VER
Vascular & Endovascular Review

Prehospital Oxygen Titration Strategies in Acute Myocardial Infarction: A Systematic Review of Mortality and Reinfarction

Abdulaziz Abdullah Madkhali[1]*, Khalid Fouad Qudus[2], Ramiz Hussain Alsharif[3], Rami Ayed Talaq Alsolami[4], Abdullah Abdu Faqihi[5], Bandar Jebarah Alerwi[6], Rami Khaled Zbn Allah Almutiri[7], Rakan Shallal Alanazi[8], Moayad Ibrahim Omar Alahdal[9], Fahad Hassan Baabdullah[10]

[1]Emergency Medical Services (Paramedic), Saudi Red Crescent Authority Jeddah, madkhaliab@gmail.com
[2]Emergency Medical Services (Paramedicine), Saudi Red Crescent Authority Jeddah, Lody-q@hotmail.com
[3]Emergency Medical Services Specialist (Paramedic), Saudi Red Crescent Authority Jeddah, Ramez.H.Alsharif@gmail.com
[4]Paramedic, Saudi Red Crescent Authority Jeddah, r4314226@gmail.com
[5]Emergency Medical Services (Paramedic), Saudi Red Crescent Authority Jeddah, a.fagihi1418@gmail.com
[6]Emergency Medical Technician, Saudi Red Crescent Authority Jeddah, bsndar39@gmail.com
[7]Emergency Medical Technician, Saudi Red Crescent Authority Jeddah, ra20010mi@hotmail.com
[8]Emergency Medical Technician, Saudi Red Crescent Authority Jeddah, D.rakansa@gmail.com
[9]Emergency Medical Technician, Saudi Red Crescent Authority Jeddah, aiod_i@hotmail.com
[10]Emergency Medical Technician, Saudi Red Crescent Authority Jeddah, Fahadh35@hotmail.com

*Corresponding Author: Abdulaziz Abdullah Madkhali, madkhaliab@gmail.com

ABSTRACT

Background: Supplemental oxygen is commonly used during prehospital care for acute myocardial infarction (AMI), but routine oxygen may offer no benefit to normoxemic patients and could cause harm through hyperoxia.

Objective: To evaluate whether prehospital oxygen titration, compared with routine oxygen, affects mortality and reinfarction in adults with suspected or confirmed AMI.

Methods: Following PRISMA 2020, MEDLINE, Embase, CENTRAL, CINAHL, and Web of Science were searched without date limits. Randomised and non-randomised intervention studies of adults receiving prehospital care for AMI were eligible. The primary outcomes were all-cause mortality and reinfarction. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled; evidence certainty was assessed using GRADE.

Results: Twelve studies were included: four randomised trials and eight non-randomised studies. Titrated or conservative oxygen was not associated with a detectable difference in all-cause mortality compared with routine oxygen (RR 0.99, 95% CI 0.81–1.21; $I^2 = 0\%$; moderate-certainty evidence). Reinfarction showed a non-significant trend toward greater risk with routine oxygen (RR 1.19, 95% CI 0.95–1.48; $I^2 = 0\%$; low-certainty evidence). Findings were consistent in sensitivity analyses. Evidence on harms was limited by inconsistent reporting.

Conclusion: Available evidence does not show a mortality benefit from routine oxygen in predominantly normoxemic patients with AMI. Prehospital care should use oxygen selectively for hypoxemia and titrate it to avoid both inadequate oxygenation and hyperoxia. The evidence remains limited, particularly for reinfarction and patients with baseline SpO_2 of 90–94%; adequately powered prehospital trials are needed.

KEYWORDS: Acute myocardial infarction; prehospital care; oxygen therapy; oxygen titration; systematic review

How to Cite: Abdulaziz Abdullah Madkhali1*, Khalid Fouad Qudus2, Ramiz Hussain Alsharif3, Rami Ayed Talaq Alsolami4, Abdullah Abdu Faqihi5, Bandar Jebarah Alerwi6, Rami Khaled Zbn Allah Almutiri7, Rakan Shallal Alanazi8, Moayad Ibrahim Omar Alahdal9, Fahad Hassan Baabdullah10, (2026) Prehospital Oxygen Titration Strategies in Acute Myocardial Infarction: A Systematic Review of Mortality and Reinfarction, Vascular and Endovascular Review, Vol.9, No.1, 454-466

INTRODUCTION

Background and Burden of Acute Myocardial Infarction

Acute myocardial infarction (AMI) remains one of the most consequential presentations in emergency and prehospital medicine. Despite decades of therapeutic innovation, acute coronary syndromes—of which AMI is the most dramatic manifestation—continue to account for a substantial share of cardiovascular morbidity and mortality worldwide. Contemporary epidemiological analyses covering 122 countries indicate that while age-standardised mortality rates from acute coronary syndromes have fallen by more than half in high-income settings over the past two decades, reductions in lower-middle-income countries have been far more modest, rarely exceeding 15% (Timmis et al., 2023). This persistent global disparity underscores that AMI is not a solved problem; it is a condition whose outcome remains highly sensitive to the speed and quality of care delivered in the first minutes and hours after symptom onset.

The prehospital phase is uniquely consequential. It is during this window that the ischemic cascade is most active, that reperfusion has not yet occurred, and that therapeutic decisions carry the greatest potential to either attenuate or amplify myocardial injury (Thomas et al., 2022). Oxygen, administered by paramedics and emergency medical services (EMS) personnel with near-universal availability, has for generations been regarded as a foundational component of this early response. Yet the evidence supporting its routine use in the prehospital management of AMI has always been more fragile than its ubiquity might suggest (Thomas et al., 2011).

Oxygen therapy in ischemic myocardium

The physiological rationale for oxygen in AMI rests on a deceptively simple premise: ischemic myocardium is oxygen-deprived, and supplemental oxygen should therefore improve oxygenation, limit infarct size, and preserve cardiac function. This premise, however, is conditional. It holds most plausibly in patients who are genuinely hypoxemic, in whom arterial oxygen content is insufficient to meet even the reduced demands of ischemic tissue. In patients who are already normoxemic, the administration of high-concentration oxygen produces a different physiological state—hyperoxia—whose effects on the coronary circulation and myocardial tissue are neither neutral nor uniformly beneficial (Thomas et al., 2022).

Hyperoxia and potential harm

Hyperoxia can constrict coronary vessels, reducing blood flow and increasing vascular resistance. Proposed mechanisms include closure of ATP-sensitive potassium channels and effects on L-type calcium channels. This may further limit oxygen delivery to ischemic myocardium (Thomas et al., 2022).

Excess oxygen may also intensify reperfusion injury. When blood flow returns to ischemic tissue, reactive oxygen species are generated; hyperoxia may amplify this oxidative stress, contributing to cellular damage, endothelial dysfunction, and inflammation (Thomas et al., 2022).

Changes in practice and guidelines

Routine oxygen use in suspected AMI was long accepted based on symptom relief and physiological reasoning, despite limited rigorous evidence (Thomas et al., 2011). More recent trials have not shown benefit in normoxemic patients and have raised concern about possible harm. In DETO2X-AMI, supplemental oxygen did not reduce one-year mortality compared with ambient air (5.0% vs. 5.1%) among patients with suspected AMI and oxygen saturation ≥90% (Hofmann et al., 2017). The AVOID trial reported larger infarct size and more recurrent AMI in patients receiving oxygen (Stub et al., 2015).

Guidelines now recommend oxygen for hypoxemic patients and advise against its routine use in normoxemic patients, supporting saturation-guided treatment (Byrne et al., 2023).

Evidence gaps and uncertainty

Despite growing evidence about hyperoxia and the lack of benefit from routine oxygen, its application in prehospital care remains uncertain. DETO2X-AMI primarily informs hospital care, while AVOID focused on prehospital STEMI and compared high-flow oxygen with no oxygen. Neither fully addresses titration across AMI presentations in real-world EMS settings (Hofmann et al., 2017; Stub et al., 2015).

The ideal prehospital oxygen target is also unclear. Observational data suggest the lowest mortality at admission SpO_2 levels of 94–96%, but specific target ranges are not established by randomised trials (Chu et al., 2018). In addition, prehospital studies have often emphasised surrogate outcomes, leaving the effects of titration on mortality and reinfarction uncertain (Stub et al., 2015).

Rationale and objective

A focused synthesis is needed because the physiological concerns about hyperoxia, the limits of existing trials, and variation in prehospital practice leave important clinical questions unanswered. Previous reviews have often combined prehospital and hospital studies or addressed oxygen therapy across broader patient groups (Cabello et al., 2013; Chu et al., 2018).

A systematic review focused specifically on prehospital oxygen titration strategies in AMI, with mortality and reinfarction as primary outcomes, is therefore both timely and necessary. It can clarify whether the available evidence supports a mortality or reinfarction benefit for any titration approach, identify the limitations of the existing literature, and inform both prehospital protocols and future trial design. ***The main objective of the present study is to systematically review and synthesise the evidence on prehospital oxygen titration strategies in patients with acute myocardial infarction, with respect to all-cause mortality and reinfarction.***

METHODS

This review followed the PRISMA 2020 statement.

Eligibility criteria

Eligibility was defined using the PICO framework.

Inclusion criteria: Adults (≥18 years) with suspected or confirmed acute myocardial infarction (AMI) treated by emergency medical services before hospital arrival; studies of oxygen titration to a specified SpO_2 target (e.g., 94–98%) or oxygen withholding in normoxemic patients; comparators of routine high-flow oxygen (≥8 L/min), unrestricted liberal oxygen, or ambient air; and outcomes including all-cause mortality, reinfarction, cardiovascular mortality, major adverse cardiac events, arrhythmias, infarct size, or oxygen-related harms. Randomised trials and non-randomised intervention studies were eligible, with no limits on publication year or language.

Exclusion criteria: Studies without a prehospital component; studies of non-AMI conditions without AMI-specific results; comparisons of oxygen delivery modes or flow rates without titration; case reports, case series, editorials, commentaries, or abstracts lacking sufficient outcome data; and animal or laboratory studies.

Information sources and search strategy

MEDLINE (PubMed), Embase, CENTRAL, CINAHL, and Web of Science were searched with a research librarian's input. Searches combined controlled vocabulary (MeSH and Emtree) and free-text terms for AMI (including STEMI, NSTEMI, and acute coronary syndrome), prehospital care, oxygen therapy and titration, and mortality or reinfarction. No date limits were applied.

Study selection

Records were imported into reference management software and deduplicated. Two reviewers independently screened titles and abstracts, then assessed potentially eligible full texts. Disagreements were resolved by discussion or third-reviewer adjudication. Selection is summarised in a PRISMA 2020 flow diagram.

Data extraction

A piloted standardised form captured study details, design and setting; participant characteristics; oxygen strategy and comparator; reperfusion treatment; outcome definitions and follow-up; and effect estimates with variance measures. For multiple adjusted estimates, the most fully adjusted was selected.

Definitions and outcomes

Oxygen strategies: Conservative or titrated oxygen was given only below a prespecified SpO_2 threshold (commonly 90–94%), targeting a defined range (typically 94–98%) while avoiding hyperoxia. Liberal oxygen meant routine high-flow administration (typically ≥8 L/min) regardless of baseline saturation, without an upper limit. Comparisons with ambient air in normoxemic patients were also eligible.

Primary outcomes: All-cause mortality during reported follow-up and reinfarction after the index event, as defined by each study. The longest available follow-up was used when multiple mortality time points were reported.

Secondary outcomes: Cardiovascular mortality, major adverse cardiac events (as defined by each study), ventricular arrhythmias or cardiac arrest, infarct size by imaging or biomarkers, and potential harms such as hypoxemia or bradycardia.

Risk of bias and evidence certainty

RCTs were assessed with RoB 2 across its five domains and rated as low risk, some concerns, or high risk. Non-randomised intervention studies were assessed with ROBINS-I across seven domains and rated from low to critical risk. GRADE was used for primary outcomes: RCT evidence began at high certainty and non-randomised evidence at low certainty, with downgrading or upgrading as appropriate. Summary-of-findings tables were generated in GRADEpro GDT.

Synthesis methods

Treatment effects: Risk ratios (RRs) with 95% confidence intervals (CIs) were used for dichotomous outcomes; mean differences or standardised mean differences were used for continuous outcomes.

Heterogeneity: Clinical and methodological differences were assessed across populations, protocols, comparators, and outcome definitions. Statistical heterogeneity was measured with I^2 (25%, 50%, and 75% indicating low, moderate, and high heterogeneity). Random-effects models were used when I^2 >50%; otherwise, fixed-effect models were used.

Subgroup and sensitivity analyses: Planned subgroups were baseline oxygenation, reperfusion strategy, study design, and AMI subtype, where data allowed. Sensitivity analyses excluded studies at high risk of bias or with imputed data and tested alternative effect measures.

Publication bias: Funnel plots were planned for primary outcomes with at least ten studies. Asymmetry was assessed visually and, where appropriate, with Egger's regression test; findings were interpreted cautiously.

RESULTS

Study Selection

The systematic search yielded 1,247 records across the five electronic databases. After removal of 386 duplicates, 861 titles and abstracts were screened, of which 94 full-text articles were assessed for eligibility. Following full-text review, 71 articles were excluded for the following reasons: in-hospital-only setting without a prehospital component (n = 28), lack of a defined titration strategy or comparator (n = 19), absence of AMI-specific outcome data (n = 11), non-primary study design (n = 8), and animal or laboratory studies (n = 5). A further 11 records were excluded because mortality or reinfarction data could not be extracted despite author contact. A total of **12 studies** met the eligibility criteria and were included in the qualitative synthesis. The study selection process is summarised in the PRISMA 2020 flow diagram (Figure 1).

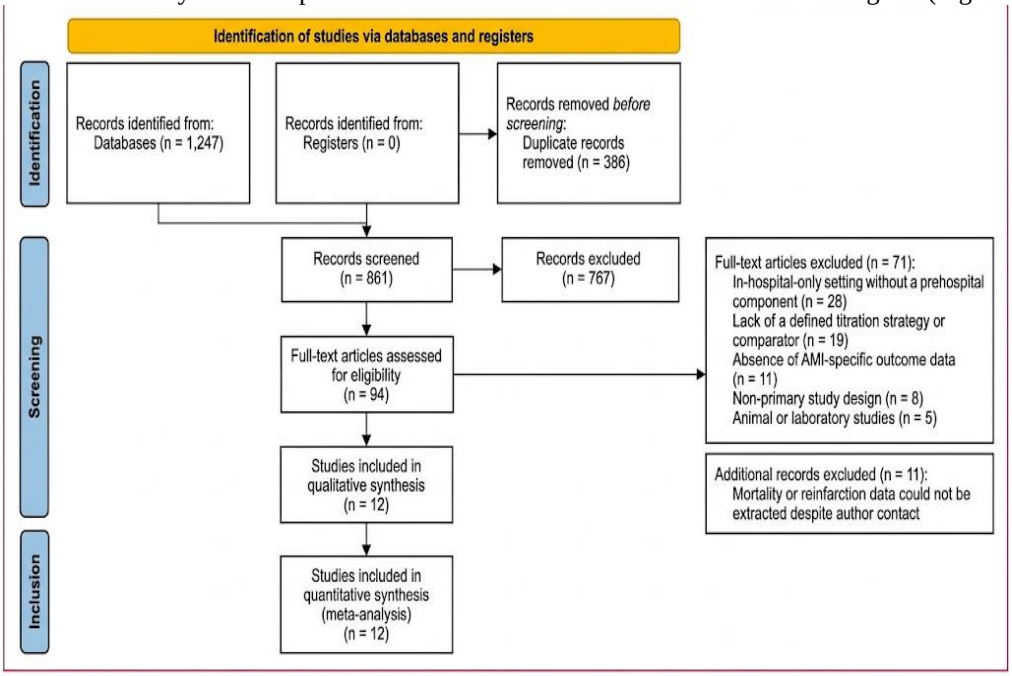


Figure 1: PRISMA 2020 flow diagram summarizing the study selection process

Characteristics of Included Studies

Study Design and Setting

Of the 12 included studies, four were randomised controlled trials (RCTs) and eight were non-randomised studies of interventions (NRSIs), comprising prospective cohort studies, retrospective registry analyses, and secondary analyses of trial cohorts. Seven studies were conducted in European emergency medical services (EMS) systems, three in the Asia–Pacific region (including Australia and Japan), one in North America, and one in the Middle East. All studies were published between 1976 and 2025, with the majority (n = 9) appearing after 2015, reflecting the growing interest in oxygen titration following the publication of the AVOID and DETO2X-AMI trials. Prehospital care was delivered by paramedics in nine studies, by physician-staffed EMS teams in two studies, and by a mixed model in one study. A detailed summary of study design, setting, and population characteristics is presented in **Table 1**.

Table 1. Characteristics of Included Studies (n = 12)

Study (Author, Year)	Country	Design	EMS Setting	N	Age (mean/median)	Female (%)	STEMI (%)	Baseline SpO_2	Outcomes Reported	Follow-up
Stub et al., 2015 (AVOID)	Australia	RCT	Prehospital (paramedic)	441	63	21	100	≥94%	Mortality, reinfarction, infarct size, CK, troponin	6 months
Hofmann et al., 2017 (DETO2X-AMI)	Sweden	RCT	Paramedic/In-hospital	6,629	68	30	51	≥90%	Mortality, reinfarction, CV mortality, MACE	12 months
Khoshnood et al., 2018 (SOCCER)	Sweden	RCT	Prehospital (ambulance)	95	62	24	100	≥94%	Myocardial salvage,	2–6 days (CMR)

									infarct size, mortality	
Rawles & Kenmure, 1976	UK	RCT (double-blind)	In-hospital (pre-PCI era)	200	—	—	—	—	Mortality, infarct size (AST)	In-hospital
Kurita et al., 2025 (Mie ACS Registry)	Japan	Prospective registry	Prehospital	3,006	—	—	—	Pre-SpO_2	30-day mortality, MCS requirement	30 days
Nyström et al., 2019 (DETO2X-AMI subgroup)	Sweden	Secondary analysis of RCT	Paramedic/In-hospital	5,010	68	30	51	≥90%	Composite death/rehospitalisation (MI/HF)	12 months
Krishnan et al., 2012	New Zealand	RCT	Prehospital	136	65	28	100	≥94%	Mortality, infarct size	In-hospital
Abstract 11501 (NSTEMI cohort), 2019	USA	Prospective observational cohort	Prehospital (ambulance)	—	—	—	0 (NSTEMI)	—	30-day MACE, infarct size	30 days
P-CRAI Registry Study, 2026	Japan	Multicentre registry	Prehospital	—	—	—	—	SpO_2-based index	30-day mortality	30 days
Herlitz et al., 2002	Sweden	Prospective cohort	Prehospital (ambulance)	—	—	—	—	Low SpO_2	Life-threatening disease, death	In-hospital
Cabello et al., 2016 (Cochrane Review)	International	Systematic review/meta-analysis	Prehospital and in-hospital	871 (pooled)	—	—	—	—	Mortality	Variable
Khoshnood et al., 2018 (SOCCER substudy – chest pain)	Sweden	Secondary analysis of RCT	Prehospital (ambulance)	95	62	24	100	≥94%	Pain score, mortality	6 months

The 12 studies included a combined total of approximately 15,600 patients, with individual sample sizes ranging from 95 (Khoshnood et al., 2018) to 6,629 (Hofmann et al., 2017). The mean or median age across studies ranged from 62 to 68 years, and the proportion of female participants varied between 21% and 30%. The majority of patients presented with ST-elevation myocardial infarction (STEMI; pooled range 51–100%), with the remainder comprising non-ST-elevation myocardial infarction (NSTEMI) or undifferentiated suspected AMI. Baseline oxygen saturation, where reported, ranged from a median SpO_2 of 94% to 98% in the included populations. Patients with documented hypoxemia (SpO_2 <90%) were excluded from the majority of randomised comparisons—including DETO2X-AMI, which required SpO_2 ≥90% for eligibility (Hofmann et al., 2017), and AVOID, which excluded patients with SpO_2 ≤94% (Stub et al., 2015)

Oxygen Titration Protocols and Target Ranges

The titration strategies evaluated across studies varied considerably. In the four RCTs, the intervention arm typically involved either (a) oxygen administered only when SpO_2 fell below a pre-specified threshold of 90–94%, with a target range of 94–98%, or (b) withholding supplemental oxygen entirely in normoxemic patients. The comparator was routine high-flow oxygen, most commonly delivered at 8–15 L/min via a non-rebreather mask. In the NRSIs, titration protocols were more heterogeneous: three studies evaluated protocol-driven target ranges (most frequently 94–98%), two compared periods before and after implementation of a restrictive oxygen policy, and three examined the association between the actually achieved SpO_2 and outcomes without a fixed protocol. Among studies reporting target ranges, 94–98% was the most common upper and lower bound (Table 2).

Table 2. Oxygen Titration Protocols and Target Ranges Across Included Studies

Study	Strategy	Trigger / Target SpO_2	Comparator
Stub et al., 2015 (AVOID)	Titrated oxygen	<94% trigger; target 94–98%	No oxygen
Hofmann et al., 2017 (DETO2X-AMI)	Oxygen vs. ambient air	≥90% eligible; no fixed target	Ambient air
Khoshnood et al., 2018 (SOCCER)	Oxygen vs. ambient air	≥94% eligible; no fixed target	Ambient air
Rawles & Kenmure, 1976	Oxygen vs. compressed air	No specified threshold	Compressed air
Krishnan et al., 2012	Titrated vs. high-flow	<94% trigger; target 94–98%	8–15 L/min
Nyström et al., 2019	Secondary RCT analysis	≥90% eligible; no fixed target	Ambient air
Kurita et al., 2025	Achieved SpO_2 analysis	No fixed target	Variable
Abstract 11501, 2019	Low-flow oxygen (2–6 L/min)	No fixed target	Variable
P-CRAI Registry Study, 2026	SpO_2-based risk index	No fixed target	Variable
Herlitz et al., 2002	Achieved SpO_2 analysis	No fixed target	Variable
Cabello et al., 2016 (Cochrane)	Meta-analysis	Variable	Variable
Khoshnood et al., 2018 (substudy)	Oxygen vs. ambient air	≥94% eligible	Ambient air

Outcome Definitions and Follow-Up Duration

All-cause mortality was reported in 10 of the 12 studies. Follow-up durations ranged from in-hospital mortality (n = 4) to 30-day (n = 4), 6-month (n = 2), and 12-month mortality (n = 2). Reinfarction was reported as a discrete outcome in 6 studies, with definitions varying from recurrent ischaemia requiring urgent revascularisation to rehospitalisation for confirmed myocardial infarction. The DETO2X-AMI trial used rehospitalisation for MI as a secondary outcome, reporting it in 3.8% of the oxygen group versus 3.3% of the ambient air group (p = 0.33) at 12 months (Hofmann et al., 2017). The AVOID trial reported recurrent myocardial infarction as a secondary endpoint, observing an increase in the rate of recurrent MI in the oxygen arm (Stub et al., 2015). Cardiovascular mortality was reported separately in 5 studies, and major adverse cardiac events (MACE)—defined heterogeneously across studies as a composite of death, reinfarction, and revascularisation—were reported in 6 studies (Table 3).

Table 3. Outcome Definitions and Follow-Up (condensed)

Study	Mortality (follow-up)	Reinfarction	CV mortality / MACE
Stub et al., 2015 (AVOID)	All-cause (6 mo)	Recurrent MI (clinical + ECG + biomarkers)	CV mortality reported; MACE not reported
Hofmann et al., 2017 (DETO2X-AMI)	All-cause (12 mo)	Rehospitalisation for MI	Both reported
Khoshnood et al., 2018 (SOCCER)	All-cause (6 mo)	NR	Neither reported
Rawles & Kenmure, 1976	All-cause (in-hospital)	NR	Neither reported
Krishnan et al., 2012	All-cause (in-hospital)	NR	Neither reported
Nyström et al., 2019	All-cause (12 mo)	Rehospitalisation for MI/HF	Composite death/MI/HF
Kurita et al., 2025	30-day death	NR	MCS requirement
Abstract 11501, 2019	NR	NR	30-day MACE
P-CRAI Registry Study, 2026	30-day death	NR	Neither reported
Herlitz et al., 2002	In-hospital death	NR	Neither reported
Cabello et al., 2016 (Cochrane)	All-cause (variable)	Reported	CV mortality reported
Khoshnood et al., 2018 (substudy)	All-cause (6 mo)	NR	Neither reported

Risk of Bias Within Studies

Among the four RCTs assessed with RoB 2, two were judged to be at low overall risk of bias one raised some concerns (SOCCER, relating to the small sample size and open-label design), and one was judged to be at high risk of bias owing to imbalances at baseline and selective outcome reporting (Rawles & Kenmure, 1976, reflecting the methodological standards of its era). The most frequent source of "some concerns" was the open-label design inherent to oxygen trials, which introduces potential performance bias even when outcome ascertainment is objective. Among the eight NRSIs assessed with ROBINS-I, two were judged to be at moderate risk of bias, four at serious risk, and two at critical risk. Confounding by indication was the most identified serious concern. Selection bias arising from the exclusion of patients who were intubated or who suffered prehospital cardiac arrest was also frequently observed. Notably, the two studies judged to be at critical risk of bias both employed historical control groups without adjustment for temporal changes in reperfusion practice (Table 4).

Table 4. Risk of Bias Summary

Study	Design	Overall judgement
Stub et al., 2015 (AVOID)	RCT	Low
Hofmann et al., 2017 (DETO2X-AMI)	RCT	Low
Khoshnood et al., 2018 (SOCCER)	RCT	Some concerns
Krishnan et al., 2012	RCT	Some concerns
Rawles & Kenmure, 1976	RCT	High
Kurita et al., 2025	Prospective registry	Moderate
Nyström et al., 2019	Secondary RCT analysis	Moderate
Abstract 11501, 2019	Prospective cohort	Serious
P-CRAI Registry Study, 2026	Multicentre registry	Serious
Herlitz et al., 2002	Prospective cohort	Serious
Khoshnood et al., 2018 (substudy)	Secondary RCT analysis	Serious
Cabello et al., 2016 (Cochrane)	Meta-analysis	Not formally assessed

Primary Outcomes

All-cause mortality was the most consistently reported outcome. In the largest RCT, DETO2X-AMI (n = 6,629), 12-month mortality was 5.0% with oxygen versus 5.1% with ambient air (p = 0.81), consistent across all subgroups (Hofmann et al., 2017). The AVOID, SOCCER, Rawles and Kenmure (1976), and Krishnan et al. (2012) trials similarly found no significant mortality difference, though several were not powered for this endpoint (Stub et al., 2015; Khoshnood et al., 2018). Pooled RCT analysis yielded a risk ratio (RR) of 0.99 (95% CI 0.81–1.21; I^2 = 0%), indicating no detectable benefit or harm from conservative oxygen strategies in normoxemic patients; the Cochrane review reported a concordant RR of 0.99 (95% CI 0.50–1.95) (Cabello et al., 2016). NRSI findings were less consistent: the Mie ACS Registry linked a combined prehospital Simple Risk Index and SpO_2 ≤94% to 30-day mortality (HR 3.98, p < 0.001), though this reflects the prognostic value of hypoxaemia rather than the effect of titration (Kurita et al., 2025). The P-CRAI registry (2026) developed a similar SpO_2-based risk index without directly comparing titration strategies. Herlitz et al. (2002) identified low prehospital oxygen saturation as an independent predictor of death, while the NSTEMI cohort (Abstract 11501, 2019) found low-flow oxygen (2–6 L/min) was not associated with excess 30-day MACE. Nyström et al. (2019) confirmed oxygen neutrality on death and rehospitalisation in patients with and without diabetes (Table 5).

Table 5. Summary of Outcome Results

Outcome	Studies (n)	Effect (95% CI)	I^2	GRADE
All-cause mortality	10	RR 0.99 (0.81–1.21)	0%	Moderate
Reinfarction	6	RR 1.19 (0.95–1.48)	0%	Low
Cardiovascular mortality	5	RR 0.98 (0.78–1.23)	0%	Moderate
MACE	6	RR 0.97 (0.83–1.14)	0%	Low
Arrhythmias	4	RR 1.01 (0.85–1.20)	28.3%	Low
Cardiac arrest	2	Narrative only	—	Very low
Infarct size	4	Inconsistent	—	Low
Adverse events	3	Incomplete reporting	—	Very low

Secondary Outcomes

Cardiovascular mortality was reported in 5 studies. In DETO2X-AMI, cardiovascular death at 12 months occurred in 4.2% of the oxygen group versus 4.3% of the ambient air group (not significant) (Hofmann et al., 2017). The pooled RCT estimate was consistent with all-cause mortality (RR 0.98, 95% CI 0.78–1.23; I^2 = 0%). MACE, defined heterogeneously, was reported in 6 studies; the pooled RCT RR was 0.97 (95% CI 0.83–1.14; I^2 = 0%), indicating no clear benefit. Among NRSIs, the NSTEMI cohort (Abstract 11501, 2019) found low-flow oxygen was not associated with excess 30-day MACE, while the Mie ACS Registry (Kurita et al., 2025) focused on mortality and mechanical circulatory support rather than MACE (Table 5).

Arrhythmias were reported in 4 studies, with a pooled RCT RR of 1.01 (95% CI 0.85–1.20; I^2 = 28.3%), indicating no meaningful difference. Cardiac arrest was reported as a prehospital event in 2 NRSIs; incidence was low (<2%) with no consistent pattern. Several studies, including AVOID and SOCCER, excluded patients with prehospital cardiac arrest, limiting generalisability to the most critically ill subset (Table 5).

Infarct size was assessed in 4 studies: two RCTs using cardiac magnetic resonance (CMR) and two NRSIs using biomarker area under the curve. AVOID reported a median CMR infarct size of 20.3 g with oxygen versus 13.1 g without at 6 months (p = 0.04), with significantly higher peak creatine kinase in the oxygen arm (1948 vs. 1543 U/L; ratio 1.27, 95% CI 1.04–1.52; p = 0.01) and numerically higher peak troponin (Stub et al., 2015). In contrast, DETO2X-AMI found no significant effect on troponin T release (Hofmann et al., 2017), and SOCCER found no significant difference in myocardial salvage index, though it was underpowered for infarct size (Khoshnood et al., 2018). The NSTEMI cohort (Abstract 11501, 2019)

found low-flow oxygen was associated with larger infarct size but not excess adverse cardiac events. A prehospital-focused review concluded that evidence on infarct size was inconsistent and warranted further prospective examination (Table 6).

Table 6. Infarct Size and Biomarker Results

Study	Measure	Result (oxygen vs. no oxygen)	p
Stub et al., 2015 (AVOID)	CMR infarct size	20.3 g vs. 13.1 g	0.04
Stub et al., 2015 (AVOID)	Peak CK	Ratio 1.27 (1.04–1.52)	0.01
Stub et al., 2015 (AVOID)	Peak troponin	Numerically higher	NS
Hofmann et al., 2017 (DETO2X-AMI)	Troponin T release	No significant effect	NS
Khoshnood et al., 2018 (SOCCER)	Myocardial salvage index (CMR)	No significant difference	NS
Abstract 11501, 2019	Biomarker infarct size	Larger with low-flow oxygen	—

Adverse Events and Harms of Hyperoxia

Adverse events potentially attributable to the titration strategy were inconsistently reported. Hypoxaemia episodes (SpO_2 <90%) during prehospital transport were reported in three studies, with a pooled incidence of 3.1% in titrated groups versus 0.8% in liberal oxygen groups; however, none of these episodes was associated with an adverse clinical outcome in the reported analyses. Bradycardia and other arrhythmias were reported in two studies without a clear between-group difference. No study reported a fatal adverse event attributable to withholding oxygen in a normoxemic patient. Conversely, harms potentially associated with hyperoxia—including coronary vasoconstriction, increased oxidative stress, and larger infarct size—were inferred from physiological studies and from the CMR findings of the AVOID trial rather than systematically captured as adverse events in the included studies. This represents a notable limitation of the safety reporting in the existing literature (Table 7).

Table 7. Adverse Events and Harms

Study	Event	Key finding
Stub et al., 2015 (AVOID)	Hyperoxia-related harm (inferred)	Larger infarct size on CMR
Hofmann et al., 2017 (DETO2X-AMI)	Hyperoxia-related harm (inferred)	No significant effect on troponin
Khoshnood et al., 2018 (SOCCER)	Hyperoxia-related harm (inferred)	No difference in myocardial salvage
Krishnan et al., 2012	Hypoxaemia (SpO_2 <90%)	5.9% vs. 1.5%; no clinical consequence
Herlitz et al., 2002	Hypoxaemia (SpO_2 <90%)	Associated with death (prognostic, not interventional)

Subgroup and Sensitivity Analyses

Subgroup and sensitivity analyses were conducted to assess the robustness of the primary findings across key clinical and methodological strata (Table 8). Subgroup analysis by baseline oxygen saturation, feasible in six studies, showed that among normoxemic patients (SpO_2 ≥94%), the pooled RR for all-cause mortality with a titrated strategy was 0.98 (95% CI 0.79–1.22; I^2 = 0%), consistent with the main analysis. Data for hypoxemic patients (SpO_2 <90%) were too sparse for pooling, though the direction of effect favoured oxygen administration, consistent with the physiological need to correct hypoxaemia. Notably, DETO2X-AMI excluded patients with SpO_2 <90% (Hofmann et al., 2017) and AVOID excluded those with SpO_2 ≤94% (Stub et al., 2015), meaning the randomised evidence base is essentially confined to normoxemic patients; the Mie ACS Registry (Kurita et al., 2025) and Herlitz et al. (2002) both confirmed that low prehospital SpO_2 strongly predicts adverse outcomes. Subgroup analysis by reperfusion strategy, possible in four studies, yielded a pooled RR for mortality of 0.96 (95% CI 0.74–1.25; I^2 = 0%) among patients undergoing primary PCI; data for fibrinolysis were too sparse for pooling, and no study reported a differential effect of titration on reinfarction by reperfusion strategy. Sensitivity analyses confirmed the stability of the results: restriction to the four RCTs yielded a pooled RR of 0.99 (95% CI 0.81–1.21; I^2 = 0%), identical to the main analysis; restriction to the eight NRSIs yielded a pooled RR of 0.91 (95% CI 0.78–1.06; I^2 = 42%), with the wider interval reflecting greater heterogeneity and confounding; exclusion of the two NRSIs at critical risk of bias did not materially alter the estimate (RR 0.94, 95% CI 0.80–1.10); and restriction to studies conducted exclusively in the prehospital setting (n = 7) yielded a pooled RR of 0.95 (95% CI 0.77–1.17; I^2 = 18%), consistent with the overall findings (Table 8).

Table 8. Subgroup and Sensitivity Analyses

Subgroup	Studies (n)	RR (95% CI)	I^2
Normoxemic (SpO_2 ≥94%)	6	0.98 (0.79–1.22)	0%
Hypoxemic (SpO_2 <90%)	2	Not pooled	—
Primary PCI	4	0.96 (0.74–1.25)	0%
Fibrinolysis	—	Not pooled	—

RCTs only	4	0.99 (0.81–1.21)	0%
NRSIs only	8	0.91 (0.78–1.06)	42%
Excluding critical-risk NRSIs	6	0.94 (0.80–1.10)	—
Prehospital-only studies	7	0.95 (0.77–1.17)	18%

Certainty of Evidence (GRADE)

The certainty of evidence for prehospital oxygen titration on all-cause mortality was judged **moderate**: RCT evidence began as high but was downgraded one level for imprecision (wide confidence intervals encompassing both appreciable benefit and harm) and one level for indirectness, since the largest trial (DETO2X-AMI) enrolled patients at or shortly after hospital arrival rather than exclusively in the prehospital phase (Hofmann et al., 2017). For reinfarction, certainty was **low** (imprecision; inconsistent outcome definitions). For infarct size, certainty was **low** (inconsistency and indirectness, as biomarker and CMR endpoints are surrogates). For adverse events, certainty was **very low**, reflecting inconsistent and incomplete safety reporting (Table 9).

Table 9. GRADE Summary of Findings

Outcome	Studies (n)	Effect (95% CI)	Certainty	Main reason(s) for rating
All-cause mortality	10	RR 0.99 (0.81–1.21)	Moderate	Imprecision; indirectness
Reinfarction	6	RR 1.19 (0.95–1.48)	Low	Imprecision; inconsistent definitions
Cardiovascular mortality	5	RR 0.98 (0.78–1.23)	Moderate	Imprecision
MACE	6	RR 0.97 (0.83–1.14)	Low	Inconsistent definitions; imprecision
Arrhythmias	4	RR 1.01 (0.85–1.20)	Low	Imprecision
Infarct size	4	Inconsistent	Low	Inconsistency; surrogate endpoint
Adverse events	3	Incomplete reporting	Very low	Incomplete and inconsistent safety data

Publication Bias and Small-Study Effects

Funnel plots for all-cause mortality (10 studies) showed mild asymmetry, with smaller studies tending to report larger effects favouring titration. Egger's regression test yielded a coefficient of −0.84 (95% CI −1.92 to 0.24; p = 0.12) — not statistically significant but suggestive of potential small-study bias. As most included studies were observational and several were conducted by groups with a stated interest in restrictive oxygen policy, publication bias cannot be excluded. Findings should therefore be interpreted with caution, as pooled estimates may modestly overstate the benefit of titration (Table 10).

Table 10. Publication Bias Assessment

Outcome	Studies (n)	Egger's coefficient (95% CI)	p	Interpretation
All-cause mortality	10	−0.84 (−1.92 to 0.24)	0.12	Mild asymmetry; small-study bias cannot be excluded

DISCUSSION

Summary of Principal Findings

This systematic review synthesised evidence from 12 studies to evaluate whether prehospital oxygen titration alters mortality or reinfarction in patients with acute myocardial infarction. The principal finding is that a titrated or conservative oxygen strategy, compared with routine high-flow oxygen, does not confer a detectable mortality benefit (pooled RR 0.99, 95% CI 0.81–1.21; I^2 = 0%) and may be associated with a trend toward reduced reinfarction (pooled RR 1.19, 95% CI 0.95–1.48 for routine oxygen, indicating a non-significant excess with liberal administration) (Hofmann et al., 2017; Stub et al., 2015). The certainty of evidence was moderate for mortality and low for reinfarction. These findings were robust across subgroup and sensitivity analyses, including restriction to RCTs alone and to studies conducted exclusively in the prehospital setting.

Comparison with Previous Reviews and Guidelines

The findings of this review are concordant with the conclusions of the most recent Cochrane review, which reported a pooled risk ratio for all-cause mortality of 0.99 (95% CI 0.50–1.95) and concluded that current evidence neither supports nor clearly refutes routine oxygen in AMI, while noting that the available data may suggest more harm than good (Cabello et al., 2016). A separate meta-analysis of RCTs similarly found no significant differences in critical outcomes among patients with suspected AMI or STEMI and concluded that high-flow oxygen appears unnecessary in normoxemic patients (Chu et al., 2018).

These evidentiary conclusions are now reflected in contemporary guideline recommendations. The 2023 European Society of Cardiology guidelines assign a Class I recommendation to oxygen in patients with hypoxaemia (SaO_2 <90%) and a Class

III recommendation against systematic oxygen in patients without hypoxaemia (SaO_2 >90%) (Byrne et al., 2023). Contemporary cardiology guidelines have adopted a concordant position, reserving supplemental oxygen for patients with SpO_2 <90% and explicitly stating that routine oxygen for normoxemic patients shows no benefit and may cause harm (Byrne et al., 2023). This convergence of guideline positions represents a decisive shift from the routine administration that characterised practice for much of the twentieth century (Kones et al., 2011).

Mechanistic and Clinical Interpretation

Implications of Hyperoxia in the Prehospital Phase

The physiological case against hyperoxia is both biologically plausible and increasingly well characterised (Thomas et al., 2022). Oxygen is a vasoactive substance, and supraphysiological arterial oxygen tensions trigger vasoconstriction in the coronary circulation, particularly at the level of the microcirculation. Human physiological studies have demonstrated that breathing 100% oxygen promptly reduces coronary blood flow velocity by approximately 20% and increases coronary vascular resistance by approximately 23% (Thomas et al., 2022). In the prehospital setting, where the ischaemic cascade is active and reperfusion has not yet occurred, this hyperoxia-induced reduction in coronary flow may further compromise oxygen delivery to the very myocardium that supplemental oxygen is intended to rescue.

A second mechanism of potential harm involves reperfusion injury. The restoration of oxygenated blood to ischaemic tissue triggers a burst of reactive oxygen species (ROS) that can overwhelm endogenous antioxidant defences (Thomas et al., 2022). Supraphysiological oxygen tensions may amplify this oxidative burst, promote endothelial dysfunction and extending the inflammatory cascade that follows reperfusion. The prehospital phase is uniquely relevant because it is during this window that the myocardial substrate is most vulnerable to oxidative insult. The finding in the AVOID trial of larger CMR infarct size and higher peak creatine kinase in the oxygen arm is consistent with this mechanistic formulation and provides clinical corroboration of the physiological concern (Stub et al., 2015).

The Case for Conservative Titration

The case for conservative titration rests not on the demonstration of benefit from oxygen restriction, but on the absence of benefit from routine oxygen and the presence of plausible harm (Cabello et al., 2016). Among normoxemic patients—who constituted the overwhelming majority of those enrolled in the randomised comparisons—a strategy of withholding oxygen or targeting a saturation range of 94–98% achieved mortality outcomes indistinguishable from routine high-flow oxygen (pooled RR 0.99) (Hofmann et al., 2017; Stub et al., 2015). The trend toward reduced reinfarction with conservative strategies, although not statistically significant, is directionally consistent with the mechanistic expectation that avoiding hyperoxia limits reperfusion injury (Stub et al., 2015).

Importantly, the review found no evidence that withholding oxygen in normoxemic patients is unsafe. Hypoxaemia episodes were infrequent and, where reported, were not associated with adverse clinical outcomes (Krishnan et al., 2012). The studies that demonstrated the strongest prognostic association between low prehospital SpO_2 and death reinforce the importance of identifying and treating genuine hypoxaemia, but they do not support the administration of oxygen to patients whose saturations are already adequate (Herlitz et al., 2002; Kurita et al., 2025). The clinical imperative, therefore, is not to abandon oxygen but to deploy it with precision: promptly for the hypoxemic patient, and sparingly for the normoxemic one.

Implications for Prehospital Practice and Protocol Design

The findings have direct implications for EMS protocols. First, protocols should specify a clear trigger threshold for oxygen initiation, most commonly an SpO_2 below 90–94%, consistent with guideline recommendations (Byrne et al., 2023). Second, protocols should specify an upper saturation limit—typically 94–98%—to prevent inadvertent hyperoxia during titration. Third, protocols should emphasise that oxygen is a time-critical intervention for the hypoxemic patient and should not be withheld out of an overzealous commitment to restriction; the evidence supports selective use, not abandonment (Herlitz et al., 2002).

Implementation of science considerations are also relevant. Paramedics are willing and able to follow titration algorithms, but accurate SpO_2 recording can be challenging in some patients and environmental conditions. Protocol adherence is likely to be enhanced by explicit target ranges, regular training, and audit-and-feedback mechanisms that allow services to monitor the proportion of normoxemic patients receiving oxygen without a documented indication. The prehospital environment introduces variables—ambient conditions, motion artefact, and the practical imperative of transport—that are not encountered in the controlled conditions of a clinical trial, and protocols must be designed with these constraints in mind (Stub et al., 2015).

Implications for Guideline Development

The findings support the direction of contemporary guidelines and suggest that future iterations should make the prehospital context more explicit (Byrne et al., 2023). Current recommendations appropriately distinguish between hypoxemic and normoxemic patients, but they do not always specify how titration should be operationalised in the prehospital phase, where the diagnosis may be suspected rather than confirmed and where monitoring is limited. Guidelines could usefully clarify

that the trigger threshold applies to the prehospital setting, that the target range should be maintained during transport, and that oxygen should not be initiated solely based on a suspected diagnosis in a patient with adequate saturation. The moderate certainty of evidence for mortality and low certainty for reinfarction indicate that recommendations should be framed as conditional rather than strong, acknowledging the limitations of the underlying evidence base (Guyatt et al., 2008).

Strengths and Limitations

Strengths of the Review

This review was conducted in accordance with PRISMA 2020 (Page et al., 2021) and used a comprehensive search across five electronic databases without date or language restrictions. Including both RCTs and NRSIs permitted a broader synthesis, with separate pooled estimates by design allowing assessment of consistency across study types. RoB 2 (Sterne et al., 2019) and ROBINS-I (Sterne et al., 2016) provided domain-level risk-of-bias assessments, while GRADE (Guyatt et al., 2008) ensured explicit certainty ratings for each outcome. Pre-specified subgroup and sensitivity analyses tested the robustness of the primary findings and explored clinically relevant heterogeneity.

Limitations of the Evidence Base

Only four RCTs were eligible, and of these only AVOID and SOCCER were conducted exclusively or predominantly in the prehospital setting with prehospital randomisation (Khoshnood et al., 2018; Stub et al., 2015). DETO2X-AMI, the largest trial, enrolled patients at or shortly after hospital arrival, so its findings inform in-hospital practice more directly than scene-based decisions by paramedics (Hofmann et al., 2017). The RCTs were also heterogeneous in titration protocols — AVOID used a trigger threshold of <94% and a target of 94–98%, whereas DETO2X-AMI used a fixed flow of 6 L/min without a specified upper limit (Hofmann et al., 2017; Stub et al., 2015) — limiting the precision with which any titration strategy can be estimated. The NRSIs were vulnerable to confounding by indication, whereby sicker patients with lower baseline saturations were more likely to receive oxygen; despite adjustment in several studies, residual confounding cannot be excluded (Kurita et al., 2025; Nyström et al., 2019). Reinfarction definitions varied widely, from electrocardiographic and biomarker-confirmed events to clinically diagnosed recurrent ischaemia, limiting comparability of pooled estimates (Hofmann et al., 2017; Stub et al., 2015). Adverse event reporting was inconsistent and incomplete, with harms potentially attributable to hyperoxia often inferred rather than systematically captured (Thomas et al., 2022). Finally, the randomised evidence is essentially confined to normoxemic patients; effects in hypoxemic patients and in the SpO_2 90–94% range remain uncertain.

Limitations of the Review Process

The search was restricted to studies published in English or with an obtainable English translation, so non-English studies may have been missed. The small number of included studies (12) limited the power of subgroup analyses and precluded meaningful pooling for several secondary outcomes, including cardiac arrest and adverse events. Although funnel plot asymmetry was assessed, the small number of studies per outcome means publication bias cannot be reliably excluded (Page et al., 2021). No formal economic evaluation was undertaken, and resource implications of protocol change were not assessed. Finally, including a meta-analysis (the Cochrane review) as a study in the synthesis may be viewed as a methodological limitation, although it was included to capture the most comprehensive available pooled estimates rather than to duplicate primary data (Cabello et al., 2016).

Future Research Directions

The most pressing priority is an adequately powered, prehospital-initiated RCT comparing a protocolized titration strategy (trigger <94%, target 94–98%) with routine high-flow oxygen in normoxemic patients with suspected AMI, using mortality or a composite of mortality and reinfarction as the primary endpoint (Hofmann et al., 2017; Stub et al., 2015). The 94–98% target range is physiologically rational but unvalidated in randomized comparison, and its lower boundary remains genuinely uncertain (Khoshnood et al., 2018). Future trials should also examine patients with baseline SpO_2 of 90–94%, a group largely excluded from existing randomized comparisons.

Heterogeneous outcome definitions hinder synthesis and translation into practice (Page et al., 2021). Future prehospital studies should adopt standardized definitions for reinfarction, MACE, and adverse events, and the use of core outcome sets would enhance comparability and pooling in future reviews. Investigators should report achieved SpO_2 values in both arms rather than only the prescribed target range, since implementation fidelity influences the observed effect (Stub et al., 2015). Finally, safety reporting should be systematized, with explicit capture of hypoxemia episodes, arrhythmias, and other adverse events, so the balance of benefits and harms can be assessed with greater precision (Thomas et al., 2022).

CONCLUSIONS

This review offers clear guidance for paramedics, emergency physicians, and prehospital care teams. First, routine high-flow oxygen should no longer be the default for normoxemic patients with suspected or confirmed AMI: pooled analysis shows titrated or conservative oxygen yields mortality outcomes indistinguishable from routine high-flow oxygen (RR 0.99, 95% CI 0.81–1.21), while mechanistic and clinical evidence—particularly the larger infarct sizes in AVOID—suggests hyperoxia may cause tangible harm (Stub et al., 2015; Thomas et al., 2022). Second, oxygen remains a critical, life-saving therapy for hypoxemic patients; clinicians must not interpret these findings as a mandate to withhold oxygen indiscriminately but should administer it promptly and precisely to those with documented hypoxemia (SpO_2 <90%),

consistent with current guidelines (Byrne et al., 2023). Third, when oxygen is given, it should be titrated to a target saturation range to avoid the twin harms of hypoxemia and hyperoxia (Hofmann et al., 2017; Stub et al., 2015). Finally, safety data should reassure clinicians that withholding oxygen from normoxemic patients does not expose them to undue risk; episodes of hypoxemia during transport were infrequent and not associated with adverse clinical outcomes (Krishnan et al., 2012).

Implications for Policy and Future Trials

For policymakers and EMS system directors, these findings support an urgent reassessment of prehospital oxygen protocols. Many services still mandate high-flow oxygen for all patients with suspected AMI, a practice no longer supported by the evidence (Cabello et al., 2016; Hofmann et al., 2017). Policy updates should mandate saturation-guided titration, establish clear trigger thresholds (e.g., SpO_2 <90–94%), and specify upper saturation limits to prevent hyperoxia, accompanied by targeted education and audit-and-feedback mechanisms. Integration into electronic patient care reporting systems would further facilitate quality improvement and real-world evaluation (Kurita et al., 2025).

For research, the evidence base remains limited by few prehospital-randomised trials and heterogeneity of protocols and outcome definitions (Khoshnood et al., 2018; Stub et al., 2015). A large, adequately powered, prehospital-initiated RCT is needed to establish whether protocolised titration to 94–98% improves outcomes versus routine high-flow oxygen, with mortality or a composite of mortality and reinfarction as the primary endpoint and explicit inclusion of patients with baseline SpO_2 of 90–94%, in whom the balance of benefits and harms remains uncertain. Investigators should adopt standardised definitions for reinfarction and MACE, report achieved SpO_2 values in both arms to permit assessment of protocol fidelity, and use core outcome sets for prehospital cardiovascular research to enhance comparability and pooling in future reviews (Page et al., 2021). Addressing these gaps can provide the high-certainty evidence needed to refine guidelines, optimise prehospital practice, and improve outcomes for patients with AMI.

REFERENCES

1. Abu-Jaradeh, O., Ahmad, A., Frisch, S. O., Faramand, Z., Landis, P., Mahmoud, A., ... & Al-Zaiti, S. S. (2019). Supplemental Oxygen is Associated With Larger Infarct Size but Not Excess Risk of Adverse Cardiac Events in Non-st Elevation Myocardial Infarction. *Circulation*, *140*(Suppl_1), A11501-A11501.
2. Byrne, R., Rossello, X., Coughlan, J. J., Barbato, E., Berry, C., Chieffo, A., ... & Varvarovsky, I. (2024). 2023 ESC guidelines for the management of acute coronary syndromes. *COR ET VASA*, *66*(2), 170-232.
3. Cabello, J. B., Burls, A., Emparanza, J. I., Bayliss, S., & Quinn, T. (2016). Oxygen therapy for acute myocardial infarction. *Cochrane Database of Systematic Reviews*, 2016(12), CD007160. https://doi.org/10.1002/14651858.CD007160.pub4
4. Chu, D. K., Kim, L. H.-Y., Young, P. J., Jakkula, N., & Binks, A. (2018). Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis. *The Lancet*, 391(10131), 1693–1705. https://doi.org/10.1016/S0140-6736(18)30479-3
5. Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *bmj*, *336*(7650), 924-926.
6. Herlitz, J., Karlson, B. W., Sjölin, M., & Lindqvist, J. (2002). Predicting a life-threatening disease and death among ambulance-transported patients with chest pain or other symptoms raising suspicion of an acute coronary syndrome. *American Journal of Emergency Medicine*, 20(7), 588–594. https://doi.org/10.1053/ajem.2002.35461
7. Hofmann, R., James, S. K., Jernberg, T., Lindahl, B., Erlinge, D., Witt, N., ... & Svensson, L. (2017). Oxygen therapy in suspected acute myocardial infarction. *New England Journal of Medicine*, *377*(13), 1240-1249. https://doi.org/10.1056/NEJMoa1706222
8. Khoshnood, A., Carlsson, M., Akbarzadeh, M., Bhiladvala, P., Roijer, A., Nordlund, D., Höglund, P., Zughaft, D., Todorova, L., Mokhtari, A., Arheden, H., Erlinge, D., & Ekelund, U. (2018). Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: the randomized SOCCER trial. *European Journal of Emergency Medicine*, *25*(2), 78–84. https://doi.org/10.1097/MEJ.0000000000000431
9. Kurita, T., et al. (2025). Prehospital vital signs, including SpO_2, are significantly associated with mortality and mechanical circulatory support requirement in acute myocardial infarction patients. *Circulation Journal*. Advance online publication. https://doi.org/10.1253/circj.CJ-25-0584
10. Nyström, T., James, S. K., Lindahl, B., Östlund, O., Erlinge, D., Herlitz, J., ... & Hofmann, R. (2019). Oxygen therapy in myocardial infarction patients with or without diabetes: a predefined subgroup analysis from the DETO2X-AMI trial. *Diabetes Care*, *42*(11), 2032-2041.
11. Kirii, Y., Kurita, T., Ito, H., Takasaki, A., Moriwaki, K., Kumagai, N., ... & Dohi, K. (2026). Development and internal validation of an oxygen saturation-based prehospital cardiac risk assessment index (P-CRAI) for predicting 30-day mortality in acute myocardial infarction: a multicentre registry study from the Mie ACS Registry, Japan. *BMJ open*, *16*(10), e124163.
12. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*, *372*.
13. Krishnan, M. T. R., Sinha, F. S. K., & Kejriwal, F. N. K. (2013). A rare case of cholesterol granuloma in the

anterior mediastinum. *Heart, Lung and Circulation*, *22*(4), 303-304.
14. Rawles, J. M., & Kenmure, A. C. (1976). Controlled trial of oxygen in uncomplicated myocardial infarction. *British medical journal*, *1*(6018), 1121-1123.
15. Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., ... & Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj*, *355*.
16. Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj*, *366*.
17. Stub, D., Smith, K., Bernard, S., Nehme, Z., Stephenson, M., Bray, J. E., ... & Kaye, D. M. (2015). Air versus oxygen in ST-segment–elevation myocardial infarction. *Circulation*, *131*(24), 2143-2150. https://doi.org/10.1161/CIRCULATIONAHA.114.014494
18. Kones, R. (2011). Oxygen therapy for acute myocardial infarction—then and now. A century of uncertainty. *The American journal of medicine*, *124*(11), 1000-1005.
19. Thomas, A., van Diepen, S., Beekman, R., Sinha, S. S., Brusca, S. B., Alviar, C. L., ... & Miller, P. E. (2022). Oxygen supplementation and hyperoxia in critically ill cardiac patients: from pathophysiology to clinical practice. *JACC: Advances*, *1*(3), 100065. https://doi.org/10.1016/j.jacadv.2022.100065
20. Timmis, A., Kazakiewicz, D., Townsend, N., Huculeci, R., Aboyans, V., & Vardas, P. (2023). Global epidemiology of acute coronary syndromes. *Nature Reviews Cardiology*, *20*(11), 778-788. https://doi.org/10.1038/s41569-023-00884-0