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Systematic review on the risk-benefit ratio of morphine for acute heart failure

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ABSTRACT

Objective: To evaluate morphine's risk-benefit profile in the treatment of acute heart failure.

Method: Different electronic databases, including PubMed, MEDLINE, Cochrane Library, and Google Scholar, as well as clinicaltrails.gov, were searched for articles published between 2012 and 2022. The risk of bias in the present study was evaluated by employing randomized controlled trials (RCTs) checklist that assesses the effectiveness of new interventions through random assignment of participants to different treatment groups. The two-part tool was used to address the five specific domains such as selection bias, performance bias, detection bias, attrition bias, and selective reporting bias. Evaluation of the quality of diagnostic accuracy studies was conducted using the RevMan software (version 5.4), a quality assessment tool.

Results: A total of 13 studies were included in the present review, in which there were 5 retrospective studies, 3 randomized-control studies, 2 prospective studies, 1 multicenter pharmacodynamics study, 1 multicenter cardiac magnetic resonance imaging study, and 1 open-label, cross-over study. The mortality of acute heart failure patients treated with morphine was higher compared to those without morphine.

Conclusions: Acute heart failure patients who do not receive morphine have a lower mortality rate compared to those who receive morphine. Considering the adverse effects, including mortality associated with morphine, there is a pressing need for further research to explore alternative and effective treatment options in acute heart failure.

KEYWORDS: Acute heart failure; Hospital mortality; Morphine; Side-effects; Invasive ventilation

1. Introduction

Acute heart failure (AHF) is characterized by an unexpected deterioration of cardiac function along with a sudden onset of its symptoms and signs[1]. As a result of AHF, patients often experience dyspnea (shortness of breath) and fatigue, as well as typical physical symptoms, including pulmonary rales (abnormal crackling sounds), peripheral edema, or distended jugular veins[2].

It is estimated that heart failure affects 2% of the adult population in developed countries and hospital admissions due to heart failure have tripled since the 1990s[3]. Globally, AHF's mortality hovers around 4% which later rises to 10% at 60-90 days after discharge, and it may increases to 25%-30%[4-8]. The International Congestive Heart Failure prospective cohort study found that countries with a higher percentage of young people have a higher 1-year mortality due to heart failure, such as India and Africa[9]. Since AHF frequently results in cardiogenic shock, it is regarded as a high-risk factor for mortality[10] and requires immediate diagnosis and treatment.

Based on the class-IIb level of evidence, morphine has been recommended for several decades to improve severe pulmonary

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edema in AHF patients[11,12]. Several studies have revealed that morphine has some vasodilatory properties (described between the 1960s and 1980s)[12-14] suggesting that it is beneficial for the treatment of AHF. Morphine can reduce venous tone and increase peripheral venous pooling, thereby decreases cardiac filling pressure. AHF therapy must reduce the filling pressure as soon as possible; hence the use of morphine might be beneficial. Furthermore, it has an anti-anxiety effect and could decrease both the preload and afterload by decreasing the action of the sympathetic nervous system[15].

Despite a shortage of evidence to support its prolonged usage, morphine has long been utilized in patients with AHF due to its anxiolytic and vasodilatory effects. But like any other drugs, morphine also comes with adverse effects such as central nervous system suppression as well as depression of ventilation[16,17]. For these reasons, several studies advised against the use of morphine in treating AHF patients[18,19]. The risk-benefit ratio should be kept in mind when morphine is used to treat heart failure patients[20,21]. Hence, the present review was conducted to highlight the risk as well as the benefit of morphine in treatment of AHF.

2. Methods

This systematic review was piloted in accordance with the preferred reporting for the systematic review guiding principles.

2.1. Search strategy

We conducted a literature search on major electronic databases such as MEDLINE, PubMed, Scopus, Web of Science, Wiley, Embase, the Cochrane Library, as well as clinicaltrails.gov, for articles that were published between 2012 and 2022. A geographic restriction was not applied to the search. We combined terms such as "morphine" and "mortality" with "AHF", and used the boolean operator "AND" to combine keywords in the search. The following terms were used for the literature search: "effect of morphine in treatment of AHF", "risk of AHF", and "benefits of morphine in AHF".

2.2. Inclusion and exclusion criteria

The articles that met the following inclusion criterion were

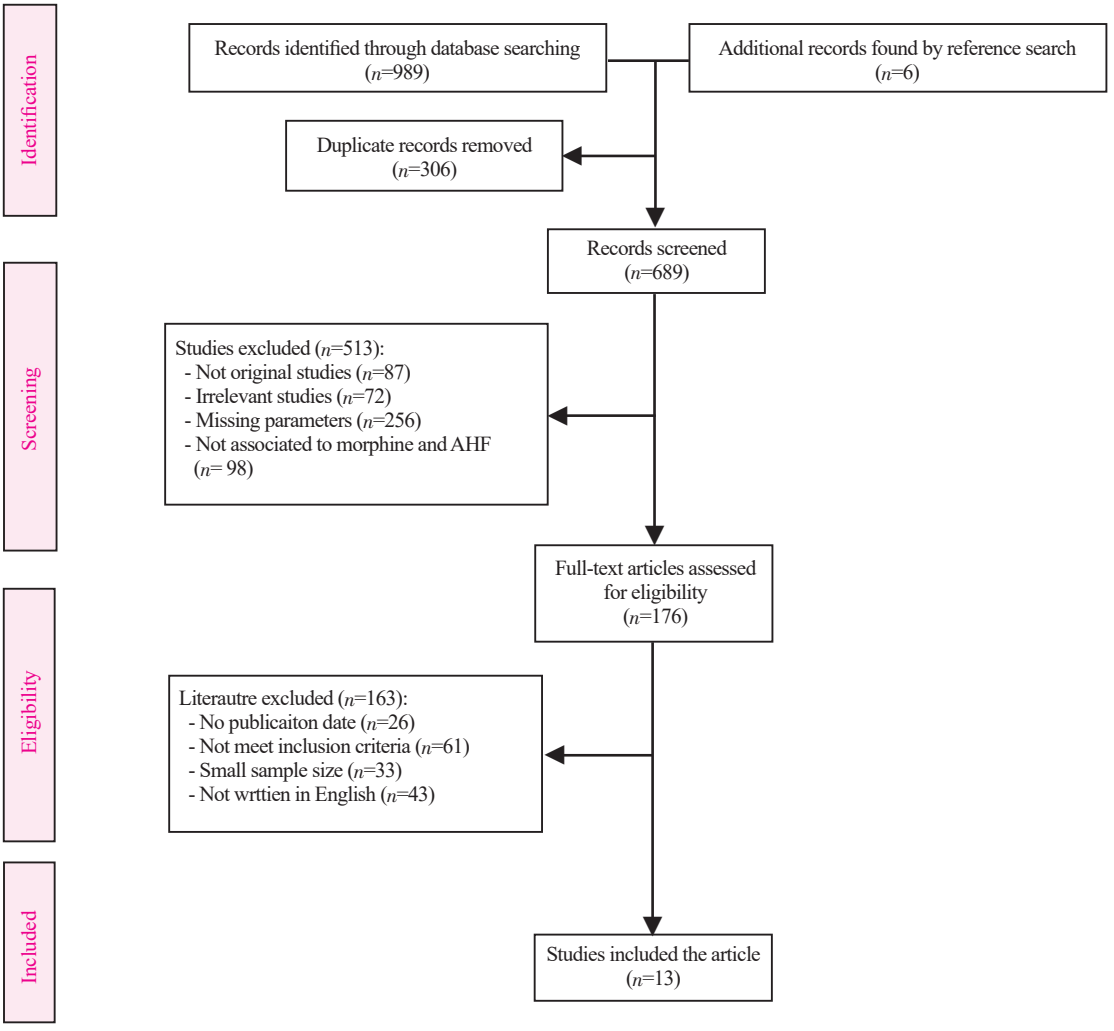

Figure 1. The study flowchart.

selected: 1) human-based studies; 2) written in English; 3) published after 2012; 4) containing extractable data, such as all-cause mortality and in-hospital deaths, 5) providing information about the effects of morphine on the treatment of AHF, and 6) describing the risk or benefit of morphine in the treatment of AHF.

Articles that were not relevant to morphine or AHF and written in languages other than English, as well as not providing sufficient data such as abstract, editorial, and comment, were excluded.

2.3. Statistical analysis

In this study, risk of bias was evaluated using the tool RevMan 5.4.1 according to the Cochrane Review Guidelines (Higgins 2011). Five specific domains were addressed by the two-part tool. "Risk of bias" tables were included in each domain. A study entry begins with a description of what was reported to have happened during the research. Second, the tool includes assigning a judgment about the entry's bias risk: low risk, unclear risk, or high risk.

3. Results

3.1. Study selection

On the initial search, 989 records were found and 6 additional records were found by reference search. After the initial search, 306 duplicates were excluded. Among the remaining 689 records, 513 were excluded because of that some articles are not original studies (n=87), had missing parameters (n=256), were irrelevant to the present study (n=72), and about 98 articles were removed for not relating to "morphine" or "acute heart failure". The contents of 176 articles were fully assessed. Upon reviewing the full texts, articles that have a small sample size (n=33), have no publication date (n=26), are not written in English (n=43), as well as are letters, case reports or reviews (n=61), were excluded for the final review. After completing the screening, a total of 13 studies, published between 2012 to 2022, were included for data analysis in this present systematic review (Figure 1).

3.2. Studies characteristics

The present systematic review included 13 studies, in which there were 5 retrospective studies, 3 randomized-control studies, 2 prospective studies, 1 multicenter pharmacodynamics study, 1 multicenter cardiac magnetic resonance imaging study, and 1 open-label, cross-over study. Among the included studies, 3 024 patients were treated with morphine, and 14 323 patients were not treated with morphine. The mean age was 68.17 years in the morphine group and 64.92 years in the control group. The basic features of the included studies are presented in Table 1.

3.3. Mortality rate

Among the 3 024 patients who received morphine, 534 (17.65%) of them died. Out of 14 323 patients without morphine, 1 160 (8.09%) died.

3.4. Quality assessment

Figure 2 shows the bias assessment for the 13 included trials. Serious procedural inadequacies were established in all trials for at least one bias domain. In this review, 10.76% of the trials, randomization was inadequate or nonexistent, blinding of outcome assessors was missing in 58.46% of trials and the risk was unclear in 30.76%.

4. Conclusion

According to Gil *et al.*, morphine has anti-anxiety, vasodilator, pain-relieving, sedative qualities that make it an effective treatment for acute pulmonary edema as well as AHF[34]. However, contrasting protocols for morphine administration are noted by the American Heart Association/American College of Cardiology and European Society of Cardiology which supports the use of morphine only for the palliative therapy of end-stage heart failure[35]. However, some other guidelines suggested that only use morphine for cases with severe breathing complications or prominent pulmonary edema[10],

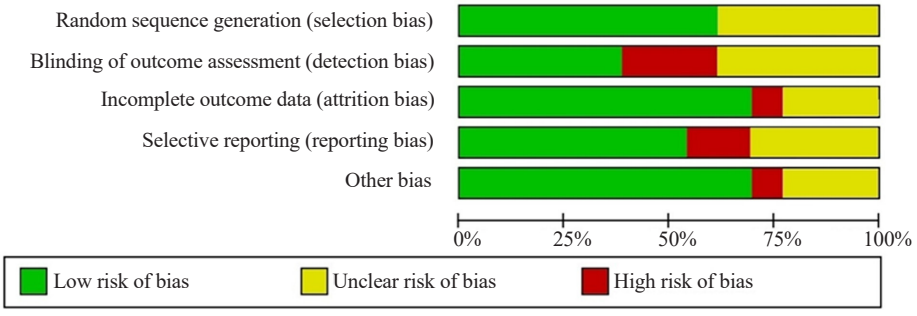

Figure 2. Risk of bias review of included studies.

Table 1. Basic features of included studies.

Author and year	Ref	Study design	Sample size (*n*)	Age, year (Mean±SD)/(Median, Q1, Q3)	Sex	Mortality cases/ratio	Outcome
Miró *et al.* (2017)	[18]	Retrospective study	MG: 416 CG: 6 100	MG: 80.7±10.2 CG: 81.1±10.1	M/F	MG: 55 deaths CG: 35 deaths	The use of intravenous morphine in AHF may be linked to an increased 30-day mortality.
Parodi *et al.* (2014)	[22]	Multicenter pharmacodynamic study	MG: 95 CG: 205	MG: 62.0±13.0 CG: 61.1±12.6	M	MG: 2 deaths CG: 7 deaths	The use of morphine is associated to a delayed onset of the oral antiplatelet medicines' actions. After morphine propensity adjustment and exclusion of individuals who had vomited, this connection remained.
Puymirat *et al.* (2016)	[23]	Prospective multicenter study	MG: 453 CG: 1 985	MG: 59.3±13.9 CG: 64.2±14.6	M/F	At 1 year, crude mortality rates were reduced in patients with morphine (3.3%) than in the ones without morphine (8.7%)	Morphine pre-hospital-use in STEMI patients has been shown not to result in worse hospital outcomes or higher mortality.
Kubica *et al.* (2016)	[24]	Randomized, double-blind, placebo-controlled IMPRESSION trial	MG: 35 CG: 35	MG: 60.7±10.5 CG: 62.5±10.5	M/F	MG: 0 death CG: 0 death	All three methods of platelet reactivity assessment showed a stronger antiplatelet effect in the control group and a greater prevalence of high platelet reactivity in patients receiving morphine.
Thomas *et al.* (2016)	[25]	Open-label, cross-over study	MG: 6 CG: 6	MG: 64 (59, 66) CG: NR	M/F	NR	The administration of intravenous morphine considerably delayed the onset of action of prasugrel. Intravenous drugs may be essential to decrease the risk of acute stent thrombosis in morphine-treated STEMI cases suffering from primary percutaneous coronary intervention.
Le Corvoisier *et al.* (2018)	[26]	Randomized controlled trial	MG: 45 CG: 45	MG: 59.9±13.2 CG: 56.5±10.6	M/F	MG: 0 death CG: 1 death	The effect of intracoronary morphine at reperfusion on infarct size and left ventricle systolic function was not significantly reduced in patients with STEMI.
Caspi *et al.* (2019)	[27]	Retrospective study	MG: 672 CG: 72	MG: 78±11 CG: 75±12	M	MG: 17.4% in-hospital mortality CG: 13.4% in-hospital mortality (*OR*=1.43, 95% *CI*: 1.05-1.98, *P*=0.024)	Among AHF patients, morphine administration significantly increased the risk of in-hospital mortality and mechanical ventilation was essential due to hemodynamic deterioration.
Johnson *et al.* (2019)	[28]	Randomized placebo-controlled trial	MG: 21 CG: 24	MG: 74.4±6.0 CG: 70.1±14.0	M/F	MG: 0 death CG: 1 death	The use of morphine should be restricted to those who are unable to address their symptoms through other methods, as well as with early management of side effects.
Dong *et al.* (2020)	[29]	Retrospective study	MG: 125 CG: 150	MG: 61.70±13.67 CG: 58.71±13.03	M	MG: 19 deaths CG: 10 deaths	In STEMI patients with AHF, it was warranted to increase consciousness of the potential adverse clinical effects of intravenous morphine-use in the hospital, such as cardiac mortality as well as invasive mechanical ventilation.

Table 1. Continued.

Author and year	Ref	Study design	Sample size (*n*)	Age, year (Mean±SD)/(Medium, Q1, Q3)	Sex	Mortality cases/ratio	Outcome
Kawaguchi *et al.* (2020)	[30]	Retrospective study	MG: 47 CG: NR	MG: 73.5 ±11.4 CG: NR	M	NR	In advanced heart failure patients, morphine treatment for persistent dyspnea may be an option for palliative care.
Furtado *et al.* (2020)	[31]	Prospective study	MG: 617 CG: 4821	MG: 66.1±NR CG: 67.2±NR	F	MG: 66 (10.7%) death, MI, RIUR, or TBO at 96 h; 76 (12.3%) deaths or MI at 30 days. CG: 411 (8.5%) death, MI, RIUR, or TBO at 96 h; 500 (10.4%) deaths or MI at 30 days.	When used concomitantly with clopidogrel pre-treatment, morphine was associated with higher rates of ischemic events in patients with non-ST elevation acute coronary syndrome.
Eitel *et al.* (2020)	[32]	Multicenter cardiac magnetic resonance imaging study	MG: 454 CG: 280	MG: 61 (51, 70) CG: 66 (52, 72)	M	NR	Myocardial damage or clinical prognosis were not affected by morphine administration in acute reperfused STEMI. There may be a cardio protective effect of morphine in patients who present early (120 min) according to smaller infarct size, but this needs to be further explored in well-designed clinical trials.
Gotou *et al.* (2022)	[33]	Retrospective study	MG: 38 CG: NR	MG: 78±NR CG: NR	M	NR	Among the study population, 37% of cases with the end-stage heart failure receiving continuous intravenous/subcutaneous morphine infusion experienced the ADRs, particularly drowsiness. A baseline eGFR< 32 mL/min/1.73 m^2 was significantly related to morphine-related ADRs.

NR: not reported; MG: morphine group; CG: control group; M/F: male/female; AHF: acute heart failure; STEMI: ST-elevation myocardial infarction; MI: myocardial infarction; RIUR: recurrent ischemia with urgent revascularization; TBO: thrombotic bailout; ADRs: adverse drug reactions; eGFR: estimated glomerular filtration rate.

for morphine treatment in AHF patients have known to have several harmful effects like vomiting, myocardial depression, and respiratory depression as well as the attenuated platelets inhibition.

In the present review, it was observed that morphine as a treatment modality for AHF comes with its own set of risks as well as benefits. To further analyze the efficacy of morphine, the mortality of AHF patients who received morphine treatment was compared with those who did not receive it. In this review, most of the studies found that AHF patients who used morphine had higher mortality rates. Patients with AHF were found to have no benefit from morphine, instead, a risk of invasive ventilation which is associated with the mortality was detected, as Caspi *et al.* found a significant linear relationship between the dose of morphine administration and the incidence of invasive mechanical ventilation[27]. Miró *et al.* discovered the evidence showing that the use of intravenous morphine in AHF may increase mortality after 30 days based on a propensity score-matched analysis. In their study, mortality rate was higher in the morphine group than in the control group[18]. In addition, Dong *et al.* showed that the patients who received morphine were much more likely to suffer from cardiogenic shock and even die from cardiac arrest[29]. There are also other disadvantages of morphine-use, such as delaying or diminishing the effect of other drugs. For example, Parodi *et al.* reported that in cases with ST-segment-elevation myocardial infarction (STEMI), morphine-use delayed the onset of the oral antiplatelet drugs' actions[22], and Kubica *et al.* demonstrated that in patients with myocardial infarction, morphine delayed as well as attenuated the effects of ticagrelor[24]. Moreover, Gotou *et al.* suggested that the continuous administration of intravenous morphine in heart failure patients may lead to adverse drug reactions[33]. These foundlings were similar to those of the previous studies conducted by Zhang *et al.*[36] as well as Orso *et al.*[37], suggesting that morphine should be used cautiously and should be avoided wherever possible in patients with AHF.

Whereas, in some other included studies, morphine-use in

the treatment of AHF patients was found to be not associating with negative outcomes. As the study done by Puymirat *et al.* demonstrated, for pre-hospital safety, administering intravenous morphine in patients with a STEMI would not result in worse hospital outcomes or higher mortality[23]. Similarly, Eitelet *et al.* found that ischemic myocardial injury and clinical outcome were not negatively influenced by morphine administration in acute reperfused STEMI patients[32].

Different from the results of the studies mentioned above, some studies found the benefits of morphine-use in patients with cardiovascular disease. For example, according to the study conducted by Thomas *et al.*, in STEMI patients receiving morphine treatment who were undergoing primary percutaneous coronary intervention, the use of intravenous morphine may be essential to lower the incidence of initial stent thrombosis[25]. Likewise, Kawaguchi *et al.* proved that low-doses morphine is effective for the treatment of refractory dyspnea in patients with advanced heart failure[30].

In our study, 3 024 patients in the group were receiving morphine treatment for AHF, out of which 534 (17.65%) succumbed to death. On the other hand, in the control group, 1 160 (8.09%) out of 14 323 patients had died. Our review showed that AHF patients who did not receive morphine as a mean of treatment had a lower mortality rate as compared to the patients in which morphine was administered as an AHF treatment.

The limitations of this review included that 1) there was no established treatment protocol regarding to morphine infusion, 2) a majority of studies did not specify the dose and route of administration of morphine therapy, 3) patients with AHF could not be further analyzed with respect to dosage or administration approaches of morphine due to data restrictions, and 4) there were no other adverse drug reactions evaluated in this study besides the symptoms that were selected for the assessment.

Based on the outcomes of this review, we found that patients treated without morphine had a lower mortality rate as compare to the patients treated with morphine. Some studies have reported that morphine can cause adverse effects, including death. Hence, there is an urgent need for additional researchers to focus on competing effective clinical studies of morphine in AHF.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

RSH: conceptualization, formal analysis, resources. SS: validation, formal analysis. GP: writing original draft, data curation, methodology, resources. DP: formal analysis, writing, review. SD: methodology, formal analysis.

References

[1] Joffe SW, Webster K, McManus DD, Kiernan MS, Lessard D, Yarzebski J, et al. Improved survival after heart failure: A community-based perspective. *J Am Heart Assoc* 2013; **2**(3): e000053.

[2] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2016; **18**(8): 891-975.

[3] Braunwald E. Heart failure. *JACC Heart Fail* 2013; **1**(1): 1-20.

[4] Gheorghiade M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, et al. Acute heart failure syndromes: Current state and framework for future research. *Circulation* 2005; **112**(25): 3958-3968.

[5] Hamo CE, O'Connor C, Metra M, Udelson JE, Gheorghiade M, Butler J. A critical appraisal of short-term endpoints in acute heart failure clinical trials. *J Card Fail* 2018; **24**(11): 783-792.

[6] Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme—A survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003; **24**(5): 442-463.

[7] Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: Insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *J Am Coll Cardiol* 2008; **52**(5): 347-356.

[8] Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, et al. Readmission and death after an acute heart failure event: Predictors and outcomes in sub-Saharan Africa: Results from the THESUS-HF registry. *Eur Heart J* 2013; **34**(40): 3151-3159.

[9] Dokainish H, Teo K, Zhu J, Roy A, Al Habib KF, El Sayed A, et al. Global mortality variations in patients with heart failure: Results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health* 2017; **5**: e665-e672.

[10] Gray A, Goodacre S, Seah M, Tilley S. Diuretic, opiate and nitrateuse in severe acidotic acute cardiogenic pulmonary oedema: Analysis from the 3CPO trial. *QJM* 2010; **103**(8): 573-581.

[11] Timmis AD, Rothman MT, Henderson MA, Geal PW, Chamberlain DA.

Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *Br Med J* 1980; **280**(6219): 980-982.

[12]Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. *Circulation* 1976; **54**(2): 335-337.

[13]Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. *J Clin Invest* 1974; **54**(6): 1247-1258.

[14]Vasko JS, Henney RP, Oldham HN, Brawley RK, Morrow AG. Mechanisms of action of morphine in the treatment of experimental pulmonary edema. *Am J Cardiol* 1966; **18**(6): 876-883.

[15]Ellingsrud C, Agewall S. Morphine in the treatment of acute pulmonary oedema—Why? *Int J Cardiol* 2016; **202**: 870-873.

[16]Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008; **100**(6): 747-758.

[17]Pattinson KT, Governo RJ, MacIntosh BJ, Russell EC, Corfield DR, Tracey I, et al. Opioids depress cortical centers responsible for the volitional control of respiration. *J Neurosci* 2009; **29**(25): 8177-8186.

[18]Miró Ò, Gil V, Martín-Sánchez FJ, Herrero-Puente P, Jacob J, Mebazaa A, et al. Morphine use in the ED and outcomes of patients with acute heart failure: A propensity score-matching analysis based on the EAHFE Registry. *Chest* 2017; **152**(4): 821-832.

[19]Domínguez-Rodríguez 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**(6): 382-384.

[20]López-Saca JM, Centeno C. Opioids prescription for symptoms relief and the impact on respiratory function: Updated evidence. *Curr Opin Support Palliat Care* 2014; **8**(4): 383-390.

[21]McCarthy CP, Mullins KV, Sidhu SS, Schulman SP, McEvoy JW. The on- and off-target effects of morphine in acute coronary syndrome: A narrative review. *Am Heart J* 2016; **176**: 114-121.

[22]Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2014; **8**(1): e001593.

[23]Puymirat E, Lamhaut L, Bonnet N, Aissaoui N, Henry P, Cayla G, et al. Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI programme. *Eur Heart J* 2016; **37**(13): 1063-1071.

[24]Kubica J, Adamski P, Ostrowska M , Sikora J, Kubica JM, Sroka WD, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: The randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016; **37**(3): 245-252.

[25]Thomas MR, Morton AC, Hossain R, Chen B, Luo L, Shahari NN, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb Haemost* 2016; **116**(1): 96-102.

[26]LeCorvoisier P, Gallet R, Lesault PF, Audureau E, Paul M, Ternacle J, et al. Intra-coronary morphine versus placebo in the treatment of acute ST-segmentelevation myocardial infarction: The MIAMI randomized controlled trial. *BMC Cardiovasc Disord* 2018; **18**(1): 193.

[27]Caspi O, Naami R, Halfin E, Aronson D. Adverse dose-dependent effects of morphine therapy in acute heart failure. *Int J of Cardiol* 2019; **293**: 131-136.

[28]Johnson MJ, Cockayne S, Currow DC, Bell K, Hicks K, Fairhurst C, et al. Oral modified release morphine for breathlessness inchronic heart failure: A randomized placebo-controlled trial. *ESC Heart Fail* 2019; **6**(6): 1149-1160.

[29]Dong S, Lin Y, Yuan J, Zhu Y, Liu H, Pang X. Correlations between morphine use and adverse outcomes in acute ST-segment elevation myocardial infarction with acute heart failure: A retrospective study. *Research Square* 2020. DOI: 10.21203/rs.3.rs-74896/v1. Preprint.

[30]Kawaguchi J, Hamatani Y, Hirayama A, Nishimura K, Nakai E, Nakamura E, et al. Experience of morphine therapy for refractory dyspnea as palliative care in advanced heart failure patients. *J Cardiol* 2020; **75**(6): 682-688.

[31]Furtado RH, Nicolau JC, Guo J, Im K, White JA, Sabatine MS, et al. Morphine and cardiovascular outcomes among patients with non-ST-segment elevation acute coronary syndromes undergoing coronary angiography. *J Am Coll Cardiol* 2020; **75**(3): 289-300.

[32]Eitel I, Wang J, Stiermaier T, Fuernau G, Feistritzer HJ, Joost A, et al. Impact of morphine treatment on infarct size and reperfusion injury in acute reperfused ST-elevation myocardial infarction. *J Clin Med* 2020; **9**(3): 735.

[33]Gotou M, Suzuki A, Shiga T, Wakabayashi R, Nakazawa M, Kikuchi N, et al. Adverse drug reactions in Japanese patients with end-stage heart failure receiving continuous morphine infusion: A single-center retrospective cohort study. *Drugs Real World Outcomes* 2022; **9**(1): 1-8.

[34]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. *Curr Heart Fail Rep* 2019; **16**(4): 81-88.

[35]Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2013; **62**(16): e147-e239.

[36]Zhang D, Lai W, Liu X, ShenY, 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.

[37]Orso D, Boaro G, Cassan E, Guglielmo N. Is morphine safe in acute decompensated heart failure? A systematic review of the literature. *Eur J Intern Med* 2019; **69**: e8-e10.

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