**UAMS EM Journal Club**
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# Safety of Morphine in Patients with Acute Coronary Syndrome

**Bottom Line:** The evidence that suggests that the use of morphine in acute coronary syndrome (ACS) may lead to an increase in in-hospital mortality and/or recurrent MI is of low quality and potentially not reproducible. However, since these studies suggest a possible risk and there are alternatives available, we suggest considering an alternative method for pain control in ACS until higher quality studies are performed.

**Background:** Morphine has been widely used for pain management in patients with acute coronary syndromes. Other studies have found reduced efficacy of P2Y12 agents with use of Morphine. These following studies were performed to assess risk of morphine use in ACS.

## Study 1

Ghadban R, Enezate T, Payne J, et al. The safety of morphine use in acute coronary syndrome: a meta-analysis. *Heart Asia*. 2019;11(1):e011142. Published 2019 Mar 19. doi:10.1136/heartasia-2018-011142

**Pubmed Link:** https://pubmed.ncbi.nlm.nih.gov/31031833/

**Validity Rating:** Moderate to high risk of bias due to lower quality of included studies

**The Basics:** This article was a systematic review and meta-analysis of studies evaluating the impact of morphine in patients with ACS. Recurrent MI, all-cause mortality, stroke, major bleeding, minor bleeding and dyspnea were studied. Of 166 articles assessed for full-text screening, 8 were included. These consisted for 1 RCT and 7 observational studies.

**Inclusion Criteria:** MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trails were searched for randomized, prospective or retrospective studies, and double-arm studies that compared morphine with nonmorphine use in the setting of ACS.

**Exclusion Criteria:** Single-arm studies, studies evaluating stable CAD and studies that used any narcotic agent other than morphine.

**Primary Outcomes:** Primary outcomes included recurrent MI, all-cause mortality, stroke, major bleeding, minor bleeding and dyspnea.

**Results:** A total of 64 323 patients with ACS were included from eight studies, seven of which were observational studies and one was a randomized controlled trial. The use of morphine was associated with increased risk of in-hospital recurrent MI (OR 1.30, 95% CI 1.18 to 1.43, p <

0.00001). There was, however, no significant difference in terms of all-cause mortality (OR 0.87, 95% CI 0.62 to 1.22, p = 0.44), stroke (OR 0.81, 95% CI 0.39 to 1.66, p = 0.57), major bleeding (OR 0.49, 95% CI 0.24 to 1.00, p = 0.05), minor bleeding (OR 0.98, 95% CI 0.41 to 2.34, p = 0.97), or dyspnoea (OR 0.55, 95% CI 0.16 to 1.83, p = 0.33).

**Limitations/Bias:** Most studies were observational. There was heterogeneity between the studies in size, type of ACS, patient characteristics, severity of illness, treatment modality for ACS management, dosing, timing of morphine, and antiplatelet medication used. Intermediate to high risk of bias in regards to population matching in two studies.

## Trial 2

Duarte G, Nunes-Ferreira A, et al. Morphine in acute coronary syndrome: systematic review and meta-analysis. *BMJ Open*, 2019 Mar 15;9(3):e025232. doi: 10.1136/bmjopen-2018-025232

**Pubmed Link:** https://pubmed.ncbi.nlm.nih.gov/30878985/

**Validity Rating:** Multiple included studies had high/critical risk of bias. Two of the five included randomized control trials were judged to have a high risk of bias. Overall poor validity due to the quality of included studies.

**The Basics:** This article was a systematic review of longitudinal studies evaluating the impact of morphine on cardiovascular outcomes or platelet reactivity in ACS. Studies were required to evaluate morphine against placebo, control, or any other analgesic non-opioid drug. Of 53 articles assessed for full-text screening, 17 were included. These consisted for 5 RCTs and 12 observational studies.

**Inclusion Criteria:** CENTRAL, MEDLINE, EMBASE, and clinicaltrials.gov were searched for longitudinal studies (ie, RCTs and observational studies) evaluating the impact of morphine in cardiovascular outcomes or platelet reactivity measures. Two reviewers independently screen the titles and abstracts and assessed full texts of the included to determine the appropriateness for inclusion. Disagreements were handled by a third reviewer serving as a final arbitrator.

**Exclusion Criteria:** Exclusion of studies selected in the initial search was at the discretion of the independent reviewers and the final arbitrator.

**Primary Outcomes:** Primary outcomes included in-hospital mortality and major adverse cardiovascular events (MACE).

**Secondary Outcomes:** Secondary outcomes included bleeding, nausea/emesis, bradycardia, hypotension, respiratory insufficiency, and platelet reactivity.

**Results:** Adjusted pooled results showed an increased risk of in-hospital mortality in the morphine group (RR 1.45; 95% CI 1.10 to 1.91; $I_2$=0%). However, when studies at critical risk of bias were excluded, sensitivity analysis showed no difference between morphine and control

(RR 1.41; 95% CI 0.87 to 2.27; $I_2$ = 0%). For risk of MACE, adjusted pooled results showed an increased risk of MACE I the morphine group (RR 1.21, 95% CI 1.02 to 1.45; $I_2$=0). However, subgroup analysis based on study design and ACS subtype were both non-significant. When studies at critical risk for bias were excluded, risk of MACE was not significantly different between morphine and control groups (RR 1.40, 95% CI 0.85 to 2.30; $I_2$=0%). Platelet reactivity was increased at one hour and two hours after administration mean difference (MD) of 59.37 in platelet reactivity (PRU) and 68.28 PRU, respectively (95% CI 36.04 to 82.71 and 37.01 to 99.55). Subgroup analysis based on study design and ACS subtype were non-significant at both time-points. No differences were found in major or minor bleeding. There were no differences associated with morphine use and risk of cardiogenic shock (RR 1.48; 95% CI 1.00 to 2.18), heart failure (RR 1.17; 95% CI 0.91 to 1.51), hypotension (RR 0.93; 95% CI 0.49 to 1.74), nausea/emesis (RR 1.84; 95% CI 0.80 to 4.23), respiratory insufficiency (RR 0.77; 95% CI 0.31 to 1.91), or stent thrombosis (RR 1.13; 95% CI 0.67 to 1.92).

**Limitations/Bias:** Most studies were rated to be at least a moderate risk of bias with some rated as high and critical risk. When studies judged to be at a critical risk of bias were removed from the analysis, primary outcomes were not significant. All subgroup analyses were insignificant. The majority of the patients included came from one study that consisted of over 57,000 participants.