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Clinical Investigation

CRITICAL CARE

Early noninvasive ventilation in general wards for acute respiratory failure: an international, multicentre, open-label, randomised trial

Giacomo Monti[1,2], Luca Cabrini[3,4], Yuki Kotani[1,2,5], Claudia Brusasco[6], Assiya Kadralinova[7,8], Giuseppe Giardina[1], Athanasios Chalkias[9,10], Cristina Nakhnoukh[1], Ioannis Pantazopoulos[11,12], Federico Mattia Oliva[1], Federico Dazzi[13], Agostino Roasio[14], Martina Baiardo Redaelli[1], Vincenzo Francesco Tripodi[15,16], Giada Cucciolini[13], Alessandro Belletti[1], Rosanna Vaschetto[17], Giulia Maj[18], Giovanni Borghi[1], Francesco Savelli[19], Silvia Boni[20], Filippo D'Amico[1], Sarah Cavallero[21], Rosa Labanca[1], Moreno Tresoldi[1], Marilena Marmiere[1], Matteo Marzaroli[1], Elena Moizo[1], Fabrizio Monaco[1], Pasquale Nardelli[1], Marina Pieri[1,2], Valentina Plumari[1], Anna Mara Scandroglio[1], Stefano Turi[1], Francesco Corradi[13], Aidos Konkayev[7,8], Giovanni Landoni[1,2,*], Rinaldo Bellomo[22,23], Alberto Zangrillo[1,2] for the NAVIGATE Study Group

[1]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy, [2]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy, [3]Department of Biotechnologies and Life Science, University of Insubria, Varese, Italy, [4]Azienda Ospedaliera Ospedale di Circolo e Fondazione Macchi di Varese, Varese, Italy, [5]Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Japan, [6]Anaesthesia and Intensive Care Unit, Galliera Hospital, Genoa, Italy, [7]Department of Anesthesiology and Intensive Care, Astana Medical University, Astana, Kazakhstan, [8]Department of Anesthesiology and Intensive Care, National Scientific Center of Traumatology and Orthopedics named after N. Batpenov, Astana, Kazakhstan, [9]Institute for Translational Medicine and Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, [10]OUTCOMES RESEARCH Consortium®, Houston, TX, USA, [11]Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Larisa, Greece, [12]Department of Emergency Medicine, Faculty of Medicine, University of Thessaly, Larisa, Greece, [13]Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy, [14]Department of Anesthesia and Intensive Care Medicine, Cardinal Massaia Hospital, Asti, Italy, [15]Cardiac Anesthesia and Intensive Care, Cardio-Thoraco-Vascular Department, 'Bianchi-Melacrino-Morelli' Hospital, Reggio Calabria, Italy, [16]Anesthesia and Intensive Care, Surgery Department, 'Gaetano Martino' University Hospital, Messina, Italy, [17]Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, Novara, Italy, [18]Department of Anesthesia and Intensive Care, Sant'Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy, [19]First Aid and Emergency Medicine, Ospedale 'degli Infermi' Di Faenza, Faenza, Italy, [20]Department of Infectious Disease, Galliera Hospital, Genoa, Italy, [21]Department of Orthopedic Surgery, Cardinal Massaia Hospital, Asti, Italy, [22]Department of Critical Care, The University of Melbourne, Melbourne, VIC, Australia and [23]Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia

*Corresponding author. E-mail: landoni.giovanni@hsr.it, @giovannilandoni; @SRAnesthesiaICU

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Abstract

Background: The impact of noninvasive ventilation (NIV) managed outside the intensive care unit in patients with early acute respiratory failure remains unclear. We aimed to determine whether adding early NIV prevents the progression to severe respiratory failure.

Methods: In this multinational, randomised, open-label controlled trial, adults with mild acute respiratory failure (arterial oxygen partial pressure/fraction of inspiratory oxygen [Pa_{O_2}/FiO_2] ratio ≥200) were enrolled across 11 hospitals in Italy, Greece, and Kazakhstan. Patients were randomised to receive early NIV or usual care. Patients in the early NIV group received 2-h cycles of NIV applied every 8 h for up to 12 days. The primary outcome was the progression to severe acute respiratory failure, defined by severe hypoxaemia, severe respiratory distress, or hypercapnic acidaemia during hospitalisation.

Results: Between May 6, 2012, and July 18, 2023, we randomised 524 patients (44.8% female; median age 73 yr, interquartile range [IQR] 63–83 yr). One patient withdrew consent. Progression to severe acute respiratory failure occurred in 49/265 (18.5%) patients randomised to early NIV, compared with 73/258 (28.3%) patients receiving usual care (relative risk 0.65, 95% confidence interval 0.48–0.90, P=0.0080). Median length of hospital stay was 10 (IQR 6–16) days in the early NIV group and 9 (IQR 5–16) days in the usual care group (P=0.30). Respiratory complications, 28-day mortality, and adverse events were not different between early NIV and usual care.

Conclusions: In patients with mild acute respiratory failure treated in nonintensive care wards, early NIV reduced the progression to severe acute respiratory failure.

Clinical trial registration: NCT01572337.

Keywords: continuous positive airway pressure; intensive care unit; intubation; noninvasive ventilation; respiratory insufficiency

Editor's key points

- The authors examined whether NIV in early respiratory failure (Pa_{O_2}/FiO_2 ratio ≥200) prevented the progression to severe respiratory failure in adult patients managed outside the intensive care unit.
- This multinational trial randomised patients to receive either 2-h cycles of NIV every 8 h for up to 12 days or usual care.
- The primary outcome was the progression to severe hypoxaemia, severe respiratory distress, or hypercapnic acidaemia during hospitalisation.
- Progression to severe acute respiratory failure occurred in 49/265 (18.5%) patients randomised to early NIV compared with 73/258 (28.3%) patients receiving usual care (relative risk 0.65, 95% confidence interval 0.48–0.90).
- Early NIV reduces the progression to severe acute respiratory failure in patients initially treated in nonintensive care wards.

Acute respiratory failure (ARF) is the most common cause of deterioration in hospitalised patients[1] and a frequent indication for intensive care unit (ICU) admission. The incidence of ARF is increasing in the UK.[2] The efficacy of NIV in preventing deterioration and progression to invasive ventilation in ARF patients has been demonstrated in specific forms of hypoxaemic or hypercapnic ARF.[3–8] NIV is now considered the first-line treatment for acute pulmonary oedema and chronic obstructive pulmonary disease (COPD) exacerbations by multiple international guidelines.[9] However, even for these conditions, most trials focused on severe ARF and on patients admitted to the ICU,[3–7] leaving its role in patients with mild ARF admitted to non-ICU wards unclear.

The early application of NIV at mild stages of ARF (e.g. arterial oxygen partial pressure/fraction of inspiratory oxygen [Pa_{O_2}/FiO_2] ratio ≥200) may prevent worsening of ARF through alveolar recruitment, by reducing the work of breathing,[10–12] maintaining upper airways patency, and improving left ventricular function.[13] In contrast, when applied late, its efficacy is diminished and NIV may delay intubation and increase mortality.[7,14] In this regard, if the required skills are available,[15] NIV for mild ARF can be delivered early outside the ICU.[16,17] Two small, single-centre randomised controlled trials (RCTs), excluding those involving COPD patients, reported improved oxygenation with NIV outside the ICU but yielded mixed results for patient-centred, clinically relevant outcomes.[18,19] The small sample size and single-centre design limit the generalisability of these findings.[18,19]

Accordingly, we performed a multicentre, international, RCT in patients in non-ICU wards with mild ARF. We tested the primary hypothesis that early NIV would decrease progression to severe ARF, defined as severe hypoxaemia, severe respiratory distress while on oxygen, or hypercapnic acidaemia.

Methods

Study design

The NAVIGATE trial was an international, multicentre, parallel-group, open-label RCT performed in 11 hospitals in three countries (Italy, Greece, and Kazakhstan). The ethics committee of each centre approved the trial protocol, which was published with the statistical analysis plan before trial conclusion.[20] The trial was registered at ClinicalTrials.gov (NCT01572337). The reporting was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT).[21] Written informed consent was obtained from all patients or their legal representatives before enrolment.

Inclusion criteria

Patients aged ≥18 yr with mild ARF admitted in non-ICU wards were eligible for the study. Mild ARF was defined by at least one of the following criteria: radiological evidence of new pulmonary consolidation or atelectasis; peripheral oxygen saturation <92% while breathing room air; arterial oxygen partial pressure/fraction of inspiratory oxygen (Pa_{O_2}/FiO_2) ratio <300 on arterial blood gas analysis; arterial carbon dioxide partial pressure (Pa_{CO_2}) >6 kPa (45 mm Hg) and pH <7.35; clinical signs of respiratory distress while on room air (i.e. dyspnoea, utilisation of accessory respiratory muscles, or paradox movements of thoracoabdominal wall).

Exclusion criteria

We excluded patients with respiratory failure resulting from acute exacerbation of COPD, severe hypoxaemia (Pa_{O_2}/FiO_2 ratio <200), hypercapnic acidaemia (Pa_{CO_2} >6 kPa [45 mm Hg] and pH <7.30), and immediate need for mechanical ventilation or ICU admission based on clinical judgement. Additional exclusion criteria are provided in Supplementary Table S1.

Randomisation

Patients were randomised in a 1:1 ratio either to receive early NIV or usual care. An independent epidemiologist provided a computer-generated randomisation list with a permuted-block design, stratified according to centre. Study personnel at each site enrolled patients and assigned them to the treatment group using a web-based computerised interactive response system. The assigned group was revealed only after filling in the required fields (sex and date of birth). The trial was overseen by a data and safety monitoring board.

Intervention

Following a previously described protocol for early NIV outside the ICU,[18] which we modified after conducting a pilot study,[22,23] patients assigned to the early NIV group received 2-h cycles of early NIV every 8 h in addition to usual care. During the intervals between the early NIV cycles, patients breathed room air or received oxygen via a low-flow nasal cannula or oral masks. The preferred early NIV treatment was continuous positive airway pressure (CPAP) with positive end-expiratory pressure of 5–8 cm H_2O, whereas biphasic positive airway pressure (BiPAP) was applied in patients with hypercapnia. High-flow nasal cannula was not considered as NIV, its use was not widespread in the study centres, and the few patients who received it were reported as protocol deviations. Ventilatory settings were adjusted according to clinical judgement to reach a target peripheral oxygen saturation >92% and Pa_{CO_2} <6 kPa (45 mm Hg). Early NIV treatment had to be continued for at least the first 24 h (2-h cycles of early NIV applied every 8 h) even in case of sudden improvement. The maximum length of early NIV treatment was 12 days (Supplementary Fig. S1). Discontinuation criteria are provided in Supplementary methods.

Both groups received low-flow oxygen therapy, diuretics, antibiotics, and other therapies as indicated to treat the underlying ARF cause. Patients in the usual care group only received NIV therapy if deemed clinically necessary and after reaching the primary endpoint.

Data collection

Data were collected by trained investigators and stored electronically. Evaluations were conducted three times a day (before each NIV cycle for patients in the early NIV group) on the first day of the study and then daily. Arterial blood gas analysis was performed at the discretion of the attending physician. We also collected data on ventilator settings together with any complications or contraindications to NIV. Telephone follow-ups were performed at 28 and 90 days after randomisation.

Primary outcome

The primary outcome was progression to severe respiratory failure during the index hospitalisation. Severe respiratory failure was defined by the presence of one or more of the following criteria: severe hypoxaemia (Pa_{O_2}/FiO_2 ratio <200), severe respiratory distress (persistent marked dyspnoea, use of accessory respiratory muscles, or paradoxical movements while on oxygen), or hypercapnic acidaemia (Pa_{CO_2} >6 kPa [45 mm Hg] and pH <7.30). We present the primary endpoint also through a bar plot depicting the worst respiratory outcome occurring to patients who developed the primary outcome: death for respiratory reasons, intubation for respiratory reasons, severe respiratory distress, and hypoxaemia (if a patient developed more than one respiratory outcome, only the most serious one was presented).

Prolonged NIV was defined as at least 12 h per day of NIV treatment and was administered after reaching the primary endpoint to patients who developed severe respiratory distress. The attending physician, in collaboration with the emergency medical team, determined whether to administer prolonged NIV as CPAP or BiPAP and whether to admit patients to the ICU or manage them in the general ward, based on the patient's condition, local protocols, and available resources.

Secondary outcomes

Prespecified secondary outcomes were all-cause mortality at day 28, length of hospital stay, and other respiratory complications (a composite of atelectasis, nosocomial pneumonia, new pneumothorax, pleural effusion, intubation for respiratory reasons, tracheostomy, and acute respiratory distress syndrome).

Statistical analysis

Analyses were performed by an independent statistician blinded to intervention allocation. We did not apply any imputation for missing data. Primary analyses were conducted on the intention-to-treat population. Primary and secondary outcomes were also analysed using per-protocol analysis, excluding participants who did not undergo the assigned treatment and those identified post randomisation as meeting the exclusion criteria. Categorical variables are presented as absolute numbers and percentages. Unadjusted univariate analysis (Pearson's χ^2 test or Fisher's exact test) was used to compare the two groups. Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR) and were examined using the Student's t-test or the Wilcoxon signed rank test, as appropriate. The Shapiro–Wilk normality test was used to assess normality. Treatment effect on the primary endpoint was estimated using a multivariable logistic regression model with forward

stepwise selection. Pre-randomisation clinical variables were added to the model if their univariate *P*-value was <0.2. We used the log-rank test for time-to-event analysis and displayed this comparison using Kaplan–Meier curves. Data were analysed using STATA (Stata Statistical Software, version 18, College Station, TX, USA).

Sample size estimation

We estimated that 22% of patients in the usual care group and 11% of patients in the early NIV group would meet the primary endpoint.[18,19] We calculated a sample size of 256 patients per group, assuming a two-sided alpha error of 0.05 and a power of 90% using Pearson's χ^2 test. Considering potential protocol deviations and loss to follow-up, we rounded the sample size to a total of 520 patients.

Sensitivity analyses

We investigated heterogeneity in treatment effects on the primary outcome in the following prespecified subgroups[20]: patients aged ≥ or <75 yr; patients with body mass index of ≤20, >20 and <30, or ≥30 kg m^{-2}; respiratory rate of ≥ or <25 per minute at baseline; and postoperative or nonsurgical patients.

Results

Study characteristics

From May 6, 2012, to July 18, 2023, a total of 1317 patients were assessed for eligibility, and 524 underwent randomisation (Fig. 1). As informed consent was withdrawn by one patient, 523 patients (265 patients in the early NIV group and 258 in the usual care group) were included in the intention-to-treat analysis. No patient was lost to follow-up for assessment of 90-day mortality. Baseline characteristics, including the main reason for ARF, FIO2 at randomisation, and respiratory rate, were similar between groups (Table 1).

Trial intervention

In early NIV patients, 238/265 (89.8%) received CPAP with a median positive end-expiratory pressure of 7 (IQR 5–8) cm H_2O and without additional pressure support (Table 2). Only 27/265 patients (10.2%) received BiPAP with median expiratory and inspiratory positive airway pressures of 5 (IQR 5–5)

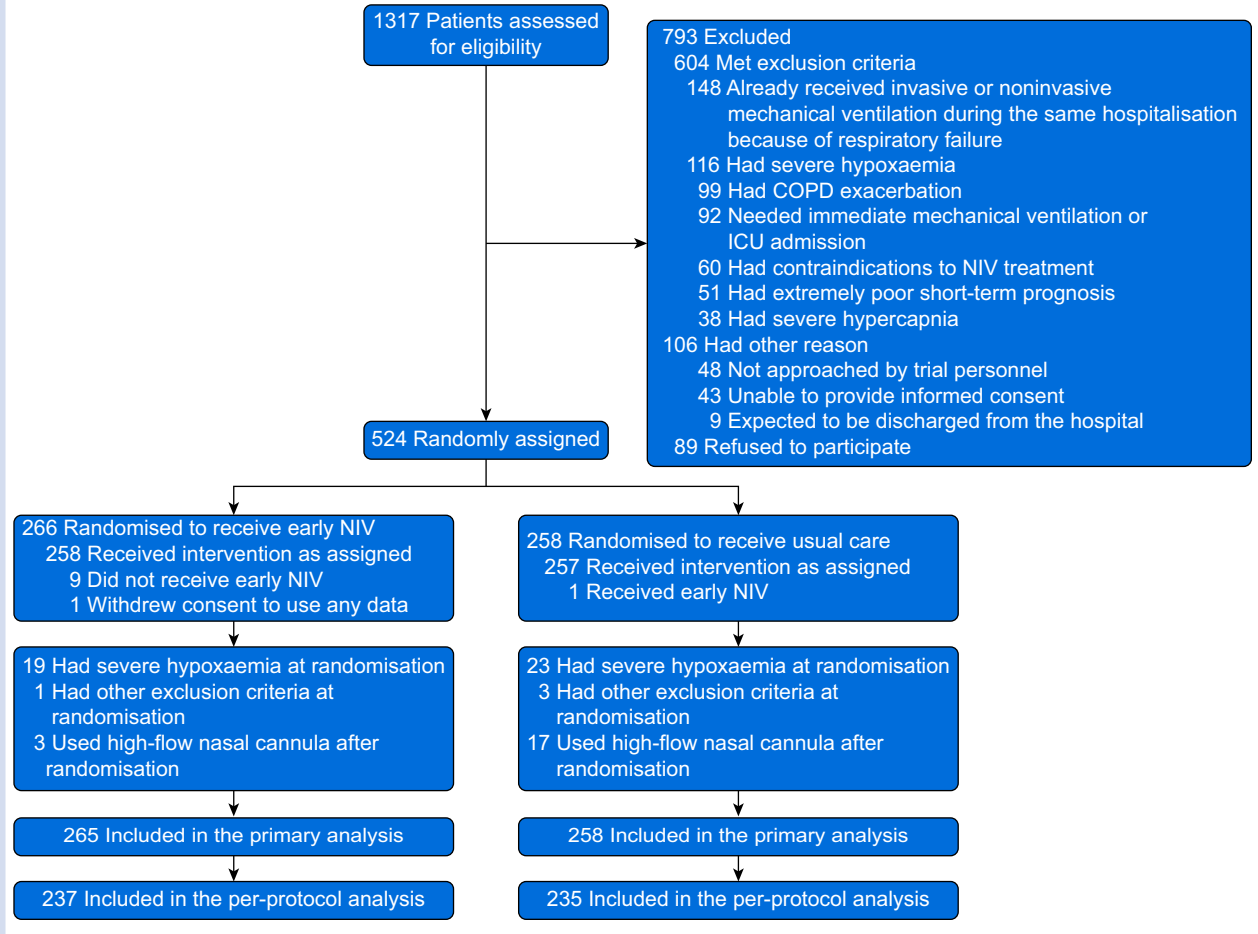

Fig 1. CONSORT flow diagram. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NIV, noninvasive ventilation.

Table 1 Participant characteristics. ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; FiO_2, fraction of inspired oxygen; IQR, interquartile range; NIV, noninvasive ventilation; Pao_2, arterial oxygenation partial pressure. *The body mass index is the weight in kilogrammes divided by the square of the height in metres. †The mild decompensated hypercapnia is defined as Pao_2 >6 kPa (45 mm Hg) and pH <7.35.

	Early NIV (*n*=265)	Usual care (*n*=258)
Sex, *n* (%)		
Male	145 (54.7)	143 (55.4)
Female	120 (45.3)	115 (44.6)
Age (yr), median (IQR)	74 (63–82)	73 (63–83)
Body mass index* (kg m^{-2}), median (IQR)	26 (23–29)	26 (24–29)
Ethnic origin, *n* (%)		
White	234 (90.0)	234 (93.2)
Hispanic or Latino	6 (2.3)	3 (1.2)
Black or African American	3 (1.2)	1 (0.4)
Asian	17 (6.5)	13 (5.2)
Comorbidities, *n* (%)		
COPD	52 (19.6)	42 (16.3)
Chronic heart failure	65 (24.5)	66 (25.6)
Malignancy	43 (16.2)	40 (15.5)
Chronic liver disease	11 (4.2)	9 (3.5)
Chronic immunosuppressive therapy	3 (1.1)	4 (1.6)
Main reason for ARF, *n* (%)		
Pneumonia	104 (39.2)	118 (45.7)
Postoperative respiratory failure	54 (20.4)	48 (18.6)
Cardiogenic pulmonary oedema	46 (17.4)	45 (17.4)
Other	61 (23.0)	47 (18.2)
COVID-19 as hospital admission diagnosis, *n* (%)	51 (19.2)	52 (20.2)
FiO_2 at randomisation, median (IQR)	0.30 (0.21–0.36)	0.28 (0.21–0.36)
On room air at randomisation, *n* (%)	74 (27.9)	86 (33.3)
Vital signs at randomisation		
Systolic blood pressure (mm Hg), median (IQR)	125 (110–140)	127 (115–140)
Diastolic blood pressure (mm Hg), median (IQR)	70 (62–80)	70 (65–80)
Median heart rate (beats min^{-1}), median (IQR)	81 (72–92)	83 (72–95)
Peripheral oxygen saturation (%), median (IQR)	92 (90–95)	92 (90–95)
Respiratory rate (breaths min^{-1}), median (IQR)	21 (18–25)	22 (18–24)
Glasgow Coma Scale, median (IQR)	15 (15–15)	15 (15–15)
Duration from hospital admission to randomisation (days), median (IQR)	3 (1–5)	2 (1–6)
Mild ARF criteria, *n* (%)		
Peripheral oxygen saturation <92% while breathing room air or Pao_2/FiO_2 ratio <300 on arterial blood gas analysis	256 (96.6)	244 (94.6)
Radiological evidence of new pulmonary consolidation or atelectasis	138 (52.1)	157 (60.9)
Signs of respiratory distress while breathing room air	80 (30.2)	76 (29.5)
Mild decompensated hypercapnia†	6 (2.3)	6 (2.3)

and 10 (IQR 10–15) cm H_2O, respectively. Patients received early NIV for 3 (IQR 2–5) days with 40/265 (15.1%) not tolerating or refusing to continue NIV (Table 2 and Supplementary Table S2). No patients developed pressure sores during early NIV.

Primary outcome

The primary outcome occurred in 49 patients (18.5%) in the early NIV group and 73 (28.3%) in the usual care group (relative risk 0.65, 95% confidence interval [CI], 0.48–0.90, *P*=0.008; Table 3). The benefit of early NIV was mainly driven by reducing severe respiratory distress (Table 3 and Fig. 2). Early NIV reduced the risk of developing severe respiratory failure (Fig. 3), compared with usual care (hazard ratio 0.64, 95% CI 0.44–0.91, *P*=0.014, by log-rank.

Secondary outcomes

No differences were found in length of hospital stay, 28-day mortality or other predefined respiratory complications including pleural effusions, atelectasis, and nosocomial pneumonia.

Post hoc exploratory outcomes

Prespecified *post hoc* subgroup and per-protocol analyses found results consistent with the primary analysis (Supplementary Figs S3–S5 and Table S3). After adjustment for relevant predictors on univariate and multivariable analysis, randomisation to the early NIV group was associated with a reduced risk of progression to severe ARF (odds ratio 0.56, 95% CI 0.36–0.86; Supplementary Tables S4 and S5). When patients reached the primary endpoint of severe respiratory distress, clinicians often decided to manage these patients with prolonged NIV (>12 h per day) outside the ICU (Table 3), resulting in similar intubation rates and mortality between groups (Table 3). There was also no difference in adverse events, including respiratory arrest, unstable haemodynamic status, and new pneumothorax (Supplementary Table S6). Additionally, we present a cumulative incidence function of the primary outcome combined with death (Supplementary Figure 6). No patients developed pressure sores during early NIV.

Table 2 Respiratory support by NIV. BiPAP, biphasic positive airway pressure; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure.

	Early NIV (n=265)	Usual care (n=258)	P-value
NIV modality, n (%)			
CPAP	238 (89.8)	–	–
PEEP (cm H_2O), median (IQR)	7 (5–8)	–	–
BiPAP	27 (10.2)	–	–
IPAP (cm H_2O), median (IQR)	10 (10–15)	–	–
EPAP (cm H_2O), median (IQR)	5 (5–5)	–	–
Interface type, n (%)		–	–
Oronasal mask	225 (84.9)	–	–
Helmet	36 (13.6)	–	–
Full face mask	4 (1.5)	–	–
Time from randomisation to protocol discontinuation (days), median (IQR)	3 (2–5)	4 (2–7)	0.034
High-flow nasal cannula, n (%)	3 (1.1)	17 (6.6)	0.001
Reasons for discontinuation of protocol, n (%)			
Clinical improvement	170 (64.2)	118 (45.7)	<0.001
Intolerance and refusal	40 (15.1)	–	–
Clinical deterioration	41 (15.5)	86 (33.3)	<0.001
Protocol discontinued because 12 days elapsed	5 (1.9)	25 (9.7)	<0.001
Hospital discharge	6 (2.3)	29 (11.2)	<0.001
Occurrence of contraindications to NIV	2 (0.8)	–	–
Only palliative treatments	1 (0.4)	–	–

Discussion

In this multicentre RCT of early NIV applied in nonintensive wards in patients with mild ARF, we found that, compared with usual care, early NIV reduced progression to severe ARF. The beneficial effect of early NIV on the primary outcome appeared consistent across prespecified subgroup analyses. Early NIV also reduced the occurrence of severe respiratory distress and hypoxaemia. There was no difference in respiratory arrest, unstable haemodynamic status, new pneumothorax, or mortality.

NIV provides respiratory support through multiple mechanisms[3] and leads to reduced ARF deterioration and decreased intubation rates.[3–7,24,25] Some experts recommended the application of NIV at an earlier stage of ARF,[4] and a meta-analysis showed greater success rates when NIV was used early in patients with ARF.[7] However, almost all relevant studies were performed in the ICU,[7] and in a recent international observational study, failure rates doubled when NIV was used in moderate to severe hypoxaemic ARF compared with mild ARF.[26] Thus, guidelines have not issued any recommendation for *de novo* ARF owing to limited evidence,[5] highlighting the need for focused investigation on non-ICU settings.

To our knowledge, outside of the management of COPD exacerbations, only two small RCTs compared NIV with standard oxygen therapy in early ARF in non-ICU settings. The first was performed in 40 haematological patients, and using a very similar NIV protocol to ours, it found that NIV improved oxygenation and reduced the risk of intubation and ICU admission.[18] The second was performed in 86 haematological patients and found that NIV improved oxygenation but that intubation rates and mortality were unaffected.[19] Our trial confirmed the improved oxygenation effect of NIV observed in both previous trials[18,19] and found a reduction in the development of severe respiratory distress, an important patient-centred outcome, without increasing adverse events and mortality. Unlike the previous two trials, which were limited by their small size and single-centre nature, our trial is the first international, multicentre trial with a larger sample size and more inclusive eligibility criteria, all of which increased the generalisability of this trial's findings.

In the present trial, early NIV decreased the progression to a severe stage of ARF in patients with mild ARF admitted to nonintensive wards. The result was driven mainly by a reduction in the rate of severe respiratory distress (persistent marked dyspnoea, use of accessory respiratory muscles, or paradoxical movements while on oxygen) and severe hypoxaemia. Moreover, early NIV did not increase other respiratory complications or any adverse events, including pneumothorax, vomiting, and excessive airway secretions, which was consistent with previous findings obtained in more severe populations.[27–29] These observations imply that early NIV can be delivered to such patients without increasing the risk of adverse events. Implementation of early NIV in non-ICU wards may offer a potentially affordable treatment, improving the management of patients with ARF. However, early NIV therapy did not improve other outcomes. A possible explanation might be an increased use of prolonged NIV in the control group. Although early prophylactic NIV prevented ARF worsening, prolonged NIV (implemented after progression to severe ARF) could have prevented further respiratory deterioration, leading to similar results in terms of intubation, mortality, and length of hospital stay between groups.

We acknowledge that our study has limitations, mostly resulting from the pragmatic approach of our trial, adopted to make our study closer to real-world conditions. We did not standardise patient monitoring, ward staff training, or ventilatory settings, including the choice of CPAP or BiPAP for the prolonged NIV treatment. In addition, the ICU admission

Table 3 Clinical outcomes. ARF, acute respiratory failure; CI, confidence interval; ICU, intensive care unit; NIV, noninvasive ventilation. *The hypercapnic acidaemia is defined as $Paco_2$ >6 kPa (45 mm Hg) and pH <7.30. †A composite endpoint comprising atelectasis, nosocomial pneumonia, new pneumothorax, pleural effusion, intubation for respiratory reasons, tracheostomy, and acute respiratory distress syndrome. ‡Prolonged NIV was defined as at least 12 h per day of NIV treatment resulting from severe respiratory distress (persistent marked dyspnoea, use of accessory respiratory muscles, or paradoxical movements), which occurred after reaching the primary endpoint. ¶Two patients in the early NIV group and three patients in the usual care group met the criteria for invasive mechanical ventilation but were not intubated for 'do not intubate' decision.

	Early NIV (*n*=265)	Usual care (*n*=258)	Relative risk (95% CI)	Difference (95% CI)	*P*-value
Primary outcome					
Development of severe ARF during hospitalisation, *n* (%)	49 (18.5)	73 (28.3)	0.65 (0.48–0.90)	Absolute, −9.8 (−17 to −2.6)	0.008
Components of the primary outcome (at the time of reaching the primary outcome)					
Severe hypoxaemia, *n* (%)	33 (12.5)	55 (21.3)	0.58 (0.39–0.87)	Absolute, −8.9 (−15 to −2.5)	0.007
Severe respiratory distress while on oxygen, *n* (%)	39 (14.7)	62 (24.0)	0.61 (0.43–0.88)	Absolute, −9.3 (−16 to 2.6)	0.007
Hypercapnic acidaemia*, *n* (%)	8 (3.0)	5 (1.9)	1.56 (0.52–4.70)	Absolute, 1.1 (−1.6 to 3.7)	0.58
Secondary outcomes					
Length of hospital stay (days), median (IQR)	10 (6–16)	9 (5–16)	–	Mean, 0.14 (−1.6 to 1.9)	0.30
All-cause mortality at day 28, *n* (%)	30 (11.3)	27 (10.5)	1.08 (0.66–1.77)	Absolute, 0.9 (−4.5 to 6.2)	0.75
Other respiratory complications†, *n* (%)	82 (31.1)	84 (32.6)	0.95 (0.74–1.23)	Absolute, −1.5 (−9.5 to 6.5)	0.71
Components of other respiratory complications, *n* (%)					
Pleural effusion	46 (17.4)	51 (19.8)	0.88 (0.62–1.26)	Absolute, −2.6 (−8.1 to 3.0)	0.49
Atelectasis	28 (10.6)	34 (13.2)	0.80 (0.50–1.29)	Absolute, −2.6 (−8.1 to 3.0)	0.36
Nosocomial pneumonia	18 (6.8)	15 (5.8)	1.17 (0.60–2.27)	Absolute, 1.0 (−3.2 to 5.1)	0.65
Intubation for respiratory reasons	13 (4.9)	11 (4.3)	1.15 (0.53–2.52)	Absolute, 0.6 (−2.9 to 4.2)	0.73
Acute respiratory distress syndrome	8 (3.0)	3 (1.2)	2.60 (0.70–9.68)	Absolute, 1.9 (−0.6 to 4.3)	0.22
New pneumothorax	2 (0.8)	4 (1.6)	0.49 (0.09–2.64)	Absolute, −0.8 (−2.6 to 1.0)	0.45
Tracheostomy	4 (1.5)	1 (0.4)	3.91 (0.44–34.74)	Absolute, 1.1 (−0.5 to 2.8)	0.37
Post hoc exploratory outcomes					
Treatment with prolonged NIV‡, *n* (%)	30 (11.3)	60 (23.3)	0.49 (0.33–0.73)	Absolute, −12 (−18 to −5.5)	<0.001
Treatment with invasive mechanical ventilation¶, *n* (%)	18 (6.8)	16 (6.2)	1.10 (0.57–2.10)	Absolute, 0.6 (−3.6 to 4.8)	0.78
ICU admission, *n* (%)	22 (8.3)	18 (7.0)	1.19 (0.65–2.17)	Absolute, 1.3 (−3.2 to 5.9)	0.57
In-hospital all-cause mortality, *n* (%)	24 (9.1)	25 (9.7)	0.93 (0.55–1.59)	Absolute, −0.6 (−5.6 to 4.4)	0.80
All-cause mortality at day 90, *n* (%)	41 (15.5)	40 (15.5)	1.00 (0.67–1.49)	Absolute, 0.0 (−6.2 to 6.2)	0.99
Length of hospital stay among survivors at hospital discharge (days), median (IQR)	9 (6–16)	8 (5–15)	–	Mean, 0.10 (−1.6 to 1.8)	0.29

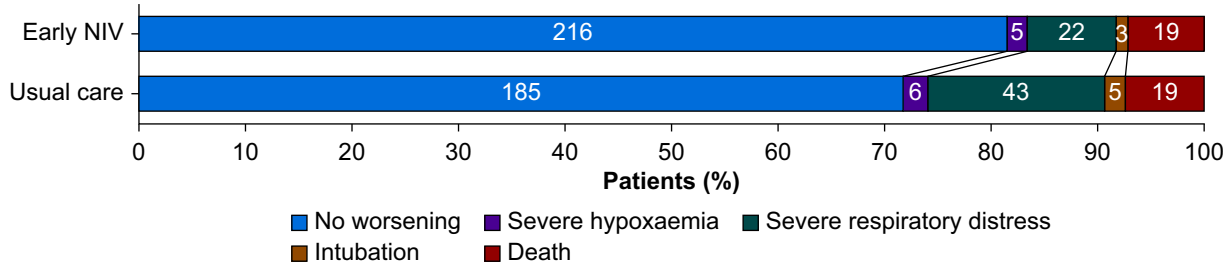

Fig 2. Bar plot with a visual representation of the distribution of all the respiratory patient-centred outcomes contributing to the primary outcome: death for respiratory reasons, intubation for respiratory reasons, severe respiratory distress, and hypoxaemia. If a patient developed more than one respiratory outcome, only the most serious one was indicated. NIV, noninvasive ventilation.

criteria were left to each participating centre. We included heterogeneous forms of ARF so that different effects of NIV among different types of ARF could not be fully explored. We also could not collect data on the time lapse between mild ARF development and trial enrolment. This may have differed between study years, hospitals, and days of the week and influenced the primary outcome. Even if one of the three components of severe ARF (severe respiratory distress) might

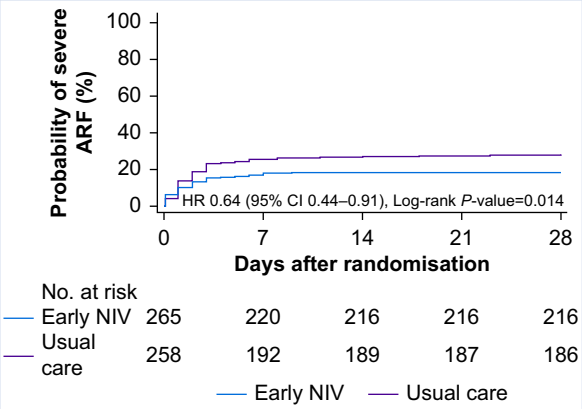

Fig 3. Cumulative incidence of the primary outcome: severe respiratory failure. ARF, acute respiratory failure; CI, confidence interval; HR, hazard ratio; NIV, noninvasive ventilation.

be associated with bias in an unblinded study, it was accompanied by objective measurements (severe hypoxaemia or hypercapnic acidaemia) and followed by therapeutic strategies (prolonged NIV) administered by a physician not involved in the protocol. Given the potential subjectivity of severe respiratory distress assessment, establishment of consensus criteria will help evaluate this important endpoint in future trials. It might be argued that using NIV on general wards requires additional resources and training, but the opposite is also true, as we found a decrease in prolonged NIV use in the early NIV group. The COVID-19 pandemic occurred during the study. Although patients with pneumonia in general seem less responsive to NIV,[3,4,22] it is still debated if those with COVID-19 benefit from NIV in terms of reduced tracheal intubation and mortality.[30–33] However, the inclusion of COVID-19 patients in this trial may have inflated the benefits of NIV. Patient recruitment lasted for 11 yr, even if most patients were recruited in the last 6 yr, introducing the potential for impact of change in usual care over time, particularly for high-flow nasal oxygen and awake prone positioning. Finally, we found no significant differences in most secondary outcomes. However, these results should be interpreted cautiously, as the study was powered only for the primary outcome.

In conclusion, the NAVIGATE trial shows that the application of early NIV to patients with mild ARF in non-ICU wards reduced the progression of ARF to more severe stages without increasing the occurrence of respiratory arrests, unstable haemodynamic status, new pneumothorax, or mortality. These findings support the consideration of early NIV in selected patients in non-ICU wards.

Authors' contributions

Contributed to study conception or design and have directly assessed and verified the data reported in the manuscript: LC, GM, GL, AZ, CB, AK, AR, RV, FC, MT, RB, AC
Contributed to data acquisition, analysis, or interpretation: YK, AK, GG, CN, IP, FMO, FD, MBR, VFT, GC, AB, GM, GB, FS, SB, FD, SC, RL, MM, MM, EM, FM, PN, MP, VP, MS, ST
Drafted and critically revised the manuscript: all authors
Reviewed and approved the final version of the manuscript: all authors

Declaration of interest

All authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.11.023.

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Appendix 1.

Non-author collaborators

Silvia Ajello[1], Maria Grazia Calabrò[1], Sergio Colombo[1], Martina Crivellari[1], Ambra Licia Di Prima[1], Annalisa Franco[1], Stefano Fresilli[1], Carola Galbiati[1], Luigi Olper[1], Alessandro Oriani[1], Alessandro Ortalda[1], Gloria Panozzo[1], Domenico Pontillo[1], Alessandro Pruna[1], Erica Ronca[1], Greta Sabato[1], Rosario Losiggio[1], Simone Vietri[1], Alessandro Marinosci[1], Giuseppe Alvise Ramirez[1], Filippo Consolo[1], Tommaso Scquizzato[1], Mariachiara Antonini[1], Paola Rienzo[1], Umberto Benedetto[2], Marco Gemma[3], Katia Donadello[4, 5], Andrea Parisini[6], Roberta Pienovi[7], Elisa Corsino[7], Federica Gandolfo[8], Maria, Lidia Bologna[9], Virginia Brizzi[9], Alessandro Isirdi[9], Stefano Bosso[10], Aigerim Yeltayeva[11, 12, 13], Gaziza Abdirakhym[11], Nazerke Zhanarystan[11], Athanasios Pagonis[13], Konstantinos Tourlakopoulos[13], Georgios Mavrovounis[13], Gaia Furlan[14], Matteo Filippini[15], Gabriele Farina[16], Mariacristina Vadalà[17, 18], Valery Likhvantsev[19], Daria Yavorovskaya[20], Federica Ferrod[21], Porta Sabrina[21], Gianluca Paternoster[22], Tiziana Bove[23, 24], Nikola Bradić[25, 26] and Federico Longhini[27]

Department(s) and institution(s)

[1]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
[2]Department of Cardiac Surgery, University of G. d'Annunzio Chieti and Pescara, Chieti, Italy
[3]Department of Neuro Anesthesia and Intensive Care, Istituto Neurologico Carlo Besta Fondazione IRCCS, Milan, Italy
[4]Department of Surgery, Dentistry, Gynecology and Pediatrics, University of Verona, Verona Italy
[5]Anaesthesia and Intensive Care B, AOUI—University Hospital Integrated Trust of Verona, Verona, Italy
[6]Department of Infectious Disease,
[7]Anesthesia and Intensive Care Unit, and
[8]Department of Geriatric Care, Orthogeriatrics and Rehabilitation, Galliera Hospital, Genoa, Italy
[9]Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy
[10]Department of Anesthesia and Intensive Care Medicine, Cardinal Massaia Hospital, Asti, Italy
[11]Department of Anesthesiology and Intensive Care, Astana Medical University, Astana, Kazakhstan
[12]Department of Anesthesiology and Intensive Care, National Scientific Center of Traumatology and Orthopedics named after N. Batpenov, Astana, Kazakhstan
[13]Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Larisa, Greece

[14]Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, Novara, Italy
[15]Department of Anesthesia and Critical Care Medicine, Spedali Civili, Brescia, Italy
[16]First aid and Emergency Medicine, Ospedale 'degli Infermi' Di Faenza, Faenza, Italy
[17]Cardiac Anesthesia and Intensive Care, Cardio-Thoraco-Vascular Department, 'Bianchi-Melacrino-Morelli' Hospital, Reggio Calabria, Italy
[18]Anesthesia and Intensive Care, Surgery Department, 'Gaetano Martino' University Hospital, Messina, Italy
[19]V. Negovsky Reanimatology Research Institute, Moscow, Russia
[20]I.M. Sechenov First Moscow State Medical University, Ministry of Public Health of Russia, Moscow, Russia
[21]S.C. Anestesia e Rianimazione Cardiovascolare, A.O. Ordine Mauriziano Umberto I di Torino, Turin, Italy
[22]Cardiovascular Anesthesia and ICU, San Carlo Hospital, Potenza, Italy
[23]Department of Anesthesia and Intensive Care Medicine, ASUFC University Hospital of Udine, Udine, Italy
[24]Department of Medicine (DAME), University of Udine, Udine, Italy
[25]Clinical Department of Anesthesiology, Resuscitation and Intensive Medicine, University Hospital Dubrava, Zagreb, Croatia
[26]University North, Varazdin, Croatia
[27]Department of Nursing, University North, Varazdin, Croatia

Handling Editor: Gareth Ackland