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Letter to the Editor

Is morphine safe in acute decompensated heart failure? A systematic review of the literature

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Acute decompensated heart failure (ADHF) is one of the most common diseases in the emergency department worldwide. Historically one of the most recommended therapeutic drugs, in addition to diuretics and nitrates, is morphine. Despite some handbooks and guidelines still accept its use [1,2], morphine has never demonstrated a benefit on mortality of patients treated for ADHF. Furthermore, recent studies have highlighted some potential deleterious effects of morphine [3].

We conducted a systematic review of clinical studies regarding the use of morphine in patients with ADHF to verify its safety. Details of the protocol were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018106091. We searched the Medline (Pubmed), CINAHL, Cochrane Library, Embase, SPORTDiscus, ScienceDirect and Web of Science databases from the inception to May 30, 2018. The main outcomes were the effect on in-hospital mortality, 30-day mortality and the need for mechanical ventilation. The control group was made up of patients with ADHF treated without morphine. Seven hundred and forty-six articles were found by the systematic search. Fifteen articles were assessed for eligibility. Five studies were included in the systematic review [4–8]. We considered 157,447 pooled patients. All but one was multicentre studies. Over the years there has been a trend towards an increase in the average age of patients included: from 70 years in Sacchetti to 81 years in Mirò et al. (Table 1). The selection criteria were mostly clear and respected in the considered studies. However, only one study [8] used an independent validation process for cases inclusion. None of the considered studies specified whether patients with ADHF in the control group were ever previously treated with morphine.

The individual studies relative risk (RR) for the in-hospital mortality ranged from 1.17 (95%CI 0.81–1.70) to 5.42 (95%CI 5.16–5.70); and the pooled RR was 2.15 (95%CI 1.06–4.35; *p*-value = .03). The individual studies RR for the 30-day mortality ranged from 1.57 (95%CI 1.06–2.31) to 1.62 (95%CI 1.12–2.34); and the pooled RR was 1.60 (95%CI 1.22–2.09; p-value < .001). The individual studies RR for the need for mechanical ventilation ranged from 0.66 (95%CI 0.28–1.60) to 5.47 (95%CI 5.26–5.75); and the pooled RR was 2.01 but the statistical significance has not been reached (95%CI 0.25–15.85; *p*-value = .51).

Current guidelines for heart failure established by the European Society of Cardiology (ESC) do not recommend the routine use of morphine in the treatment of heart failure. Opioids can be considered with caution in severe dyspnea to alleviate anxiety (class IIb recommendation, level of evidence B) [1]. The same guidelines highlight the occurrence of side effects such as nausea and hypopnea. The two most common mechanisms on the presumed vasodilating effect of opioids are the release of histamine by mast cells and the reduction of catecholamine production by the central nervous system. A decrease in the venous tone would allow for the reduction of preload, and therefore morphine would reduce the filling pressure of the cardiac ventricles. Vismara et al., comparing patients with ADHF and healthy individuals treated with morphine, found that there was no statistically significant difference in the reduction of venous pressure between the two groups [9]. Moreover, Timmis et al., through the measurement of pulmonary arterial pressure, had shown that the administration of morphine in some patients with acute myocardial infarction complicated by severe left ventricular failure had not reduced the left ventricular filling pressure nor the stroke index [10]. While the vasodilating effect of morphine has not been demonstrated in clinical trials, there is no evidence that even the reduction of the adrenergic tone occurs through a direct effect on the central nervous system.

Some concerns about an increase in in-hospital mortality for the patients treated with morphine were pointed out. It must be emphasized that these data derive from studies that generally tried to reduce confounding factors through propensity score matching analysis or other forms of adjustment. Thus, albeit it is not possible to exclude the presence of non-evident confounding factors, the results seem sufficiently robust. Furthermore, the patients who received morphine have a relative risk of death at 30 days greater than those patients to whom morphine has not been administered. Evidence has accumulated that the morphine could attenuate the platelet inhibition of some antiplatelet agents such as clopidogrel, ticagrelor and prasugrel. As a portion of cases of ADHF can be attributed to acute myocardial ischemia, this effect could play a significant role in the deleterious effect of the morphine. More studies in this field are

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Table 1
Summary characteristics of the included studies.

Study	Year	Sampling	Sample size	Exp. group	Mean age (yy)	Gender (% male)	Incl. criteria	Primary outcome	Mech. Vent.	In Hosp mort	30-d mort
Sacchetti et al	1999	Registry	181	88	70	nr	ADHF	ICU/Hosp	na	na	na
Peacock et al	2008	Registry	147,362	20,782	73	47	ADHF	ICU/Hosp/IHMort	5.47 (5.26,5.75)	5.42 (5.16,5.70)	na
Gray et al	2010	Registry	1052	541	78	45	ADHF	IHMort[a]	na	1.17 (0.81,1.70)[a]	na
Iakobishvili et al	2011	Registry	2336	218	76	48	ADHF	IHMort	na	2.29 (1.52,3.46)	1.62 (1.12,2.34)
Mirò et al	2017	Registry	6516	275	81	40	ADHF	30dMort	0.66 (0.28,1.60)	1.34 (0.81,2.20)	1.57 (1.06,2.32)

Exp. group: experimental group; yy: years; % male: male percentage; incl. criteria: inclusion criteria; ICU: admission in ICU; Hosp: hospitalization; IHMort: in-hospital mortality; 30dMort: 30-day mortality; mech. vent.: need for invasive mechanical ventilation; In Hosp Mort: in-hospital mortality; 30-d Mort: 30-day mortality; nr: not reported; na: not available. Results are expressed as Relative Risk. The 95% confidence interval is indicated in round brackets.

[a] 7-day mortality was approximated to in-hospital mortality.

required to clarify this aspect. In particular, it would be useful to know if some phenotypes of ADHF could benefit from morphine. Finally, regarding the need for mechanical ventilation, we noticed a very discordant result in included studies. In Peacock et al. [5] the rate of mechanically ventilated patients was 15% compared to 2.9% in Mirò et al. [8]. In recent years the evidence of the beneficial effect of the Continuous Positive Airway Pressure (CPAP) and its wider diffusion also in the pre-hospital environment has probably reduced the need for orotracheal intubation and invasive mechanical ventilation. It is noteworthy that in Mirò et al. over 33% of the patients have been subjected to some type of ventilation [8]. Since CPAP is now widely used as a first-line treatment for ADHF, probably the use of any pharmacological agent (as well as morphine) could not change the use of this type of ventilator support.

We must point out that none of the studies considered in our systematic review were randomized controlled trials. However, the evidence collected so far does not seem to support the safety of morphine in the treatment of patients with ADHF. Randomized controlled trials with adequate sample sizes are needed to resolve the concerns about morphine safety in this clinical scenario. Until then, morphine should be used cautiously (or even not be used at all) in the treatment of patients with ADHF.

Contributors statement

Dr. Orso conceptualized and designed the study, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Boaro conceptualized the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Cassan conceptualized the study, collected data, and reviewed and revised the manuscript. Dr. Guglielmo coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

No competing interests for the Authors.

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