## Online supplement table 1: Study characteristics

<table>
<thead>
<tr>
<th>Main author</th>
<th>Year</th>
<th>Country &amp; 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>
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<tbody>
<tr>
<td><strong>RCT</strong></td>
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</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**

2011

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
<table>
<thead>
<tr>
<th>Johnson</th>
<th>2002</th>
<th>Heart failure clinic, Glasgow, United Kingdom</th>
<th>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)</th>
<th>CG: placebo for 4 days</th>
<th>IG: 10</th>
<th>CG: 10</th>
<th>Breathlessness</th>
<th>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)</th>
<th>• Age (years): 67 (range 45-85)</th>
<th>• Sex (men/women): 10/0</th>
<th>• NYHA class III:8</th>
<th>IV:2</th>
</tr>
</thead>
<tbody>
<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</td>
<td>CG: placebo</td>
<td>IG: 11</td>
<td>C: 12</td>
<td>Difference in mean breathlessness scores “right now” on Visual Analogue Scale</td>
<td>• Optimally treated pulmonary artery hypertension for several months and were still breathless</td>
<td>• 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</td>
<td>• Calculated creatinine clearance of &gt;10 mmol/L</td>
<td>• Optimized hemoglobin levels</td>
<td>• On stable medications over the previous seven days</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
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<td>Olson</td>
<td>2014</td>
<td>Mayo Clinic, Minnesota, United States</td>
<td>IG: 0.05 mg fentanyl intrathecal injection</td>
<td>CG: sham injection</td>
<td>VO2 peak (B)</td>
<td>Ischaemic or dilated cardiomyopathy with duration of HF symptoms &gt;1 year, Stable HF symptoms (&gt;3 months), Left ventricular ejection fraction ≤35% (from clinical records within 3 months), Body mass index &lt;35 kg/m² (at enrolment), Current non-smokers with a past smoking history of &lt;15 pack-years (at time of enrolment)</td>
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<tr>
<td>Smith</td>
<td>2020</td>
<td>Mayo Clinic, Minnesota, United States</td>
<td>IG: 0.05 mg fentanyl intrathecal injection</td>
<td>CG: sham injection</td>
<td>VO2 peak (B)</td>
<td>Ischaemic or dilated cardiomyopathy with symptom duration &gt;1 year, Stable HF symptoms (&gt;3 months), Left ventricular ejection fraction ≤40%, Body mass index &lt;35 kg/m², Non-smokers with a smoking history of &lt;15 pack-years, No diagnosis of coexisting pulmonary disease</td>
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<td>Chua</td>
<td>1997</td>
<td>United Kingdom</td>
<td>IG: 1 mg/kg dihydrocodeine solution</td>
<td>CG: placebo</td>
<td>Dyspnea, exercise tolerance (B)</td>
<td>Not reported</td>
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- Age (years): 60 ± 2
- Sex (men/women): 7/2
- NYHA class I:3, II:3, III:3
- Age (years): 61 ± 9
- Sex (men/women): 9/2
- NYHA class I:3, II:8
- Age (years): 65.5 ± 1.5 (range 58-75)
- Sex (men/women): 12/0
- NYHA class II:6, III:6
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<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>
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</table>

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

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