# Online supplement table 1: Study characteristics

<table>
<thead>
<tr>
<th>Main author</th>
<th>Year</th>
<th>Setting of recruitment</th>
<th>Intervention &amp; Comparator</th>
<th>Sample Size</th>
<th>Primary outcome</th>
<th>Inclusion criteria</th>
<th>Sample Characteristics (Mean age, sex distribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Johnson     | 2019 | 13 centres in England and Scotland, hospital/community cardiology or palliative care clinics or hospices | IG: modified release morphine 10 mg, twice per day for 12 weeks, CG: placebo capsules identical in appearance, taste, and smell twice per day for 12 weeks | IG: 21, CG: 24 | Primary: average numerical rating scale breathlessness intensity score over the previous 24 h assessed at 4 weeks. | • Aged ≥18 years  
• New York Heart Association (NYHA) class III/IV symptoms  
• Had either left ventricular systolic dysfunction defined as left ventricular ejection fraction <40% or left ventricular ejection fraction >40% and left ventricular hypertrophy, left atrial dilation or abnormal diastolic function  
• N-terminal-pro-B-type natriuretic peptide ≥1000 pg/mL or B-type natriuretic peptide ≥250 pg/mL within the last 3 months  
• Were on a guideline-recommended medical treatment for chronic heart failure and unchanged for ≥2 weeks;  
• Had a glomerular filtration rate ≥30 mL/min/(1.73m2) within 2 weeks | • Age (years) ± SD:  
IG: 74.4 ± 6  
CG: 70.1 ± 14  
• Sex (men/women):  
IG: 18/3  
CG: 20/4  
• NYHA class III:  
IG: 20  
CG: 24  
• NYHA class IV  
IG: 1  
CG: 0 |
• Scored ≥grade 2 on the modified Medical Research Council (mMRC) breathlessness scale

| Cross-over RCT | Oxberry | Castle Hill Hospital, Hull, United Kingdom | IG 1: oral morphine solution 5 mg four times per day | IG 1: 39
| | IG 2: oral Oxycodone solution 2.5 mg four times per day | IG 2: 39
| | CG: oral placebo | CG: 39
| Mean change from baseline to Day 4 in NRS average breathlessness over the past 24 h | • Adults with a diagnosis of NYHA III–IV CHF
| | • Impairment of left ventricular systolic function (defined as an ejection fraction of <45% on trans-thoracic echocardiography) on standard medical therapy (diuretics and an inhibitor of the renin-angiotensin system at stable dose for at least 1 month)
| | • Age (years): 70.2 ± 11.1 (range 41-89)
| | • Sex (men/women): 30/5
| | • NYHA class
| | III: 31
| | IV: 4

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Location</th>
<th>Intervention</th>
<th>Participants</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson</td>
<td>2002</td>
<td>Heart failure clinic, Glasgow, United Kingdom</td>
<td>IG: 5 mg oral morphine solution for 4 days; if creatinine &lt;200 µmol/l: 2.5mg oral morphine (min. 2 participants received lower dose) CG: placebo for 4 days</td>
<td>IG: 10 CG: 10</td>
<td>Patients attending the heart failure clinic with NYHA stage III or IV heart failure, clinically stable (NYHA status unchanged for 1 month and medication unchanged for 2 weeks) on optimum therapy (diuretic and ACE inhibitor or losartan)</td>
</tr>
<tr>
<td>Ferreira</td>
<td>2018</td>
<td>Southern Adelaide Palliative Services &amp; Austin Health, Australia</td>
<td>IG: oral sustained release morphine once-daily for seven consecutive days CG: placebo</td>
<td>IG: 11 C: 12</td>
<td>Difference in mean breathlessness scores &quot;right now&quot; on Visual Analogue Scale</td>
</tr>
</tbody>
</table>

- Optimally treated pulmonary artery hypertension for several months and were still breathless
- Secondary heart failure class III or IV of the New York Heart Association functional classification corresponding to marked limitation of physical activity due to breathlessness or breathlessness at rest
- Calculated creatinine clearance of >10 mmol/L
- Optimized hemoglobin levels
- On stable medications over the previous seven days

- Age (years): 67 (range 45-85)
- Sex (men/women): 10/0
- NYHA class III:8 IV:2

- Age (years): 64 ± 11
- Sex (men/women): 7/16
- Australian Karnofsky Performance Status
  - AKPS 50: 2
  - AKPS 60: 4
  - AKPS 70: 9
  - AKPS 80: 5
  - AKPS 90: 3
<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Location</th>
<th>Treatment IG</th>
<th>Treatment CG</th>
<th>Primary Study End Points</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
</table>
| Olson | 2014 | Mayo Clinic, Minnesota, USA  | 0.05 mg fentanyl intrathecal injection | sham injection | Ischaemic or dilated cardiomyopathy with duration of HF symptoms >1 year | Age (years): 60 ± 2  
Sex (men/women): 7/2  
NYHA class: I:3  
II:3  
III:3 |
| Smith | 2020 | Mayo Clinic, Minnesota, USA  | 0.05 mg fentanyl intrathecal injection | sham injection | Ischaemic or dilated cardiomyopathy with symptom duration >1 year | Age (years): 61 ± 9  
Sex (men/women): 9/2  
NYHA class: I:3  
II:8 |
| Chua  | 1997 | United Kingdom               | 1 mg/kg dihydrocodeine solution     | placebo      | Dyspnea, exercise tolerance | Age (years): 65.5 ± 1.5 (range 58-75)  
Sex (men/women): 12/0  
NYHA class: II:6  
III: 6 |
<table>
<thead>
<tr>
<th>Williams</th>
<th>2003</th>
<th>Not reported</th>
<th>IG: 1 or 2 mg diamorphine intravenous injection</th>
<th>CG: placebo, intravenous injection</th>
<th>IG: 16</th>
<th>CG: 16</th>
<th>Ventilatory responses to exercise (e.g. VO2, Tidal Volume)</th>
<th>Not reported</th>
</tr>
</thead>
</table>

- Age (years): 61 ±2 (range 38-75)
- Sex (men/women): 15/1
- Ejection fraction: 35.3% (range 16-45%)

Legend: IG: intervention group, CG: control group, HF: heart failure, SD: standard deviation