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Clinical paper

The cost-effectiveness of mild hypercapnia after out-of-hospital cardiac arrest: a health economic evaluation alongside the TAME study

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Abstract

Background: Out of hospital cardiac arrest (OHCA) is a significant public health problem associated with high mortality and high healthcare costs. The Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) randomised clinical trial showed that targeted mild hypercapnia did not lead to better neurologic outcomes at 6 months compared to normocapnia after OHCA. We aimed to estimate the cost-effectiveness of mild hypercapnia compared to targeted normocapnia using data from the TAME trial.

Methods: Pre-specified, prospective cost-effectiveness analysis alongside the TAME RCT from a healthcare perspective using a 6-month time horizon. The analysis included 1586 patients across 63 intensive care units (ICUs), in 17 countries. The primary measure of cost-effectiveness was the cost per quality-adjusted life year (QALY). Costs were estimated for each patient by multiplying resource use data by the relevant country-specific resource unit cost. QALYs were calculated using utility scores derived from the EQ-5D-5L administered at 6-month follow-up.

Findings: There were no significant differences in costs or QALYs at 6 months between groups. The incremental net monetary benefit was also not significant at a willingness-to-pay threshold of $50,000 per QALY, with the 95 % CI including both negative and positive values.

Interpretation: This analysis found that the cost-effectiveness of mild hypercapnia is highly uncertain when compared with normocapnia in adult patients following OHCA, with no significant differences in either costs or outcomes. Further research is required to determine the specific circumstances under which mild hypercapnia may provide value for money.

Keywords: Cost-effectiveness, Cardiac arrest, Hypercapnia, Normocapnia

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Introduction

Out of hospital cardiac arrest (OHCA) is a significant public health problem associated with high mortality and high healthcare costs. In Europe, the estimated hospital survival from OHCA is only 8 %.[1] Costs for the management of patients following OHCA are significant – a study in Denmark found healthcare costs in the first year of €62,439 (95 %CI: 60,889 to 63,988), with hospitalisation as the largest proportion with €56,692 (95 %CI: 55,158 to 58,226) per OHCA survivor.[2] In addition, there are significant additional economic losses associated with OHCA – e.g., in the United States, the total annual economic productivity loss due to OHCA in 2018 was estimated at $11.3B.[3] There is an urgent need to identify interventions that can both improve outcomes for OHCA patients and provide value for money in a constrained healthcare system.

Survival rates from OHCA are increasing, with improved pre-hospital care including increased rates of bystander CPR, public defibrillators, and rapid transport to hospital.[4,5] The increase in hospitalisations following OHCA has resulted in a steady rise in associated healthcare costs for the management of OHCA.[6] A recent systematic review of the economic evidence surrounding interventions for OHCA identified 46 economic evaluations of interventions for OHCA, of which only three were trial-based economic evaluations, however none involved interventions within the ICU.[7] These evaluations were of varying quality, with less than one-third of evaluations considered high quality.[7] Most evaluations reported cost-effectiveness ratios which fell below commonly accepted willingness-to-pay thresholds; thus signifying that these interventions were cost-effective and represented good value for money.

The Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest (TAME) trial was a multinational randomised trial comparing targeted mild hypercapnia to normocapnia in comatose adults admitted to the intensive care unit (ICU) after OHCA.[8] It showed no difference in favourable neurological outcome (measured using the Glasgow Outcome Scale-Extended [GOSE]) or mortality at six months after OHCA. A within-trial cost-utility analysis was included as part of the statistical analysis plan for the TAME clinical trial protocol.[9] Conducting a cost-utility analysis alongside a clinical trial can provide important insights to clinicians and policy makers, even when null differences are observed for the primary outcome (note: henceforth the term 'cost-effectiveness analysis' will be used as an umbrella term that refers to 'cost-utility analysis'). For example, a cost-effectiveness analysis that examines quality-adjusted life years (QALYs) as the outcome of interest, adopts a generic health measure encompassing aspects of health-related quality of life that typically extend beyond the primary outcome of a clinical trial. Furthermore, demand for healthcare services will always exceed available resources. Economic analyses can subsequently uncover hidden costs or inefficiencies even when a trial shows no clinical benefit.[10] Mild hypercapnia is an intervention that requires minimal resources to implement and it may reduce costs through downstream effects, including reduced use of healthcare resources over time. Within the TAME study, the median time to hospital discharge was 7.8 days [IQR 4.0 to 15.8] in the mild hypercapnia group compared to 9.3 days [4.2 to 16.8] in the targeted normocapnia group.[8] It follows that patients in the mild hypercapnia group may experience differing trajectories in healthcare resource use, and thus healthcare costs, over time. Accordingly, and in line with CONSORT guidelines,[11] we aimed to estimate the cost-effectiveness of mild hypercapnia compared to targeted normocapnia from the perspective of healthcare payers using data from the TAME trial.

Methods

Intervention trial

A pre-specified, within-trial economic evaluation was conducted alongside an international, multi-centre, randomised controlled trial comprising 1700 patients, across 63 ICUs, in 17 countries (ClinicalTrials.gov identifier NCT03114033; first registered 11 April 2017). The TAME trial was approved by the ethics committee in each country or at each participating institution with written informed consent deferred or obtained from a legal surrogate, depending on the circumstances and local requirements, with consent to continue obtained from each patient who regained capacity to consent. Details of the TAME trial have been published previously.[8] In brief, hospitalised adults (≥18 years of age) with coma who had been resuscitated after OHCA of a presumed cardiac or unknown cause and who had a sustained return of spontaneous circulation were assigned to receive targeted mild hypercapnia ($PaCO_2$, 50 to 55 mm Hg; $n = 847$) or targeted normocapnia ($PaCO_2$, 35 to 45 mm Hg; $n = 853$) for a 24-h period beginning at randomisation. The list of TAME study investigators and sites is provided in Appendix S1, while Appendix S2 presents the accompanying CONSORT diagram. The primary outcome involved a favourable neurologic outcome, defined as a Glasgow Outcome Scale-Extended (GOSE) score of 5 to 8 at 6 months.

Health outcomes

The quality-adjusted life year (QALY) was the main health outcome of interest, with one QALY equalling one year in full health. QALYs were calculated using utility scores derived from the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) administered at 6-month follow-up and valued using an Australian tariff involving a discrete choice experiment of best-and-worst options.[12] In line with other studies in critically ill populations, all patients were assumed to have a utility score of zero at randomisation.[13,14] Patients who died were assigned a utility score of zero at follow-up. Area-under-the-curve methods were used to convert utility scores into QALYs, assuming a linear change in utility scores from randomisation to follow-up.[15]

Cost analysis

Data on healthcare resource use was recorded at discharge from the index hospitalisation and 6-month follow-up. Data was collected on the total number of days spent: in ICU and the hospital ward (including readmissions); receiving care at a rehabilitation facility or nursing home; and receiving care at home. Costs were estimated for each patient by multiplying data for each resource use item by the relevant unit cost within the country where the patient was randomised. Unit costs were either obtained from hospital staff, where possible, or national databases (see Appendix S3). All costs were adjusted to 2021 prices using the health-related consumer price index from each country,[16] and purchasing power parity conversion rates were then used to convert costs into United States dollars (US$).[17] As the study

timeframe was <1 year, costs were not discounted. Further details on the methods used for costing healthcare resources are provided in Appendix S3.

Statistical analysis

This study is conducted according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (see Appendix S4).[18] Statistical analyses were performed using Stata 17 (College Station, Texas, USA), with researchers unblinded to treatment arm allocation. A healthcare sector perspective was adopted in the base case analysis and analyses were conducted using an intention-to-treat approach. All patients were analysed in the base case analysis, alongside subgroup analyses for the following regions: 'Australia/NZ' (Australia and New Zealand); and 'Europe' (Belgium, Denmark, Finland, France, Ireland, Italy, Netherlands, Norway, Slovenia, Sweden, Switzerland and the United Kingdom). The analysis excluded 82 (4.9 %) patients who were alive and had missing GOSE scores at 6 months when a GOSE assessment could not be completed; and a favourable (range: 1–4) or unfavourable (range: 5–8) GOSE score could not be imputed based on a clinical judgement following a review of all available medical records/data. In line with the primary trial manuscript, imputations involved assigning a GOSE score of 4 to those with favourable outcomes ($n = 15$) and 8 to those with unfavourable outcomes ($n = 31$). The intention-to-treat population consequently comprised 1586 patients – i.e., 784 in the mild hypercapnia and 802 in the normocapnia group. EQ-5D-5L data were missing at follow-up for 82 patients (5.2 %) and were deemed 'missing at random' following several exploratory analyses (see Appendix S5). Multiple imputation by chained equations (MICE) with predictive mean matching, stratification by treatment group and adjustment for covari-

Table 1 – Sample characteristics of patients at baseline.

Characteristic	Mild Hypercapnia($n = 784$)	Normocapnia ($n = 802$)
Demographic characteristics		
Age, mean ± SD	61.6 ± 14.1	61.7 ± 13.3
Male sex, n (%)	597 (76.2)	653 (81.4)
Medical history		
Hypertension, n / N (%)	257 / 756 (34.0)	285 / 789 (37.6)
Diabetes, n (%)	136 (17.4)	155 (19.3)
Percutaneous coronary intervention, n / N (%)	104 / 756 (13.8)	113 / 759 (14.9)
Myocardial infarction, n (%)	94 (12.0)	124 (15.5)
Chronic obstructive pulmonary disease, n (%)	79 (10.1)	83 (10.4)
Heart failure, n (%)	56 (7.1)	71 (8.9)
Coronary-artery bypass grafting, n / N (%)	46 / 756 (6.1)	56 / 759 (7.4)
NYHA class III or IV heart failure, n / N (%)	10 / 762 (1.3)	17 / 775 (2.2)
Charlson comorbidity index [a], mean ± SD	2.8 ± 2.2	2.8 ± 2.2
Characteristics of the cardiac arrest		
Location of the cardiac arrest, n (%)		
Place of residence	447 (57.0)	442 (55.1)
Public place	254 (32.4)	262 (32.7)
Workplace	54 (6.9)	65 (8.1)
Other	29 (3.7)	33 (4.1)
Bystander-witnessed cardiac arrest, n (%)	686 (87.5)	710 (88.5)
Bystander-performed CPR, n (%)	628 (80.1)	655 (81.7)
First monitored rhythm, n (%)		
Shockable rhythm	550 (70.2)	580 (72.3)
ROSC after bystander-initiated defibrillation	26 (3.3)	25 (3.1)
Unknown rhythm, shock administered	22 (2.8)	19 (2.4)
Nonshockable rhythm	172 (21.9)	169 (21.1)
Unknown rhythm, no shock administered	14 (1.8)	9 (1.1)
Time from cardiac arrest to sustained ROSC (minutes), mean ± SD	34 ± 25	31 ± 23
Time from cardiac arrest to randomisation (minutes), mean ± SD	154 ± 45	150 ± 44
Other characteristics		
Region, n (%)		
Australia and New Zealand	277 (35.3)	277 (34.5)
Europe	487 (62.1)	506 (63.1)
Other	20 (2.6)	19 (2.4)
Total number of deaths at follow-up, n (%)	388 (49.5)	377 (47.0)
Time from randomisation to death across patients who died at follow-up (days), mean ± SD	9.0 ± 14.9	10.3 ± 17.5
Missing EQ-5D-5L data at follow-up, n (%)	42 (5.4)	40 (5.0)

Abbreviations: CPR cardiopulmonary resuscitation; EQ-5D-5L EuroQoL 5-Dimension 5-Level; ICU intensive care unit; NYHA New York Heart Association; ROSC return of spontaneous circulation; SD standard deviation.

[a] Each comorbidity category on the Charlson comorbidity index is weighted from 1 to 6 based on the adjusted risk of death or resource use, with the sum of the weights producing the final score. A score of 0 indicates an absence of known co-existing conditions, while higher scores indicate an increased risk of death and greater resource use.

ates (trial site; concomitant enrolment in the TTM2 trial; and baseline characteristics) was used to account for missing EQ-5D-5L data.

The difference in mean QALYs between the groups was estimated using a mixed-effects linear regression model; while the difference in mean costs was estimated using a mixed-effects generalised linear model (GLM) involving the gamma family and log link. Both the analysis of mean QALYs and mean costs incorporated robust standard errors, alongside adjustments for: concomitant enrolment in the TTM2 trial as a fixed covariate; and trial site as a random effect. Incremental cost-effectiveness ratios (ICERs) were estimated as the difference in mean costs between the two groups, divided by the difference in mean QALYs. A resampling method involving single imputation nested in bootstrapping was used to estimate 95 % confidence intervals (95 % CIs) around each ICER.[19]

A total of 10,000 bootstrap replications (stratified by treatment group and clustered by trial site) were generated and used to produce a cost-effectiveness plane to visually represent dispersion around the differences in mean costs/QALYs and resulting ICERs.[20] Mild hypercapnia was considered cost-effective if the resulting ICER was less than a willingness-to-pay threshold of US$50,000 per QALY. Cost-effectiveness acceptability curves were used to show the probability of mild hypercapnia being cost-effective under different willingness-to-pay thresholds. Cost-effectiveness results were also presented as an incremental net monetary benefit (INMB), which is the difference between the monetary value of incremental QALYs and total expected costs,[20] with a positive INMB signifies that mild hypercapnia is cost-effective compared to targeted normocapnia at the given willingness-to-pay threshold.

Sensitivity analysis

A complete case analysis was performed as a sensitivity analysis to explore the impact of not imputing missing data when analysing costs and QALYs. An additional sensitivity analysis was done to examine the impact of incorporating longer-term data. Trial sites located in New Zealand collected additional data from 200 patients at 24 months. These data were used to compare resulting ICERs that occur at 6 months versus 24 months (see Appendix S6).

Results

Intervention trial

We included 1586 patients who had dichotomised GOSE data available at 6 months, comprising 784 in the mild hypercapnia group and 802 in the targeted normocapnia group (Table 1). The majority of patients were from Europe ($n = 993$, 62.6 %). At 6-month follow-up, there were 388 deaths (49.5 %) in the mild hypercapnia group and 377 deaths (47.0 %) in the normocapnia group. Approximately one-in-twenty (~5%) patients had missing EQ-5D-5L data across both groups.

Health outcomes

Health outcomes are presented in Table 2, for the trial-wide sample and the two regional subsamples. Mortality did not differ significantly between groups across the trial-wide or regional samples. Similarly, EQ-5D utility scores for the trial-wide sample were not significantly different (mean 0.431, SE 0.017 versus mean 0.457, SE 0.017; $P = 0.288$). No significant differences were observed between groups for utility scores in the two regional subsamples.

Cost analysis

Healthcare resource use across the two trial groups (until death or follow-up) are summarised in Table 3. In the trial-wide sample, the majority of resource use days across both groups involved care at home (mean 79.6, SE 2.0); followed by days spent in the hospital ward (mean 8.6, SE 0.3), ICU (mean 7.6, SE 0.2), rehabilitation (mean 1.3, SE 0.1) and nursing home (mean 0.4, SE 0.1). No significant differences were observed between the two groups across any of these resource use parameters in the overall and regional samples.

Cost-effectiveness analysis

Cost-effectiveness results from the bootstrapping analysis are presented for the trial-wide sample and two regional subsamples in Table 4. Negative incremental costs were consistently observed across the trial-wide sample (−$1724, 95 % CI −6598 to 1865); and the two regional subsamples. Negative incremental QALYs were

Table 2 – Summary of health outcomes at follow-up.

Region	Trial group	Deaths, n (%)	EQ-5D utility score [a] –Overall, mean ± SE	EQ-5D utility score [b] –Alive at 6 months, mean ± SE
Pooled	Mild hypercapnia ($n = 784$)	388 (49.5)	0.431 ± 0.017	0.904 ± 0.009
	Normocapnia ($n = 802$)	377 (47.0)	0.457 ± 0.017	0.904 ± 0.009
	P value [c]	0.323	0.288	0.964
Australia/NZ	Mild hypercapnia ($n = 277$)	134 (48.4)	0.465 ± 0.029	0.919 ± 0.012
	Normocapnia ($n = 277$)	122 (44.0)	0.497 ± 0.029	0.921 ± 0.010
	P value [c]	0.306	0.427	0.915
Europe	Mild hypercapnia ($n = 487$)	242 (49.7)	0.421 ± 0.022	0.906 ± 0.012
	Normocapnia ($n = 506$)	242 (47.8)	0.446 ± 0.022	0.904 ± 0.012
	P value [c]	0.556	0.410	0.899

Abbreviations: EQ-5D – EuroQol 5-Dimension; NZ – New Zealand; SE – standard error.

[a] Descriptive statistics are presented for complete cases only – i.e., Mild hypercapnia ($n = 742$) and Normocapnia ($n = 762$).

[b] Descriptive statistics are presented for complete cases only among those still alive at 6 months – i.e., Mild hypercapnia ($n = 354$) and Normocapnia ($n = 385$).

[c] The P values for continuous variables were derived using two-sample t-tests, while P values for categorical variables were derived using Pearson's chi-squared test.

Table 3 – Summary of resource use at follow-up.

Region	Trial group	ICU days, mean ± SE	Hospital ward days, mean ± SE	Rehabilitation days, mean ± SE	Nursing home days, mean ± SE	Care at home days, mean ± SE
Pooled	Mild hypercapnia ($n = 784$)	7.4 ± 0.2	8.4 ± 0.5	1.3 ± 0.2	0.4 ± 0.2	77.6 ± 2.8
	Normocapnia ($n = 802$)	7.8 ± 0.2	8.8 ± 0.5	1.3 ± 0.2	0.5 ± 0.2	81.6 ± 2.8
	P value [a]	0.297	0.503	0.733	0.698	0.297
Australia/ NZ	Mild hypercapnia ($n = 277$)	6.2 ± 0.3	6.5 ± 0.6	1.5 ± 0.3	0.1 ± 0.1	82.1 ± 4.8
	Normocapnia ($n = 277$)	6.3 ± 0.3	7.7 ± 0.7	1.6 ± 0.3	0.6 ± 0.3	88.8 ± 4.7
	P value [a]	0.802	0.182	0.778	0.157	0.326
Europe	Mild hypercapnia ($n = 487$)	8.0 ± 0.3	9.1 ± 0.6	1.3 ± 0.3	0.6 ± 0.3	76.2 ± 3.5
	Normocapnia ($n = 506$)	8.3 ± 0.3	9.1 ± 0.5	1.1 ± 0.2	0.5 ± 0.3	79.4 ± 3.4
	P value [a]	0.465	0.954	0.652	0.804	0.515

Abbreviations: ICU intensive care unit; NZ New Zealand; SE standard error.

[a] The P values for continuous variables were derived using two-sample t-tests.

Table 4 – Cost-effectiveness results for each region (presented by analytic method).

Region(by analytic method)	Incremental costs, US$ [a](95 % CI)	Incremental QALYs(95 % CI)	Mean ICER, US$ per QALY [a](95 % CI)	Mean INMB, US$ [a] (95 % CI)
Pooled				
Bootstrapping [b]	−$1724 (−6598 to 1865)	−0.006 (−0.020 to 0.009)	$298,587 [d] (*Not defined* [e])	$1436 (−2054 to 6178)
SA Complete case analysis [c]	−$2277 (−6111 to 1557)	−0.006 (−0.018 to 0.006)	$389,543 [d] (*Not defined* [f])	$1985 (−1793 to 5762)
Australia/NZ				
Bootstrapping [b]	−$2367 (−7369 to 2247)	−0.010 (−0.033 to 0.017)	$246,373 [d] (*Not defined* [e])	$1887 (−2405 to 7066)
SA Complete case analysis [c]	−$1802 (−8594 to 4990)	−0.008 (−0.030 to 0.015)	$239,732 [d] (*Not defined* [f])	$1426 (−5264 to 8116)
Europe				
Bootstrapping [b]	−$1270 (−10,218 to 4517)	−0.004 (−0.025 to 0.013)	$303,969 [d] (*Not defined* [e])	$1061 (−4629 to 9534)
SA Complete case analysis [c]	−$2899 (−7715 to 1917)	−0.005 (−0.019 to 0.009)	$553,655 [d] (*Not defined* [f])	$2637 (−2109 to 7384)
New Zealand				
SA 6-month follow-up [b]	$2223 (−13,503 to 11,889)	0.007 (−0.027 to 0.041)	$304,266 [g] (*Not defined* [e])	−$1858 (−11,868 to 13,953)
SA 24-month follow-up [b]	$353 (−11,884 to 16,765)	0.040 (−0.207 to 0.282)	$8741 [g] (*Not defined* [f])	$1667 (−20,737 to 20,525)

Abbreviations: 95 % CI – 95 % confidence interval; ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; SA – sensitivity analysis; QALYs – quality-adjusted life years; US$ – United States dollars.

[a] Monetary units are denominated in 2021 United States dollars.

[b] This analytic method involved single imputation nested within bootstrapping (10,000 iterations).

[c] This analytic method involved a complete case analysis with no imputation of missing data.

[d] This positive ICER is situated in the South-West quadrant of the cost-effectiveness plane, which signifies that the intervention is simultaneously less costly and less effective than the comparator. In this scenario, large positive ICERs indicate that an intervention is more cost-effective than a comparator, while small positive ICERs indicate the opposite.

[e] The 95 % confidence interval could not be defined when using the bootstrap percentile method to calculate the confidence interval of the ICER (i.e., bootstrap replicates span all four quadrants of the cost-effectiveness plane).

[f] The 95 % confidence interval could not be defined when using Fieller's theorem to calculate the confidence interval of the ICER.

[g] This positive ICER is situated in the North-East quadrant of the cost-effectiveness plane, which signifies that the intervention is simultaneously more costly and more effective than the comparator. In this scenario, small positive ICERs indicate that an intervention is more cost-effective than a comparator, while large positive ICERs indicate the opposite.

similarly observed across the trial-wide sample (−0.006, 95 % CI −0.020 to 0.009) and two regional subsamples. Even so, no significant differences were observed between groups for either incremental costs or incremental QALYs. Non-significant findings across both incremental costs and QALYs resulted in bootstrap iterations spanning all four quadrants of the cost-effectiveness plane (see Fig. 1), with 95 % confidence intervals for the resulting ICERs being undefined (see Table 4). Likewise, the mean INMB was not significantly different in the trial-wide sample or the regional subsamples (see Appendix S7 for INMBs occurring across a range of different

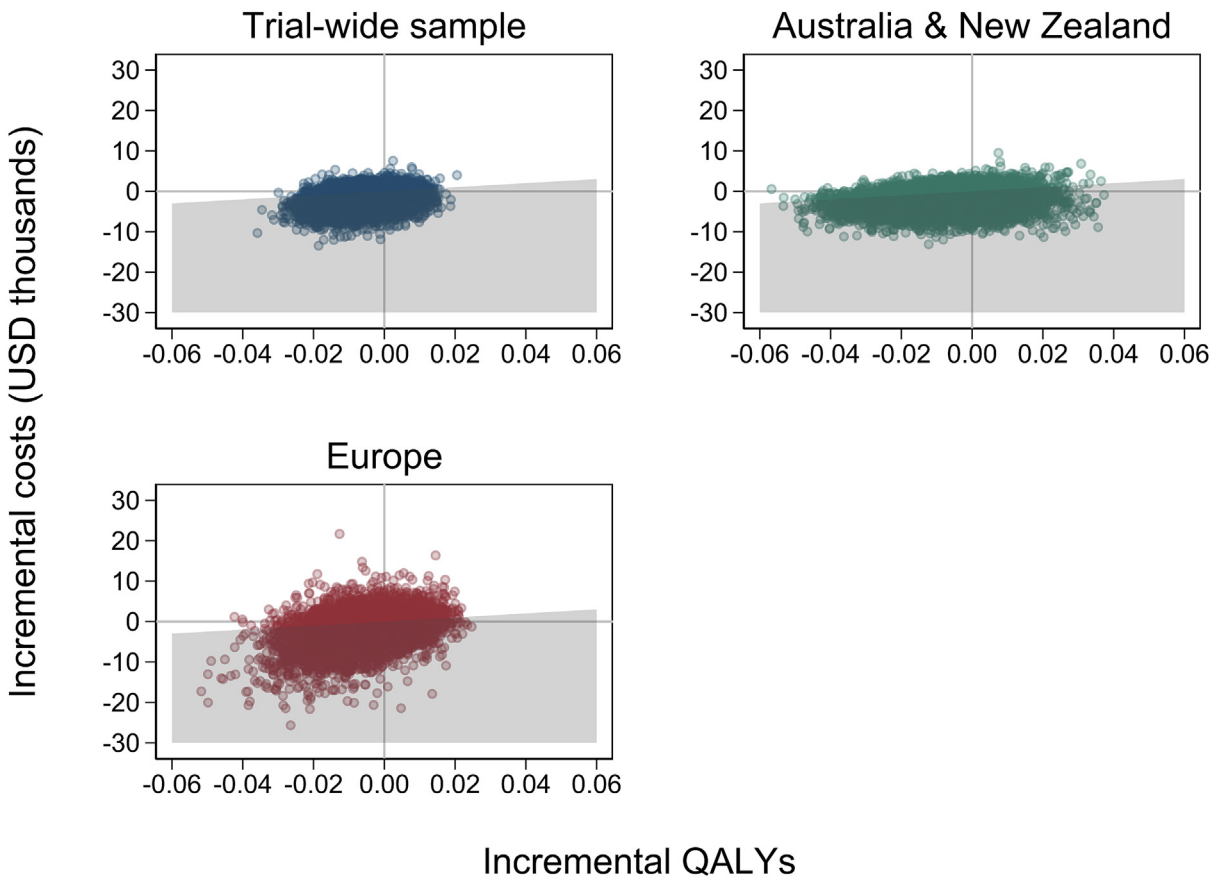

Fig. 1 – Cost-effectiveness planes for the trial-wide sample and two regional subsamples.
Abbreviations: QALYs – quality-adjusted life years; USD – United States dollars.
Note: The cost-effectiveness plane is based on 10,000 bootstrap replications (stratified by treatment group and hospital site). The y-axis presents the incremental costs of treatment compared to control, while the x-axis presents the incremental QALYs of treatment compared to control. The shaded region denotes bootstrap replications that are cost-effective at a willingness-to-pay threshold of US$50,000 per QALY.

willingness-to-pay thresholds). The cost-effectiveness acceptability curve for the trial-wide sample indicated that the probability of mild hypercapnia being cost-effective was greater than 60 %, even at a willingness-to-pay threshold of $200,000 per QALY (see Appendix S7). However, interpretation of these cost-effectiveness findings is limited by the absence of statistically significant differences in costs and outcomes. Similar results were observed for the two regional subsamples.

Sensitivity analysis

The results of the complete case analysis and the sensitivity analysis incorporating longer-term data from New Zealand are presented in Table 4. No substantive changes were observed between the results of the complete case analysis when compared to the base case analysis. By contrast, incorporating longer-term data at 24 months led to the cost-effectiveness of mild hypercapnia remaining highly uncertain, with 95 % confidence intervals around incremental costs and incremental QALYs continuing to include both positive and negative values. A widening of these confidence intervals was also observed due to a reduction in the sample size for this subgroup analysis.

Discussion

Summary of findings

This economic evaluation found that the probability that mild hypercapnia is a more cost-effective intervention than targeted normocapnia for patients following OHCA is >60 % across a range of willingness-to-pay thresholds. However, there is a high degree of uncertainty around these results. The costs and QALYs at 6 months were not significantly different between groups. The INMB similarly indicated that the cost-effectiveness of the mild hypercapnia intervention was highly uncertain at a willingness-to-pay threshold of $50,000 per QALY, with the 95 % CI including both negative and positive values. Sensitivity analyses incorporating follow up to 24 months also indicated high uncertainty around the cost-effectiveness of mild hypercapnia.

Comparison to previous research

There is no pre-existing data on the cost-effectiveness of mild hypercapnia for OHCA. A recent systematic review of the cost-effectiveness of interventions for the management of OHCA identified 46 economic evaluations, however the review focused on inter-

ventions in the pre-hospital setting. There are few economic evaluations of in-hospital interventions for OHCA. A systematic review of hospital-based extracorporeal cardiopulmonary resuscitation (E-CPR) for OHCA included four studies and concluded that E-CPR was cost-effective when compared to conventional CPR.[21] Conversely, a recent trial-based economic evaluation alongside the INCEPTION RCT found that hospital-based ECPR in refractory OHCA had a low probability of being cost-effective.[22] Previous economic evaluations of targeted temperature management (TTM) have found TTM to be a cost-effective intervention for OHCA;[23] though these evaluations were completed prior to the TTM2 trial which has subsequently shown that TTM does not lead to improved outcomes following OHCA.[24] In general, economic evaluations are constrained by the availability of high-quality evidence from RCTs and the availability of data on long-term outcomes such as quality of life.

Implications of findings

OHCA is associated with a significant societal and public health burden. As the number of patients suffering from OHCA increases, there is an urgent need to evaluate interventions which may provide value for money. This is particularly the case for interventions such as mild hypercapnia where the intervention can be easily implemented within existing systems. However, decisions need to be made about when to implement such interventions. While the primary outcome of the TAME trial found no difference in neurologic outcomes at 6 months between mild hypercapnia and targeted normocapnia, a rationale to implement mild hypercapnia for OHCA patients may still persist if mild hypercapnia can lead to lower costs while producing non-inferior outcomes. Nevertheless, no significant differences were detected between groups in either costs or outcomes, and the uncertainty in the results suggest that further research is needed to determine the clinical profile of patients and/or circumstances under which mild hypercapnia may be effective/cost-effective. Additional data on longer-term outcomes and the use of a lifetime time horizon may provide further evidence if trajectories in healthcare resource use and health outcomes were observed to diverge between treatment and control groups over time. However, the paucity of data on ongoing healthcare resource utilisation and longer-term quality of life outcomes limits the ability to conduct such an analysis.

Strengths and limitations

Our economic evaluation has several strengths. It is the first analysis of cost-effectiveness of mild hypercapnia for OHCA; and was a pre-specified evaluation alongside a large international, multicentre, high-quality, pragmatic randomised trial. We collected costs at an individual country level, and conducted regional subgroup analyses, providing information relevant to local policy-makers, a practice that has been recommended for multinational studies.[25] Quality of life was collected as an outcome allowing determination of QALYs at an individual patient level.

We acknowledge several limitations. The time horizon was short, being limited to 6 months. A sensitivity analysis with data from a subset of patients in New Zealand observed over a longer time horizon found that uncertainty around the probability of cost-effectiveness remained high; with widening confidence intervals due to the reduction in sample size for this subgroup analysis. Additional data on longer-term outcomes and healthcare resource utilisation was not available, but future research would benefit from collecting data over a longer time horizon if there is a long-term divergence in trajectories between patients receiving mild hypercapnia versus normocapnia. The TAME trial was powered for the primary outcome of favourable neurological outcome, and likely underpowered for the cost-effectiveness analysis. Further, our evaluation was conducted from a healthcare payer perspective, and the inclusion of costs incurred by patients and their carers may alter the assessment of cost-effectiveness.

Conclusion

This economic evaluation found that the cost-effectiveness of mild hypercapnia is highly uncertain when compared with normocapnia in adult patients following OHCA, with no significant differences in either costs or outcomes. Further research is required to determine the specific circumstances under which mild hypercapnia may provide value for money.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing inter-

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2025.110878.

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