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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 (I^2 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.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Opioids are recommended as symptomatic treatment for breathlessness in patients with advanced heart failure (HF).
⇒ Data from meta-analyses to confirm these recommendations are still lacking.

WHAT THIS STUDY ADDS

⇒ This meta-analysis did not show any significant benefit of opioid therapy on the management of breathlessness in patients with advanced HF.
⇒ Opioids strongly increased the risk for adverse events in patients with HF, for example, nausea, vomiting and constipation.
⇒ If conducted at all, future studies could follow suggestions for alternate protocols as provided in the Discussion section.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The use of opioids should be explored in more detail, while considering the multidimensionality of breathlessness.
⇒ Variables such as sex, ethnicity, HF aetiology and types of breathlessness need to be considered in future trials on the benefit of opioids in advanced heart failure.

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.[5] 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.[6] 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 performed in Rayyan.[7] Full-text publications of all records were 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).[8] 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.[9]

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.[10] Additionally, the I^2 statistic was calculated, describing the percentage of the total variation across trials due to heterogeneity rather than sampling error. We considered I^2 values of ≥50% as substantial statistical heterogeneity.[11]

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*[12] and package *meta*[13] 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.[14]

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).[15]

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 al*[16] had a low RoB).
- Dose (not applicable since all studies in category medium >10–30 mg oral morphine equivalent daily dose).

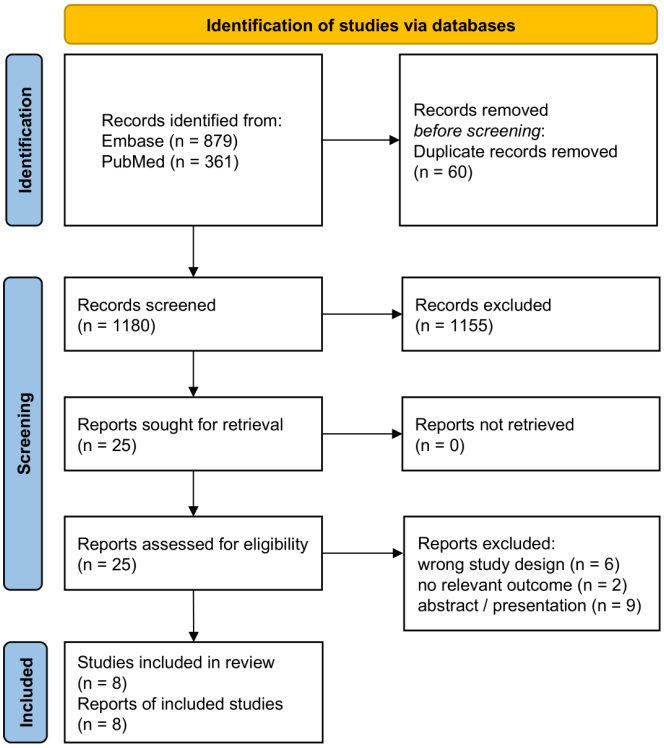

Figure 1 Study identification and selection process (PRISMA flowchart).

- HF aetiology: mixed aetiology (ischaemic and dilatative cardiomyopathy patients) or not reported versus pulmonary hypertension.
- Time point of effect: short term (up to 1 day) versus long term (>1 day) versus unclear.

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.

Study characteristics

We identified eight RCTs (271 randomised patients). Seven were conducted as cross-over RCTs,[16–22] of which one was a tree-arm trial[17] and one was a parallel group RCT[23] (online supplemental table 1).

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.

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 satuation.

Johnson and colleagues also reported methodologically adequate randomisation but identified significant differences in study groups, leading to a judgement of some concerns.[23] In other studies, no information on randomisation and allocation procedures was provided.[18 20 21] Williams and colleagues did not provide any information on randomisation or allocation and additionally reported differences in the characteristics between study groups at baseline (VO_2 at peak exercise significantly greater in the intervention group).[19]

Bias due to deviations from intended interventions

Six studies[16–19 22 23] reported a double-blind design, and in two studies,[20 21] only patients were blinded. Despite side effect-related dropouts, Oxberry *et al*[17] and Ferreira *et al*[22] 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*[17] and Ferreira *et al*[22] 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*[20] neither reported the method of analysis (ITT or PP) nor provided 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.

Bias in selection of the reported result

Johnson *et al*[23] and Ferreira *et al*[22] reported the registration of a study protocol and no differences between the protocol and final report were identified. None of the remaining studies provided a reference to a study protocol or analysis plan, leading to a judgement of some concerns.

Additional bias due to cross-over designs

No additional bias specific for cross-over trials were identified, since the group allocation was equal and a sufficient period between treatments was present.

Additional bias

Johnson *et al*[16] reported the use of different doses of oral morphine, depending on the creatinine level of patients (2.5 mg instead of 5 mg if creatinine level was <200 µmol/L). Williams *et al*[19] reported that participants received 1 or 2 mg diamorphine. Both studies did not present results separately for lower and higher opioid doses or provided the number of patients who received either dose. Therefore, evaluating effects in relation to doses was hampered. Less than one-quarter of the study participants (23.9%) were female and outcome data were not presented separately for each sex. Additionally, studies did not report on race or other potentially sociodemographic characteristics of participants.

Assessment of funnel plot asymmetry

The main finding for the primary endpoint is displayed as forest plot (figure 3). We also prepared funnel plots to detect signals for non-reporting bias for all outcomes in the table on summary of findings (table 1) except for QoL and mortality because of the lack of studies (figures 4–6 and online supplemental figures 8–13). The studies were rather well distributed (e.g., breathlessness and respiratory rate) and did not give a clear signal for non-reporting bias. Furthermore, few studies on side effects were included in the meta-analyses to make a reasonable judgement (e.g., constipation and vomiting).

Primary outcome: breathlessness

We included seven of the eight retrieved studies in the meta-analysis for the primary endpoint breathlessness (n=151 in intervention groups and n=120 in control groups), with Oxberry and colleagues[17] reporting two different interventions (oral morphine and oral oxycodone). The results were analysed as SMD since

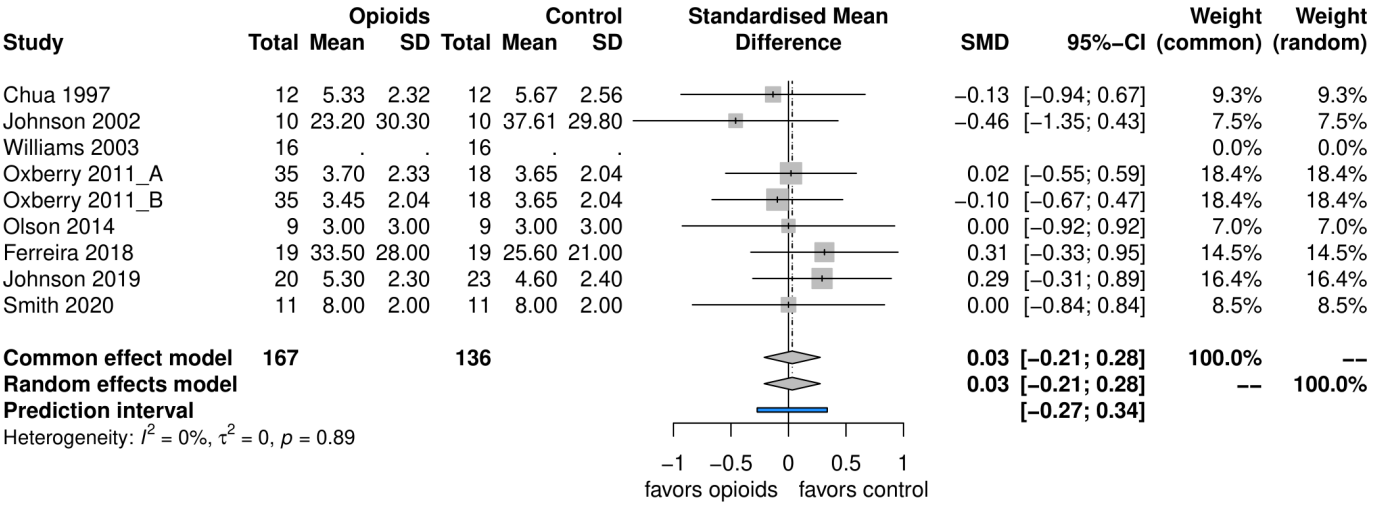

Figure 3 Forest plot with breathlessness as primary outcome. SMD, standardised mean difference.

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants, n (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with opioids				
Dyspnoea		MD 0.03 SD higher (0.21 lower to 0.28 higher)	–	271 (7 RCTs)	⨁⨁OO Low†‡	All studies but Johnson *et al*[23] (n=45) were cross-over studies.
QoL follow-up: 4 weeks	The mean QoL was 44.1 (SD 12.9) points	MD 2.7 points lower (9.7 lower to 4.3 higher)	–	45 (1 RCT)	⨁⨁OO Low§	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]
Mortality (not reported)	No study reported deaths			–	–	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.
Oxygen saturation assessed with (%) (0–100%)		MD 0.92% lower (1.79 lower to 0.06 lower)	–	261 (6 RCTs)	⨁⨁⨁O Moderate†	Outcome of clinical relevance but there is moderate certainty of evidence that the intervention (opioids) does not alter this outcome significantly or relevantly.
Nausea	92 per 1.000	289 per 1.000 (65 to 1.000)	RR 3.13 (0.70 to 14.07)	127 (4 RCTs)	⨁OOO Very low†¶	Outcome of relevance because it is a leading reason for patients to discontinue opioid therapy.
Vomiting	11 per 1.000	48 per 1.000 (13 to 180)	RR 4.29 (1.15 to 16.01)	209 (5 RCTs)	⨁⨁OO Low†**	Outcome of relevance because it is a leading reason for patients to discontinue opioid therapy.
Constipation	67 per 1.000	322 per 1.000 (133 to 777)	RR 4.77 (1.98 to 11.53)	209 (5 RCTs)	⨁⨁⨁O Moderate†	Outcome of relevance because it is a leading reason for patients to discontinue opioid therapy. Effect favouring placebo might be higher in real practice, since opioid-induced constipation need some time to develop.
Respiratory rate assessed with (breaths/min)		MD 0.25 breaths/min lower (1.22 lower to 0.72 higher)	–	313 (8 RCTs)	⨁⨁⨁O Moderate†	Outcome of relevance for potential clinical harms (bradypnea). Though overall, the net effect seems negligible and the 95% CI is very narrow.

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.
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†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 of this single study 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 serious imprecision, i.e., the number of participants was small and 95% CI include a small and large effect
GRADE, Grading of Recommendations Assessment, Development and Evaluation; HF, heart failure; MD, mean difference; QoL, quality of life; RCT, randomised controlled trial; RR, risk ratio.

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 I^2 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

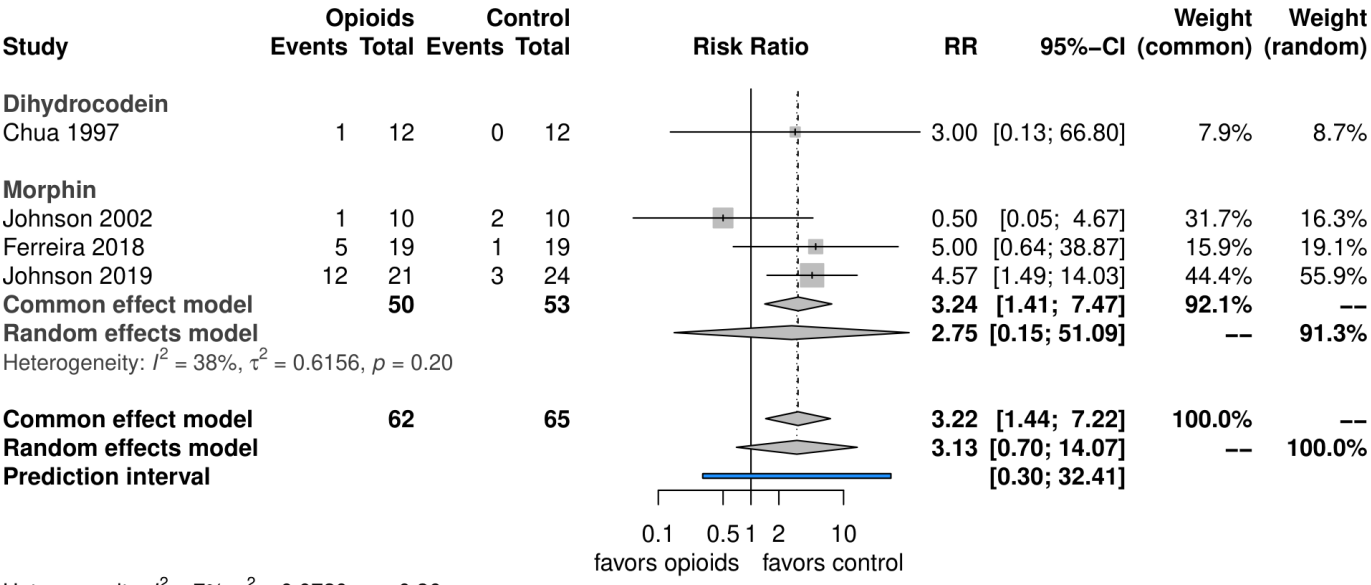

Figure 4 Forest plot with nausea as secondary outcome.

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[19] and the other did not report SDs.[16]

Key secondary outcomes

Quality of life

Only four studies provided data for this endpoint,[16 17 22 23] 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.[16–22]

Key adverse events: nausea, vomiting, constipation and withdrawal

Statistically significant and clinically relevant differences for nausea, vomiting and constipation between the intervention and the 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 (I^2=0%). Subgroup analyses for these findings on type of opioid administered or route of administration did not show any differences

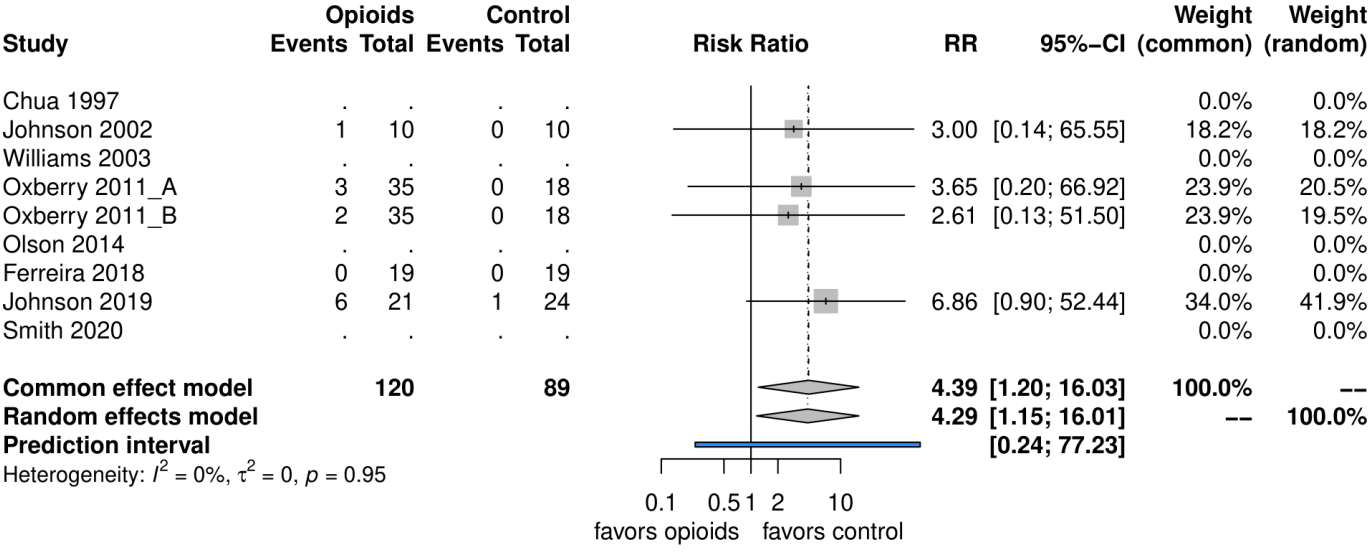

Figure 5 Forest plot with vomiting as secondary outcome.

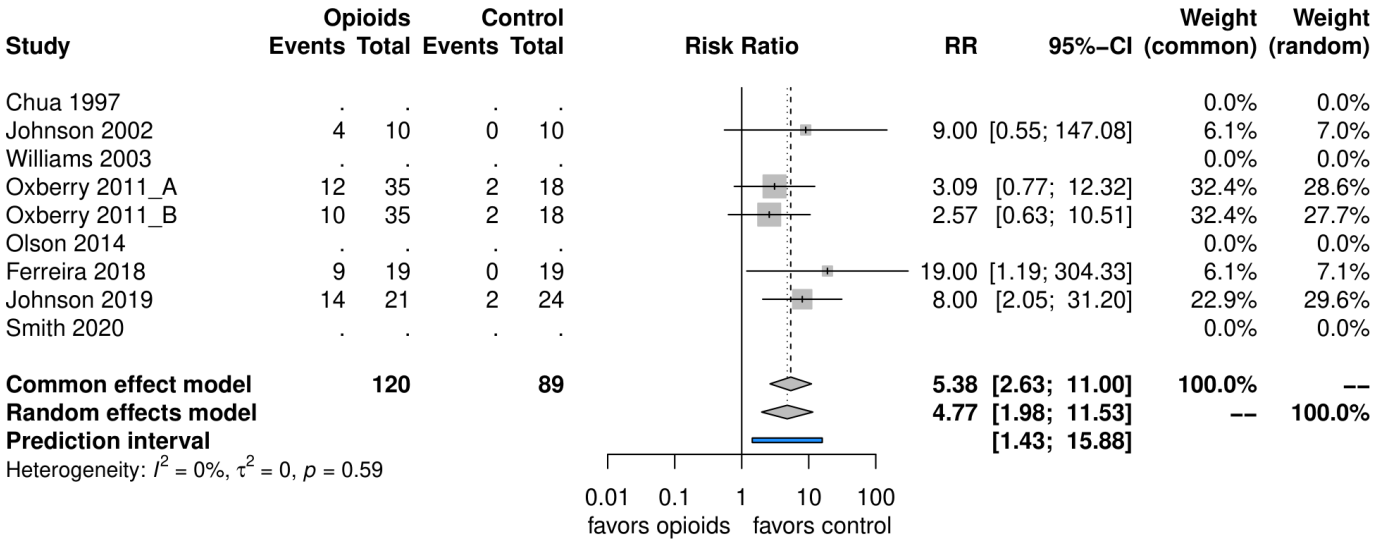

Figure 6 Forest plot with constipation as secondary outcome.

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 study. For example, the recent study by Johnson and colleagues[2323] provided a 12-week follow-up. Here, the median time to treatment withdrawal was 12 (range 4–56) days for morphine and 48 (range 7–57) days for placebo. Although the random-effects model is more appropriate for this research question and was chosen for the primary analysis, we provided additional information from sensitivity analyses using the common-effects model. Results for all outcomes were consistent between the models except for nausea (figure 4).

Notably, many included studies were of limited quality. Three RCTs (four intervention groups, IGs) were from the same working group.[16 17 23] It may be argued that the inclusion of studies that apply interventions with intrathecal drug delivery is clinically not relevant. On the other hand, this may also be seen as a strength, because it gives further information and exclusion of theses studies would not have changed results of this meta-analysis. Long-term intrathecal opioid application with the means of implanted devices is absolutely possible and a well-established option to treat chronic pain.[24] Moreover, the removal of this subgroup of studies[20 21] from our meta-analysis does not alter the findings.

Suggestion for practice and for a future research agenda

First, opioids for the treatment of breathlessness in HF should be the very last resort, if other interventions, non-pharmacological and pharmacological treatments have failed. If administered at all, clinicians should be alert to stop treatment very soon in case of unresponsiveness and severe adverse events. Of note, for acute HF, in 2021 alone, three large studies reported that the use of opioids led to increased mortality in this population.[25–27] A recent study from Domínguez-Rodríguez *et al*[28] found that morphine, compared with midazolam, doubled the incidence of adverse events when used to treat breathlessness in patients with HF.

Second, taking into account the unequivocal PIs of our meta-analysis and the homogeneity of the included RCTs, future studies with similar study design will be unlikely to change the results of the meta-analysis. If conducted at all, we agree with Johnson and colleagues[23] that such studies should imply titration steps because of the highly variable responsiveness between individuals.[29] Also, they should be conducted as long-term studies, at least several weeks. 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[30] to distinguish, for example, 'unpleasantness' from 'severity' of breathlessness; (2) identify coexisting anxiety and depression; (3) evaluate sex and ethnic differences; (4) distinguish breathlessness rest 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.

CONCLUSION

This systematic review questions the benefits of opioids for the treatment of breathlessness in patients with HF. We suggest that opioids may only be the very last option if all 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 VV 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 VV acting as reviewers. JG performed the Grading of Recommendations Assessment, Development and Evaluation assessment with WS and VV acting as reviewers. JG, TF-S, WS and VV drafted the manuscript. After critical review by all authors, TF-S and JG revised the manuscript. JG serves as guarantor.

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