

**South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: CVS Chapters**

EVIDENCE SUMMARY

Title: The appropriate use of oxygen therapy for ST elevation myocardial infarction (STEMI): evidence from a contemporary systematic reviews and meta-analysis

Date: 09th September 2021

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Affiliation and declaration of interests:

a) NT: Division of Cardiology, Department of Medicine, Charlotte Maxeke Johannesburg Academic Hospital and the University of the Witwatersrand. NT has received honoraria for speaker and advisory board consulting fees relating to cardiovascular therapies from Acino Health Care Group, Boehringer – Ingelheim, Boston Scientific, Eli Lilly, Medtronic, Merck, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Phillips, Sanofi-Aventis, Servier and Takeda.

b) HB: Department of Family Medicine, University of the Free State. No conflict of interest to declare.

c) TL: Essential Drugs Programmer, National Department of Health, South Africa with no conflicts of interests to declare pertaining to oxygen therapy.

Background:

The current standard treatment guidelines (STG's) of STEMI, from the Adult Hospital Level Chapter 3: Cardiovascular conditions, recommends that oxygen therapy should only be started when the peripheral artery oxygen saturation is < 94%. This recommendation is based on the 2018 meta-analysis by Chu et al.¹ However, a recent external comment was received suggesting that a value < 90% in acute STEMI should be used, citing Hofmann et al (2017).² Thus, the evidence was reviewed, and an overview of the evidence follows on below:

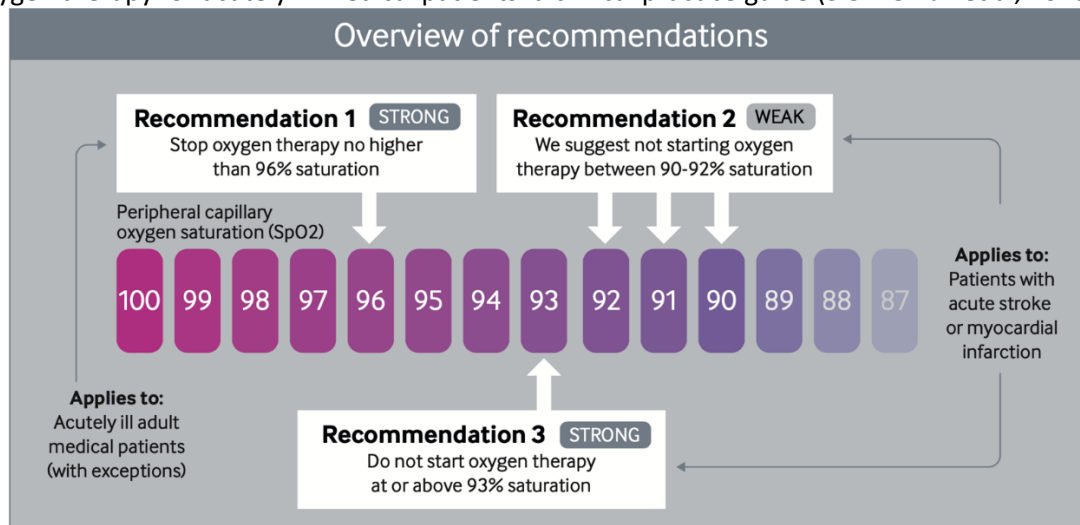
Guidelines:

A 2018 clinical guideline provided guidance based on the 2018 meta-analysis by Chu et al.

Table 1: Characteristics of guideline(s)		
Citation (date published)	Recommendation (pg 1)	AGREE II appraisal
Siemieniuk RAC, Chu DK, Kim LH-Y, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ 2018;363:k4169 – Summary of the results from the Rapid Recommendation process	The panel suggested that for patients receiving oxygen therapy, aim for peripheral capillary oxygen saturation (SpO2) of ≤96% (strong recommendation). For patients with acute myocardial infarction or stroke, do not initiate oxygen therapy in patients with SpO2 ≥90% (for ≥93% strong recommendation , for 90-92% (weak recommendation)). A target SpO2 range of 90-94% seems reasonable for most patients and 88-92% for patients at risk of hypercapnic respiratory failure; use the minimum amount of oxygen necessary.	6/7

See appendix 1: AGREE 2 appraisal and figure 1 below.

Figure 1: Oxygen therapy for acutely ill medical patients: a clinical practice guide (Siemieniuk et al, 2018)³

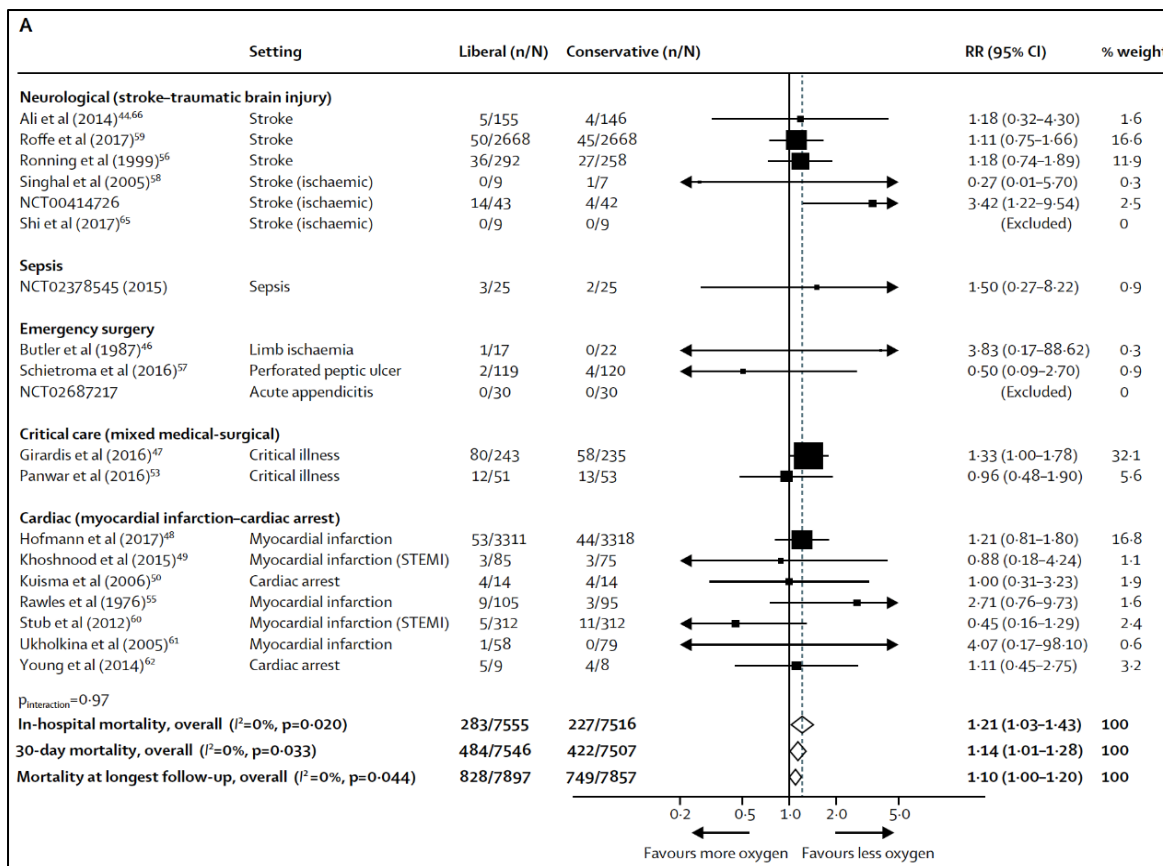


Systematic reviews and meta-analyses:

- *Chu et al (2018) systematic review and meta-analysis:*

The authors analysed 25 randomised controlled trials which enrolled 16 037 patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery. Compared with a conservative oxygen strategy, a liberal oxygen strategy (median baseline saturation of peripheral oxygen [SpO₂] across trials, 96% [range 94–99%, IQR 96–98]) increased mortality in-hospital (relative risk [RR] 1.21, 95% CI 1.03–1.43, I²=0%, high quality), at 30 days (RR 1.14, 95% CI 1.01–1.29, I²=0%, high quality), and at longest follow-up (RR 1.10, 95% CI 1.00–1.20, I²=0%, high quality). Morbidity outcomes were similar between groups. These findings were reported as robust to trial sequential, subgroup, and sensitivity analyses. The authors ultimately concluded that in acutely ill adults, high-quality evidence shows that liberal oxygen therapy increases mortality without improving other patient-important outcomes. Supplemental oxygen might become unfavourable above an SpO₂ range of 94–96%. These results support the conservative administration of oxygen therapy. See figure 1, below.

Figure 2: Forest plot of in-hospital mortality with at 30 days or longer follow-up (Chu et al, 2018)

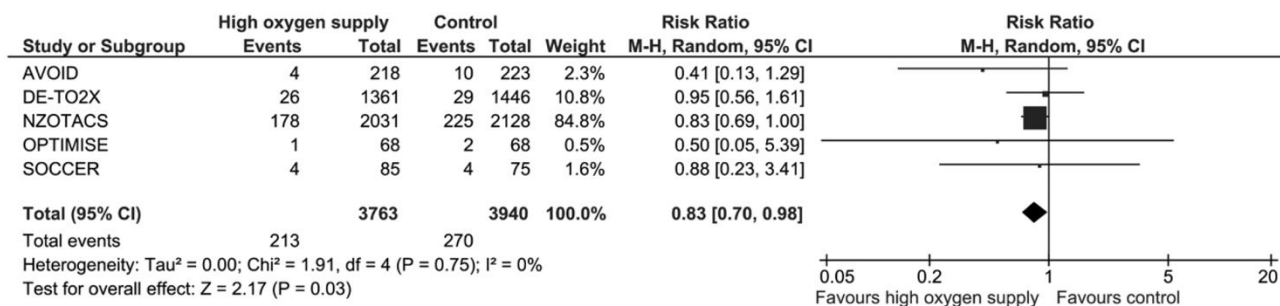


Furthermore, a search was conducted on PUBMED (search strategy – appendix 2), restricting to SRs of RCTs for oxygenation strategies in acute cardiovascular conditions to search for additional literature after 2018. Two SRs were retrieved, and a review of the most recently published SR (2021) follows below:

• *Alves et al (2021) systematic review and meta-analysis⁴:*

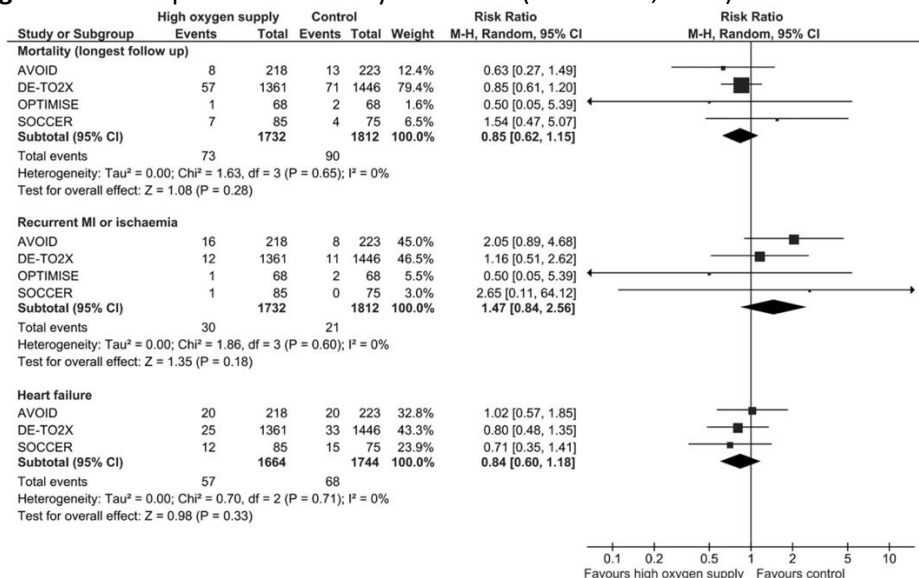
Alves et al. assessed the clinical effect of high oxygen supply in patients with STEMI using a systematic review of the available literature. All randomized controlled trials (RCTs) evaluating the systematic use of high oxygen (6 L/min or higher) versus room air or lower oxygen supply in STEMI patients were included. Systematic review with meta-analysis of trials retrieved in July 2020. Six databases were searched. Risk of bias was evaluated using the Cochrane risk of bias tool. There were five eligible RCTs (7703 patients). High oxygen supply was associated with a significant risk reduction of short-term mortality [risk ratio (RR) 0.83; 95% confidence interval (CI), 0.70–0.98; $I^2 = 0\%$]. Mortality (longest follow-up) (RR 0.83; 95% CI, 0.71–0.97; $I^2 = 0\%$) and heart failure (RR 0.84; 95% CI, 0.60–1.18; $I^2 = 0\%$) did not present a risk reduction. Recurrent MI presented a contradictory result, favouring the lower oxygen protocol (RR 1.47; 95% CI, 0.84–2.56; $I^2 = 0\%$). The GRADE analysis was very low, and the authors concluded that High oxygen supply may be associated with a decrease in short-term mortality in STEMI patients, but the pooled data are not robust enough to allow definitive conclusions. See figures 3 and 4 below.

Figure 3: Forest plot of short-term mortality (*Alves et al, 2021*)



Forest plot of short-term mortality (SOCGER data were provided by author). SOCGER, Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion.

Figure 4: Forest plot for secondary outcomes (Alves et al, 2021)



Forest plot for secondary outcomes – recurrent MI or ischemia, heart failure and mortality (longest follow-up) (SOCCER data on mortality were provided by author). SOCCER, Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion.

Table 2: Summary of findings according to GRADE (Alves et al, 2021)

Outcome no. participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
		Without high oxygen supply (%)	With high oxygen supply			
Short-term mortality no. participants: 7703 (5 RCTs)	RR 0.83 (0.70–0.98)	6.8	5.7% (4.8–6.7)	1.2% fewer (2 fewer to 0,1 fewer)	⊕○○○ VERY LOW ^{a,b}	High oxygen therapy may reduce short-term mortality, but the evidence is very uncertain
Mortality (longest follow-up) no. participants: 7703 (5 RCTs)	RR 0.83 (0.71–0.97)	8.0	6.6% (5.7–7.2)	1.4% fewer (2,3 fewer to 1,2 fewer)	⊕○○○ VERY LOW ^{a,b}	High oxygen therapy may reduce all-cause mortality but the evidence is very uncertain
Recurrent MI or ischemia no. participants: 3544 (4 RCTs)	RR 1.47 (0.84–2.56)	1.2	1.7% (1–3)	0.5% more (0,2 fewer to 1,8 more)	⊕○○○ VERY LOW ^{a,b}	The evidence is very uncertain about the effect of high oxygen therapy on recurrent MI or ischemia
Heart failure no. participants: 3408 (3 RCTs)	RR 0.84 (0.60–1.18)	3.9	3.3% (2.3–4.6)	0.6% fewer (1,6 fewer to 0,7 more)	⊕○○○ VERY LOW ^{a,b}	The evidence is very uncertain about the effect of high oxygen therapy on heart failure

CI, confidence interval; RR, risk ratio; RCT, randomized controlled trials.
^aHigh risk of bias – open label design and selective reporting risk of bias.
^bInsufficient/small sample size.

Conclusions

The main finding of the most recent SR and Meta-analysis was that high oxygen supply in patients with acute STEMI may be associated with a significant 17% risk reduction of short-term mortality (until 30 days). Despite this statistically significant difference in mortality, the trial sequential analysis showed that only 56.3% of the sample size required to assess the 17% risk reduction with a power 80% was reached, and the magnitude of the results were not large which precludes definite conclusions. This consideration and the high risk of bias of the included trials led to successive downgrading in the GRADE analysis of the confidence in the pooled data.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
			X		
<p>Recommendation: Based on this review, the PHC/Adult Hospital Level Committee recommends that the current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic.</p> <p>Rationale: Evidence suggests that acutely ill patients randomised to liberal oxygen therapy were more likely to die, without improving other patient outcomes. For pragmatic purposes the current recommendation of <94% be retained.</p> <p>Level of Evidence: Moderate certainty evidence</p> <p>Review indicator: New evidence that will change the recommendation</p>					
<p>NEMLC RECOMMENDATION (22 FEBRUARY 2022):</p> <ul style="list-style-type: none"> NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter. The PHC/Adult Hospital Level ERC review the evidence of the impact of altitude on oxygen requirements, whilst the draft documents are circulated for external comment. 					
Monitoring and evaluation considerations					
Research priorities					

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	<p>What is the certainty/quality of evidence?</p> <p>High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low <input type="checkbox"/></p> <p><i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect</p>	<p>High quality evidence not to initiate oxygen therapy in patients with acute myocardial infarction or stroke, with SpO₂ ≥ 93% (Hofmann et al, 2017). However, uncertain whether this is applicable to patients requiring oxygen therapy that do not have these conditions.</p> <p>The BMJ Guideline panel down rated the evidence for indirectness.</p>
EVIDENCE OF BENEFIT	<p>What is the size of the effect for beneficial outcomes?</p> <p>Large <input type="checkbox"/> Moderate <input type="checkbox"/> Small <input checked="" type="checkbox"/> None <input type="checkbox"/></p>	<p>No impact on length of hospitalisation or risk of hospital acquired infections.</p>
QUALITY OF EVIDENCE OF HARM	<p>What is the certainty/quality of evidence?</p> <p>High <input type="checkbox"/> Moderate <input checked="" type="checkbox"/> Low <input type="checkbox"/> Very low <input type="checkbox"/></p> <p><i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect</p>	<p>Systematic review by Chu et al (2018)¹ graded the evidence for the outcome, increased mortality in-hospital at 30 days as high quality.</p> <p>The PHC/Adult Hospital Level Committee down rated evidence as uncertain whether applies to all medically ill patients.</p>
EVIDENCE OF HARMS	<p>What is the size of the effect for harmful outcomes?</p> <p>Large <input type="checkbox"/> Moderate <input type="checkbox"/> Small <input checked="" type="checkbox"/> None <input type="checkbox"/></p>	<p>"Patients randomised to liberal oxygen therapy were more likely to die (RR 1.21 (95% confidence interval 1.03 to 1.43)). The increase in mortality was highest in the trials with the greatest increase in SpO₂; this suggests a dose-response relation and strengthens the inference that excessive oxygen is a cause of death. Providing supplemental oxygen above a SpO₂ of 96% probably increases mortality by around 1%"</p>

BENEFITS & HARMES	<p>Do the desirable effects outweigh the undesirable harms?</p> <p>Favours intervention <input type="checkbox"/> Favours control <input checked="" type="checkbox"/> Intervention = Control or Uncertain <input type="checkbox"/></p>	Guideline panel suggests a target SpO2 range of 90-94% so that “it does not require excessive attention” (Siemieniuk et al, 2018).
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	
FEASIBILITY	<p>Is implementation of this recommendation feasible?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/></p>	
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive <input type="checkbox"/> Less intensive <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/></p>	
VALUES, PREFERENCES, ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor <input type="checkbox"/> Major <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/></p>	No local survey data is available, but the Committee was of the opinion that the option would be acceptable to prescribers.
EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/></p>	No significant impact on equity in health for marginalized groups were identified.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 September 2021	NT, HB	Current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic.

References:

1. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet (London, England)* 2018; **391**(10131): 1693-705.
2. Hofmann R, James SK, Jernberg T, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med* 2017; **377**(13): 1240-9.
3. Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018; **363**: k4169.
4. Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. *Eur J Emerg Med* 2021; **28**(1): 11-8.

APPENDIX 1: AGREE II ASSESSMENT

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	94%	84%	94%	52%	92%	83%	Yes - 1, Yes with modifications - 1, No - 0

APPENDIX 2: Pubmed Search Strategy

Strategy: (((Myocardial infarction [MeSH Terms]) OR(coronary artery disease[MeSH Terms]))) AND (Oxygen[MeSH Terms]) OR (oxygen inhalation therapy[Other Term])

#	Searches
1	Myocardial infarction
2	Coronary artery disease
3	1 or 2
4	Oxygen
5	Oxygen inhalation therapy
6	4 or 5
7	Systematic review
8	Meta-analysis
9	7 or 8
10	Exp animals/not humans
11	Not 10
12	3 and 6 and 9
13	Remove duplicates from 12

Systematic Reviews and Meta-analysis Retrieved: In Chronological order.

Restricted to publications after 2018.

1. Alves M, Prada L, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Effect of oxygen supply on mortality in acute ST-elevation myocardial infarction: systematic review and meta-analysis. *Eur J Emerg Med* 2021; **28**(1): 11-8.
2. Khan AR, Abdulhak AB, Luni FK, et al. Oxygen Administration Does Not Influence the Prognosis of Acute Myocardial Infarction: A Meta-Analysis. *Am J Ther* 2019; **26**(1): e151-e60.