

# **A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial**

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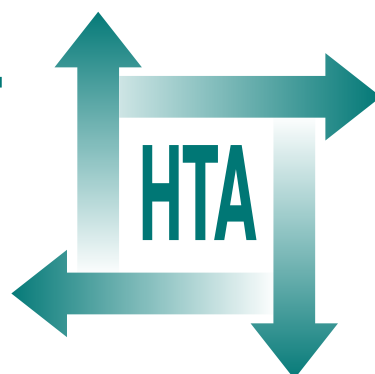
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## **Executive summary**

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## Executive summary

### Background

Non-invasive ventilation [continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV)] appears to be of benefit in the immediate treatment of patients with severe acute cardiogenic pulmonary oedema (patients with respiratory failure and distress) and may reduce mortality. Most published primary studies are small and patient populations, settings, severity of illness, interventions and outcomes vary considerably. None has been powered to detect a mortality difference as a primary outcome although meta-analyses suggest mortality benefit. Although there are mechanistic reasons for NIPPV to be superior to CPAP this has not been shown in the setting of a clinical trial.

### Objectives

We aimed to determine whether non-invasive ventilation reduces mortality and whether there are important differences in outcome by treatment modality (CPAP or NIPPV).

Specifically we aimed to assess:

- the clinical effectiveness of non-invasive ventilation (CPAP or NIPPV) in addition to standard therapy against standard therapy alone in the early management of severe acute cardiogenic pulmonary oedema
- whether there is any difference in the effectiveness of CPAP and NIPPV in the early management of acute cardiogenic pulmonary oedema
- the safety of these interventions
- quality of life and patient satisfaction after treatment with non-invasive ventilation compared with standard therapy alone
- the incremental cost-effectiveness of non-invasive ventilation versus standard therapy from a health and social care perspective, in terms of cost per quality-adjusted life-year gained.

### Design

In a multicentre open prospective randomised controlled trial, patients were randomised to one of three treatment arms: standard oxygen therapy, CPAP (5–15 cmH<sub>2</sub>O) or NIPPV (inspiratory pressure 8–20 cmH<sub>2</sub>O, expiratory pressure 4–10 cmH<sub>2</sub>O). The two primary end points were 7-day mortality, and 7-day mortality or intubation rate.

### Setting

Patients presenting with severe acute cardiogenic pulmonary oedema were recruited from 26 emergency departments in the UK.

### Participants

Inclusion criteria were age > 16 years, clinical diagnosis of acute cardiogenic pulmonary oedema, pulmonary oedema on chest radiograph, respiratory rate > 20 breaths per minute, and arterial hydrogen ion concentration > 45 nmol/l (pH < 7.35).

### Interventions

Eligible patients were consented and randomised using a telephone randomisation service to standard oxygen therapy, CPAP or NIPPV on a 1:1:1 basis. Other concomitant therapies were administered at the discretion of the treating clinician but the trial guideline advocated the use of nitrates. The interventions were for a minimum of 2 hours but the treating clinician was free to change the treatment if it was felt that it was clinically appropriate. Data collected included patient demographic, historical and physiological characteristics, intubation, mortality, diagnosis of myocardial infarction (MI), length of stay, critical care admission including length of stay, and patient symptoms measured by a dyspnoea scale. All

patients, if possible, were approached for repeat consent within 7 days of recruitment. The trial received multicentre research ethics committee approval (MREC/02/0/074) and was registered.

Repeat arterial blood gas analysis and Glasgow Coma Score were performed 1 hour after recruitment, and pulse, respiratory rate, oxygen saturation and non-invasive blood pressure were recorded at 1 and 2 hours. Patients completed a self-reported dyspnoea visual analogue scale [no breathlessness (0) to maximal breathlessness (10)] at recruitment and at 1 hour. A research nurse administered a patient satisfaction questionnaire within the following week. Patients were mailed a self-complete questionnaire at 1, 3 and 6 months after randomisation consisting of the EuroQol 5 dimensions (EQ-5D) health utility survey and a resource use questionnaire.

## Main outcome measures

The primary end point for the comparison between non-invasive ventilation (NIPPV or CPAP) and standard oxygen therapy was 7-day mortality. The primary end point for the comparison of NIPPV and CPAP was a composite end point of 7-day mortality and tracheal intubation rate. A priori secondary end points were breathlessness, physiological variables, intubation rate, length of hospital stay and critical care admission rate.

Myocardial infarction was defined according to the 1971 World Health Organization (WHO) and the European Society of Cardiology/American College of Cardiology criteria. Two cardiologists blinded to treatment allocation assigned the following categories: definite MI, probable MI, possible MI and no MI. Incident cases of MI were defined as the composite of definite and probable MI.

The economic evaluation took the form of a cost-utility analysis, taken from an NHS (and personal social services) perspective, with outcomes measured in the form of quality-adjusted life-years (QALYs). Resources used by individual patients within the trial were quantified using data from the data collection form, the hospital patient administrative system and the resource use questionnaire. These were combined with unit costs to produce a total cost for each patient. Patient-level costs were then combined with patient-level EQ-5D data to produce an incremental cost per QALY and a probability that each treatment group is cost-effective at current funding levels.

## Results

A total of 1069 patients [ $78 \pm 10$  years (mean  $\pm$  SD); 43% male] were recruited to standard oxygen therapy ( $n = 367$ ), CPAP [ $n = 346$ ;  $10 \pm 4$  cmH<sub>2</sub>O (mean  $\pm$  SD)] or NIPPV [ $n = 356$ ;  $14 \pm 5/7 \pm 2$  cmH<sub>2</sub>O (mean  $\pm$  SD)]. There was no difference in 7-day mortality for standard oxygen therapy (9.8%) and non-invasive ventilation (9.5%;  $p = 0.87$ ). The combined end point of 7-day death or intubation rate was similar, irrespective of non-invasive ventilation modality (11.7% versus 11.1% for CPAP versus NIPPV respectively;  $p = 0.81$ ). In comparison with standard oxygen therapy, non-invasive ventilation was associated with greater reductions (treatment difference, 95% confidence intervals) in breathlessness (visual analogue scale score 0.7, 0.2–1.3;  $p = 0.008$ ) and heart rate (4/min, 1–6;  $p = 0.004$ ) and improvement in acidosis (pH 0.03, 0.02–0.04;  $p < 0.001$ ) and hypercapnia (0.7 kPa, 0.4–0.9;  $p < 0.001$ ) at 1 hour. There were no treatment-related adverse events. There were no differences in other secondary outcomes such as MI rate, length of hospital stay, critical care admission rate and requirement for endotracheal intubation.

Economic evaluation showed that mean costs and QALYs up to 6 months were £3023 and 0.202 for standard therapy, £3224 and 0.213 for CPAP, and £3208 and 0.210 for NIPPV. Modelling of lifetime costs and QALYs produced values of £15,764 and 1.597 for standard therapy, £17,525 and 1.841 for CPAP, and £17,021 and 1.707 for NIPPV. These results suggest that both CPAP and NIPPV accrue more QALYs but at higher cost than standard therapy. However, these estimates are subject to substantial uncertainty.

## Conclusions

Non-invasive ventilatory support delivered by either CPAP or NIPPV safely provides earlier improvement and resolution of breathlessness, respiratory distress and metabolic abnormality. However, this does not translate into improved short- or longer-term survival. We recommend that non-invasive ventilation (CPAP or NIPPV) should be considered as adjunctive therapy in patients with severe acute cardiogenic pulmonary oedema in the presence of severe respiratory distress or when there is a failure to improve with pharmacological therapy.

Further research needs to address whether certain subgroups of patients may specifically benefit

from early application of non-invasive ventilation, for example patients with co-existent chronic obstructive pulmonary disease or particular underlying pathophysiological processes of pulmonary oedema (hypertensive heart failure).

### **Trial registration**

This trial is registered as ISRCTN07448447.

### **Publication**

Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al.*, on behalf of the 3CPO study investigators. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. *Health Technol Assess* 2009;**13**(33).



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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 01/43/01. The contractual start date was in June 2003. The draft report began editorial review in May 2008 and was accepted for publication in January 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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