### 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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<tr>
<td>Johnson</td>
<td>2019</td>
<td>13 centres in England and Scotland, hospital/communtiy cardiology or palliative care clinics or hospices</td>
<td>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</td>
<td>IG: 21; CG: 24</td>
<td>Primary: average numerical rating scale; breathlessness intensity score over the previous 24 h assessed at 4 weeks.</td>
<td>• Aged ≥18 years • New York Heart Association (NYHA) class III/IV symptoms • Had either left ventricular systolic dysfunction defined as left ventricular ejection fraction &lt;40% or left ventricular ejection fraction &gt;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</td>
<td>• 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</td>
</tr>
</tbody>
</table>
- Scored ≥ grade 2 on the modified Medical Research Council (mMRC) breathlessness scale

**Cross-over RCT**

<table>
<thead>
<tr>
<th>Oxberry</th>
<th>2011</th>
<th>Castle Hill Hospital, Hull, United Kingdom</th>
<th>IG 1: oral morphine solution 5 mg four times per day</th>
<th>IG 2: oral Oxycodone solution 2.5 mg four times per day</th>
<th>CG: oral placebo</th>
<th>IG 1: 39</th>
<th>IG 2: 39</th>
<th>CG: 39</th>
<th>Mean change from baseline to Day 4 in NRS average breathlessness over the past 24 h</th>
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- 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: 2.5 mg oral morphine (min. 2 participants received lower dose) CG: placebo for 4 days</th>
<th>Breathingness</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 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 CG: placebo</td>
<td>Difference in mean breathlessness scores &quot;right now&quot; on Visual Analogue Scale</td>
<td>• Optimally treated pulmonary artery hypertension for several months and were still breathless</td>
<td>• Age (years): 64 ± 11</td>
<td>• Sex (men/women): 7/16</td>
<td>• Australian Karnofsky Performance Status AKPS 50: 2 AKPS 60: 4 AKPS 70: 9 AKPS80: 5 AKPS 90: 3</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Inclusion Criteria</td>
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<td>Demographics</td>
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| Olson   | 2014 | Mayo Clinic, Minnesota, United States of America | IG: 0.05 mg fentanyl intrathecal injection | CG: sham injection | • Ischaemic or dilated cardiomyopathy with duration of HF symptoms >1 year  
• Stable HF symptoms (>3 months)  
• Left ventricular ejection fraction ≤35% (from clinical records within 3 months)  
• Body mass index <35 kg/m2 (at enrolment)  
• Current non-smokers with a past smoking history of <15 pack-years (at time of enrolment) |                                       | Age (years): 60 ± 2  
Sex (men/women): 7/2  
NYHA class I:3  
II:3  
III:3 |
| Smith   | 2020 | Mayo Clinic, Minnesota, United States of America | IG: 0.05 mg fentanyl intrathecal injection | CG: sham injection | • Ischaemic or dilated cardiomyopathy with symptom duration >1 year  
• Stable HF symptoms (>3 months)  
• Left ventricular ejection fraction ≤40%  
• Body mass index <35 kg/m2  
• Non-smokers with a smoking history of <15 pack-years  
• No diagnosis of coexisting pulmonary disease |                                       | Age (years): 61 ± 9  
Sex (men/women): 9/2  
NYHA class I:3  
II:8 |
| Chua    | 1997 | United Kingdom            | IG: 1 mg/kg dihydrocodeine solution | CG: placebo      | • Dyspnea, exercise tolerance (B) | Not reported | 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>Ventilatory responses to exercise (e.g. VO2, Tidal Volume)</th>
<th>CG: 16</th>
<th>Not reported</th>
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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%)