

Supplementary Table 1: Key clinical trials on clinically available, novel or investigational agents in acute heart failure with neutral outcomes. Only the largest study per drug is reported.

Acronym	Drug	Primary Endpoint
OPTIME-CHF	Milrinone	Cumulative hospitalization days
SURVIVE	Levosimendan	All-cause mortality
EVEREST	Tolvaptan	All-cause mortality; CV death or HF hospitalization
PROTECT	Rolofylline	All-cause death; HF status; renal function
ASCEND-HF	Nesiritide	Death or HF hospitalization; dyspnea relief
TRUE-AHF	Ularitide	CV death
RELAX-AHF-2	Serelaxin	CV death, worsening HF
DAD-HF II	Dopamine	All-cause death and HF hospitalization
ATOMIC-AHF	Omecamtiv mecarbil	Dyspnea relief

Supplementary Table 2: Updated definition of advanced heart failure by the Heart Failure Association of the European Society of Cardiology (from Crespo-Leiro et al. [2])

All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF $\leq 30\%$, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.⁹
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWT (<300 m) or pVO_2 ($<12-14$ mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

ARVC, arrhythmogenic right ventricular cardiomyopathy; BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; HFA, Heart Failure Association; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2 , peak exercise oxygen consumption; RV, right ventricular; 6MWT, 6-minute walk test distance.