# Appendixes

# **Appendix 1: Search Strategy**

|  |
| --- |
| **Ovid MEDLINE**  1 Pulmonary Edema/ 17628  2 (pulmonary adj2 (edema or oedema)).tw. 19427  3 decompensated heart failure.mp. 3870  4 decompensated cardiac failure.mp. 37  5 exp Heart Failure/ 135224  6 1 or 2 or 3 or 4 or 5 161564  7 Morphine/ 39357  8 morphin\*.tw. 55512  9 7 or 8 62460  10 6 and 9 332  11 randomized controlled trial.pt. 558117  12 controlled clinical trial.pt. 94685  13 (randomized or placebo or randomly or trial or groups).ab. 3175308  14 drug therapy.fs. 2440064  15 11 or 12 or 13 or 14 5255383  16 exp animals/ not humans.sh. 4955382  17 15 not 16 4572999  18 10 and 17 152  19 Meta-Analysis as Topic/ 20787  20 meta-analysis/ or "systematic review"/ 257861  21 meta analy\*.tw. 223648  22 metaanaly\*.tw. 2381  23 (systematic adj (review\* or overview\*)).tw. 232823  24 19 or 20 or 21 or 22 or 23 389013  25 10 and 24 7  26 18 or 25 152 |
| **Embase**  1 lung edema/ 51465  2 (pulmonary adj2 (edema or oedema)).tw. 31414  3 decompensated heart failure.mp. 8216  4 decompensated cardiac failure.mp. 73  5 exp Heart Failure/ 597104  6 1 or 2 or 3 or 4 or 5 641888  7 Morphine/ 116360  8 morphin\*.tw. 78128  9 7 or 8 130930  10 6 and 9 3362  11 (random\* or factorial\* or placebo\* or assign\* or allocat\* or crossover\*).tw. 2281083  12 ((blind\* or mask\*) and (single or double or triple or treble)).tw. 301379  13 crossover procedure/ 69726  14 double blind procedure/ or single blind procedure/ 237518  15 randomization/ or placebo/ 471387  16 parallel design/ or Latin square design/ 15682  17 randomized controlled trial/ 697078  18 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 32230501  19 exp human/ 24589730  20 18 not 19 7640771  21 11 or 12 or 13 or 14 or 15 or 16 or 17 2588211  22 21 not 20 2254143  23 10 and 22 360  24 exp Meta Analysis/ 237876  25 ((meta adj analy\*) or metaanalys\*).tw. 289477  26 (systematic adj (review\* or overview\*)).tw. 283463  27 "systematic review"/ 331371  28 24 or 25 or 26 or 27 559508  29 10 and 28 106  30 23 or 29 417 |
| **Cochrane Database of Systematic Reviews**  #231 MeSH descriptor: [Pulmonary Edema] explode all trees 273  #232 (pulmonary edema):ti,ab,kw 1925  #233 ("pulmonary œdema"):ti,ab,kw 262  #234 MeSH descriptor: [Heart Failure] explode all trees 10224  #235 (decompensated heart failure):ti,ab,kw 1337  #236 (decompensated cardiac failure):ti,ab,kw 407  #237 #231 or #232 or 233 or #234 or #235 or #236 25707  #238 MeSH descriptor: [Morphine Derivatives] explode all trees 7372  #239 (morphin\*):ti,ab,kw 15665  #240 #238 or #239 17651  #241 #240 and #237 208 |

## Appendix 2: Characteristics of included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Citation** | **Study design** | **Population** | **Treatment** | **Main Findings** | **Comments** |
| Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72. | Systematic review and Meta-analysis | 5 studies (3 propensity-matched cohorts, 2 retrospective analysis (1 unpublished)).  Total n=149,967 (intravenous morphine group, n=22,072; no-morphine group, n=127,895)  All studies provided the primary clinical endpoints, 4 studies provided secondary endpoints; 3 studies had follow-up durations from 30 days to 12 months  Patients with AHF | Intravenous morphine used in treatment group (dosage*≥*0.5 mg/kg) vs no morphine used in the control group. | **In-hospital mortality**  OR = 2.14, 95% CI: 0.88–  5.23, *p* = 0.095, I2 = 97.1 %;  Very low certainty of evidence  Total group:  2899/22072 in intervention group  3180/127895 in control group.  Subgroup analysis in score matching studies:  178/1165 in intervention group  132/1165 in control group  (OR=1.41, 95% CI: 1.11–1.80, p =0.005, I2 = 0%)  **ICU Length of stay**  Not reported  **Hospital Length of stay**  Not reported | All included studies represented a low risk of bias in selective outcome reporting and outcome assessment. The scores of NOS for study quality assessment of included studies ranged from 7 to 9. However, the funnel plot asymmetry for in-hospital mortality and invasive mechanical ventilation indicated publication bias. Between-study heterogeneity  in in-hospital mortality was *I*2 = 97.1%. Accordingly, subgroup analyses including score-matching studies only were conducted, for which in-hospital mortality was *I*2 = 0%, suggesting low heterogeneity. |
| Gao D, David C, Rosa MM, Costa J, Pinto F, Caldeira D. The Risk of Mortality Associated With Opioid With Acute Heart Failure: Systematic Review and Meta-analysis. J Cardiovasc Pharmacol Volume 77, Number 2, February 2021 | Systematic Review and Meta-analysis | 6 studies (observational retrospective studies)  Total n=151735  Patients with AHF defined as acute signs/or symptoms of low cardiac output and/or congestion, either de novo or as a heart failure exacerbation, or as reported by investigators irrespective of the details reported. | Treatment: IV morphine  Control: Standard of care was not stated. | **In-hospital mortality**  OR 1.78; 95% CI 1.01–3.13. very low certainty of Evidence, 151 735 participants, 6 studies  Sensitivity analysis (OR 1.46; 95% CI 1.19–1.79; I2= 0%.  Total n=151735  Intervention n=22649  Control n=129086  **30-day mortality**  OR 1.56; 95% CI 1.14–2.15  Very low certainty of evidence, 986 participants, 6 studies  Total n=986  Intervention n=493  Control n=493  **ICU length of stay**  No reported  **Hospital length of stay**  Not reported | Opioids seem to be associated with a higher risk of in-hospital mortality; however, the true effect may be substantially different from the estimated  effect.  Opioids seem to be associated with a higher risk of 30-d mortality; however, the true effect may be substantially different from the estimated effect. |
| Gil V, Domínguez—Rodríguez A, Masip J, Peacock WF, Miró O. Morphine Use in the Treatment of Acute Cardiogenic Pulmonary Edema and its Effects on Patient Outcome: A Systematic Review. Current Heart Failure Reports (2019) 16:81–88  [https://doi.org/10.1007/s11897-019-00427-0](about:blank) | Systematic Review (7 studies) | 1 randomized controlled trial  1 non-randomized controlled trial  5 observational studies  Total n=150639  Intervention n=22080  Control n=128559  Unable to determine total number of males and females as not all studies provide this information | Treatment:  Morphine with or without other drugs  Control:  Other drugs without morphine, but the drugs were not stated. | All studies with the exception of Sachetti et al. evaluated mortality in the patients.  The conclusion from the review was that administration of morphine to patients with acute pulmonary oedema could lead to worse outcomes in the patients ranging from increased length of hospital stay to death | A meta-analysis not performed but a narrative review of each study was done |
| Zhang D, Lai W, Liu X, Shen Y,  Hong K. The safety of morphine in patients with acute heart  failure: A systematic review and meta-analysis. Clin Cardiol.  2021;44(9):1216-1224. [https://doi.org/10.1002/clc.23691](about:blank) | Systematic review and meta-analysis | Seven studies (all retrospective case-control studies)  Total n=172226  Morphine group n=22967  Control group n=149259  Mean age range from 73 to 81 years  Sample size range from 181 to 147 362. | Treatment  Morphine and intravenous morphine.  Dosage not stated  Control treatment was not stated. | **In-hospital mortality**  Five studies  Total n=170993  Morphine n=22338  Control n= 148655  (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, I2 = 96%)  **7-day and 30-day all-cause mortality**  Three studies included  Total n= 9904  Morphine n= 1175  Control n=8729  **For 7-day all-cause mortality**  (OR: 1.69; 95% CI 0.89 to 3.22; p = 0.11, I2 = 61%)  **For 30-day all-cause mortality**  OR: 1.59; 95% CI 1.16 to 2.17; p = 0.004, I2 = 0%  **SAE**  Risk of invasive mechanical ventilation  4 studies  Total n=167847  Morphine n=22047  Control n= 145800  OR 2.72; 95% CI 1.09 to 6.80; p = 0.03, I2 = 93%  **ICU length of stay**  Not reported  **Hospital length of stay**  Not reported | Publication bias could not be ascertained as the number of included studies was less than 10  The Newcastle-Ottawa Scale (NOS) for observational studies was used to assess the quality of the studies based on selection of the population, the comparability of the study, and the assessment of the outcome.  The study scored an average of 6.43  For the in-hospital mortality, risk of invasive mechanism and 7-day all-cause mortality outcomes the results showed significant heterogeneity  There was no heterogeneity for the 30-day all-cause mortality outcome |

## Appendix 3: Characteristics of excluded studies

|  |  |  |
| --- | --- | --- |
| **Citation** | **Type or record** | **Reason for exclusion** |
| Agewall S. *Morphine in acute heart failure*. J Thorac Dis 2017;9(7):1851-1854. | Journal article | Wrong study design |
| Berger PE, et al. *ARE narcotics harmful in the treatment of acute pulmonary edema? A critically appraised topic*. Scientific Abstracts (163). CJEM.JCMU 2010;12(3): 277. | Conference abstract | Wrong study design |
| Dominquez-Rodriquez A, , et al. Study Design and Rationale of *A”Multicenter, Open-labelled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema”:* MIMO Trial. Cardiovasc Drugs Ther 2017; 31:209-213 | Protocol | Wrong comparator |
| Dominquez-Rodriquez A, et al. *Influence of morphine treatment on in-hospital mortality among patients with acute heart failure*. Med Intensiva 2017;41:382-384. | Letter | Wrong comparator |
| Ellingsrud C, et al *Morphine in the treatment of acute pulmonary edema*. Tidsskr Nor Legeforen 23-24, 2014; 134:2272-2275. | Journal article | Wrong study design |
| Graham CA, et al. *Morphine should be abandoned as a treatment for acute cardiogenic pulmonary oedema*. Emergency Medicine Australasia 2009;21:160. | Letter | Wrong study design |
| Hall M, et al. *Is Morphine indicated in acute pulmonary oedema*. Emerg Med J 2005; 22:391-392. | Letter | Wrong study design |
| Herlitz J, et al*. Is pre-hospital treatment of chest pain optimal in acute coronary syndrome? The relief of both pain and anxiety is needed*. International Journal of Cardiology 2011;(149): 147–151. | Journal article | Wrong study design |
| Holm M, et al. *The* *Movement Trial*. J Am Heart Assoc. 2019;8:1-11. | Journal article | Wrong intervention |
| Johnson MJ, et al. *Morphine for the relief of breathlessness in patients with chronic heart failure – a pilot study*. The European Journal of Heart Failure 2002; (4):753–756. | Journal article | Wrong patient population |
| Johnson MJ, et al. *Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial*. ESC Heart Failure 2019: 6:1149-1160. | Journal article | Wrong intervention |
| Kubica J, et al. *Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial*. European Heart Journal 2016; 37:245–252. | Journal article | Wrong patient population |
| León-Delgado M, et al. *Opioids for the management of dyspnea in patients with heart failure: a systematic review of the literature*. Colombian Journal of Anesthesiology 2019; 47(1): 49-56 | Journal article | Wrong comparator |
| Mattu A, et al. *Prehospital Management of Congestive Heart Failure*. Heart Failure Clin 5 2009; 19–24. | Journal article | Wrong study design |
| Orso D, et al. *Is morphine safe in acute decompensated heart failure? A systematic review of the literature*. European Journal of Internal Medicine 2019; 69:e8–e10. | Journal article | Wrong study design |
| Oxberry SG, et al. *Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial*. European Journal of Heart Failure 2011;13:1006–1012. | Journal article | Wrong patient population |
| Oxberry SG, et al. *Minimally clinically important difference in chronic breathlessness: Every little helps*. American Heart Journal 2012; 164(2):229-235. | Journal article | Wrong outcomes |
| Oxberry SG, et al. *Repeat Dose Opioids May Be Effective for Breathlessness in Chronic Heart Failure if Given for Long Enough*. Journal of Palliative Medicine 2013; 16(3): 250-255. | Journal article | Wrong intervention |
| Poole-Wilson PA. *Treatment of Acute Heart Failure. Out with the Old, in With the New*. JAMA 2002; 287(12):1578-1580. | Journal article | Wrong study design |
| Triposkiadis F, et al. *Current drugs and medical treatment algorithms in the management of acute decompensated heart failure.* Expert Opin Investig Drugs 2009; 18(6):695-707. | Journal article | Wrong study design |
| Vicicevic Z. Is it necessary to use Morphine in acute pulmonary edema? Lijec Vjesn 2003; 125(47):1-2. | Journal article | Not in English |

## Appendix 4: AMSTAR II for included studies

|  |  |
| --- | --- |
| **STUDY** | **AMSTAR RESULT** |
| Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72. | Critically Low-quality review |
| Gao D, David C, Rosa MM, Costa J, Pinto FJ, Caldeira D. The risk of mortality associated with opioid use in patients with acute heart failure: systematic review and meta-analysis. Journal of Cardiovascular Pharmacology. 2021 Feb 1;77(2):123-9. | Moderate quality review |
| Gil V, Domínguez-Rodríguez A, Masip J, Peacock WF, Miró Ò. Morphine use in the treatment of acute cardiogenic pulmonary edema and its effects on patient outcome: a systematic review. Current heart failure reports. 2019 Aug;16(4):81-8. | Critically Low-quality review |
| Zhang D, Lai W, Liu X, Shen Y, Hong K. The safety of morphine in patients with acute heart failure: A systematic review and meta‐analysis. Clinical cardiology. 2021 Sep;44(9):1216-24. | Moderate quality review |