inhibitors						
Empagliflozin						

20	EMPA-RESPONSE-AHF	Damman et al 2019[29] Netherlands	RCT (n= 80 patients) with AHF, diabetic and non-diabetic. Patients were randomised to 10mg/day empagliflozin or placebo as an adjuvant to loop diuretics.	Primary endpoints - Change in the AUC of dyspnea visual analogue scale - Diuretic response - Percentage change in NT-proBNP	- No difference was seen in the AUC of dyspnea VAS over the first four days (P = 0.18) in the empagliflozin and placebo groups, respectively. - Diuretic response and percentage change in NT-proBNP was comparable in empagliflozin and placebo group, (P = 0.37, 0.63, respectively).	Empagliflozin did not enhance diuretic response.
Miscellaneous						
Thiamine						
21	Smithline et al., 2019 [44] Multinational		RCT (n= 118 patients) examined the effect of adding thiamine to the standard of care	Primary endpoint - Dyspnea severity using VAS in three positions: sitting upright on supplemental oxygen, sitting upright off oxygen, or lying supine off oxygen.	- There was only one significant difference between groups over time in dyspnea measured sitting upright on oxygen (P=0.015). Dyspnea did not change in any of the other positions.	The results of this study do not support the adjuvant use of thiamine in AHF.
Clevidipine						
22	PRONTO	Peacock et al., 2014[45] Multinational	RCT to study the efficacy of Clevidipine vs standard of care in patients (n=104) with HF having SBP ≥160 mmHg and dyspnea ≥50 on a scale (VAS)	Secondary endpoint: - Dyspnea reduction (VAS score) at different time points up to 720 minutes after administration	- Clevidipine patients had more remarkable mean VAS dyspnea improvement than standard care (-37 vs -28mm, p=0.02) at 45 minutes, a difference that persisted for up to 3 h.	Clevidipine effectively lowers blood pressure and improves dyspnea in hypertensive AHF patients.
Glucocorticoid						

23	COPE-ADHF	Liu et al., 2014[46]	RCT (n=102 patients) to assess the efficacy of glucocorticoid therapy (single dose dexamethasone followed by prednisolone daily for 1week).	Other Outcomes - Patient-assessed dyspnea (7-point scale). - Physician-assessed global clinical (7-point scale).	- After seven days, the glucocorticoid-treated group had greater patient-assessed dyspnea improvement than the standard treatment group (2.71 vs 1.78 points, $P < 0.01$). - Improvement in physician-assessed global clinical status, favouring glucocorticoids, were also found ($P < 0.01$).	This preliminary trial shows the potential benefit of short-term use of glucocorticoid in patients with ADHF.

AHF: Acute heart failure; RCT: randomised controlled trial; UOP: urine output; BNP: Brain natriuretic peptide; PCWP: pulmonary capillary wedge pressure; VAS: visual analogue scale; AUC: area under the curve; ADHF: Acute decompensated heart failure; SBP: systolic blood pressure; NT-proBNP: NT-proB-type natriuretic peptide; LVEF: Left ventricular ejection fraction (LVEF); WHF: worsening heart failure; CrCl creatinine clearance.