South African National Essential Medicine List
Adult Hospital Level and PHC Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

Executive Summary

Date: May 2022
Medicine (INN): Morphine
Medicine (ATC): N02AA01
Indication (ICD10 code): J81 (The relief of moderate to severe pain in patients with acute pulmonary oedema).
Patient population: Adult patients with acute pulmonary oedema with distress, anxiety, or restlessness
Prevalence of condition: According to the Global Health Data Exchange (GHDx) registry, a search with the keyword "heart failure", the current worldwide prevalence of HF is 64.34 million cases (8.52 per 1,000 inhabitants), or 0.8%. The overall prevalence of clinically identified heart failure is estimated to be 3–20 cases/1000 population, but rises to > 100 cases/1000 population in those aged ⩾65 years. The PICO population ONLY includes those patients with distress, anxiety or restlessness - there is limited prevalence data for this cohort but it is estimated as a small proportion of the total APE cohort.[28]
The average incidence of hospitalized ADHF was 11.6 per 1,000 persons, aged ≥55 years, per year.[29,30,31] Considering only the population with anxiety, restlessness and distress, no prevalence of these symptoms cold be found in literature. As approximately 15% of patients with acute decompensated heart failure has morphine prescribed - one can assume that anxiety could be present in around 15% of acute decompensated heart failure. So, 15% of 0.8% is approximately 0.12%.
Level of Care: PHC, Adult Hospital Level
Prescriber Level: Clinician (Doctor)
Current standard of Care: SL or IV Nitrates; IV or PO Furosemide, IV Morphine
Efficacy estimates: (preferably NNT): 67 NNH (mortality)
Motivator/reviewer name(s): Michael McCaul, Clint Hendrikse, Gustav Thom, Idriss Kallon, Veranyuy Ngah, Rephaim Mpofu Trudy Leong.
PTC affiliation: Gustav Thom – KZN PTC

Key findings

- We conducted a rapid review of clinical evidence on whether intravenous/intra-osseus morphine should be used in the treatment of acute pulmonary distress
- We identified four systematic reviews of observational studies. The two most relevant, up-to-date, and highest quality reviews were used to inform recommendations for critical outcomes.
- Morphine may increase in-hospital and all-cause mortality (OR 1.78; 95% CI 1.01 to 3.13; 15 more per 1000, from 0 fewer to 40 more; n=151 735 participants) and may result in a large increase in need for invasive mechanical ventilation (OR 2.72; 95% CI 1.09 to 6.80; 45 more per 1000, from 2 more to 136 more; n=167 847 participants) compared to not using morphine.
- No available data could be sourced on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use morphine for the treatment of acute pulmonary distress.
Rationale: Available evidence shows that morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. No available data could be found on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.
Level of Evidence: Low certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECCOMENDATION – 23 JUNE 2022:

NEMLC MEETING OF 23 JUNE 2022:

NEMLC accepted the proposal to amend the remove morphine the treatment of acute pulmonary distress. However, recommended that a caution be included in the STG, accordingly:

CAUTION

Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm.

Furthermore, once the respetive chapter is finalised, it was recommended that a circular be drafted and disseminated regarding the harms associated with use of morphine for distress in pulmonary oedema.

Monitoring and evaluation considerations

Research priorities

Authors: Idriss Kallon[1], Veranyuy Ngah[1], Clint Hendrikse[2, 5], Gustav Thom[3, 5], Michael McCaul[1,4, 5], Rephaim Mpofu[5,6], Trudy Leong [7,8]

[1]Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University
[2]Division of Emergency Medicine, University of Cape Town
[3]KwaZulu-Natal Department of Health
[4]SA GRADE Network
[5] PHC/Adult Hospital Level Committee (2019-2023)
[6] Department of Medicine, Division of Clinical Pharmacology, Groote Schuur Hospital, University of Cape Town
[7]Essential Drugs Programme, National Department of Health
[8] Secretariat to the PHC/Adult Hospital Level Committee (2019-2023); Secretariat to the National Essential Medicines List Committee (2021-)

Declarations of interest: IK, VN, GT, MM and TL have no interests pertaining to morphine.

Acknowledgments: Rephaim Mpofu (affiliated to University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa and PHC/Adult Hospital Level Committee, 2019-2023) assisted with the costing analysis.

Background

Morphine has been prescribed for patients with acute decompensated heart failure, but there is little evidence for safety and efficacy when used for this indication. The suggested mechanism is that morphine may assist with anxiolysis and reduce preload (Ellingsrun, 2016). However, a mortality benefit has not been demonstrated, and recent evidence suggests increase in adverse events and 30-day mortality. Morphine is included in both the Adult and PHC EML/STG for the management of pulmonary oedema/acute decompensated heart failure, specifically for patients who are experiencing anxiety. In the Adult Hospital EML/STG it is recommended under Acute Pulmonary Oedema "if distressed. Consider adding Morphine". In the PHC EML/STG, it is recommended "if patient is very anxious or restless". The evidence to support this is unclear/lacking (expert opinion) and recent evidence of harm has emerged (Gao *et al*, 2021 and Lin *et al*, 2021).

Research Question

Should intravenous morphine be used in the treatment of acute pulmonary distress?

Methods

We conducted a rapid review of evidence for the use of intravenous morphine in patients with acute pulmonary oedema. We systematically searched Ovid MEDLINE, Embase and the Cochrane Database of Systematic Reviews on February 12, 2022 for Randomised Controlled Trials (RCTs) and Systematic Reviews (SRs) of RCtTs or observational studies. Additionally, we searched the Pan African Clinical Trial registry for any ongoing studies from 2021. The search strategy can be seen in Appendix 1. Screening of title and abstracts and full text screening, selection of studies and data extraction was conducted

independently and in duplicate by two reviewers (IK and VN). Title and abstract, including full text screening was done using the Covidence systematic review software. AMSTAR II was used to appraise all the systematic reviews included in the study by a single reviewer (VN), checked by a second reviewer (IK). GRADE was applied to determine the certainty of evidence and the GRADEPro software was used to generate evidence profiles. Relevant study data were extracted into a narrative table of results. MM, IK, VN and CH reviewed the overall report. Where multiple eligible SRs were included, we reported evidence from the most relevant, recent and high-quality review or reviews in order to provide evidence across all *a priori* outcomes.

Eligibility criteria for review

Population:	Adult 18 years and older patients with acute pulmonary oedema with distress, anxiety, or restlessness in-hospital or prehospital. **Exclusion**: post-op complications, non-cardiogenic, congested cardiac failure*
Intervention:	Standard of care without Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide)
Comparator:	Standard of care with intravenous/intra-osseus Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide
Outcomes:	Mortality, AEs, SAEs, ICU length of stay, Hospital length of stay
Studies:	RCTs and SRs

**This question is restricted to acute pulmonary oedema*

Results

The search produced 709 records where 683 reports were irrelevant. We included 25 reports for full text review, excluded 21, and included four systematic review reports for data extraction and synthesis. See the PRISMA (Appendix 2) for further details, which include reasons for exclusions. Also, refer to table of excluded studies with reasons (Table 2). Gao *et al*., (2021) and Zhang *et al* (2021) were assessed to be of moderate quality (according to AGREE II) of the four included systematic reviews and were considered most relevant and up-to-date. AMSTAR II assessment results in Appendix 4. Relevant pooled outcomes from Gao and Zhang were re-GRADED (see Appendix 5)

Description of included studies

We found no RCTs addressing this question. The four included studies were systematic reviews of observational studies, with three using meta-analyses to aggregate results. The effect estimates in the meta-analysis were adjusted. Standard of care was not stated in the reviews.

Gao *et al* (2021) investigated the risk of mortality associated with opioid use in acute heart failure. They included 6 observational retrospective studies, with 15 1735 participants in total. Treatment given to the control groups was not described. The authors report extracting adjusted measures of effect from primary studies for meta-analysis where reported, however do not report on which factors were adjusted for. Gil *et al* (2019) assessed morphine use in the treatment of acute cardiogenic pulmonary edema. They included seven studies (one randomized controlled trial, one non-randomized control trial and five observational studies), and 150639 participants. Lin *et al* (2021) studied intravenous morphine in heart failure and Zhang *et al* (2021) investigated the safety of morphine in patients with acute heart failure. Lin *et al* (2021) included five studies (three propensity-matched cohorts and two retrospective analysis (one unpublished) with 14 9967 participants. Zhang *et al* (2021) included seven retrospective case-control studies and 172 226 participants, including adjusted measures of effect similar to Gao (2011). The treatment given to control groups in included studies was not stated.

See Table 1 for detailed information on included studies.

Internal validity of the systematic reviews, GRADE and absolute effects

AMSTAR II was used to determine the internal validity of included SRs (Appendix 5). In an effort to reduce duplication of effort in synthesis, we used the most relevant (to the PICO), up-to-date and highest quality SRs, among those, we prioritized reviews using GRADE. If a selected review did not report on all relevant outcomes, the next best review with relevant outcomes reported was used. Where needed outcomes were re-GRADED accounting for differencing in contextual/clinical interpretation such as indirectness and imprecision. Gao et al., (2021) included one secondary analysis of a previously conducted RCT which was excluded from our list of included studies to avoid double counting.

Gao and Zang had the highest AMSTAR II scores overall (moderate quality review), however Goa was considered overall to be the most relevant, up-to-date and internally valid as they also used GRADE. Gao did not report their reasons for the selection of type of studies included in the review neither did they report on the funding sources of each study included in the review hence scored as moderate quality. The Lin and Gil reviews were of critically low quality.

Absolute effects were calculated from pooled effect data where possible. In the absence of baseline event data (control event rates for pooled effects), absolute effects were calculated using reported baseline events either (where available) from pooled baseline event data from included reviews across the same outcome or large risk observational studies for that outcome to determine baseline prevalence. This was done for mortality and SAEs.

Effect of interventions

Mortality (in-hospital mortality and 30-day mortality)

Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (Evidence Profile in Appendix 5 and Figure 1). (Gao, 2021) Gao *et al* (2021) did not report any baseline event rates for standard of care or for the intervention arms, thus to calculate absolute effects we assumed a baseline control event rate of 2% for overall mortality based on Lin (2019).

Zhang *et al* (2021) found no association between morphine and in-hospital mortality (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, Figure 2) however the direction of effect is still in line with Gao *et al* (2021).

Figure 1: Forest plot of the pooled analysis evaluating in-hospital and 30-day mortality according to opioid use. IV, inverse variance (Gao, 2021)

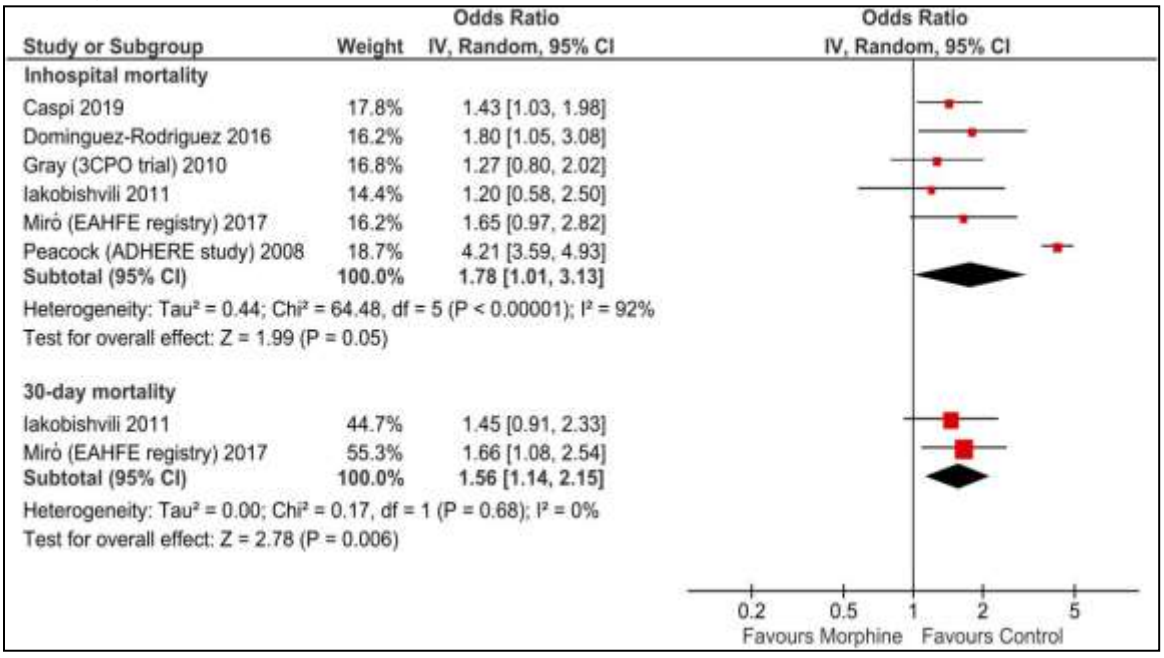


Figure 2: Forest plot of in-hospital mortality (Gao, 2021)

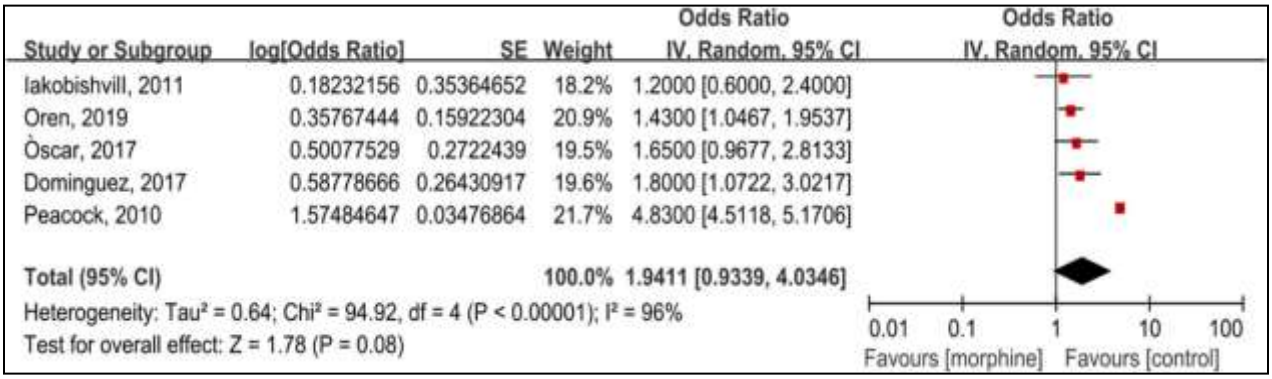
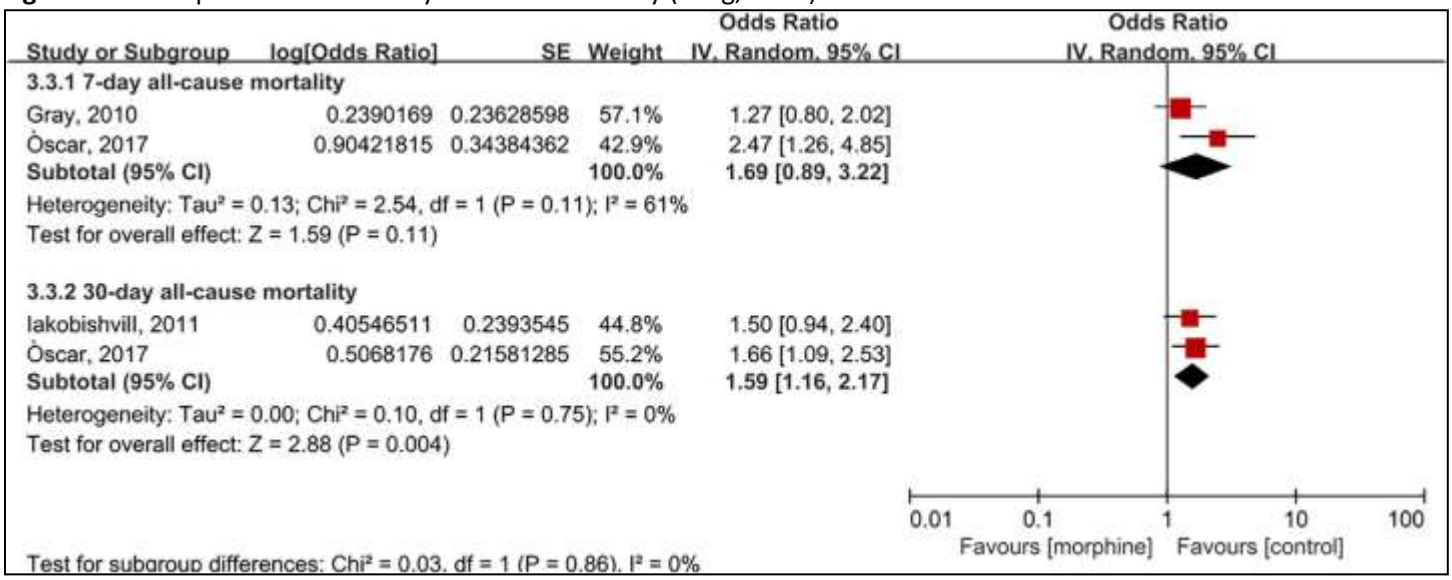


Figure 3: Forest plot of 7 and 30-day all-cause mortality (Zang, 2021)

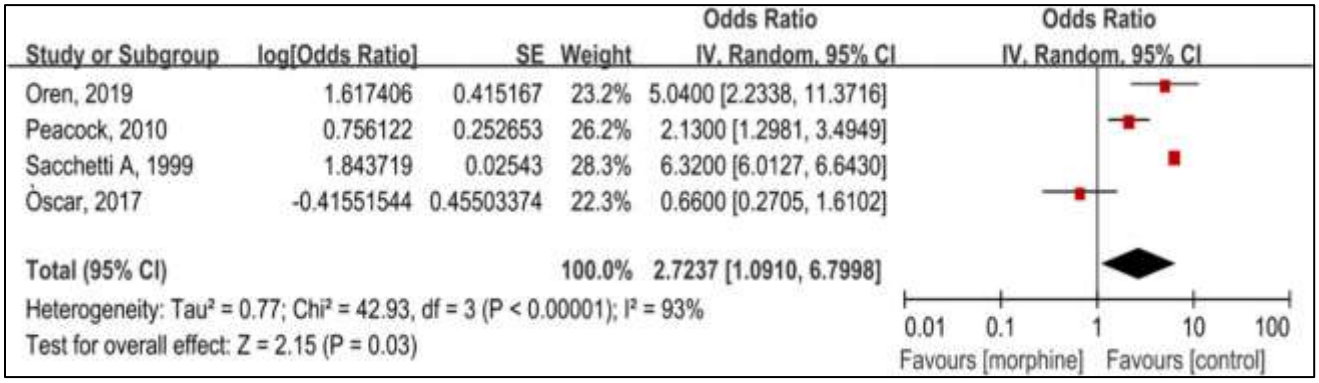


Zhang et al (2021) found that morphine treatment was associated with an increased significant 30-day all-cause mortality (OR 1.59; 95% CI 1.16 - 2.17) from three studies (n=9 904). Gao et al (2021) reported a similar association between morphine use and 30-day mortality (OR 1.56; CI 1.14 -2.15) from two studies (n=986) (Figure 3).

SAE (need for invasive mechanical ventilation)

Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) (Figure 4) (Zang, 2021). Baseline event rate not reported in review thus calculated from estimates of mechanical ventilation baseline event rate based on Gray (2008, NEJM).[27]

Figure 4: Forest plot of invasive mechanical ventilation



Adverse events
Not measured.

ICU or hospital length of stay
Not measured.

Conclusion

This evidence review of use of intravenous morphine in the treatment of acute pulmonary distress included four systematic reviews of observational studies. This review focuses on adjusted pooled evidence from two high-quality, relevant and up-to-date reviews pooling more than 150 000 participants, with direction and magnitude of effects consistent across other included systematic reviews. Based on the most recent, relevant, and highest quality reviews, morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. We have no data on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Observational evidence (using ROBINS-1) downgraded by one level for risk of bias and by one level for inconsistency. Goa (2021) judged indirectness as serious (for unclear reasons), thus scoring very low certainty. The committee did not consider this evidence as indirect as evidence has clear alignment to PICO and is across various settings, including HIC and LIMCs.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [x]	The review identified no beneficial anticipated effects.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	• Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (NNH 67) • Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) 45 more per 1,000 (from 2 more to 136 more) baseline event rate based on Gray (2008, NEJM)[27] • Absolute effects for mortality based on baseline event rates provided by Lin (assuming 2% mortality rate)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention (No Morphine) [x] Favours control (Morphine) [ ] Intervention = Control *or* Uncertain [ ]	**Desirable effects** (of morphine): None **Undesirable effects** (of morphine): moderate
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a Yes [ ] No [ ]	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	No evidence of feasibility was reviewed/sought. The Committee was of the opinion that not giving morphine is standard practice in most settings and clinicians would accept such a recommendation.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	x	

The Committee was of the opinion that removing a medicine would result in cost savings, with less mechanical ventilation.

Price/treatment course of morphine, IV per patient *(direct medicine prices only)*

Medicine	Tender price (ZAR)*
Morphine 10mg/mL ampoule	4.03**
Sodium chloride 0.9% 10 ml	1.56**
Total	**5.59**

**Weighted average tender prices*

*** Contract circular HP06-2021SVP, June 2022*

Prevalence assumptions:

- According to the Global Health Data Exchange (GHDx) registry, the current worldwide prevalence of HF is approximately 0.8%.
- Meta-analysis by Platz et al (2015) showed that the prevalence of pulmonary oedema in heart failure and reduced ejection fraction (HF-REF) trials ranged from 75% to 83% (though the criteria defining HF varied across trials).
- Experts suggest that approximately 15% of HF-REF patients are administered morphine (as per the 2019 Adult Hospital and 2020 PHC STGs and EML recommendations).

Other assumptions:

- Adult population estimated to be >19 years of age (38189762); based on StatsSA mid-year population estimates of 2021.
- 85.04% of the population is uninsured (>19 years = 32476574)
- Most patients would use a maximum dose of morphine, IV (10 mg).
- Patients would only have one episode per year.

Estimated annual budget impact (medicine costs only):

1: Lower prevalence of HF-REF 75%:
Administered morphine: 0.09 % of 32 476 574 = 28 449
Estimated medicine cost per annum: R159 033

2. Upper prevalence of HF-REF of 83%:
Administered morphine: 0.1 % of 32 476 574 = 32 347
Estimated medicine cost per annum: R180 818

Therefore, disinvesting morphine IV for the treatment of anxiety in adult patients with pulmonary oedema would result in a saving of R159 000 to R180 000 per year.

References:

- Council for Medical Schemes Annual report, 2018/9. Available at: https://www.medicalschemes.com/files/Annual%20Reports/CMSAR2018_19.pdf
- StatsSA mid-year population estimates of 2021.
- Platz E, et al. Assessment and prevalence of pulmonary oedema in contemporary acute heart failure trials: a systematic review. Eur J Heart Fail. 2015 Sep;17(9):906-16.
- Contract circular HP06-2021SVP, June 2022

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	No evidence of values and acceptability was reviewed/sought. The Committee expects minor variability in how patients value critical outcomes such as death and avoiding serious adverse events. Acceptable to stakeholders in the hospital setting (district level). However, removing morphine from practice for pulmonary oedema may result in some resistance or lack of behavior change, especially in the prehospital setting.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Removing morphine will likely result in increased equity across settings where morphine was not available or had unequal access.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	13 April 2022	ID, VN, CH, GT, MM, TL	

References:

1. Agewall S. *Morphine in acute heart failure.* J Thorac Dis 2017;9(7):1851-1854. Morphine in acute heart failure - PMC (nih.gov).
2. Berger PE, Archambault P, Poitras J. *ARE narcotics harmful in the treatment of acute pulmonary edema*? A critically appraised topic. Scientific Abstracts (163). CJEM.JCMU 2010;12(3): 277. https://regroup-production.s3.amazonaws.com/documents/ReviewReference/446507477/2010_caepacmu_scientific_abstracts_may_29jun_2_2010_montreal_que.pdf AWSAccessKeyId=AKIAJBZQODCMKJA4H7DA&Expires=1649927249&Signature=0VmxGwfBhnatQd4mhGTTFViP9Xw%3D.
3. Dominquez-Rodriquez A, Burillo-Putze G, Garcia-Saiz M, Aldea-Perona A, Harmand MG, Miro O, Abreu-Gonzalez P. *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. https://regroup-production.s3.amazonaws.com/documents/ReviewReference/446507644/Dominguez-Rodriguez2017_Article_StudyDesignAndRationaleOfAMult.pdf?AWSAccessKeyId=AKIAJBZQODCMKJA4H7DA&Expires=1649927437&Signature=jmXwEE%2FEGNk86Oiz4uqzj9H519c%3D.
4. Dominquez-Rodriquez A, Avanzas P, Burillo-Putze G, Abreu-Gonzalez P. *Influence of morphine treatment on in-hospital mortality among patients with acute heart failure*. Med Intensiva 2017;41:382-384. https://pubmed.ncbi.nlm.nih.gov/27707523/.
5. Ellingsrud C, Agewall S. *Morphine in the treatment of acute pulmonary Edema.* Tidsskr Nor Legeforen 23-24, 2014; 134:2272-2275. DOI: 10.4045/tidsskr.14.0359. https://europepmc.org/article/med/25492336.
6. Gao D, David C, Rosa MM, Costa J, Pinto FJ, Caldeira D. *Risk of Mortality Associated with Opioid Use in Patients With Acute Heart Failure: Systematic Review and Meta-analysis*. J Cardiovasc Pharmacol 2021; 77: 123-129. https://journals.lww.com/cardiovascularpharm/Fulltext/2021/02000/The_Risk_of_Mortality_Associated_With_Opioid_Use.1.aspx?casa_token=3_w9ZgnmS7MAAAAA:h69WkGI2LE5IY2iQxuqjotG33DEXDJkIfKfyWkgsIStgzGrkstUST2pO7K-uugqUlDNJbAiyXZCipcT8G7LqAGQ.
7. 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://link.springer.com/article/10.1007/s11897-019-00427-0.
8. Graham CA, Cattermole GN. *Morphine should be abandoned as a treatment for acute cardiogenic pulmonary oedema*. Emergency Medicine Australasia 2009;21:160. https://europepmc.org/article/med/19422415.
9. Hall M, Griffiths R, Appadu B. *Is Morphine indicated in acute pulmonary oedema*. Emerg Med J 2005; 22:391-392. https://emj.bmj.com/content/22/5/391.1.
10. Herlitz J, Bång A, Omerovic E, Wireklint-Sunström B. *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. https://doi.org/10.1016/j.ijcard.2010.10.012.
11. Holm M, Tomvall P, Henareh L, Jensen U, Golster N, AlstrÖm P, Santos-Pardo I, Fedchenko N, Venetsantos D, Beck O, Linden J. *The Movement Trial*. J Am Heart Assoc. 2019;8:1-11. https://regroup-production.s3.amazonaws.com/documents/ReviewReference/446507814/The%20movement%20trial.pdf?AWSAccessKeyId=AKIAJBZQODCMKJA4H7DA&Expires=1649927338&Signature=A%2B6hA7QBaWj45lkaiu22KIv9ZBg%3D.

12. Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ. *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. https://doi.org/10.1016/S1388-9842(02)00158-7.
13. Johnson MJ, Cockayne S, Currow, DC, Bell K, Hicks K, Fairhurst C, Gabe R, Togerson D, Jefferson L, Oxberry S, Ghosh J, Hogg, KJ, Murphy J, Allgar V, Cleland JGF, Clark AL. *Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial*. ESC Heart Failure 2019: 6:1149-1160. https://doi.org/10.1002/ehf2.12498.
14. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, Stankowska K, Buszko K, Navarese EP, Jilma B, Siller-Matula JM, Marszatt MP, Ros´c´D, Kozin´ski M. *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. https://doi.org/10.1093/eurheartj/ehv547.
15. León-Delgado M, Rodríguez- Campos L, Bastidas-Goyes A, Herazo-Cubillos A, Martin-Arsanios D, Muñoz-Ortíz J, Cifuentes-Serrano A, García-Ávila P, Beltrán-Caro M. *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. http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0120-33472019000100049.
16. 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; 22(3): 865-872. https://article.imrpress.com/journal/RCM/22/3/10.31083/j.rcm2203092/2153-8174-22-3-865.pdf.
17. Mattu A, Lawner B. *Prehospital Management of Congestive Heart Failure*. Heart Failure Clin 5 2009; 19–24. https://doi.org/10.1016/j.hfc.2008.08.004.
18. Orso D, Boaro G, Cassan E, Guglielmo N. *Is morphine safe in acute decompensated heart failure? A systematic review of the literature*. European Journal of Internal Medicine 2019; 69:e8–e10. https://doi.org/10.1016/j.ejim.2019.08.016.
19. Oxberry SG, Togerson DJ, Bland MJ, Clark AL, Cleland JGF, Johnson MJ. *Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial*. European Journal of Heart Failure 2011;13:1006–1012. https://doi.org/10.1093/eurjhf/hfr068.
20. Oxberry SG, Bland MJ, Clark AL, Cleland JGF, Johnson M. *Minimally clinically important difference in chronic breathlessness: Every little helps*. American Heart Journal 2012; 164(2):229-235. https://doi.org/10.1016/j.ahj.2012.05.003.
21. Oxberry SG, Bland M, Clark AL, Cleland JG, Johnson MJ. *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. https://doi.org/10.1089/jpm.2012.0270.
22. Poole-Wilson PA. *Treatment of Acute Heart Failure. Out with the Old, in With the New*. JAMA 2002; 287(12):1578-1580. https://jamanetwork.com/journals/jama/article-abstract/194759?casa_token=BCNCbvwpL5YAAAAA:1qrmmoDv0V4K_l6VN03nl3XwTWuowC7ASSJpVBMkuAlT6n4GKv6cKcbkVH2hpYQH11U-qdDRFw.
23. Triposkiadis F, Parissis JT, Starling RC, Skoularigis J, Louridas G. *Current drugs and medical treatment algorithms in the management of acute decompensated heart failure*. Expert Opin Investig Drugs 2009; 18(6):695-707. https://doi.org/10.1517/13543780902922660.
24. Vicicevic Z. *Is it necessary to use Morphine in acute pulmonary edema*? Lijec Vjesn 2003; 125(47):1-2. https://pubmed.ncbi.nlm.nih.gov/12812030/.
25. Zhang D, Lai W, Lui X, Shen Y, Hong K. *The safety of morphine in patients with acute heart failure: A systematic review and meta-analysis*. Clin Cardiol 2021; 44:1216–1224. https://doi.org/10.1002/clc.23691.
26. Dominguez-Rodriguez A, Burillo-Putze G, Garcia-Saiz MDM, Aldea-Perona A, Harmand MG, Mirò O, Abreu-Gonzalez P; MIMO investigators. Study Design and Rationale of "A Multicenter, Open-Labeled, Randomized Controlled Trial Comparing MIdazolam Versus MOrphine in Acute Pulmonary Edema": MIMO Trial. Cardiovasc Drugs Ther. 2017 Apr;31(2):209-213. doi: 10.1007/s10557-017-6722-5
27. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008 Jul 10;359(2):142-51. doi: 10.1056/NEJMoa0707992.
28. McMurray JJ, Stewart SE. pidemiology, aetiology, and prognosis of heart failure. Heart 2000;83:596-602.
29. Chang PP, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities . Am J Cardiol. 2014 Feb 1;113(3):504-10. doi: 10.1016/j.amjcard.2013.10.032.
30. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME Med J 2020;5:15.
31. Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert Rev Cardiovasc Ther. 2009 Feb;7(2):169-80. doi: 10.1586/14779072.7.2.169.

Appendix 1: Search Strategy

Ovid MEDLINE

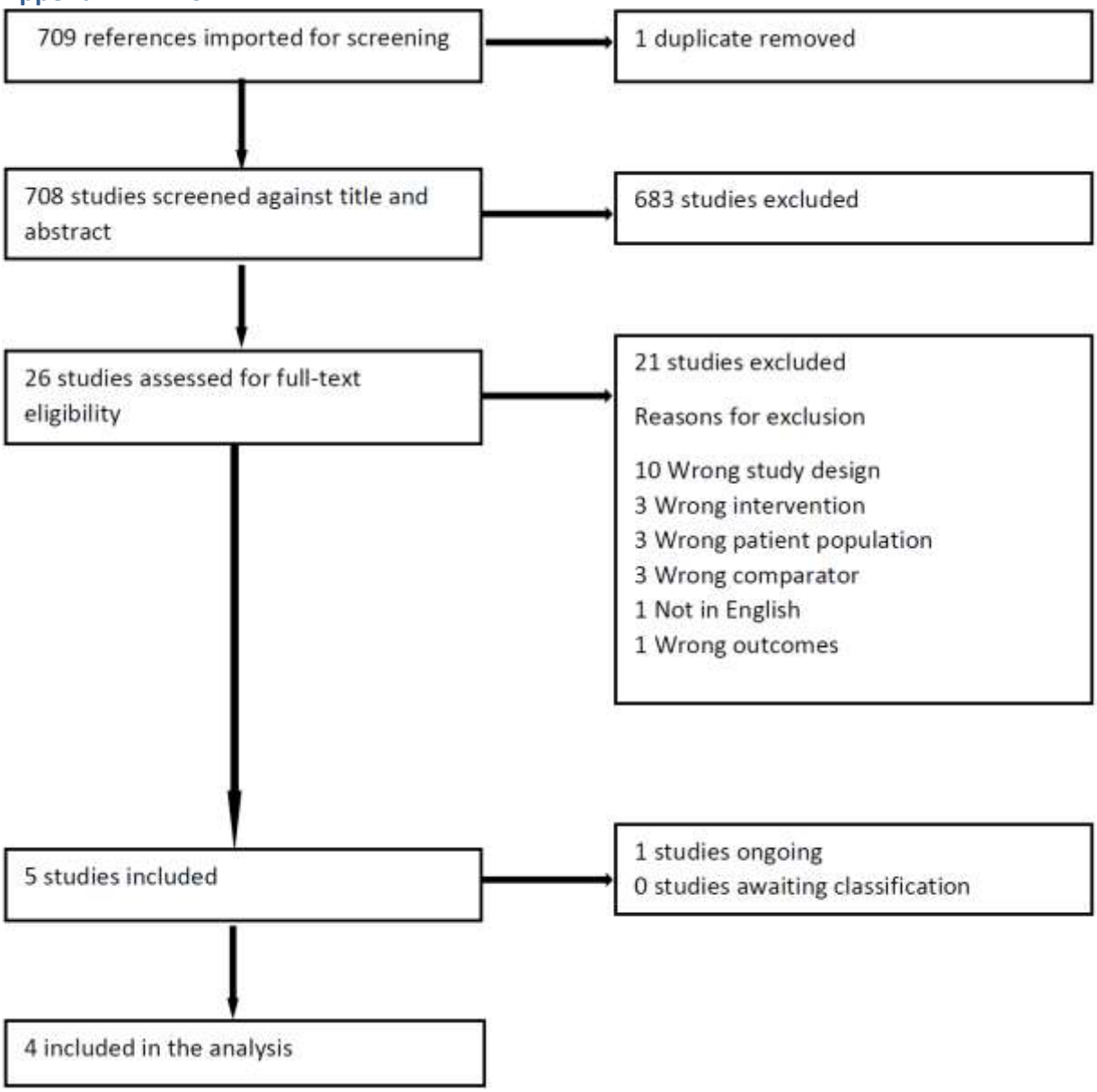
1	Pulmonary Edema/	17628
2	(pulmonary adj2 (edema or oedema)).tw.	19427
3	decompensated heart failure.mp.	3870
4	decompensated cardiac failure.mp.	37
5	exp Heart Failure/	135224
6	1 or 2 or 3 or 4 or 5	161564
7	Morphine/	39357
8	morphin*.tw.	55512
9	7 or 8	62460
10	6 and 9	332
11	randomized controlled 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: PRISMA



Appendix 3

Table 1: 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, I^2 = 97.1 %; Very low certainty of evidence <u>Total group:</u> 2899/22072 in intervention group 3180/127895 in control group. <u>Sub group analysis in score matching studies</u>: 178/1165 in intervention group 132/1165 in control group (OR=1.41, 95% CI: 1.11–1.80, p =0.005, I^2 = 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 $I2$ = 97.1%. Accordingly, subgroup analyses including score-matching studies only were conducted, for which in-hospital mortality was $I2$ = 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; I^2= 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	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	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, I^2 = 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, I^2 = 61%) **For 30-day all-cause mortality** OR: 1.59; 95% CI 1.16 to 2.17; p = 0.004, I^2 = 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, I^2 = 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 4

Table 2: 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 5: Certainty assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsist-ency	Indirectness	Imprecision	Other considerations	Morphine	SOC	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
6	observational studies	serious[a]	serious[b]	not serious	not serious[c]	none	794/22649 (3.5%)	2582/129086[g] (2.0%)	**OR 1.78 (1.01 to 3.13)**	**15 more per 1,000 (from 0 fewer to 40 more)**	⊕⊕◯◯ Low	CRITICAL
SAE												
4	observational studies	not serious[d]	serious[e]	not serious	serious[f]	none	1632/22047 (7,4%)	4083/145800[g] (2,8%)	**OR 2.72 (1.09 to 6.80)**	**45 more per 1,000 (from 2 more to 136 more)**	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio; **SOC:** standard of care

Explanations

a. Serious risk of bias: At least one domain of bias in most studies was graded as serious according to ROBINS-I tool

b. With the exception of Peacock, confidence intervals show overlapping, point estimates have a some variation and there is a significant heterogeneity in the pooling. Peacock is a study that comprises a greater sample size (147k vs. 6k, the 2nd greatest) in comparison with the aforementioned studies, and is the only study conducted in a nation that does not abide by ESC guidelines. Inconsistency may be dampened with the exclusion of Peacock as observed following the jackknife sensitivity analysis, however as no concrete justification for the discrepancy was found

c. No imprecision: Not downgraded, very low baseline risk (rare events <2%), further changes in relative effects are unlikely to result in meaningful changes in absolute effects. Furthermore, not downgrading for imprecision as to not double downgrade/penalise for both inconsistency and imprecision.

d. No serious ROB: NCOS was used, low risk of bias for this outcome of included studies

e. Serious inconsistency: Significant heterogeneity across studies specifically Oscar (2017) and Sacchetti (1999)

f. Serious imprecision: Absolute effect does not cross the null threshold, potentially large relative effect (OR >2.5) with IOS met, however absolute effect ranges from trivial harms to possible large harms.

g. Baseline risk calculated from references 16 (for in-hospital mortality)and 27 (for SAE) as this data was not provided as generic inverse variance methods was used

Appendix 6: Overall AMSTAR score for each of the 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

Appendix 7: Ongoing studies

Ongoing studies

A Multicenter, Open-Labeled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema": MIMO Trial(26)

Brief Summary: Acute pulmonary edema (APE) is a common condition in the emergency room, associated with considerable mortality. The use of intravenous morphine in the treatment of APE remains controversial and Benzodiazepines have been suggested as an alternative for morphine to relieving dyspnoea and anxiety in the patients with APE. The Midazolam versus Morphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE.
Study type: Interventional (Clinical Trial)
Estimated enrollment: 136 participants
Allocation: Randomized
Intervention model: Parallel assignment
Masking: None (Open Label)
Primary purpose: Treatment