Effect of opioids for breathlessness in heart failure: a systematic review and meta-analysis

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ABSTRACT

Background For the treatment of breathlessness in heart failure (HF), most textbooks advocate the use of opioids. Yet, meta-analyses are lacking.

Methods A systematic review was performed for randomised controlled trials (RCTs) assessing effects of opioids on breathlessness (primary outcome) in patients with HF. Key secondary outcomes were quality of life (QoL), mortality and adverse effects. Cochrane Central Register of Controlled Trials, MEDLINE and Embase were searched in July 2021. Risk of bias (RoB) and certainty of evidence were assessed by the Cochrane RoB 2 Tool and Grading of Recommendations Assessment, Development and Evaluation criteria, respectively. The random-effects model was used as primary analysis in all meta-analyses.

Results After removal of duplicates, 1180 records were screened. We identified eight RCTs with 271 randomised patients. Seven RCTs could be included in the meta-analysis for the primary endpoint breathlessness with a standardised mean difference of 0.03 (95% CI –0.21 to 0.28). No study found statistically significant differences between the intervention and placebo. Several key secondary outcomes favoured placebo: risk ratio of 3.13 (95% CI 0.70 to 14.07) for nausea, 4.29 (95% CI 1.15 to 16.01) for vomiting, 4.77 (95% CI 1.98 to 11.53) for constipation and 4.42 (95% CI 0.79 to 24.87) for study withdrawal. All meta-analyses revealed low heterogeneity (I² in all these meta-analyses was <8%).

Conclusion Opioids for treating breathlessness in HF are questionable and may only be the very last option if other options have failed or in case of an emergency.

PROSPERO registration number CRD42021252201.

INTRODUCTION

Heart failure (HF) is a chronic condition with impaired myocardial function that may progress towards a life-limiting disease trajectory. The clinical picture is characterised by severe symptoms such as breathlessness and poor quality of life (QoL).1

Refractory breathlessness
Refractory breathlessness (dyspnoea) is defined as breathlessness, persisting despite optimal treatment of the underlying cause.2

Little is known about the neurophysiology of breathlessness. Anatomical structures that might be involved in the development of breathlessness include brain stem nuclei, the thalamic system, chest wall sensors, chemoreceptors, pulmonary C-fibres (J-receptors), mechanoreceptors in ventilatory muscles, upper airway C-fibres (‘flow measures’), pulmonary stretch receptors, opioid receptors, vascular receptors in heart and vessels and many more.3 It is likely that there is neither one universal sensory nor therapeutic pathway.

Description of the intervention
Opioids bind to opioid receptors located, for example, in various central nervous structures. They are not only used as painkillers but also administered for the treatment of breathlessness in life-limiting conditions, but the mechanisms of their effect are not well explored.

Why it was important to do this review
Most textbooks and recommendations advocate the use of opioids in HF.4 Yet, so far, meta-analyses are unavailable.

Aims of the review
This systematic review aims to assess the effect of opioids in patients with HF on breathlessness and...
to evaluate whether opioids impact on mortality, QoL, adverse effects and physiological parameters.

METHODS
This systematic review and meta-analysis follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. A protocol of this review was registered before the International Prospective Register of Systematic Reviews (CRD42021252201).

Data sources and search strategy
We searched MEDLINE (PubMed) (1946 to present), and Embase (OVID) (1974 to present) in July 2021. The search terms were based on previous search strategies adapted from Cochrane reviews. We combined search terms for opioids (eg, analgesics and opioid), including all known opioid substances with a query for terms and synonyms for HF and pulmonary hypertension (eg, heart decompensation, myocardial/cardiac/HF, pulmonary/arterial hypertension). The search was limited to randomised controlled trials (RCTs) as study designs. The full search strategy is displayed in online supplemental document 1.

Selection of studies
Published and unpublished parallel group RCTs compared with placebo or other treatment, as well as crossover and cluster RCTs available in English or German, were eligible for inclusion. Participants had to be adults (≥18 years) with HF and refractory breathlessness regardless of the underlying aetiology. HF was assumed if the authors declared this, and refractory breathlessness was assumed if the studies applied an opioid for the relief of breathlessness or to increase exercise performance. As intervention, any opioids, regardless of the route of administration used for the treatment of breathlessness, compared with placebo were eligible. The detailed criteria applied in this review are displayed in online supplemental document 2. Two authors (JG and VV) independently screened all records’ titles and abstracts for potential eligibility. The title–abstract screening was independently reviewed by two authors (JG and VV). Screening and evaluation of records and full texts were documented in self-developed data extraction tables.

Data extraction and management
Two authors (JG and VV) extracted data from the included studies. A third author (WS) checked the extracted data. Data on study characteristics and outcomes were summarised in data sheets. The following information was extracted whenever available:
- Methods: study design, duration of the intervention, time frame of recruitment, study setting and date of study.
- Participants: number, age, sex, inclusion and exclusion criteria, New York Heart Association class.
- Intervention and control: intervention, dose (single, maximum daily dose), titration model, mode of administration, concomitant medications and exclusions.
- Outcomes: primary (breathlessness) and secondary outcomes (mortality, QoL, adverse effects and physiological parameters), type of assessment scales used, time points collected, means and measures of dispersion and, where appropriate, results of responder analyses.
- Funding for trial and any conflicts of interest for trial authors.

Assessment of risk of bias (RoB) in included studies
One reviewer (VV) judged the RoB of included studies using Cochrane’s revised ‘Risk of Bias’ assessment tool (RoB 2). The judgements were checked by a second reviewer (JG or WS). Disagreement was solved through discussion.

Statistical analysis
Measures of treatment effect
For continuous variables, we present results as mean difference (MD) or as standardised mean difference (SMD) with the corresponding 95% CI. For dichotomous data, we calculated risk ratios (RRs) and the number needed to treat/harm. We used data of the intention-to-treat (ITT) population for calculating treatment effects where applicable.

Unit of analysis
Most of the included studies were cross-over studies. As no correlation coefficients were available for calculating the SD of the difference between groups, we imputed a correlation of zero resulting in the most conservative scenario for 95% CIs of cross-over studies.

Assessment of heterogeneity
We assessed statistical heterogeneity in meta-analyses with 95% prediction intervals (PIs) indicating the 95% probability range of a future similar study in a random-effects model. Additionally, the I² statistic was calculated, describing the percentage of the total variation across trials due to heterogeneity rather than sampling error. We considered I² values of ≥50% as substantial statistical heterogeneity.

Data synthesis
We used the random-effects model for all meta-analyses with the Hartung-Knapp adjustment and the Paule-Mandel for estimating the between-study variance. (We used the statistical software R and package meta for calculating and plotting all meta-analyses and contour-enhanced funnel plots.)

We applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for assessing the certainty of evidence and provide ‘Summary of findings’ tables for the main outcomes of this systematic review: breathlessness, QoL, mortality, oxygen saturation, nausea, vomiting, constipation and respiratory rate. GRADE classifies certainty of evidence in the categories high, moderate, low or very low and takes into account the following domains for potentially downgrading the evidence of RCTs: RoB, inconsistency, indirectness, imprecision and publication bias.

We considered a reduction of 1 point on the Numerical Rating Scale or Borg scale of average daily breathlessness intensity as clinically relevant (minimal clinically important difference).

Subgroup analyses and investigation of heterogeneity
We conducted subgroup analyses for the following variables:
- Type of opioids used: morphine versus fentanyl versus oxycodone versus diamorphine versus dihydrocodeine.
- Mode of administration of opioid drug: intrathecal versus oral versus intravenous.
- Type of release: immediate release (i.r.) versus sustained release (s.r.) versus unclear.
- RoB (not applicable since only Johnson et al16 had a low RoB).
- Dose (not applicable since all studies in category medium >10–30mg oral morphine equivalent daily dose).
Sensitivity analysis
The common-effect model was additionally conducted in all meta-analyses as sensitivity analysis to assess the robustness of assumptions.

Patient and public involvement
Patients and the public where not involved in the development or conduct of this project.

RESULTS
Study selection
Figure 1 shows the flowchart of the study identification and selection process. We identified 1240 records through PubMed and Embase. After removal of duplicates, 1180 records were screened. Twenty-five reports were sought and screened for eligibility in full text. Seventeen reports were ineligible due to their study design (six reports), lack of relevant outcomes (two reports) or report format (nine reports). A list of excluded full-text reports is provided in online supplemental document 3. Eight studies met our inclusion criteria. All of these were also eligible for inclusion in one or more meta-analyses.

RoB in included studies
Overall, a high RoB was identified in all studies except in the study published by Johnson et al,23 (figure 2).

Bias arising from the randomisation process
A low RoB was present in three studies.16 17 22 These studies reported using (computer-generated) random number tables.

<table>
<thead>
<tr>
<th>Study</th>
<th>Bias arising from the randomization process</th>
<th>Bias due to deviations from intended interventions</th>
<th>Bias due to missing outcome data</th>
<th>Bias in measurement of the outcome</th>
<th>Bias in selection of the reported result</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua_1997*</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Johnson_2002*</td>
<td>+</td>
<td>+</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Williams_2003*</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Oxberry_2011*</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Olson_2014*</td>
<td>X</td>
<td>+</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Ferreira_2018*</td>
<td>+</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johnson_2019</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>X</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Smith_2020*</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>X</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2  Risk of bias summary. *No additional bias (eg, unequal group allocation, insufficient period between treatments) identified in cross-over trials. Oxberry 2011: high risk for nausea, constipation, drowsiness, vomiting, dizziness, headache, abdominal pain, sweating, dry mouth; some concerns for breathlessness, heart rate, blood pressure, breathing rate, arterial oxygen saturation. Ferreira 2018: high risk for nausea and constipation; some concerns for breathlessness, respiratory rate, arterial oxygen saturation.
Johnson and colleagues also reported methodologically adequate randomisation but identified significant differences in study groups, leading to a judgement of some concerns. In other studies, no information on randomisation and allocation procedures was provided. Williams and colleagues did not provide any information on randomisation or allocation and additionally reported differences in the characteristics between study groups at baseline (VO2 at peak exercise significantly greater in the intervention group).  

Bias due to deviations from intended interventions  
Six studies reported a double-blind design, and in two studies, only patients were blinded. Despite side effect-related dropouts, Oxberry et al and Ferreira et al only provided a per protocol (PP) analysis. Due to the small sample sizes in these studies, even the few dropped-out patients may have had an impact on the results. Therefore, the two aforementioned studies were rated as high risk in this domain. For all other studies, an ITT analysis or additionally a PP analysis was present, leading to a judgement of low RoB.  

Bias due to missing outcome data  
Oxberry et al and Ferreira et al reported dropouts (<5% of study participants) and did not provide an ITT analysis. For some outcomes (eg, breathlessness, heart rate, blood pressure, breathing rate and arterial oxygen saturation), there was no clear indication that deteriorations in these outcomes were a reason for these dropouts. Therefore, the RoB due to missing outcome data is rated as with some concerns. Both studies reported dropouts due to adverse events (eg, nausea, constipation and vomiting) and did not include those patients in their final analysis, which led to a rating of high RoB in the respective outcomes. Olson et al neither reported the method of analysis (ITT or PP) nor the number of analysed patients in results tables, leading to a judgement of a high RoB.  

Bias in measurement of the outcome  
All studies were at least single-blinded, and no indication for unclear measurements in the outcomes was identified. Therefore, all studies were evaluated with a low RoB in this domain.  

**Study** | Opioids Total | Opioids Mean | Opioids SD | Control Total | Control Mean | Control SD | Standardised Mean Difference | SMD | 95% CI | Weight (common) | Weight (random) |
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
Chua 1997 | 12 | 5.33 | 2.32 | 12 | 5.67 | 2.56 | -0.13 | [-0.94; 0.67] | 9.3% | 9.3% |
Johnson 2002 | 10 | 23.20 | 30.30 | 10 | 37.61 | 29.80 | -0.46 | [-1.35; 0.43] | 7.5% | 7.5% |
Williams 2003 | 16 | 3.70 | 4.95 | 16 | 4.95 | 4.95 | 0.02 | [-0.55; 0.59] | 18.4% | 18.4% |
Oxberry 2011_A | 35 | 3.70 | 2.33 | 18 | 3.65 | 2.04 | -0.10 | [-0.67; 0.47] | 18.4% | 18.4% |
Oxberry 2011_B | 35 | 3.45 | 2.04 | 18 | 3.65 | 2.04 | 0.00 | [-0.92; 0.92] | 7.0% | 7.0% |
Olson 2014 | 9 | 3.00 | 3.00 | 9 | 3.00 | 3.00 | 0.31 | [-0.33; 0.95] | 14.5% | 14.5% |
Ferreira 2018 | 19 | 33.50 | 28.00 | 19 | 25.60 | 21.00 | 0.29 | [-0.31; 0.89] | 16.4% | 16.4% |
Johnson 2019 | 20 | 5.30 | 2.30 | 23 | 4.60 | 2.40 | 0.00 | [-0.84; 0.84] | 8.5% | 8.5% |
Smith 2020 | 11 | 8.00 | 2.00 | 11 | 8.00 | 2.00 | 0.03 | [-0.21; 0.28] | 100.0% | -- |

**Figure 3** Forest plot with breathlessness as primary outcome. SMD, standardised mean difference.

**Table 1** Summary of findings: opioids compared with placebo for patients with HF

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Participants, n (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>Risk with placebo: MD 0.03 SD higher (0.21 lower to 0.28 higher)</td>
<td>–</td>
<td>271 (7 RCTs)</td>
<td>☒ ☒ ☒ O Low†‡</td>
<td>All studies but Johnson et al23 (n=45) were cross-over studies.</td>
</tr>
<tr>
<td></td>
<td>Risk with opioids: MD 0.00 SD higher (0.01 lower to 0.19 higher)</td>
<td>–</td>
<td>45 (1 RCT)</td>
<td>☒ ☒ ☒ O Low§</td>
<td>Cardiomyopathy Questionnaire (Kansas City): 1 (extremely limited) to 100 (not limited). Three studies reported QoL, but in two of these, the intervention was short (few days), which does not resemble an adequately long period to judge the relevant effects on QoL. Therefore, only one study was included in the grading of the evidence.23</td>
</tr>
<tr>
<td>QoL follow-up: 4 weeks</td>
<td>The mean QoL was 44.1 (SD 12.9) points</td>
<td>–</td>
<td>261 (6 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
<td>Outcome of clinical relevance but there is moderate certainty of evidence that the intervention (opioids) does not alter this outcome significantly or relevantly.</td>
</tr>
<tr>
<td>Mortality (not reported)</td>
<td>No study reported deaths</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No certainty of evidence assessment possible. Mortality is a highly relevant outcome for patients, but interventions and follow-up times were too short to provide meaningful results.</td>
</tr>
<tr>
<td>Oxygen saturation assessed with (%) (0–100%)</td>
<td>Risk with placebo: MD 0.92% lower (1.79 lower to 0.06 lower)</td>
<td>–</td>
<td>261 (6 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
<td>Outcome of clinical relevance but there is moderate certainty of evidence that the intervention (opioids) does not alter this outcome significantly or relevantly.</td>
</tr>
<tr>
<td></td>
<td>Risk with opioids: MD 0.00% lower (0.00 lower to 0.00 lower)</td>
<td>–</td>
<td>127 (4 RCTs)</td>
<td>☒ ☒ ☒ O Very low†¶</td>
<td>Outcome of relevance because it is a leading reason for patients to discontinue opioid therapy.</td>
</tr>
<tr>
<td>Nausea</td>
<td>92 per 1.000</td>
<td>289 per 1.000 (65 to 1.000)</td>
<td>RR 3.13 (0.70 to 14.07)</td>
<td>127 (4 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 per 1.000</td>
<td>48 per 1.000 (13 to 180)</td>
<td>RR 4.29 (1.15 to 16.01)</td>
<td>209 (5 RCTs)</td>
<td>☒ ☒ ☒ O Low†**</td>
</tr>
<tr>
<td>Constipation</td>
<td>67 per 1.000</td>
<td>322 per 1.000 (133 to 777)</td>
<td>RR 4.77 (1.98 to 11.53)</td>
<td>209 (5 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Risk with placebo: MD 0.25 breaths/ min lower (1.22 lower to 0.72 higher)</td>
<td>–</td>
<td>313 (8 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
<td>Outcome of relevance for potential clinical harms (bradypnea). Though overall, the net effect seems negligible and the 95% CI is very narrow.</td>
</tr>
<tr>
<td></td>
<td>Risk with opioids: MD 0.00 breaths/ min lower (0.00 lower to 0.00 lower)</td>
<td>–</td>
<td>313 (8 RCTs)</td>
<td>☒ ☒ ☒ O Moderate†</td>
<td>Outcome of relevance for potential clinical harms (bradypnea). Though overall, the net effect seems negligible and the 95% CI is very narrow.</td>
</tr>
</tbody>
</table>

Patient or population: patients with HF.
Setting: hospital, outpatient or home care.
Intervention: opioids.
Comparison: placebo.
GRADE Working Group grades of evidence:
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Certainty of evidence downgraded by one level because of serious risk of bias as displayed in detail in the risk of bias analysis in other parts this publication.
†Certainty of evidence downgraded by one level because of serious imprecision, i.e., 95% CI of SMD include a small effect for both directions and less than 400 trial participants.
‡Certainty of evidence downgraded by one level because of very serious imprecision, i.e., the number of participants was small and 95% CI include small effects in both directions
¶Certainty of evidence downgraded by two levels because of very serious imprecision, i.e., the number of participants was small and 95% CI include a large effect in both directions.
§Certainty of evidence downgraded by one level because of very serious imprecision, i.e., 95% CI of SMD include a small effect for both directions and less than 400 trial participants.
**Certainty of evidence downgraded by one level because of serious imprecision, i.e., the number of participants was small and 95% CI include a large effect in both directions.

Different scales for this endpoint were used in the included studies. As depicted in figure 3, none of the studies found statistically significant differences between the intervention (opioids) compared with placebo.

The estimated effect sizes for both the common-effect and random-effects models were near the null effect (0.03) and showed identical 95% CIs of −0.21 to 0.28 (certainty of evidence: low, table 1). Results were homogeneous with an I² of 0% and a 95% PI of −0.27 to 0.34 (figure 3).

Subgroup analyses on type of opioid, route of administration, modality of prescription (i.r. vs s.r. medication) and aetiology of HF did not show any differences between the
groups (online supplemental figures 1–3). It is important to highlight that two RCTs were not included in the meta-analysis because one did not report breathlessness as an outcome and the other did not report SDs.

Key secondary outcomes
Quality of life
Only four studies provided data for this endpoint, and none found significant differences between the intervention and control groups, as shown in table 1.

Mortality
No patients died during the trials, but most studies lasted for only one to several days.

Key adverse events: nausea, vomiting, constipation and withdrawal
Statistically significant and clinically relevant differences for nausea, vomiting and constipation between the intervention and control groups were found. The random-effects model revealed an RR of 3.13 (95% CI 0.70 to 14.07) for nausea, 4.29 (95% CI 1.15 to 16.01) for vomiting and 4.77 (95% CI 1.98 to 11.53) for constipation, as depicted in figures 4–6. Furthermore, data were also analysed for withdrawal from the study, with an RR of 4.42 (95% CI 0.79 to 24.87) in patients treated with opioids (online supplemental figure 4). All these meta-analyses revealed low heterogeneity (I²=0%). Subgroup analyses for these findings on type of opioid administered or route of administration did not show any differences.
## Systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Opioids Events Total</th>
<th>Control Events Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI (common)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua 1997</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>9.00</td>
<td>[0.55; 147.08]</td>
<td>0.0%</td>
</tr>
<tr>
<td>Johnson 2002</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>.</td>
<td>6.1%</td>
</tr>
<tr>
<td>Williams 2003</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>0.0%</td>
<td>.</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oxberry 2011_A</td>
<td>12</td>
<td>35</td>
<td>2</td>
<td>18</td>
<td>.</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oxberry 2011_B</td>
<td>10</td>
<td>35</td>
<td>2</td>
<td>18</td>
<td>.</td>
<td>0.0%</td>
</tr>
<tr>
<td>Olson 2014</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>19.0</td>
<td>[1.19; 304.33]</td>
<td>6.1%</td>
</tr>
<tr>
<td>Ferreira 2018</td>
<td>9</td>
<td>19</td>
<td>0</td>
<td>19</td>
<td>.</td>
<td>6.1%</td>
</tr>
<tr>
<td>Johnson 2019</td>
<td>14</td>
<td>21</td>
<td>2</td>
<td>24</td>
<td>.</td>
<td>6.1%</td>
</tr>
<tr>
<td>Smith 2020</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>8.00</td>
<td>[2.05; 31.20]</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

**Common effect model** 120 89  
**Random effects model** 120 89  
**Prediction interval**  
Heterogeneity: $\tau^2 = 0$, $I^2 = 0$, $p = 0.59$

**Figure 6** Forest plot with constipation as secondary outcome.

Other adverse events and physiological parameters
The meta-analyses for other adverse events did not show significant differences between the interventions and placebo groups (online supplemental figures 1–7). No study reported respiratory depression, cardiac failure, severe arterial hypertension or any other adverse respiratory or cardiac adverse event.

Significant but clinically not relevant differences could be identified for heart rate (MD $-4.90$, 95% CI 8.90 to $-0.90$) and arterial oxygen saturation (MD in random-effects model: $-0.92$, 95% CI $-1.79$ to $-0.06$) (online supplemental figures 6, 7). An overview of all subgroup analyses conducted for this systematic review can be found in online supplemental file 6.

**DISCUSSION**

The meta-analysis failed to identify a treatment effect of opioids on relieving breathlessness in patients with HF. Moreover, none of these trials proved superiority of opioid therapy over placebo; heterogeneity was low; and the estimated 95% CI of the SMD, as well as the PI, was remarkably narrow (figure 3).

Instead, a significantly and clinically relevant increased risk for side effects such as nausea, vomiting and constipation was found (figures 4–6). Patients receiving opioids were more likely to withdraw from the studies. The longer the study intervention, the more pronounced was the reported effect for withdrawal from the studies. The longer the study intervention, the more pronounced was the reported effect for withdrawal from the studies. This is to resemble clinical practice and not only identify short-term ‘responsiveness’.

Third, we cannot exclude the possibility that opioids may have a beneficial effect in selected responders. For this, potential future studies should provide at least (1) a much more detailed breathlessness assessment including multidimensional assessment tools; (2) identify coexisting anxiety and depression; (3) evaluate sex and ethnic differences; (4) distinguish breathlessness from episodes; and (5) report and distinguish the underlying HF aetiology.

**Limitations of this review**

This systematic review and meta-analysis has minor limitations due to the available resources of the project. Only two reviewers screened independently and only two major databases were searched. Moreover, only trials available in English or German were eligible. Yet, for the latter, it was evident throughout the selection process that no studies written in other languages could be identified.

## Figure 6

Forest plot with constipation as secondary outcome.
CONCLUSION
This systematic review questions the benefits of opioids for the treatment of breathlessness in patients with HF with HF. We suggest that opioids may only be the very last option if all other options have failed or in case of an emergency.

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Contributors JG developed the research question, JG, WS, VV and SS developed the research protocol and the search strategy, JG and VW screened the studies for inclusion, extracted the data and conducted the qualitative synthesis with WS acting as a reviewer, WS conducted the meta-analyses with JG and VW acting as reviewers. JG performed the Grading of Recommendations Assessment, Development and Evaluation assessment with WS and VW acting as reviewers. JG, TF-S, WS and VW drafted the manuscript. After critical review by all authors, TF-S and JG revised the manuscript. JG serves as guarantor.

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