Effect of intravenous almitrine on intubation or mortality in patients with COVID-19 acute hypoxemic respiratory failure: A multicentre, randomised, double-blind, placebo-controlled trial

Pierre Kalfon,[a] Jean-François Payen,[b] Alexandra Rousseau,[c] Benjamin Chousterman,[d] Marine Cachanado,[c] Annick Tibi,[e] Juliette Audibert,[a] François Depret,[f] Jean-Michel Constantin,[g] Emmanuel Weiss,[h] Francis Remerand,[i] Yonathan Freund,[j] Tabassome Simon,[c,k] and Bruno Riou[j]*

[a]Service de Réanimation polyvalente, Hôpital Louis Pasteur, Centre Hospitalier de Chartres, Le Coudray, France
[b]Department of Anesthesiology and Intensive Care, Grenoble Alpes University Hospital, and Grenoble Alpes University, Grenoble Institut des Neurosciences, INSERM U1216, Grenoble, France
[c]Department of Clinical Pharmacology and Clinical Research Platform (URC-CRC-CRB), Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Saint Antoine, Paris, France
[d]Université Paris Cité, INSERM UMR 942, and AP-HP, Department of Anesthesiology and Critical Care, Groupe Hospitalier Saint-Louis-Lariboisière, Paris, France
[e]Université Paris Cité, and AP-HP, Agence Générale des Équipements et Produits de Santé, Département Essais Cliniques, Paris, France
[f]Université Paris Cité, and AP-HP, service d'Anesthésie-Réanimation-Centre de traitement des brûlés, Hôpital Saint Louis, Paris, France
[g]Sorbonne Université, GRC 29, and AP-HP, Department of Anesthesiology and Critical Care, Hôpital Pitié-Salpêtrière, Paris, France
[h]Université Paris Cité, and AP-HP, Department of Anesthesiology and Critical Care, Hôpital Beaujon, Paris, France
[i]Université de Tours and CHRU de Tours, Department of Anesthesiology and Critical Care, Hôpital Trousseau, Tours, France
[j]Sorbonne Université, INSERM UMRS 1166, IHU ICAN, and AP-HP, Department of Emergency Medicine, Hôpital Pitié-Salpêtrière, Paris, France
[k]Sorbonne Université, France

eClinicalMedicine 2022;52: 101663
Published online 21 September 2022
https://doi.org/10.1016/j.eclinm.2022.101663

Summary

Background Severe hypoxemia in patients with COVID-19 pneumonia might result from hypoxic pulmonary vasoconstriction, contributing to ventilation/perfusion (V/Q) mismatch. Because almitrine improves V/Q, it might reduce the risk for mechanical ventilation (MV) in such patients. Our primary objective was to determine the effect of almitrine on the need for MV at day 7.

Methods In a randomised double-blind placebo-controlled trial involving 15 ICUs, patients hospitalized for COVID-19 pneumonia and experiencing acute hypoxemic respiratory failure were randomly assigned to receive 5 days of intravenous low-dose (2 $\mu g.kg^{-1}.min^{-1}$) almitrine or placebo. The primary outcome was endotracheal intubation for MV or death within 7 days after randomisation. Secondary outcomes included in-hospital mortality, 28-day mortality, number of ventilator-free days, number of days in the ICU and the hospital, and treatment discontinuation for pre-specified adverse effects. This trial was registered with ClinicalTrials.gov, NCT04357457.

Findings Between September 3, 2020 and September 25, 2021 181 patients were enrolled and randomly assigned to almitrine (n=89) or placebo (n=92). 179 patients (excluding two who withdrew from the study) were included in the intention-to-treat analysis (mean age: 60·1 years; 34% women) and analyzed. On day 7, the primary endpoint occurred in 32 patients assigned to almitrine (36%) and in 37 patients assigned to placebo (41%), for a difference of −4·3% (95% confidence interval: −18·7% to 10·2%). Secondary outcomes (28-day mortality, in-hospital mortality, ventilator-free days at day 28, days in the ICU and the hospital, and treatment discontinuation for pre-specified adverse effects) did not differ between the two groups.

*Corresponding author at: Réanimation polyvalente, Centre Hospitalier de Chartres, 28018 Chartres Cedex, France.
E-mail addresses: pierrekalfon@sfr.fr, pierrekalfon@sfr.fr (P. Kalfon).

Interpretation In patients with COVID-19 acute hypoxemic respiratory failure, low-dose almitrine failed in reducing the need for MV or death at day 7.

Funding Programme Hospitalier de Recherche Clinique (PHRC COVID 2020) funded by the French Ministry of Health, Les Laboratoires Servier (Suresnes, France) providing the study drug free of charge.

Keywords: COVID-19; ARDS; Almitrine; Pneumonia; Hypoxemia

Research in context

Evidence before this study

Severe COVID-19 pneumonia can lead to acute respiratory distress syndrome (ARDS), partly a result of vascular dysfunction, thrombosis, and dysregulated inflammation. This vascular disease process alters hypoxic pulmonary vasoconstriction, contributing to ventilation/perfusion mismatch. Using a drug that enhances hypoxic pulmonary vasoconstriction to improve the ventilation/perfusion ratio might slow the worsening of hypoxemia, thus avoiding the use of mechanical ventilation and potentially reducing the number of days in the ICU and mortality.

Low dose (2 $\mu g.kg^{-1}.min^{-1}$) of almitrine has been shown to reduce intrapulmonary shunt by enhancing hypoxic pulmonary vasoconstriction in patients with ARDS with no or a slight increase in mean pulmonary arterial pressure (MPAP)). Pilot studies have also reported that almitrine improves oxygenation in mechanically ventilated patients with COVID-19 −related ARDS. We did not identify any randomised controlled trial designed to determine whether almitrine reduces the combined incidence of intubation for mechanical ventilation (MV) or death in patients with severe COVID-19-related ARDS.

Added value of this study

In this multicentre, randomised, double-blind, placebo-controlled trial, intravenous low-dose almitrine did not reduce endotracheal intubation for MV or death in patients with COVID-19 pneumonia experiencing acute hypoxemic respiratory failure. Adverse effects were mild, infrequent, and occurred at similar rates between almitrine and placebo groups.

Implications of all the available evidence

Intravenous low-dose almitrine administration does not reduce the risk of treatment failure in patients with COVID-19 pneumonia experiencing acute hypoxemic respiratory failure. Our findings do not support routine administration of intravenous low-dose almitrine in those patients.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic greatly affected public health in many countries.[1] Although the more recent variants appear to have a reduced risk of intensive care unit (ICU) admission,[2] their increased contagiousness and immune escape through reduced vaccine efficacy might still cause ICU bed shortages that can lead to additional mortality.[3]

Severe COVID-19 pneumonia can lead to acute respiratory distress syndrome (ARDS), partly a result of vascular dysfunction, thrombosis, and dysregulated inflammation.[4] Patients with ARDS might require endotracheal intubation for mechanical ventilation (MV), which is associated with a high mortality rate.[5] The contrast between profound hypoxemia at an early disease stage and relatively preserved pulmonary compliance has suggested that vascular mechanisms at least partly underlie COVID-19-related ARDS.[4,6] This vascular disease process alters hypoxic pulmonary vasoconstriction, contributing to ventilation/perfusion (V/Q) mismatch.[7] Using a drug that reinforces hypoxic pulmonary vasoconstriction to improve the (V/Q) ratio might slow the worsening of hypoxemia, thus avoiding the use of MV and potentially reducing the number of days in the ICU and mortality.

Almitrine has been shown to reduce intrapulmonary shunt by enhancing hypoxic pulmonary vasoconstriction in patients with ARDS.[8–11] Low dose (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) almitrine improved oxygenation with no or a slight increase in mean pulmonary arterial pressure.[11] Pilot studies have also reported that almitrine improves oxygenation in mechanically ventilated patients with COVID-19-related ARDS.[12–17] Treatment with almitrine for up to 5 days in atypical pneumonia entailing ARDS has been reported without adverse effects.[18]

We thus assessed the efficacy of 5-day low-dose (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) intravenous almitrine in avoiding MV or death on day 7 in patients with COVID-19 pneumonia experiencing acute hypoxemic respiratory failure.

Methods

Study design and patients

This study was a randomised, double-blind, placebo-controlled, multicentre trial involving 15 ICUs between

September 2020 and September 2021. It was approved by the Comité de Protection des Personnes Ile-de-France VIII (Boulogne-Billancourt, France) and the French competent authority (Agence Nationale de Sécurité du Médicament et des produits de santé, Saint Denis, France). The French Ministry of Health funded the trial, and Les Laboratoires Servier (Suresnes, France) provided almitrine. Assistance Publique-Hôpitaux de Paris was the sponsor. Study reporting followed the CONSORT statement.[19] An independent data safety monitoring committee provided trial oversight. The trial protocol and statistical analysis plan are available in Appendix 1, and Appendix 2, respectively.

Adult patients aged 80 years or less experiencing acute hypoxemic respiratory failure and COVID-19 pneumonia admitted into the participating ICUs were screened for inclusion. All the patients had been diagnosed with COVID-19 within the 14 days before hospital admission, either by positive real-time polymerase chain reaction testing for SARS-CoV-2, COVID-19–compatible or typical chest computed tomography (CT) pattern, or positive serology for COVID-19 antibodies. Acute hypoxemic respiratory failure was defined as an oxygen saturation of 92% or less under oxygen therapy (flow rate: ≥6 L/min). Exclusion criteria were hypersensitivity to almitrine or any of its excipients; current pregnancy or breastfeeding; known hepatic failure (prothrombin time <50%, factor V <50%), last known plasma total bilirubin >21 µmol/L, blood lactate >4 mmol/L, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) exceeding 3 times the upper limit of normal, pulmonary hypertension or right ventricular dysfunction, history of pulmonary embolism, current diagnosis of pulmonary embolism or ongoing anticoagulant therapy at a curative dose for thromboembolism when hospitalized, $PaCO_2$ >45 mmHg, exacerbation of asthma or chronic respiratory failure, cardiogenic pulmonary edema, systolic arterial blood pressure ≤90 mmHg; or use of vasopressors, urgent need for endotracheal intubation at the discretion of the treating physician, do-not-intubate order or estimated life expectancy <6 months, and participation in another interventional research trial. Cardiac echocardiography was performed before inclusion to rule out pulmonary hypertension (systolic pulmonary arterial pressure ≥37 mmHg and/or maximum tricuspid regurgitation velocity (V_{max}IT) ≥2.9 m/s) and right ventricular dysfunction. Chest CT angiography on the day of randomisation was not required to rule out pulmonary embolism but was performed at the discretion of the treating physician either for suspected pulmonary embolism or for assessing or reassessing the extent of COVID-19-related lung lesions. A blood gas analysis within the 4 hours before inclusion was mandatory to confirm the absence of exclusion criteria with respect to lactate and $PaCO_2$.

Each patient provided written informed consent before inclusion. If the patient could not consent, informed agreement was sought from the next of kin. If no surrogate was available, emergency inclusion was authorized and the patient's informed consent was obtained as soon as his/her clinical state allowed it. The study was conducted in accordance with Good Clinical Practice guidelines, French regulations, and the Declaration of Helsinki.

Randomisation and masking

Patients were screened either in the emergency department or in the medical ward or after admission into the ICU. A blood gas analysis within 4 hours prior to inclusion were mandatory to confirm the absence of non-inclusion criteria with respect to lactate level and $PaCO_2$. Patients who met all criteria for enrolment were randomly assigned (1:1) by the study investigator to receive low-dose intravenous almitrine (almitrine group) or placebo (placebo group). Inclusion and randomization were concomitant and facilitated by a computer-generated random sequence using an interactive web-response system (CleanWeb: Telemedecine Technologies SAS, Boulogne-Billancourt, France). Centralized blocked balanced randomisation with blocks of varying size (range: 4–8; 1:1 ratio) was used and patients were stratified by hospital site. Patients, study staff, and investigators, and all the treating physicians and nurses were masked to the study group assignment.

Procedures

The study treatment was given within 4 hours after randomisation in addition to standard and supportive therapy (increase in oxygen delivery and, if necessary, respiratory support based on high-flow nasal oxygen to achieve an SpO_2 greater than 92%) were initiated without delay before study inclusion. The almitrine bismesylate (Vectarion Injectable®: Les Laboratoires Servier, Suresnes, France), provided by the manufacturer, or placebo was administered by electronic syringe pump set to the hourly rate corresponding to a dose of µg. $kg^{-1} \cdot min^{-1}$ over a planned period of 5 days. A multilumen central venous catheter (or at least a dedicated peripheral venous access) was encouraged for the administration of the study treatment to avoid precipitation related to drug interactions or almitrine-induced venous intolerance that might unintentionally break the blinding. For patients assigned to almitrine, each vial (15 mg) was reconstituted with a vial of solvent (5 mL) and then diluted with 5% glucose to a target concentration of 2 mg/mL in a 60 mL syringe. For patients assigned to placebo, a 60 mL syringe containing only 5% glucose was prepared. To maintain blinding, unrecognizable study medications were prepared in the hospital pharmacy.

Study outcomes

The primary outcome was endotracheal intubation for MV or death within 7 days after randomisation. To

ensure the consistency of indications across sites and to reduce the risk of delayed intubation, the following pre-specified criteria for endotracheal intubation were used: hemodynamic instability (systolic arterial blood pressure <90 mmHg, or mean arterial blood pressure <65 mmHg, or requirement for vasopressors), deterioration in neurologic status (Glasgow coma scale score < 12), or signs of persistent or worsening respiratory failure (at least two signs of high respiratory-muscle workload, development of copious tracheal secretions, acidosis [pH < 7·35], SpO_2 at rest <90% for more than 5 min under reservoir mask with a flow rate of at least 10 L/min, or a poor response or intolerance to other oxygenation techniques [high-flow nasal oxygen, or continuous positive airway pressure or noninvasive ventilation] allowed during the study at the discretion of the treating physician).

Pre-specified secondary outcomes included in-hospital death, death within 28 days, ventilator-free days during the first 28 days, days in the ICU to day 28, days in hospital to day 28, severe adverse events, and discontinuation of study treatment for pre-specified causes (blood lactate > 4 mmol/L, SGOT or SGPT exceeding three times the upper limit of normal, pulmonary hypertension, acute *cor pulmonale*, or pulmonary embolism). Post-hoc secondary outcomes were change in the sequential organ failure assessment (SOFA) score at days 3 and 7 compared with the score at inclusion, and change in the respiratory component of the SOFA score at days 3 and 7 compared with the score at inclusion.[20,21]

Statistical analysis

The primary outcome was assumed to occur in 50% of patients in the placebo group, acknowledging a high level of uncertainty given the unprecedented nature of COVID-19. The trial was designed to test the superiority of almitrine over placebo based on an assumed rate of 30% in the almitrine group, with 84% power and a 5% 2-sided type 1 error rate. Given 10% non-evaluable patients, two futility analyses using non-binding O'Brien–Fleming boundaries, and sample size reassessment after enrollment of 25% and 50% of patients, the required sample size was 212.

Categorical variables are expressed as frequencies with percentages, and quantitative variables, as means with standard deviation (SD) or medians with interquartile range (IQR), depending on distribution. Distributions were assessed graphically using histograms. Proportions in the groups were compared using the Pearson chi-squared test. Effect sizes and their 95% confidence intervals (CIs) were calculated using the exact Clopper–Pearson method.

Ventilator-free days, days in the ICU, and days in hospital were calculated from randomisation to day 28. Median differences between the groups and their 95% CIs were calculated using the Brookmeyer–Crowley method. Comparisons between groups were performed using the Wilcoxon rank sum test. If a patient died before day 28, ventilator-free or ICU-free days at day 28 were imputed as 0. If the patient had several distinct periods of MV, the MV days during each period were summed. Survival at days 7 and 28 were estimated using the Kaplan–Meier method, and the Greenwood formula for variance was used to calculate the 2-sided 95% CIs. Time to death was calculated starting at randomisation. All patients were censored at the last observation or at day 28. A log-rank test was used to compare survival between the groups.

Due to the design of the study (primary outcome assessed at day 7 in hospitalized patients), few missing data for the primary endpoint were expected. Thus, a single imputation was planned and performed to analyze the full data set. Missing data for the primary outcome in both groups were replaced with the worst possible outcome as proposed by the European Medicines Agency[1], so as not to favour one group over the other. Therefore, missing data for the primary endpoint were replaced by endotracheal intubation for MV or death. Other missing data were not replaced.

The intention-to-treat population (ITT) was defined as all randomised patients, regardless of the strategy received by the patient. The per-protocol population was defined as all randomised patients treated without predefined protocol violations/deviation (eligibility criteria not respected, randomised treatment allocation and/or duration such as wrong treatment given, premature treatment discontinuation [except for death, endotracheal intubation for MV, or improvement] not respected, and missing data for the primary outcome). If other major protocol deviations were identified, they would have been classified into a new class during a blinded data review before final database lock. The safety population was defined as all randomised patients started on study treatment. Sensitivity analyses of the primary endpoint were performed on ITT population with available data and on per protocol population. An additional sensitivity analysis was performed to take the centre into account; a generalized linear mixed model with a binomial distribution was performed using the group as fixed effect and the centre as random effect.

Analyses were performed using the SAS (version 9.4: SAS Institute, Cary, NC) and R (version 3.6.3: The R Foundation for Statistical Computing, Vienna, Austria) software applications. All P values were two-sided, and a P value less than 0.05 was considered significant.

[1] Guideline on Missing Data in Confirmatory Clinical Trials, European medicines agency, 2 july 2010 EMA/CMP/EWP/1776/99 Rev.1, Committee for medicinal products for human use (CHMP)

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. Les Laboratoires Servier provided the study drug free of charge. The funder and Les Laboratoires Servier ~~(Suresnes, France)~~ had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of data; the preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Results

Before reaching the planned number of 212 patients, the steering committee decided to discontinue the study in September 2021 due to the limited number of new patients admitted for COVID-19 pneumonia in the participating ICUs at the end of an epidemic wave.

Overall, 2042 patients were admitted into the participating ICUS during the study period, and 181 patients were enrolled, among whom 2 emergency included patients (1 in each group) did not give their consent and were thus excluded from the ITT analysis that comprised 179 patients (88 patients randomised to almitrine and 91 patients randomised to placebo) (Figure 1). Among them, 138 patients were included in the per-protocol analysis (Figure 1, and Appendix 3, eTable S1). Baseline demographic and disease characteristics of the patients were similar in the two groups. Mean age was 60·1 years, and 34% were women (Table 1). At enrolment, a total of 70

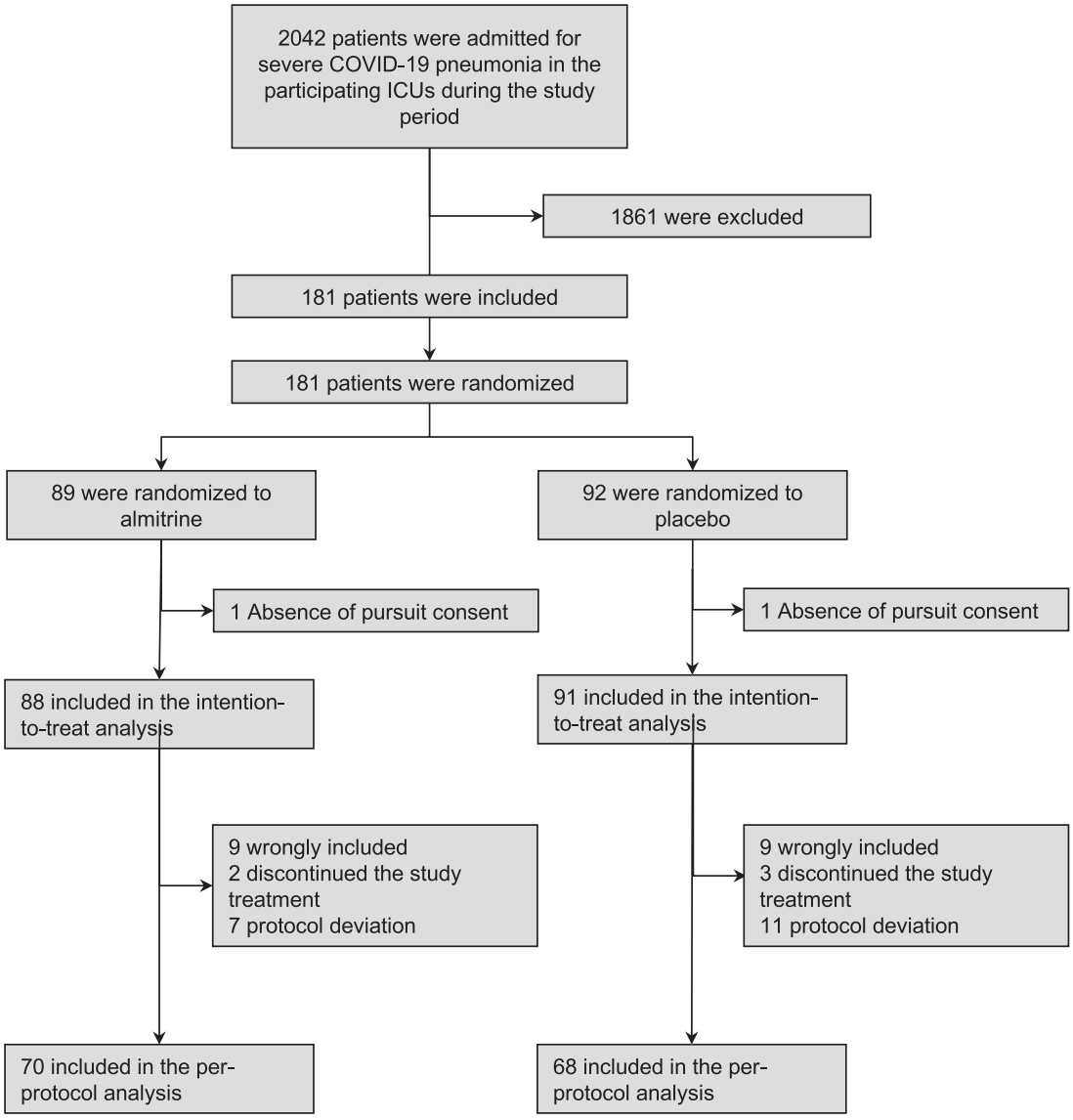

Figure 1. Flow of participants through the study.

	Almitrine group (n=88)	Placebo group (n=91)
Age, years	59·9 (11·6)	60·3 (11·9)
Sex		
Male	58/88 (66%)	61/91 (67%)
Female	30/88 (34%)	30/91 (33%)
Body mass index, kg/m^2	30·3 (6·5) [n=85]	31·6 (7·2) [n=90]
Preexisting conditions		
Hypertension	43/88 (49%)	48/91 (53%)
Other cardiovascular disease	17/88 (19%)	20/91 (22%)
Diabetes, type 2	21/88 (24%)	28/91 (31%)
Malignancy[a]	1/88 (2%)	4/91 (4%)
COPD	3/88 (3%)	3/91 (3%)
Chronic kidney disease	9/88 (10%)	6/91 (7%)
Chronic liver disease	2/88 (2%)	2/91 (2%)
Time from symptoms onset to hospitalization, median days	7·0 (4·5 to 10·0)	7·0 (5·0 to 9·0)
Time from symptoms onset to randomization, median, median days	9·5 (7·0 to 12·0)	9·0 (7·0 to 12·0)
Use of glucocorticoids for treatment of COVID-19 prior to inclusion	84/88 (95%)	91 (100%)
Clinical data at inclusion		
Respiratory rate, breaths/min	33 (8) [n=86]	33 (9) [n=88]
Temperature,°C	37·5 (0·9)	37·5 (0·8)
SOFA score, median (IQR)	4·0 (3·0 to 4·0)	4·0 (3·0 to 4·0)
Respiratory SOFA (PaO_2/FiO_2 ratio)	4·0 (3·0 to 4·0)	4·0 (3·0 to 4·0)
>400	3/85 (4%)	1/87 (1%)
301 to 400	2/85 (2%)	2/87 (2%)
201 to 300	10/85 (12%)	10/87 (11%)
101 to 200	38/85 (45%)	33/87 (38%)
≤100	32/85 (38%)	41/87 (37%)
COVID-19 diagnosis[b]		
RT-PCR positive	78/79 (99%)	81/84 (96%)
Compatible or typical chest CT pattern	78/79 (99%)	78/78 (100%)
Positive serology	4/4 (100%)	4/6 (67%)
Laboratory values at inclusion[c]		
C-reactive protein, mg/L	96·0 (62·0 to 179·0) [n=75]	101·4 (51·0 to 164·0) [n=74]
Procalcitonin, ng/mL	0·2 (0·1 to 0·3) [n=61]	0·2 (0·1 to 0·3) [n=53]
SGOT, UI/L	50·0 (32·0 to 68·0) [n=73]	53·0 (36·0 to 75·0) [n=81]
SGPT, UI/L	42·5 (25·5 to 66·5) [n=80]	41·0 (27·0 to 68·5) [n=84]
Arterial pH	7.50 (0.0) [n=85]	7·50 (0·0) [n=90]
PaCO2, mm Hg	35·5 (32·0 to 38·0) [n=86]	34·0 (31.0 to 38·0) [n=90]
PaO2, mm Hg	71·0 (62·0 to 83·0) [n=86]	69·0 (59·0 to 88·0) [n=90]
D-dimer, ng/mL	957 (670 to 1575) [n=59]	1026 (690 to 1770) [n=65]
Creatinin, mg/dL	0·76 (0·69 to 0·98) [n=87]	0·72 (0·62 to 0·95) [n=91]

***Table 1*: Characteristics of patients at enrolment.**
Data are mean (SD), (%), or median (IQR). RT-PCR=reverse transcriptase-polymerase chain reaction. SGOT= serum glutamic oxaloacetic transaminase. SGPT=serum glutamic pyruvic transaminase. SOFA=sequential organ failure assessment. The respiratory component of SOFA score (or respiratory SOFA) is 0, 1 and 2 if the PaO_2/FiO_2 ratio reaches 400, 300, 200, respectively. In case of patients requiring respiratory support (mechanical ventilation, non invasive ventilation or high flow nasal oygen), the respiratory component of SOFA score is 3 if the PaO_2/FiO_2 ratio is betweenl00 and 200, and 4 if the ratio PaO_2/FiO_2 is inferior to 100.
[a] Malignancy includes active neoplasia or antineoplastic therapy less than 1 year ago.
[b] Patients could have several diagnostic criteria.
[c] Laboratory values are presented as median (IQR) unless otherwise indicated.

among 85 patients (82%) in the almitrine group and 74 among 87 patients (85%) in the control group presented with ARDS according to the PaO_2/FiO_2 ratio for identifying moderate or severe ARDS (PaO_2/FiO_2 ratio between 101 et 200, and ≤100, respectively).

The primary outcome occurred in 32 of 88 patients (36%) randomised to almitrine and in 37 of 91 patients (41%) randomised to placebo (difference: −4·3% [95% CI: −18·7% to 10·2%], p=0·56) (Table 2). Sensitivity analyses performed on ITT population with available

	Almitrine group (n=88)	Placebo group (n=91)	Difference in proportions % (CI)	*p* value
Primary outcome				
Endotracheal intubation for MV or death within 7 days after randomization	32/88[a] (36%)	37/91(41%)	−4·3% (−18·7% to 10·2%)	0·56
Secondary outcomes[b]				
Mortality at day 28, [95% CI][c]	7/88 (8%) [3·9% to 16·1%]	15/91 (16%) [10·3% to 25·8%]		0·09[d]
In-hospital death, [95% CI][c]	7/88 (8%) [3·9% to 16·1%]	15/91 (16%) [10·3% to 25·8%]		0·09[d]
			Mean Difference (95% CI)	
Median days by day 28				
Ventilator-free	28·0 (6·0 to 28·0) [n=87]	28·0 (3·0 to 28·0) [n=91]	0·0[d]	0·38
In the ICU by day 28	9·0 (5·0 to 17·0) [n=87]	9·0 (6·0 to 25·0) [n=91]	0·0 (−2·8 to 2·8)	0·38
ICU-free	19·0 (0·0 to 23·0) [n=87]	18·0 (0·0 to 22·0) [n=91]	1·0 (−4·4 to 6·4)	0·19
In the hospital	14·0 (9·0 to 28·0)	14·0 (9·0 to 28·0)	0·0 (−5·1 to 5·1)	0·84
Hospital-free	10·0 (0·0 to 19·0)	11·0 (0·0 to 18·0)	−1·0 (−11·3 to 9·3)	0·50
Vital status at day 28				
Alive, outside the hospital	54/87 (62%)	51/91 (56%)		
Alive, hospitalized	26/87 (30%)	25/91 (27%)		
Dead	7/87 (8%)	15/91 (16%)		

***Table 2*: Primary and secondary outcomes.**
Data are n (%), or median (IQR). MV=mechanical ventilation. ICU=intensive care unit. IQR=interquartile range.
[a] For the primary outcome, the single missing outcome in the almitrine group (due to the patient who withdrew consent censored on the last reported date) was imputed as endotracheal intubation for MV or death.
[b] All censored at 28 days.
[c] All deaths by day 28 occurred in hospital.
[d] Using log-rank test.
[e] Not estimated.

data and on per protocol population and taking into account the center, produced similar results (Appendix 3, eTable S2). In the pre-specified subgroup analyses in the ITT population, treatment effect did not differ significantly by chest CT findings, time from symptom onset to hospitalization, respiratory component of the SOFA score at inclusion, and body mass index (Appendix 3, eTable S3).

Overall, 79 patients (44%) were intubated within 28 days after randomisation. No significant between-group differences were observed in the rate of intubation at day 28, ventilator-free days at day 28, days in the ICU at day 28, days in hospital at day 28 (Table 2), in the changes in the SOFA score at days 3 and 7 (Appendix 4, eTable S4,), or in the respiratory component of the SOFA score at days 3 and 7 (Appendix 4, eTable S5). During the 28 days of follow-up, death occurred in 22 patients, all at the hospital, with no difference between the two groups (Table 2, Figure 2).

Concomitant therapies were used similarly within 28 days after randomisation in the two groups, such glucocorticoids for treatment of COVID-19 or non-invasive respiratory strategies such as awake prone positioning and non-invasive ventilation, whether between randomisation and day 28 for non-intubated patients, or between randomisation and first intubation for intubated patients (Appendix 4, eTable S6).

Treatment discontinuation occurred in 78 patients, 38 (43%) in the almitrine group and 40 patients (44%) in the placebo group. The events most frequently leading to treatment discontinuation were the need for MV (30%) and hepatic cytolysis (8%). Pulmonary arterial hypertension was diagnosed in only 1 patient in each group (Table 3). Among the 62 serious adverse events (SAE) reported during the study period (32 in the almitrine group, 30 in the placebo group), 24 SAE occurred during administration of the study treatment, and only 4 were considered by the investigators to be possibly or probably related solely to the study treatment (Appendix 5, eTable S6,). At the patient level, 50 of 179 patients experienced at least 1 SAE, 24 (27%) in the almitrine group, and 26 (29%) in the placebo group (Appendix 5, eTable S7).

Discussion

In this first double-blind, randomised, multicentre study involving patients with COVID-19 pneumonia experiencing acute hypoxemic respiratory failure, intravenous low-dose almitrine failed in reducing the need

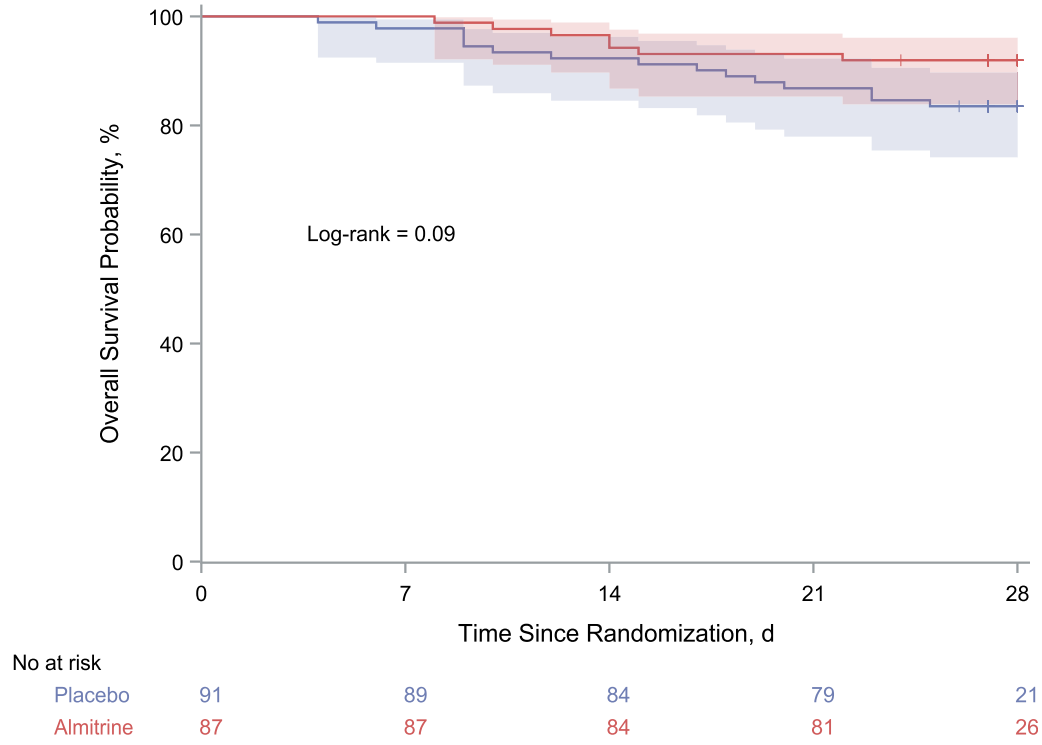

Figure 2. The 28-day survival curves for patients not undergoing endotracheal intubation for mechanical ventilation or death in the almitrine (n=87) and placebo (n=91) groups after randomisation. P value refers to between-group difference (log rank test).

	Almitrine (n=88)	Placebo (n=91)	Difference in proportions, %(CI)[a]
Investigational treatment discontinuation before the end of the planned 5-day period	38[b] (43%)	40[b] (44%)	−0·8% (−15·6% to 13·8%)
Reason for investigational treatment discontinuation			
Arterial blood lactate level >4 mmol/L	1 (1%)	0 (0%)	1·1% (−3·1% to 6·3%)
SGOT and SGPT levels >3 times the upper limit	6 (7%)	9 (10%)	−3·1% (−12·1% to 5·8%)
Pulmonary hypertension	1 (1%)	0 (0%)	1·1% (−3·1% to 6·3%)
Acute cor pulmonale	0 (0%)[c]	0 (0%)[c]	
Pulmonary embolism	0 (0%)	1 (1%)	−1·1% (−6·0% to 3·3%)
Poor tolerance of venous access to the investigational treatment	4 (5%)	0 (0%)	4·5% (0·2% to 11·3%)
Endotracheal intubation	26 (30%)	28 (31%)	−1·2% (−14·8% to 12·4%)
Death	0 (0%)	1 (1%)	−1·1% (−6·0% to 3·3%)
Other reason for investigational treatment discontinuation	2 (2%)	1 (1%)	1·2% (−4·0% to 7·0%)

***Table 3*: Treatment discontinuation and severe adverse events.**
Data are n (%). CI=confidence interval. SGOT=serum glutamic oxaloacetic transaminase. SGPT=serum glutamic pyruvic transaminase.
[a] No statistical test was used for the safety outcomes according to the statistical analysis plan.
[b] A patient can combine several reasons for treatment discontinuation.
[c] Difference is not estimated because of absence of the event.

for MV or death at day 7. Moreover, almitrine was not associated with an improvement of any of the clinically relevant secondary outcomes.

These results did not confirm those of recent studies,[12–17] with the exception of one,[22] that suggested an efficacy of almitrine in COVID-19-related ARDS based on the rationale of impaired hypoxic pulmonary vasoconstriction as a preponderant pathophysiological mechanism. Noteworthy, all of these studies were monocentric, recruited a limited number of patients, had a non-randomised design, and assessed the efficacy of almitrine only on oxygenation. Moreover, these studies enrolled patients already intubated for moderate or severe ARDS, except for 2 patients (of 32 enrolled in the

study having the largest enrollment) who were receiving continuous positive airway pressure.[15] The dose of almitrine in most of these preliminary studies was relatively high (range: 4–16 $\mu g.kg^{-1}.min^{-1}$). Only one study used low-dose almitrine (2 $\mu g.kg^{-1}.min^{-1}$).[13] Some of the study authors suggested considering almitrine for the treatment of SARS-Cov2 infection[23,24] and called for a randomised controlled trial with a clinical endpoint related to disease progression, such as intubation rate, duration of invasive MV, or use of extracorporeal oxygenation.[24]

The present study fulfills precisely these objectives, using a clinically relevant primary endpoint (intubation for MV or death at day 7) in a randomised design. Almitrine was used in patients with severe hypoxemia, most fulfilling the Berlin criteria, based mainly on the PaO_2/FiO_2 ratio for identifying moderate or severe ARDS,[25] but not yet under invasive MV as was already proposed more than two decades ago,[26] suggesting that most of the patients were in a relatively early phase of the respiratory disease, contrary to previous studies.[12–17,22] The results showed that almitrine is not the target drug for treating this population when there is a threatened ICU bed shortage due to a massive influx of patients with COVID-19. Because the decision for intubation depends on the treating physician (and potentially changed with each epidemic wave and new, well-documented care strategies[27]), respecting double-blind randomisation, is essential even if criteria for endotracheal intubation are pre-specified. However, the nature of some interventions (such as prone position) prevents the physician from being blind to the assigned treatment. The strength of our study, given its primary endpoint, is its double-blind design.

The lack of effect on the primary clinical endpoint might be explained by the lack of a significant effect on oxygenation, in contrast with the preliminary studies in patients presenting with COVID-19-related ARDS. Whether this failure to improve oxygenation in our patients was related to the lower almitrine dose used or to the preserved hypoxic pulmonary vasoconstriction or to an advanced vascular disease process causing lung tissue insensitive to almitrine remains unclear. We used the lowest almitrine dose, for which an efficacy on oxygenation had been reported for the treatment of acute hypoxemic respiratory failure, in order to minimize the dose-dependent adverse effects,[11] in particular, pulmonary hypertension and acute *cor pulmonale*. This choice was efficient in terms of safety with no difference among groups, but it remains unknown whether a higher dose would have a better efficacy/safety profile.

Our study has several limitations. First, the trial was stopped early, leading to a lack of power. However, there is no indication that the results would have been different if the pre-specified number of patients had been included. Considering occurrence of endotracheal intubation for MV or death within 7 days after randomisation of 41% in the control group and 36% in the almitrine group, and 2-sided alpha of 5%, a posteriori estimated power was 10·5% in the ITT population. Additionally, the number of included patients is lower than expected, the observed difference between groups is also lower than the expected difference. Second, during the study year, enrolled patients were from several pandemic waves: on the one hand, they might have been treated with newly developed non-invasive respiratory strategies or awake prone positioning that might have a positive impact on endotracheal intubation or mortality[2,27,28] and reduce the impact of the study drug, and on the other hand the virulence of SARS-CoV-2 taking into account the vaccination effect could differ between variants that were predominantly involved in the three epidemic waves succeeding each other in France during the study year.[3] The conclusion of our study might not be generalizable to the current and future epidemic waves due to SARS-CoV2 depending of the properties of new variants. Although more than 80% of our study patients presented with moderate or severe ARDS according to the Berlin criteria (PaO_2/FiO_2 ratio < 200 with respiratory support), the primary outcome in the placebo group turned out to be 10% lower than expected when the trial was designed during the first wave of COVID-19. Third, the trial design led to the potential inclusion of non-responders to almitrine. Whether the selection solely of almitrine responders (in terms of oxygenation) had an effect on the failure to detect a difference between the groups remains unclear. Fourth, for patients who were intubated before day 7, we did not collect which criteria among the pre-specified criteria for endotracheal intubation were used. Nevertheless randomisation with stratification by hospital site must have prevented the risk for imbalance between groups in case of different care strategies depending on the hospital site.

In conclusion, intravenous low-dose almitrine in patients with COVID-19 pneumonia experiencing acute hypoxemic respiratory failure did not reduce endotracheal intubation for MV or death at day 7.

Contributors

AR, MC, TS, PK, BR, JFP, BC, and YF had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors vouch for accuracy and adherence to the protocol during the trial. PK, YF, TS, BR contributed to the concept and the design of the trial. AT organized the double-blind design of the trial, the validation of the stability of the active solutions in their use conditions, the traceability of the preparation and administration operations performed on site, and contributed to the analysis of protocol deviations according to the study protocol. PK, JFP, BC, JA, FD, JMC, EW, and FR contributed significantly to data acquisition. All authors significantly contributed

to analysis, and interpretation of data. AR, MC, and TS conducted the statistical analysis. PK, and BR drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final manuscript.

Data sharing statement

The research protocol are available in the appendix. De-identified data will be available from 9 months to 36 months after article publication to researchers who provide a methodologically sound and ethically approved proposal, for any purpose of analysis.

AIRVM COVID investigators

Alphabetically by institution, all in France: from Centre Hospitalo-Universitaire (CHU) Beaujon, AP-HP: Jean-Denis Moyer; CHU Bicêtre, AP-HP: Anatole Harrois, and Marie Werner; Centre Hospitalier (CH) de Chartres: Hend Ben Lakhal, and Adelaïde Lenain; CHU Grenoble: Géraldine Dessertaine, and Dominique Falcon; CHU Cochin, AP-HP: Pierre-Régis Burgel, and Jonathan Marey; CHU de Dijon: Belaid Bouhemad, and Maxime Nguyen; CHU Lariboisière, AP-HP: Manuel Kindermans, Romain Barthélémy; CH de Melun: Mehran Monchi, and Jean Serbource-Goguel; CHU de Nancy: Matthieu Delannoy, and Marie-Reine Losser; CHU Pitié-Salpêtrière, AP-HP: Mona Assefi, Fanny Charbonnier, Pierre-Romain Delmotte, and Antoine Monsel; CHU Saint-Antoine, AP-HP: Léa Satre Buisson, and Franck Verdonk; CHU Saint-Louis, AP-HP: Alexandre Vagh Weinmann, and Maxime Coutrot; CH Sud Francilien: Cécilia Billiou, and Guillaume Chevrel; Centre Hospitalier Régional Universitaire (CHRU) de Tours: Martine Ferrandière, and Anne-Charlotte Tellier; CH de Troyes: Alexandra Lavalart, and Georges Simon.

Declaration of interests

PK received personal fees from General Electric Healthcare outside of the submitted work. JFP: Nothing to disclose. AR: Nothing to disclose. BC: Nothing to disclose. MC: Nothing to disclose. AT: Nothing to disclose. JA: Nothing to disclose. FD: personal fees from Sedana medical and Biomerieux; research grant from French Ministry of Health, European Society of Intensive Care Medicine, and Société Française d'Anesthésie Réanimation. JMC: personal fees and non-financial support from Drager, GE Healthcare, Sedana Medical, Baxter, and Amomed; personal fees from Fisher and Paykel Healthcare, Orion, Philips Medical, and Fresenius Medical Care; and nonfinancial support from LFB and Bird Corporation, outside of the submitted work. EW: personal fees from MSD, Akcea therapeutics, and LFB; nonfinancial support from LFB and Akcea therapeutics, outside of the submitted work. FR: Nothing to disclose. YF: Nothing to disclose. TS: research grants or contracts from AstraZeneca, Bayer, Boehringer, Daiichi-Sankyo, Eli-Lilly, GSK, Novartis, and Sanofi; personal fees from Servier, and Novartis; participation on a Data Safety Monitoring Board or Advisory Board from Ablative solutions, Air Liquide, AstraZeneca, Sanofi, Novartis, and 4Living Biotech, outside of the submitted work. BR: Nothing to disclose.

Acknowledgements

This research was financially supported by a grant from the Programme Hospitalier de Recherche Clinique (PHRC COVID 2020) funded by the French Ministry of Health. The almitrine bismesylate (Vectarion Injectable®) was provided free of charge by Les Laboratoires Servier (Suresnes, France). The sponsor was Assistance Publique-Hôpitaux de Paris (AP-HP).

We particularly thank Sarah Salhi, project manager of the AIRVM COVID trial, for her major and invaluable role in providing technical and educational support to all the all the investigators under the supervision of the lead investigator, Dominique Damas for the data management, Matthieu Le Lay for the monitoring coordination, and the entire monitoring team (Dehia Amrani-Kabiche, Malick Cissé, Nouara Djouadi, Atif Douakha, Lynda Hamouni, Tawba Korichi, Sylia Mouzaoui, Noémie Sirot, Khelidja Yahioune), all from Clinical Research Platform (URC-CRC-CRM), Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Saint Antoine, Paris. We also particularly thank Florence Capelle (Agence Générale des Equipements et Produits de Santé, Département Essais Cliniques, AP-HP and Paris Cité University, Faculté de Pharmacie, Paris, France) for her major and invaluable role for making the double-blind design feasible.

We thank the members of the data and safety monitoring board for their commitment and responsiveness: Karim Asehnoune (Université de Nantes and CHU de Nantes, Nantes, France); Stéphane Gaudry (Université Sorbonne Paris Nord and CHU Avicenne, AP-HP, Bobigny, France); Youri Yordanov (Sorbonne Université and CHU Saint Antoine, AP-HP, Paris, France). None of these individuals received compensation for their role in the study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101663.

References

1 Kandel N, Chungong S, Omaar A, Xing J. Health security capacities in the context of COVID-19 outbreak: an analysis of international health regulations annual report data from 182 countries. *Lancet*. 2020;395:1047–1053.

2 COVID-19 Lombardy ICU NetworkGrasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern. Med*. 2020;180:1345–1355.

3 IMProving Emergency Care (IMPEC) FHU Collaborators GroupBouzid D, Visseaux B, Kassasseya C, et al. Comparison of patients infected with Delta versus Omicron COVID-19 variants presenting to Paris emergency departments : a retrospective cohort study. *Ann Intern Med*. 2022;175:831–837.

4 COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med*. 2021;47:60–73.

5 Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med*. 2020;46:1105–1108.

6 Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46:1099–1102.

7 Sylvester JT, Shimoda LA, Aaronson PI, Ward JP. Hypoxic pulmonary vasoconstriction. *Physiol Rev*. 2012;92:367–520. https://doi.org/10.1152/physrev.00041.2010.

8 Reyes A, Roca J, Rodriguez-Roisin R, Torres A, Ussetti P, Wagner PD. Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;137:1062–1067.

9 Payen DM, Gatecel C, Plaisance P. Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome. *Lancet*. 1993;341:1664.

10 Wysocki M, Delclaux C, Roupie E, et al. Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. *Intensive Care Med*. 1994;20:254–259.

11 Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby JJ. Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. The NO Almitrine Study Group. *Am J Respir Crit Care Med*. 1998;158:1770–1777.

12 Bagate F, Tuffet S, Masi P, et al. Rescue therapy with inhaled nitric oxide and almitrine in COVID-19 patients with severe acute respiratory distress syndrome. *Ann Intensive Care*. 2020;10:151.

13 Barthelemy R, Blot PL, Tiepolo A, et al. Efficacy of almitrine in the treatment of hypoxemia in Sars-Cov-2 acute respiratory distress syndrome. *Chest*. 2020;158:2003–2006.

14 Losser MR, Lapoix C, Delannoy M, Champigneulle B, Payen D. Almitrine as a non-ventilatory strategy to improve intrapulmonary shunt in COVID-19 patients. *Anaesth Crit Care Pain Med*. 2020;39:467–469.

15 Lille Intensive Care COVID-19 GroupCaplan M, Goutay J, Bignon A, et al. Almitrine infusion in severe acute respiratory syndrome coronavirus 2-induced acute respiratory distress syndrome: a single-center observational study. *Crit Care Med*. 2021;49:e191–e198.

16 Huette P, Abou Arab O, Jounieaux V, et al. Almitrine for COVID-19 critically ill patients - a vascular therapy for a pulmonary vascular disease: three case reports. *World J Clin Cases*. 2021;9:3385–3393.

17 Laghlam D, Rahoual G, Malvy J, Estagnasié P, Brusset A, Squara P. Use of almitrine and inhaled nitric oxide in ARDS due to COVID-19. *Front Med*. 2021;8:655763.

18 Thorens JB, Jolliet P, Chevrolet JC. Prolonged treatment with almitrine for refractory hypoxemia in adult respiratory distress syndrome. *Chest*. 1994;105:1579–1580.

19 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357:1191–1194.

20 Ferreira FL, Bota DP, Bross A, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754–1758.

21 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–710.

22 Cardinale M, Esnault P, Cotte J, Cungi PJ, Goutorbe P. Effect of almitrine bismesylate and inhaled nitric oxide on oxygenation in COVID-19 acute respiratory distress syndrome. *Anaesth Crit Care Pain Med*. 2020;39:471–472.

23 Bendjelid K, Giraud R, Von During S. Treating hypoxemic COVID-19 "ARDS" patients with almitrine: the earlier the better? *Anaesth Crit Care Pain Med*. 2020;39:451–452.

24 Payen D. Coronavirus disease 2019 acute respiratory failure: almitrine drug resuscitation or resuscitating patients by almitrine? *Crit Care Med*. 2021;49:387–389.

25 ARDS Definition Task ForceRanieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526–2533.

26 Muret J, Clavier N, Beloucif S, Payen D. Intubation and mechanical ventilation avoided by using almitrine bismesylate in an acute hypoxemic pneumonia. *Intensive Care Med*. 1997;23:1008.

27 Awake Prone Positioning Meta-Trial GroupEhrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med*. 2021;9:1387–1395.

28 Bechman K, Yates M, Mann K, et al. Inpatient COVID-19 mortality has reduced over time: results from an observational cohort. *PLoS One*. 2022;17(1):e0261142. https://doi.org/10.1371/journal.pone.0261142.