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# Morphine Use in the Treatment of Acute Cardiogenic Pulmonary Edema and Its Effects on Patient Outcome: A Systematic Review

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## Abstract

**Purpose of Review** To analyze whether the use of morphine, as initial treatment in acute cardiogenic pulmonary edema (ACPE), has an impact in clinical outcomes and mortality. A systematic review of the literature was performed, including all the studies comparing clinical outcomes in patients with ACPE who were treated or not with morphine.

**Recent Findings** Seven studies were selected, none of which were a randomized trial focused on answering the aim of this systematic review. The studies consisted of clinical trial secondary analysis assessing non-invasive ventilation in ACPE, one open non-randomized trial, two propensity score evaluations from large registries, and three clinical case reviews. Most of the studies showed unfavorable results with the use of morphine in terms of adverse events and mortality, and many of them were statistically significant. Finally, the ongoing MIdazolam versus MOrphine in acute cardiogenic pulmonary edema (MIMO) trial was specifically designed to compare the results of morphine use versus midazolam.

**Summary** The potential hemodynamic and sedative benefit of the use of morphine for vasodilatation and dyspnea amelioration may be opposed by an increase in mortality, ICU admission, and adverse events. Until there is a randomized clinical trial, the use of morphine for ACPE should be limited.

**Keywords** Heart Failure · Acute Cardiogenic · Pulmonary Edema · Morphine · Outcomes

## Introduction

Today heart failure (HF) is considered to constitute the common end of multiple diseases [1–3]. It is a clinical syndrome which may be caused by the combination of different heart diseases manifesting as a series of symptoms (dyspnea) and signs (jugular regurgitation, edema, pulmonary crackling) typical of acute HF (AHF). In developed countries, the prevalence of HF [4–7] is approximately 1–2% of the population, rising to around 10% in individuals over the age of 70. It is important to note that the presence of HF is not related to ejection fraction. Recent trends demonstrate that the percentage of patients with HF with a reduced ejection fraction is declining, matched by an increase in the percentage of patients with HF with a preserved ejection fraction [8]. This is due to improvements in treatment [9–15] and care to the former individuals and an increase in the age of the population which favors the appearance of the latter [16–19].

The presentation of AHF [20] in the emergency department may involve different clinical phenotypes based on blood pressure at the time of the exacerbation, and, more recently, it has been stratified based on the severity of congestion and perfusion presented by the patient [21–23]. This division of scenarios enables better adjustment of Emergency Department (ED) treatment. Previous classifications recognized acute cardiogenic pulmonary edema (ACPE) as a well-defined clinical manifestation characterized by the abrupt appearance of a

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transudate in the pulmonary interstitium and alveoli, occurring as a consequence of a rapid acute increase in left ventricle filling pressure, which is generally associated with a reduction in cardiac output.

Overall, the prevalence of ACPE in hospitalized patients varies according to the different studies, ranging from 16 to 49.8% [24–29]. Based on the data of the Epidemiology of Acute Heart Failure in Emergency Departments (EAHFE) registry in Spain, which includes patients with AHF attended in ED, excluding only those associated with an acute coronary syndrome (ACS) with ST segment elevation, the prevalence of APE is 11% [21].

In this type of clinical presentation, morphine, as well as diuretics and vasodilators, has long been used despite the lack of clinical studies endorsing their application. The use of morphine is supported by its theoretical beneficial hemodynamic effects (reduction in pre- and afterloading) and those on the central nervous system (improvement in patient anxiety, respiratory difficulty, and chest pain) [30–32]. Nonetheless, these beneficial effects may be outweighed by the presence of adverse effects, such as hypotension, a reduction in ventilatory effort, as well as nausea and vomiting, which are often associated with its use (Fig. 1). Therefore, the use of morphine in ACPE is currently controversial, and numerous authors have warned about the potential negative impact which morphine may have on the outcomes of patients with ACPE. Indeed, the American Heart Association and the American College of Cardiology [33] only recommend the use of morphine in HF patients manifesting in a terminal stage and for palliative use. The European Society of Cardiology [23] does not recommend routine use and suggests that morphine be used with caution in patients with ACPE (class IIB recommendation; level of evidence B), taking into account the potential for increased mortality in patients receiving this drug.

This manuscript represents a systematic review of the principal studies published to date comparing the impact of morphine use on different outcome parameters in patients with ACPE.

## Method

The literature search for this investigation was made on March 25, 2019, using the database of the United States National Library of Medicine and the PubMed search engine. The search strategy consisted of the combination of the terms "morphine" and "opiate" with "AHF" and "ACPE." Among the articles initially identified, we selected only those comparing outcomes (in clinical terms or mortality) of patients receiving and not receiving morphine. Thus, studies not referring to treatment with morphine, not providing their own data (mainly editorials and reviews), those presenting experience with the use of morphine but not including its impact on patient outcome, and those limited to study designs were excluded. Studies with uncertainties as to their origin were reviewed by two investigators (VG, OM) until agreement was reached.

## Results

The initial search identified 469 citations corresponding to 277 single investigations, 5 of which met the entry criteria (Fig. 2). A secondary review of the references of these 5 documents led to the identification of 2 additional studies meeting the entry criteria. Therefore, seven studies evaluating the use of morphine in AHF and its prognostic relationship to mortality and clinical outcomes (worsening or improvement in clinical symptomatology or adverse events) were included in this systematic review. These are shown in Table 1. In the

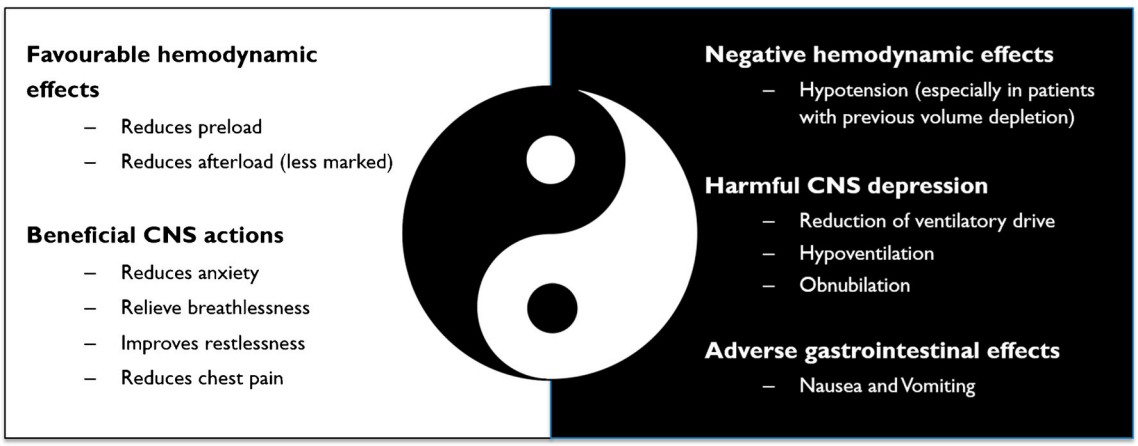


**Fig. 1** Favorable and unfavorable physiological effects associated with the use of morphine in patients with acute cardiogenic pulmonary edema

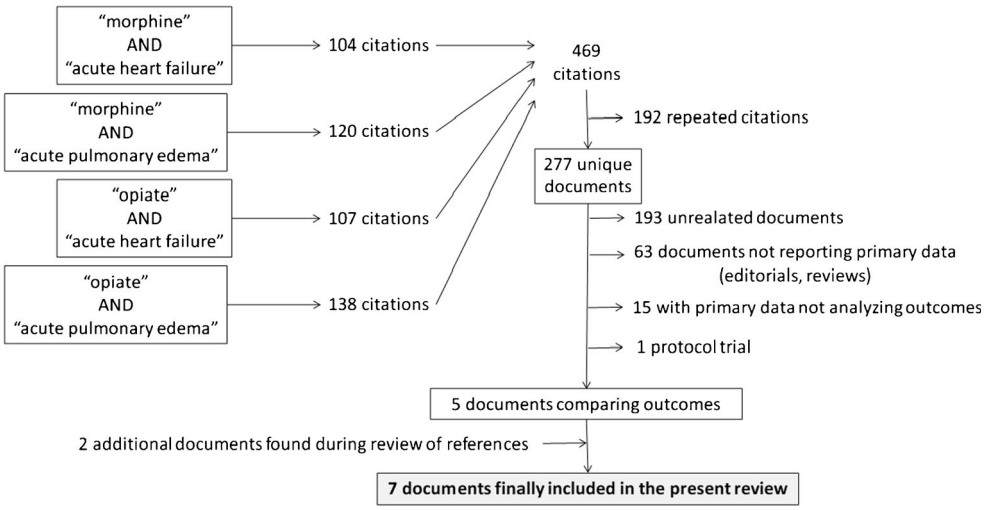


**Fig. 2** Strategy of literature searching

subsequent texts, we summarize the data and the conclusions of these articles.

In 1987, Hoffman and Reynolds [34] published a prospective, non-randomized study involving ED and paramedics in Los Angeles, USA. Their aim was to determine the most beneficial treatment during the first care to patients with a prehospital diagnosis of ACPE. They included 57 of the initially pre-selected 60 patients with a presumed diagnosis of ACPE. ACPE was confirmed in only 44 (77%), as 13 had another diagnosis as the cause of dyspnea and 3 were exclusively treated out of hospital and were discharged directly following care. Patients were divided into 4 groups of similar size based on whether they received nitroglycerin and furosemide; morphine and furosemide; nitroglycerin, furosemide, and morphine; or nitroglycerin and morphine. Results were divided into categories based on clinical response (improvement, no change, or worsening). Nitroglycerin–furosemide patients showed significantly greater subjective and objective improvement than morphine–furosemide patients, a substantial number of whom failed to improve or even worsened. There was no evident synergistic effect of any of the drugs, and some data suggested that nitroglycerin is beneficial in the management of presumed prehospital pulmonary edema, while morphine and furosemide may not add anything to its efficacy, and may be potentially deleterious in some. Thus, the adverse effects reported in the first hour of treatment were only observed in patients who received morphine and were basically hypopnea, lethargy, bradycardia, and hypotension. Twenty-four hours later, the adverse events detected were probably associated with the administration of furosemide; hypovolemia and electrolytic alterations which induced arrhythmias associated with hypokalemia in 3 patients. The results of this study suggest that while nitroglycerin was beneficial in the pre-hospital setting in cases of presumed ACPE, furosemide with morphine was not, making it unclear whether the later drugs should be routinely used.

This open non-randomized study had limitations. For example, the sample size was small, and evaluation of combinations of different drugs may be difficult because of the pitfalls of determining the effect of one drug within a combination of several drugs. On the other hand, evaluation of clinical worsening was subjective, dependent on unblinded observers, and although attempts were made to minimize this aspect, how this impacted the results is unclear. In addition, treatment groups were not homogeneous in regard to the pathological history, with a lower incidence of pre-existent heart disease in the nitroglycerin–furosemide group, as well as a lower number of diuretics and cardiac glycosides which could be a relevant confounding prognostic variable. Lastly, the initial presumed pre-hospital diagnosis was not validated with the final hospital diagnosis.

In 1999, Sacchetti et al. [35] published a retrospective study aimed at determining to what extent patient management in the emergency department influenced the need for admission to an intensive care unit (ICU) in patients with ACPE. The study included 181 cases out of 2466 patients initially evaluated with a diagnosis of AHF. In these patients, the treatments administered were analyzed, including nitroglycerin, morphine, loop diuretics, and sublingual captopril. Multiple logistic regression analysis confirmed that the use of sublingual captopril was associated with a better prognosis, a lower rate of ICU admission, and less endotracheal intubations (ETI). This was compared to the use of morphine which was associated not only with a higher rate of ICU admissions (OR 3.08; $p = 0.002$) but also a higher rate of ETI (OR 5.04; $p = 0.01$). In addition, 93 patients received some type of respiratory support (40 received non-invasive pressure support ventilation [NPSV] with a bilevel positive airway pressure system [BiPAP] and 60 ETI), and the length of ICU stay was directly proportional to the type of respiratory support used (oxygen with mask = 0.72; BiPAP = 1.48; ETI = 3.70 days).

**Table 1** Summary of the different studies' tested outcomes in relationship of morphine administration in acute heart failure

| | Hoffman et al. | Sachetti et al. | Gray et. al | Peacock et al. | Iakobishvili et al. | Doninguez-Rodriguez et al. | Miro et al. |
|---|---|---|---|---|---|---|---|
| Country | USA | USA | UK | USA | Israel | Spain | Spain |
| Year publication | 1987 | 1999 | 2010 | 2010 | 2011 | 2017 | 2017 |
| Patient source | UCLA base station | Our Lady of Lourdes Hospital in Camden | 3CPO trial | ADHERE Registry | HFSIS | Hospital Universitario de Canarias | EAHFE Registry |
| Year of patient inclusion | – | 1992–1996 | 2003–2007 | (…)–2004 | 2003 | 2013–2015 | 2011 & 2014 |
| Data source | Clinical | Clinical | Clinical | Clinical | Clinical | Clinical | Clinical |
| Data collection | Prospective | Retrospective | Prospective | Retrospective | Retrospective | Retrospective | Prospective |
| Design | Open non-randomized trial with 4 drug strategies | Care report review | Clinical randomized trial (secondary analysis) | Care report review | Case control & propensity score matching | Case report review | Propensity score matching |
| N of patients (M+/M−) | 15/42 | 88/93 | 541/521 | 20,782/126,580 | 218/2188<br>218/218 | 161/830 | 275/275 |
| N of hospitals | 1 | 1 | 26 | > 250 | 25 | 1 | 30 |
| Mean age (years) | 74.0 | 69.7 | 77.8 | 77.9 | 76.0 | 66.8 | 80.7 |
| Sex (female) | 49% | – | 56.8% | 51.8% | 51.8% | 71.8% | 42.7% |
| Outcomes assessed | -Worsening HF<br>-ED intubation<br>-In-hospital mortality | -ICU admission<br>-Need of intubation<br>-ICU length of stay | -Change in dyspnea<br>-Change in pH<br>-7-day mortality | -In-hospital mortality | -In-hospital mortality<br>-30-day mortality | -In-hospital mortality | -In-hospital death<br>-3-, 7-, 14-, and 30-day mortality |

This study showed that ED actions in ACPE patients may determine admission to an ICU and the subsequent length of stay in this unit. The negative relationship associated with the use of morphine may be its relation to respiratory depression, which subsequently leads to high rates of ETI, ICU admission, and longer hospital stay. According to their results, the authors concluded that it is difficult to justify the use of morphine in ACPE. However, the retrospective nature of the data from a single hospital and the subjectivity of the grade of respiratory insufficiency (which could lead to a higher rate of ETI) are important limitations to consider when interpreting this study.

Two studies aimed at elucidating whether morphine ACPE therapy was associated with adverse events were published in 2010. Gray et al. [36] performed a secondary analysis of the multicenter randomized, controlled cardiogenic pulmonary edema (3CPO) study. 3CPO compared the use of continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation (NIPPV), and conventional oxygen therapy in the treatment of ACPE with severe acidosis (pH < 7.35) in 26 United Kingdom EDs. They explored the effect of diuretics, nitrates, and opiates on 7-day mortality, acidosis, and respiratory function. Their adjusted analysis showed that opiate treatment was associated with less improvement in acidosis [difference in improvement in pH − 0.022, 95% confidence interval (CI) − 0.014 to − 0.030, $p < 0.001$], but no difference in 7-day mortality or improvement in respiratory distress. It should be noted that the 3CPO cohort only included patients with ACPE and severe acidosis, and, therefore, the results cannot be extrapolated to other populations or other groups of patients with milder forms of AHF. In addition, nitrates and diuretics were prescribed in 90% of the patients, and it is possible that the cohort could not detect differences in the outcomes associated with these drugs (and not to morphine).

In the second study of 2010, Peacock et al. [37] performed a retrospective analysis of the ADHERE Registry which includes 147,362 USA hospitalizations for AHF. The patients were divided into the following two groups: those receiving morphine during admission (20.782, 14.1%) and those who did not (126.580, 85.9%). The patients treated with morphine showed a higher in-hospital mortality (13% vs. 2.4%) and longer hospitalization (5.6 vs. 4.2 days), as well as a higher percentage of ICU admission (38.7% vs. 14.4%) and longer ICU stay (3.0 vs. 2.2 days). On stratifying the patients based on the severity of decompensation (assessed with the classification and regression tree [CART] risk scale), patients treated with morphine had increased adverse risk in all the subgroups analyzed. In addition, the authors adjusted the mortality for BUN, systolic blood pressure, age, creatinine, resting dyspnea, chronic dialysis, heart rate, use of inotropic drugs or vasodilators, and excluded patients receiving mechanical ventilation (to exclude the cases in whom morphine was used as an aid to ETI). Patients treated with morphine had an adjusted OR of 5.27 (95% CI 4.96–5.60) compared to the unadjusted

OR (6.08; 95% CI 5.76–6.41). When an elevation in troponins was added to these parameters, the risk of death remained high in the group receiving morphine (OR 4.84; 95% CI 4.52–5.18). In addition, the authors observed that the patients in the morphine group presented greater signs of congestion, especially in the chest X-ray. Once more, adjustment of the risk of mortality by this factor remained elevated in the group receiving morphine (OR 4.83; 95% CI 4.51–5.18). Finally, an analysis of in-hospital mortality was made for subgroups determined by the left ventricular ejection fraction (LVEF) divided into two groups (LVEF < 40% and LVEF ≥ 40%), with both groups maintaining a significant increase in mortality in patients who had received morphine.

While the data reported by Peacock et al. were obtained from a large number of patients, the retrospective and observational design of the study, the lack of data related to the morphine doses used, the reason for its use and the time from patient arrival to the emergency department and its use in the hospitalization ward are important limitations for interpreting the effect of morphine when used in the initial phase of treatment of ACPE.

In 2011, Iakobishvili et al. [38] published an analysis of a cohort of patients with AHF hospitalized in cardiology or internal medicine wards included in the Heart Failure Survey in Israel (HFSIS) and related the use of morphine to in-hospital and 30-day mortality. A total of 2336 patients were included, 218 (9.3%) of whom received morphine as treatment. The crude in-hospital mortality was increased in the group treated with morphine (5.0% vs. 1.5%, $p < 0.001$), and this increase was maintained at 30 days (13.5% vs. 8.2%, $p < 0.001$). However, on adjustment of the results for differences between groups, the increase in mortality remained in the in-hospital analysis (OR 2.0; 95% CI 1.1–3.5; $p = 0.02$) but not for 30-day mortality (OR 1.5; 95% CI 0.9–2.3). Finally, using propensity score analysis in 218 pairs of patients, we found no differences in either in-hospital or 30-day mortality.

The authors note that their cohort had certain demographic peculiarities which may have influenced the results of the study. For example, morphine was predominantly used in patients with ACS and an advanced Killip class. This suggests that morphine use may have been more analgesic than vasodilator, which would clearly influence the presence of adverse events, such as respiratory depression and the calculation of mortality. In addition, this was a retrospective study with a relatively small study sample, and data on the use of mechanical ventilation were not collected.

Recently, in 2017, two studies in Spanish centers have provided additional data related to the effects of morphine on the outcome of patients with AHF. Dominguez-Rodriguez et al. [39] retrospectively analyzed 991 patients from a Spanish ED and reported that the group receiving morphine had a greater in-hospital mortality, which was maintained after correction for other variables likely to influence mortality (age, sex, previous episode of HF, chronic kidney disease, chronic use of beta-blockers and diuretics, and LVEF < 50%).

Another study in 2017 was based on a secondary analysis of the EAHFE Registry. This registry consecutively includes all patients diagnosed with AHF in EDs independently of whether they are hospitalized or not after ED care. This analysis by Miró et al. [40] included data of 6516 patients from 34 Spanish EDs who were consecutively included and in whom clinical data were prospectively collected. This retrospective analysis compared patients treated with or without morphine and evaluated mortality rates during the first 30 days. The study cohort divided patients who received morphine during the first 3 h after ED arrival (6100; 93.6%) and those who did not (635; 9.7%). Groups were then analyzed with a propensity score, leaving two homogeneous cohorts of 275 patients who only differed in the use of morphine or not. Group analysis showed an increase in 30-day mortality in those receiving morphine (mortality 20% with morphine vs. 12.7% without; HR 1.66; 95% CI 1.09–2.54; $p = 0.017$) and was greater during the initial periods (mortality at 3 days: OR 3.330, 95% CI 1400–7.930; at 7 days; OR 2.470, 95% CI 1.260–4.850; and at 14 days: OR 1.730, 95% CI 1.010–2.960). In-hospital mortality was not affected, possibly because of the small sample size after applying the propensity score. Curiously, a sensitivity analysis of patients receiving morphine found mortality was not influenced by sex, ventilatory support, or vasoactive drugs, but it was affected by age, showing a greater risk in patients below 80 years of age. This finding was contrary to the theory that patients of older age and who are more frail (and, thus, possibly with greater therapeutic limitations) more frequently receive morphine for palliative purposes.

The EAHFE study clearly follows the current general opinion that associates the use of morphine in AHF with an increased risk of adverse events and death. However, similar to most of the previous studies, the morphine dose was not collected, and neither was the reason for use specified. Therefore, in some cases, it could have been used as palliative treatment or to control chest pain in patients with ACS (although the EAHFE Registry excludes patients presenting with AHF associated with ST segment elevation ACS). Lastly, this study was part of a cohort in a single country, and, therefore, extrapolation of the results to other populations should be made with caution.

The details of the main results of the seven studies are presented in Fig. 3. This shows the different prognostic variables analyzed and their weight in favor of or against the use of morphine in ACPE. As shown, overall, the data point towards to the potential harmful effects which morphine use may have during the initial treatment of ACPE.

Nonetheless, these results should not determine a change in either the current recommendations, categorized as IIB, or in the level of evidence (B). To change current guidelines, it is necessary to know the results of the MIMO trial which is the only trial evaluating the safety of the use of morphine versus

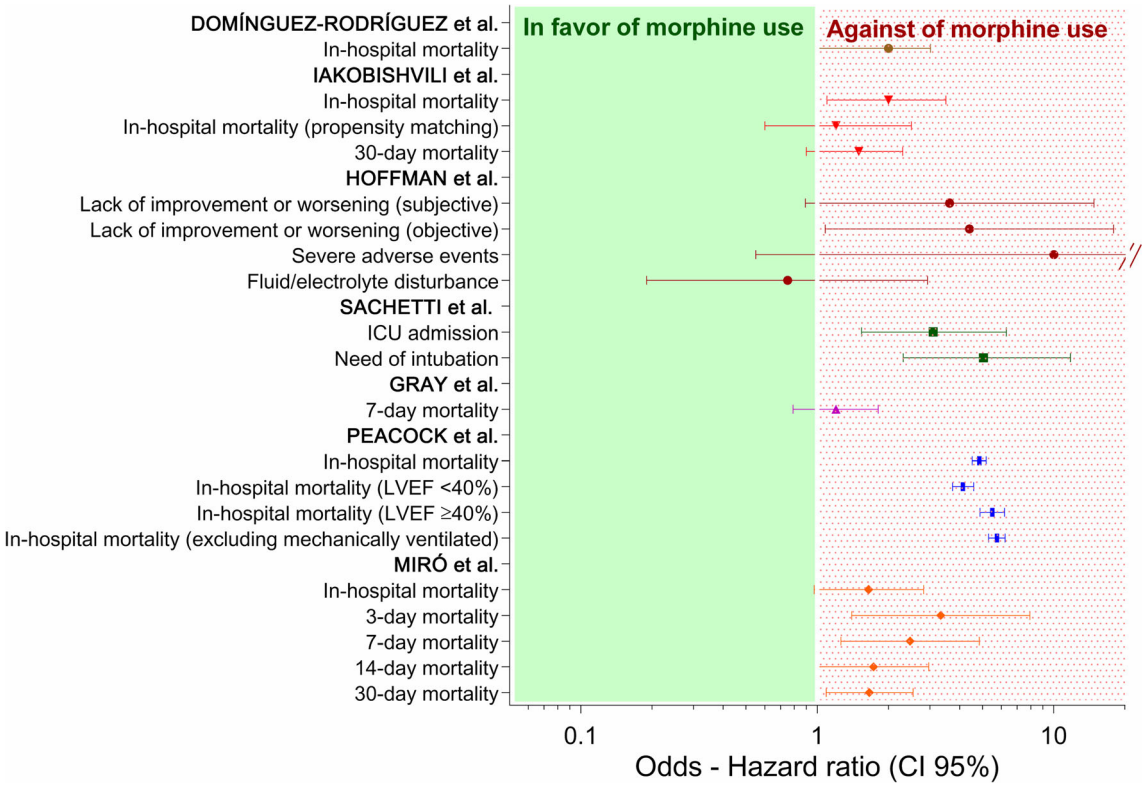


**Fig. 3** Summary of outcomes in the different studies on the use of morphine in acute heart failure

midazolam in the acute treatment of ACPE [41]. This trial is currently in the patient recruitment phase and has a prospective, multicenter, open-label, randomized design with the primary endpoint aimed at whether intravenous morphine administration improves clinical outcomes, defined as in-hospital mortality. Secondary endpoints include mechanical ventilation, cardiopulmonary resuscitation, intensive care unit admission rate, intensive care unit length of stay, and length of hospitalization.

## Conclusions

Morphine is classically a drug widely used for the treatment of ACPE. This is based on observations of improvement in pre- and after-loading, mainly in basic experimental studies. It is also given for the reduction in anxiety and respiratory function shown, although these actions are not supported by any clinical trial.

The present systematic review supports the opinion that the use of morphine could be related to worse patient outcomes with respect to a greater number of adverse events as well as an increase in not only in-hospital but also very short- and short-term mortality.

However, it should be noted that all the studies presented suffer limitations, mainly related to the lack of data regarding the dose, timing of use, and the reason for the use of morphine. None of these studies was a clinical trial in which morphine treatment was randomly assigned, and, in the best scenario, the analysis was made by matching patients using a propensity of risk analysis for adverse events.

It is only with the results of clinical trials that we will be able to obtain an answer to the question as to whether the use of morphine is necessary in ACPE [42]. In the absence of any data supporting a benefit in use of morphine for ACPE, and since every study examining it suggests an increased adverse event risk, the use of morphine in ACPE should be limited to the setting of palliative care or as a pre-intubation sedative, until there is at least a signal of utility and safety.

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## Compliance with Ethical Standards

**Conflict of Interests** VG, ADR, JM, and OM have no conflicts of interest to declare.

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