Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease
A Randomized Clinical Trial

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IMPORTANCE Acetazolamide has been used for decades as a respiratory stimulant for patients with chronic obstructive pulmonary disease (COPD) and metabolic alkalosis, but no large randomized placebo-controlled trial is available to confirm this approach.

OBJECTIVE To determine whether acetazolamide reduces mechanical ventilation duration in critically ill patients with COPD and metabolic alkalosis.

DESIGN, SETTING, AND PARTICIPANTS The DIABOLO study, a randomized, double-blind, multicenter trial, was conducted from October 2011 through July 2014 in 15 intensive care units (ICUs) in France. A total of 382 patients with COPD who were expected to receive mechanical ventilation for more 24 hours were randomized to the acetazolamide or placebo group and 380 were included in an intention-to treat analysis.

INTERVENTIONS Acetazolamide (500-1000 mg, twice daily) vs placebo administered intravenously in cases of pure or mixed metabolic alkalosis, initiated within 48 hours of ICU admission and continued during the ICU stay for a maximum of 28 days.

MAIN OUTCOMES AND MEASURES The primary outcome was the duration of invasive mechanical ventilation via endotracheal intubation or tracheotomy. Secondary outcomes included changes in arterial blood gas and respiratory parameters, weaning duration, adverse events, use of noninvasive ventilation after extubation, successful weaning, the duration of ICU stay, and in-ICU mortality.

RESULTS Among 382 randomized patients, 380 (mean age, 69 years; 272 men [71.6%]; 379 [99.7%] with endotracheal intubation) completed the study. For the acetazolamide group (n = 187), compared with the placebo group (n = 193), no significant between-group differences were found for median duration of mechanical ventilation (−16.0 hours; 95% CI, −36.5 to 4.0 hours; $P = .17$), duration of weaning off mechanical ventilation (−0.9 hours; 95% CI, −4.3 to 1.3 hours; $P = .36$), daily changes of minute-ventilation (−0.0 L/min; 95% CI, −0.2 to 0.2 L/min; $P = .72$), or partial carbon-dioxide pressure in arterial blood (−0.3 mm Hg; 95% CI, −0.8 to 0.2 mm Hg; $P = .25$), although daily changes of serum bicarbonate (between-group difference, −0.8 mEq/L; 95% CI, −1.2 to −0.5 mEq/L; $P < .001$) and number of days with metabolic alkalosis (between-group difference, −1; 95% CI, −2 to −1 days; $P < .001$) decreased significantly more in the acetazolamide group. Other secondary outcomes also did not differ significantly between groups.

CONCLUSIONS AND RELEVANCE Among patients with COPD receiving invasive mechanical ventilation, the use of acetazolamide, compared with placebo, did not result in a statistically significant reduction in the duration of invasive mechanical ventilation. However, the magnitude of the difference was clinically important, and it is possible that the study was underpowered to establish statistical significance.

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Chronic obstructive pulmonary disease (COPD) is a frequent cause of intensive care unit (ICU) admission.[1] Noninvasive mechanical ventilation has altered the outcomes of patients with acute COPD exacerbation by reducing the need for intubation.[2,3] Nevertheless, patients with COPD may still require invasive mechanical ventilation when noninvasive ventilation fails or for an unrelated pathology.

Respiratory acidosis and metabolic alkalosis are the principal acid-base disturbances in patients with COPD receiving mechanical ventilation. Metabolic alkalosis can be caused by many conditions encountered during ICU stays, including diuretic or glucocorticoid use, vomiting or nasogastric suctioning, and permissive hypercapnia induced by lung-protective strategies.[4] Furthermore, the acid-base disorders most frequently observed while weaning patients with COPD off mechanical ventilation are mixed (ie, chronic respiratory acidosis and metabolic alkalosis).[5] Metabolic alkalosis may inhibit the activity of the central nervous respiratory command center and cardiac output or alter oxyhemoglobin dissociation and favors the development of hypokalemia and hypophosphatemia, thereby prolonging the weaning period and mechanical ventilation duration for critically ill patients.[6-10]

Acetazolamide, a carbonic anhydrase inhibitor, has been used for decades as a respiratory stimulant in patients with COPD and metabolic alkalosis.[11] The classic mechanism of acetazolamide's action as a respiratory stimulant is based on the inhibition of the renal carbonic anhydrase enzyme, which in turn decreases serum bicarbonate and arterial pH, leading to increased minute ventilation via stimulation of peripheral and central chemoreceptors. However, data from uncontrolled clinical studies yielded inconsistent effects when acetazolamide was administered at usual doses (250 to 500 mg once or twice daily).[12] Recent pharmacodynamics models indicated that patients with COPD breathing with the aid of mechanical ventilation might benefit from its respiratory stimulant effect after administration of higher doses.[13,14] In designing the DIABOLO trial, we hypothesized that higher acetazolamide doses (≥1000 mg/d) would shorten the mechanical ventilation duration in critically ill patients with COPD (trial protocol in Supplement 1).

Methods

Study Design

This multicenter, double-blind (participants, caregivers, investigators, and outcome assessors), parallel-group, randomized clinical trial was approved for all centers by the Comité de Protection des Personnes Paris-Ile-de-France VI (ethics committee: No. 2011-000492-14). The French National Committee for Health Research funded the study and convened a trial steering committee and independent data monitoring committee. A safety monitoring committee was not considered necessary because the acetazolamide doses had adhered to the marketing authorization and the study design included daily patient evaluation for adverse events or temporary contraindications. The European Georges Pompidou Hospital Clinical Research Center managed the study, from October 2011 to July 2014. Patients were enrolled (day 0) at 15 adult ICUs in France. Written informed consent was obtained from all patients or from their next of kin for patients unconscious at inclusion. Definitive post hoc written consent was ultimately obtained from patients who survived but were initially unable to provide informed consent.

Participants

Patients older than 18 years with a history of COPD according to the American Thoracic Society criteria[15] (smoking, other environmental risk factors, chronic cough, acute chest illnesses, dyspnea, physical examination, and laboratory investigations such as chest radiography, lung function tests, or arterial blood gases) were enrolled if they required invasive ventilation via an intubation or tracheotomy tube and were evaluated within 24 hours after its onset. Exclusion criteria were judicial guardianship, no affiliation with the French health care system, pregnancy, cystic fibrosis or diffuse bronchiectasis, previous allergy to acetazolamide or sulfonamides, permanent acetazolamide contraindication, recent participation in another interventional study with mechanical ventilation duration as the primary end point, or investigator's decision not to resuscitate.

Randomization and Allocation

Within 24 hours of starting invasive ventilation, patients were randomized via a computer-generated assignment sequence in a centralized, blinded fashion (Figure 1). The randomization sequence was programmed in advance and generated by a statistician independent of the study. One-for-one randomization was carried out, with stratification for centers, respiratory status of the patients before hospitalization (no respiratory assistance at home vs respiratory assistance at home, whatever its nature [oxygen supplementation, noninvasive ventilation, tracheotomy + ventilation]), and disease severity at inclusion assessed with Simplified Acute Physiology Score (SAPS) II less than 50 or 50 or higher. The list was balanced by blocks of different sizes alternated in a random manner. Physicians assigned the treatment after randomization, which was accessible through dedicated web-based software. Investigators, patients, and research staff were masked to the randomization list.

Intervention

After inclusion, patients were assigned to receive either 500 mg or 1000 mg (when loop diuretics were coprescribed) of acetazolamide twice daily or placebo (10 mL of saline) in case of pure or mixed metabolic alkalosis (serum bicarbonate >26 mEql/L and arterial pH ≥ 7.35), monitored according to arterial blood gases determined on mechanical ventilation between 7 AM and 8 AM from day 1 to the day invasive ventilation ended (eFigure 1 in Supplement 2). Physicians in charge were different from the investigators who monitored and prescribed the tested treatment. Tested treatment was prepared and blinded in each local pharmacy. Acetazolamide was supplied as a freeze-dried powder. The product was reconstituted with saline and then administered immediately in the ICU, as a slow intravenous injection. The placebo was sup-

plied in the form of a solvent (saline) and was administered in the same manner. If a contraindication for the test treatment arose (for details, see Supplement 2), it was temporarily suspended until the contraindication had resolved. Patients with pure or mixed metabolic alkalosis received acetazolamide or placebo intravenously twice daily for a maximum of 28 days. Treatment doses were based on recent pharmacodynamics models predicting that 500 mg twice daily (or double-dose when loop diuretics were coprescribed) were required to significantly lower serum bicarbonate and raise minute ventilation in patients with COPD breathing with the aid of a ventilator, regardless of the ventilation mode (volume-assisted or pressure-support ventilation) used.[13,14] Other treatments were left to the discretion of the treating physicians and had to be in accordance with classic guidelines.[1] Investigators were aware of the need to correct hypokalemia.

Readiness to wean was defined according to the criteria of the Sixth International Consensus Conference on Intensive Care Medicine held in 2005.[16] The weaning strategy consisted of the progressive decrease of pressure-support or volume-assisted ventilation with progressively longer times on a T-piece and was tailored by treating physicians, according to the difficulty of the weaning process.[17] External positive end-expiratory pressure was applied to counterbalance intrinsic positive end-expiratory pressure, typically 4 to 6 cm of H_2O. Criteria for extubation and reintubation were standardized in a written protocol (for details, see Supplement 1). Patients enrolled were extubated when they tolerated, for at least 1 hour, a spontaneous breathing trial via a T-piece oxygenated with the same inspiratory oxygen fraction (FIO_2) used during mechanical ventilation. Patients satisfying spontaneous breathing-trial criteria were extubated in the presence of a physiotherapist and received supplemental oxygen to achieve arterial oxygen saturation of 90% or more. Prophylactic use of noninvasive ventilation after extubation was permitted. Weaning was considered successful when reintroduction of invasive ventilation was not required within 48 hours after its termination.[17] Tracheotomy indication and modalities for patients with prolonged weaning failure were left to the discretion of the treating physicians. Group assignments for patients who died before being weaned off mechanical ventilation or those who received no test treatment during the study period were not modified, and data analysis was conducted on an intention-to-treat basis.

Study Outcomes

The primary end point was the duration of invasive ventilation. Secondary outcomes were the changes of serum bicarbonate, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), pH, partial pressure of oxygen in arterial blood (PaO_2):FIO_2 ratio and respiratory parameters (tidal volume, respiratory rate, and minute ventilation), weaning duration, the numbers of spontaneous breathing trials, unplanned extubations and ventilator-associated pneumonia episodes, use of noninvasive ventilation after extubation, successful weaning, the duration of ICU stay, and in-ICU mortality. Adverse events were monitored for 28 days. All outcomes are defined in Supplement 2.

Statistics

The sample size was calculated a priori based on the following assumptions: placebo group with an estimated mean (SD) duration of mechanical ventilation of 12 (5) days based of one of our preliminary studies,[5] and because we expected to include the most severely ill patients with COPD (ie, requiring invasive mechanical ventilation); acetazolamide-group patients, compared with those in the placebo group, would have a potential 15% relative risk reduction for the primary end point[5] to be clinically relevant. Based on those estimates, we calculated that 380 patients had to be enrolled to achieve 80% power to detect that difference for the acetazolamide group with a 2-sided α level of .05.

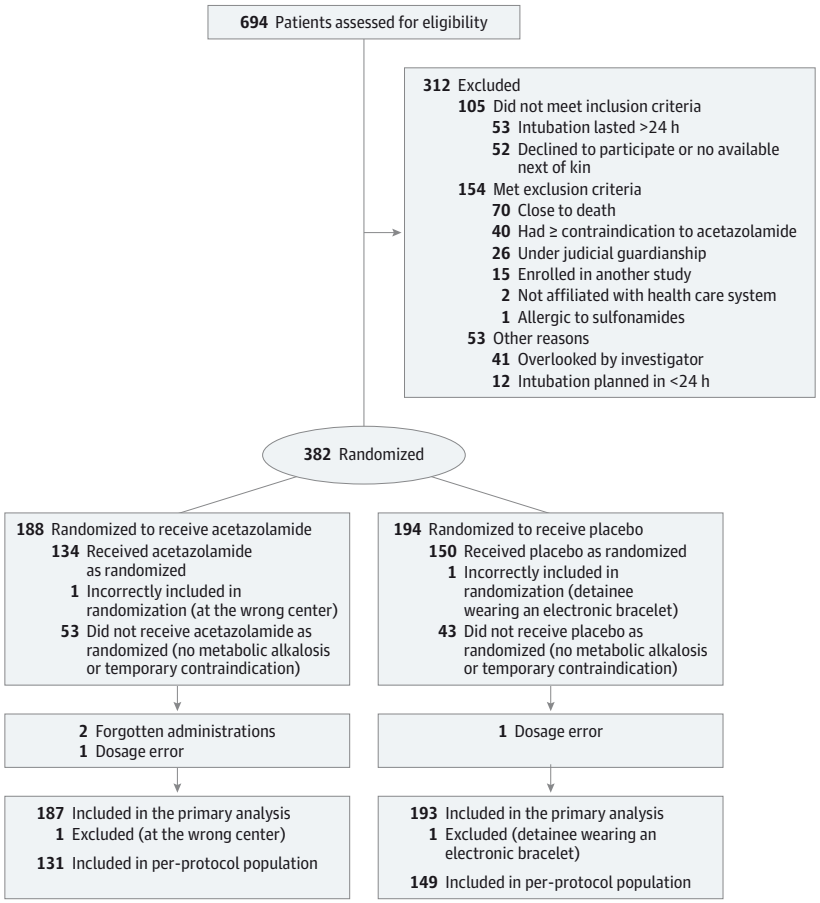
The analyses were performed on the intention-to-treat population, which was defined as all patients who had undergone randomization, excluding those erroneously included. Analyses were then confirmed on per-protocol population, which is defined as the set of patients, who did not perform any protocol violation that may interfere with primary criteria evaluation (ie, patients receiving the allocated treatment; patients with all the inclusion criteria met). Missing data were only imputed for the end of invasive mechanical ventilation. We used the mean hour of the end of invasive mechanical ventilation of the center because planned extubations were performed around the same time. To take censored data into account (patients who died before extubation), the Kaplan-Meier method was used to calculate the probabilities of being successfully weaned off invasive ventilation during the 28-day observation period. The generated Kaplan-Meier curves were compared with the log-rank test. Quantitative variables are expressed as means and standard deviation or medians and interquartile ranges (IQRs), when appropriate. Data were compared with *t* tests, when the sample size of each group was 30 or more, or Wilcoxon rank-sum tests, when one group's sample size was less than 30. All tests were 2-sided. Either χ^2 or Fischer exact tests, as appropriate, were used to compare qualitative variables, expressed as percentages. All comparisons included the entire sample stratification (as prespecified). Hazard ratios were calculated using a Cox model and the centers were taken into account as a random effect using gamma frailty model.[18] Tests of proportionality were performed including time-dependent covariates in the Cox model. Post hoc subgroups were defined according to the presence or absence (yes/no) of acute prolonged mechanical ventilation (≥96 hours),[19] the preferential use (>50% of the time) of pressure-support ventilation or not during the weaning period, the prescription or not of loop diuretics or glucocorticoids, and the presence or absence (yes/no) of pure metabolic alkalosis (pH>7.42 and serum bicarbonate >26 mEq/L) at baseline. $P < .05$ defined statistical significance. All analyses were computed using SAS software, version 9.4 (SAS Institute Inc).

Results

Patients

Among the 694 patients screened in the 15 participating French ICUs, 382 were enrolled, including 2 patients who subse-

Figure 1. Study Flow of Patients in the DIABOLO Trial



Patients who did not receive the assigned test treatment did not have metabolic alkalosis or had at least 1 temporary contraindication to that treatment during the study period.

quently withdrew from the study, resulting in an intention-to-treat population of 380 patients: 187 randomized to the acetazolamide group and 193 to receive the placebo (**Figure 1**). Baseline characteristics of the patients in the 2 study groups were comparable (**Table 1**). All 187 patients had endotracheal intubation (100%) in the acetazolamide group vs 192 (99.5%) with endotracheal intubation and 1 (0.5%) with tracheotomy in the placebo group.

Primary and Secondary Outcomes

The total durations of invasive ventilation was a median of 136.5 hours (IQR, 68.7 to 234.7 hours) in the acetazolamide group vs 163.0 hours (IQR, 86.2 to 242.9 hours) in the placebo group, for a between-group difference of −16.0 hours (95% CI, −36.5 to 4.0 hours), which did not differ significantly (**Table 2** and **Figure 2**). Acetazolamide lowered the median daily change of serum bicarbonate (−0.3 mEq/L; IQR, −1 to 0.4 mEq/L vs 0.3 mEq/L; IQR, −0.2 to 1.3 mEq/L), for a between-group difference of −0.8 mEq/L (95% CI, −1.2 to −0.05 mEq/L) and increased the median daily Pa_{O_2}:F_{IO_2} ratio (7.8 mm Hg; IQR, −1.5 to 20.5 mm Hg vs 3.5 mm Hg; IQR, −5.2 to 13.9 mm Hg), for a between-group difference of 4.6 mm Hg (95% CI, 0.6-8.6 mm Hg) more than the placebo, but had no respiratory stimulant effect on the median changes of respiratory rate 0.1 cycles/min (IQR, −0.8 to 1.0 cycles/min) vs 0.3 cycles/min (IQR, −0.3 to 1.4 cycles/min), for a between-group difference of −0.3 cycles/min (95% CI, −0.7 to 0.0 cycles/min); a tidal volume of 4.1 mL (IQR, −7.1 to 28.0 mL) vs 3.8 mL (IQR, −8.6 to 19.4 mL), for a between-group difference of 1.3 mL (95% CI, −4.2 to 7.5 mL); or median minute ventilation change of 0.2 L/min (IQR, −0.2 to 0.8 L/min) vs 0.2 L/min (IQR, −0.1 to 0.6 L/min), for a between-group difference of 0.0 L/min (95% CI, −0.2 to 0.2 L/min) (eTable 1 and eFigures 2 and 3 in Supplement 2).

Moreover, other secondary outcomes also did not differ significantly: durations of weaning off invasive ventilation, numbers of spontaneous breathing trials, use of tracheotomy or noninvasive ventilation after extubation, successful weaning rates, unplanned extubations, ventilator-associated pneumonia episodes, other laboratory-parameter values, ICU stays or in-ICU mortality rates (eTable 2 in Supplement 2). Per-protocol analysis yielded results similar to those of the intention-to-treat analysis with respect to significant findings (eTables 1 and 3 in Supplement 2).

Metabolic Alkalosis and Treatment Administration

As expected, the numbers of days with metabolic alkalosis and treatment doses were significantly lower for the acetazolamide than for the placebo group (Table 2). A total of 53

Table 1. Characteristics of the Patients at Baseline

Characteristic	Study Group, Mean (SD)	
	Acetazolamide (n = 187)	Placebo (n = 193)
Age, y	69 (10)	69 (11)
Men, No. (%)	131 (70)	141 (73.1)
SAPS II score[a]	49.4 (13.9)	50 (15.1)
SOFA score[b]	7.2 (3.1)	7.1 (3.2)
BMI	27.2 (8.0)	26.7 (9.1)
Home treatment, No. (%)		
Oxygen	49 (26.2)	52 (26.9)
Noninvasive ventilation	19 (10.1)	21 (10.9)
Tracheotomy mechanical ventilation	0	1 (0.5)
Smoker or ex-smoker, No. (%)	170 (90.9)	179 (92.7)
Smoking history, pack-years	48.3 (24.7)	50.4 (22.1)
FEV_1, mL[c]	1232 (609)	1124 (586)
FEV_1/FVC[c]	0.51 (0.15)	0.53 (0.15)
>8 Weeks, No. (%)		
Systemic glucocorticoids	32 (17.1)	39 (20.2)
Loop diuretics	51 (27.3)	67 (34.7)
β_2-Agonists	96 (51.3)	95 (49.2)
Acetazolamide	4 (2.1)	3 (1.6)
ICU stay before randomization, median (IQR), d[d]	1 (0-1)	1 (0-1)
Causes of invasive mechanical ventilation, No. (%)[e]		
Community-acquired pneumonia	83 (44.3)	83 (43.0)
Bronchitis	37 (19.8)	33 (17.1)
Left ventricular insufficiency	43 (23.0)	32 (16.6)
Surgery	12 (6.4)	13 (6.7)
Use of sedative	4 (2.1)	17 (8.8)
Pulmonary embolism	2 (1.1)	1 (0.5)
Stroke	3 (1.6)	2 (1.0)
Others	52 (27.8)	44 (22.8)
Unknown	10 (5.3)	9 (4.7)
Endotracheal intubation/ tracheotomy at inclusion, No.	187/0	192/1
Laboratory measurements at inclusion		
pH	7.32 (0.11)	7.30 (0.12)
Pao_2, mm Hg	150.5 (108)	143.6 (90)
$Paco_2$, mm Hg	52.5 (16)	55.6 (17)
Serum		
Bicarbonate, mEq/L	26.9 (6.9)	27.4 (6.6)
Potassium, mEq/L	4.2 (0.7)	4.2 (0.7)
Sodium, mEq/L	138 (5.8)	139 (4.9)
Chloride, mEq/L	100.9 (8.4)	100.6 (6.8)
Protein, g/dL	5.9 (0.9)	5.9 (0.8)
Creatinine, mg/dL	1.3 (0.9)	1.2 (0.8)
Urea, mg/dL	31.4 (25.8)	29.7 (23.2)
Glucose, mg/dL	165.8 (133.3)	165.8 (79.3)
Aspartate aminotransferase, U/L	105.2 (290.6)	115.1 (448.6)
Bilirubin, mg/dL	0.8 (0.6)	0.8 (0.9)
Uric acid, mg/dL	6.3 (2.7)	5.9 (3.1)
Thyroid-stimulating hormone, mIU/L	2.5 (8)	2.2 (5.7)
Hemoglobin, g/dL	1.2 (0.2)	1.2 (0.2)
Hematocrit, %	37.3 (8)	37.6 (8.4)
White blood cells/μL	13700 (7200)	13900 (8200)
Blood platelets, $\times 10^3$/μL	251.5 (116.6)	245.6 (118.5)
Prothrombin ratio, %	73.7 (21.6)	75.9 (22.1)
Chest radiography, No. (%)		
Distension of the lungs	147 (78.6)	148 (76.7)
Unilateral alveolar opacities	57 (30.5)	53 (27.5)
Bilateral alveolar opacities	84 (44.9)	93 (48.2)

(continued)

Table 1. Characteristics of the Patients at Baseline (continued)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; ICU, intensive care unit; IQR, interquartile range; $Paco_2$, partial carbon-dioxide pressure in arterial blood; Pao_2, partial oxygen pressure in arterial blood; SAPS, Simplified Acute Physiology score; SOFA, Sequential Organ Failure Assessment.

SI conversion factor: To convert aspartate aminotransferase from U/L to μKat/L, multiply by 0.0167; bilirubin from mg/dL to μmol/L, multiply by 17.104; creatinine from mg/dL to μmol/L, multiply by 88.4; glucose from mg/dL to mmol/L, multiply by 0.0555; Pao_2 and $Paco_2$ from mm Hg to kPA, multiply by 0.133; uric acid from mg/dL to μmol/L, multiply by 59.485.

[a] The SAPS II is based on 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.

[b] The SOFA score includes subscores ranging from 0 to 4 for each of the 5 components (circulation, lung, liver, kidneys, and coagulation). Aggregate scores range from 0 to 20, with higher scores indicating more severe organ failure.

[c] Data were available from 71 patients in the acetazolamide group and from 82 patients in the placebo group.

[d] Seventy-eight patients in the acetazolamide group and 91 patients in the placebo group were hospitalized in ICU prior to randomization.

[e] Several situations requiring invasive ventilation are possible; hence, the total can exceed 100%.

acetazolamide-group patients (28.3%) and 43 placebo-group patients (22.2%) never received the assigned treatment (P = .17) because of no metabolic alkalosis or temporary contraindication. Cotreatments with loop diuretics, glucocorticoids, β_2-agonists or catecholamines, the mechanical ventilation mode used, and the left ventricular ejection fraction at weaning were comparable for the 2 groups.

Adverse Events

No significant between-group differences were observed for the overall incidence of serious adverse events (Table 2; eTable 1 in Supplement 2).

Post Hoc Subgroup Analyses

No significant interactions were identified between study groups and any post hoc subgroup with respect to the total durations of invasive ventilation or weaning (**Figure 3** and eFigure 4A-B in Supplement 2).

Discussion

This multicenter, randomized, double-blind trial was designed to compare the respiratory effects of acetazolamide vs

Table 2. Clinical Outcomes and Serious Adverse Events[a]

Variable	Group, Median (Interquartile Range)		Between-Group Difference (95% CI)	*P* Value
	Acetazolamide (n = 187)	Placebo (n = 193)		
Primary Outcome				
Duration of invasive ventilation, h	136.5 (68.7 to 234.7)	163 (86.2 to 242.9)	−16.0 (−36.5 to 4.0)	.17
Secondary Outcomes[b]				
Daily				
Serum bicarbonate change, mEq/L	−0.3 (−1.0 to 0.4)	0.3 (−0.2 to 1.3)	−0.8 (−1.2 to −0.5)	<.001
$Paco_2$ change, mm Hg	−0.5 (−2.0 to 0.8)	−0.2 (−1.4 to 1)	−0.3 (−0.8 to 0.2)	.25
pH change	0 (−0.01 to 0.02)	0.01 (0 to 0.02)	−0.01 (−0.01 to −0.0)	.008
Pao_2:Fio_2-ratio change, mm Hg	7.8 (−1.5 to 20.5)	3.5 (−5.2 to 13.9)	4.6 (0.6 to 8.6)	.009
Respiratory rate change, cycle/min	0.1 (−0.8 to 1.0)	0.3 (−0.3 to 1.4)	−0.3 (−0.7 to 0.0)	.10
Tidal volume change, mL	4.1 (−7.1 to 28.0)	3.8 (−8.6 to 19.4)	1.3 (−4.2 to 7.5)	.72
Volume-minute change, L/min	0.2 (−0.2 to 0.8)	0.2 (−0.1 to -0.6)	0.0 (−0.2 to 0.2)	.72
Weaning duration, h	18.7 (3.0 to 46.5)	22.0 (3.0 to 44.3)	−0.9 (−4.3 to 1.3)	.36
Spontaneous breathing trials, d	1 (1 to 2)	1 (1 to 2)	0 (0 to 0)	.42
Tracheotomy, median (range), d	0 (0 to 21)	0 (0 to 9)	0 (0 to 0)	.67
Endotracheal intubation, No. (%)	187 (100)	192 (99.5)	0.05 (−0.05 to 1.5)	.99
Use of noninvasive ventilation after extubation, No. (%)	62 (33.1)	72 (37.3)	-4.2 (-13.8 to 5.5)	.39
Successful weaning, No. (%)[c]	118 (74.7)	127 (78.4)	-3.7 (-13.1 to 5.6)	.43
Unplanned extubation, median (range), d	0 (0 to 2)	0 (0 to 1)	0 (0 to 0)	.65
VAP episodes, No. (%)	23 (12.3)	33 (17.1)	-4.8 (-12.0 to 2.4)	.18
Duration of ICU stay, d	10 (6 to 17)	10 (7 to 18)	-2.1 (-6.1 to 1.9)	.30
In-ICU mortality, No. (%)	22 (11.7)	26 (13.4)	-1 (-2 to 0)	.61
Serious adverse events, No. (%)[d]	6 (0.03)	7 (0.04)	-0.4 (-4.1 to 3.2)	.82
Days receiving treatment				
Loop diuretics	1 (0 to 4)	1 (0 to 4)	0 (0 to 0)	.55
Systemic glucocorticoids	0 (0 to 3)	0 (0 to 4)	0 (0 to 0)	.29
β_2-Agonists	0 (0 to 4)	1 (0 to 6)	0 (0 to 0)	.07
Catecholamines	1 (0 to 3)	1 (0 to 3)	0 (0 to 0)	.98
Test-treatment doses	2 (0 to 5)	6 (1 to 13)	-2 (-4 to -1)	<.001
Metabolic alkalosis, d[e]	2 (1 to 4)	4 (2 to 8)	-1 (-2 to -1)	<.001
Temporary contraindication to test treatment, median (range), d	0 (0 to 10)	0 (0 to 7)	0 (0 to 0)	.16
Pressure-support ventilation, d	2 (1 to 5)	2 (1 to 5)	0 (-1 to 0)	.22
Volume-assisted ventilation, d	3 (1 to 5)	3 (1 to 6)	0 (-1 to 0)	.52
Left ventricular ejection fraction at weaning, %[f]	55 (40 to 60)	50 (42 to 60)	0 (-5 to 5)	.86

Abbreviations: Fio_2, fraction of inspired oxygen; ICU, intensive care unit; $Paco_2$, partial carbon-dioxide pressure in arterial blood; Pao_2 partial oxygen pressure in arterial blood; and VAP, ventilator-associated pneumonia (diagnostic criteria are provided in Supplement 2).

SI conversion factor: To convert $Paco_2$ and Pao_2 from mm Hg to kPA, multiply by 0.133.

[a] Range was preferred over IQR because several of the latter were (0-0). Between-group differences for quantitative variables are expressed as medians with the 95% CI around the median difference.

[b] Median daily changes of arterial blood gases or respiratory parameters corresponded to the differences between 2 consecutive days from day 1 to the end of invasive ventilation. Arterial blood gases and respiratory parameters on mechanical ventilation were measured between 7 AM and 8 AM Other laboratory-parameter changes are given in eTable 2 in Supplement 2.

[c] Weaning was considered successful when invasive ventilation reintroduction was not required within 48 hours after its termination. Criteria for extubation and reintubation are detailed in Supplement 2. Weaning-failure causes are given in eTable 2 in Supplement 2.

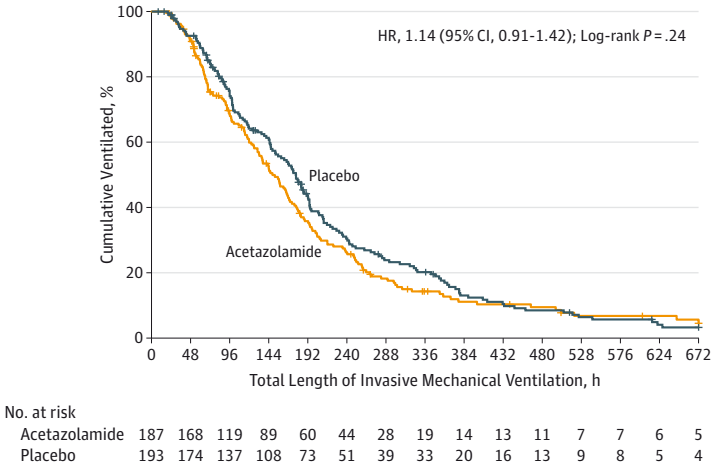
[d] Adverse events were considered serious when they required intensive care procedures (use of vasopressors, hemodialysis, central venous catheterization, cardiac pacing, or tube thoracostomy) or surgery, and those events prolonged hospitalization or resulted in persistent or major disability or incapacity.

[e] Metabolic alkalosis was defined as serum bicarbonate of more than 26 mEql/L and arterial pH of 7.35 or more.

[f] Left ventricular ejection fraction was assessed by transthoracic echocardiography during the weaning period.

placebo in mechanically ventilated patients with COPD and pure or mixed metabolic alkalosis. Acetazolamide had no significant effect on durations of mechanical ventilation or weaning, respiratory parameter-values (respiratory frequency, tidal volume, and minute ventilation) despite achieving larger decreases in serum bicarbonate and fewer days with metabolic alkalosis. In addition, the acetazolamide group's Pao_2:Fio_2 ratio was significantly increased, possibly via the drug's

Figure 2. Kaplan-Meier Curves for the Cumulative Probabilities of Being Weaned Off Invasive Ventilation

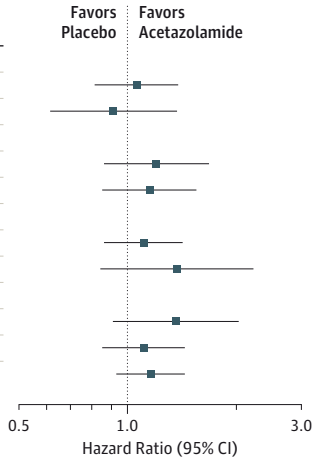


Data for the analysis, conducted on the intention-to-treat population, were censored for patients who died before extubation or were still breathing with the aid of mechanical ventilation on day 28. Successful weaning rates on day 28 (672 hours) did not differ significantly for the acetazolamide and placebo groups (P = .24, log-rank test on day 28). HR indicates hazard ratio.

Figure 3. Subgroup Analyses of the Effect of Acetazolamide on the Duration of Invasive Ventilation or Weaning

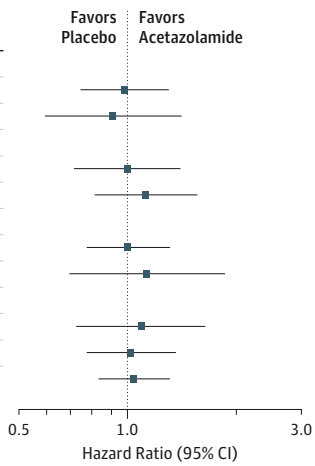
A Duration of ventilation

Subgroup	Acetazolamide Group, No. Events[a]	Acetazolamide Group, No. Patients	Placebo Group, No. Events[a]	Placebo Group, No. Patients	Hazard Ratio (95% CI)
Acute prolonged invasive ventilation, ≥96 h					
Yes	102	119	121	137	1.06 (0.81–1.38)
No	57	68	45	56	0.91 (0.61–1.37)
Pressure support ventilation >50% of the weaning period					
Yes	62	66	83	87	1.20 (0.86–1.68)
No	93	117	82	103	1.15 (0.85–1.55)
Loop diuretics or corticosteroids					
Yes	121	141	128	143	1.11 (0.86–1.42)
No	34	42	37	47	1.37 (0.84–2.23)
Pure metabolic alkalosis at baseline					
Yes	55	59	48	50	1.36 (0.91–2.03)
No	104	128	118	143	1.11 (0.85–1.44)
Overall	166	187	159	193	1.16 (0.93–1.44)



B Duration of weaning

Subgroup	Acetazolamide Group, No. Events[a]	Acetazolamide Group, No. Patients	Placebo Group, No. Events[a]	Placebo Group, No. Patients	Hazard Ratio (95% CI)
Acute prolonged invasive ventilation, ≥96 h					
Yes	93	99	111	112	0.98 (0.74–1.30)
No	50	51	42	43	0.91 (0.59–1.41)
Pressure support ventilation >50% of the weaning period					
Yes	59	62	82	83	1.00 (0.71–1.40)
No	80	84	70	71	1.12 (0.81–1.56)
Loop diuretics or corticosteroids					
Yes	108	113	118	120	1.00 (0.77–1.31)
No	31	33	34	34	1.13 (0.69–1.86)
Pure metabolic alkalosis at baseline					
Yes	51	53	45	45	1.09 (0.72–1.64)
No	92	97	108	110	1.02 (0.77–1.36)
Overall	143	150	153	155	1.04 (0.83–1.31)



The duration of weaning was the time between its onset (criteria are detailed in Supplement 2) and its termination. In the case of temporary interruption of the weaning procedure, the total duration corresponded to the number of hours of attempted withdrawal until successful weaning minus discontinued hours.

[a] An event corresponds to the termination of invasive mechanical ventilation.

diuretic effect[5,20] or the increased oxygen saturation of hemoglobin.[8,11] Taken together, these findings indicated that the inhibition of the renal carbonic anhydrase enzyme and the resulting serum bicarbonate reduction did not trigger a sufficient respiratory-stimulating effect to effect outcomes of critically ill patients with COPD. Nevertheless, this overall conclusion must be considered with prudence. Indeed, the study may have identified a clinically important benefit of acetazolamide for the primary end point that did not demonstrate statistical significance because of a possible lack of power.

The between-group difference in median durations of invasive mechanical ventilation was clinically substantial (16 hours) although it did not the reach statistical significance. Our trial was prospectively powered to detect a 15% difference in the invasive ventilation duration, considered clinically relevant in light of the usual duration of intubation in these patients.[5,21-23] However, the observed median durations of invasive mechanical ventilation in the placebo and acetazolamide groups were lower than anticipated for statistical power, complicating the study interpretation. This means that the 10% reduction of invasive mechanical ventilation by acetazolamide could have reached statistical significance if the study was designed to detect such a difference. Similar proportions of patients in the 2 groups did not develop metabolic alkalosis or have transient treatment contraindications, and intention-to-treat and per-protocol analyses findings converged. Moreover, the decision to consider weaning duration a secondary outcome was based on the fact that weaning may be discontinuous, making it difficult to measure its total time accurately. For the same reason, the test treatment was administered from day 1 in case of metabolic alkalosis.

Pharmacological factors could contribute to the absence of a stronger acetazolamide respiratory effect. First, inadequate dosing could limit the drug's effect on respiratory parameters: the serum bicarbonate decline that would cause a clinically relevant respiratory effect (ie, $Paco_2$ decrease >5 mm Hg) should be at least 5 mEq/L.[12,14] A recent case-control study showed that the use of insufficient acetazolamide dosage (500 mg/d) had no significant effect on the duration of mechanical ventilation in critically ill patients with COPD requiring invasive mechanical ventilation.[24] Herein, we administered a dose that lowered serum bicarbonate but the corresponding respiratory effect was not observed. Tissue compartmentalization of carbonic anhydrase isozymes and low acetazolamide selectivity might explain why this drug had no benefit in terms of improving minute ventilation and $Paco_2$ in patients with COPD receiving respiratory support. Indeed, only the inhibition of carbonic anhydrase isozymes II, IV, and XIII should induce a respiratory-stimulating effect by increasing the respiratory rate and tidal volume, whereas blockage of isozymes I and II can modulate erythrocyte functions.[12,25,26] Hence, our findings might support further investigations of more selective molecules targeting isozymes I, II, IV and XII, rather than relying on the traditional concept of renal isozyme inhibition. It cannot be excluded that higher acetazolamide doses could have a double-sided effect on respiratory parameters by increasing the respiratory muscle workload and causing respiratory muscle fatigue. Pertinently, we observed that, out to approximately 360 hours, the acetazolamide group performed worse than the placebo group. However, post hoc analysis did not show significant difference between patients with or without acute prolonged mechanical ventilation.

A limitation of this study is the presence of mixed metabolic alkalosis in most patients. Indeed, the lack of acetazolamide respiratory effect may be because so many of the patients had a degree of metabolic alkalosis too mild for the intervention. But previous models used to evaluate the acetazolamide effect on respiratory parameters in the present study were based on patients with COPD patients and with mixed metabolic alkalosis.[13,14] Moreover, our post hoc analysis did not show that patients with COPD and pure metabolic alkalosis at baseline responded better than others. Another possible limitation could be the presence of factors more strongly influencing the discontinuation of mechanical ventilation or ICU outcomes (eg, age, severely limited airflow, long-term glucocorticoid use or diaphragm atrophy).[13,27-29] However, our study groups had similar overall characteristics and cotreatments, and acetazolamide did not seem to have greater effect on patients with COPD mechanically ventilated for fewer than 96 hours.

Conclusions

Among mechanically ventilated patients with COPD and pure or mixed metabolic alkalosis, the use of effective acetazolamide doses, compared with placebo, did not result in a statistically significant reduction in the duration of invasive mechanical ventilation. However, the magnitude of the difference (16 hours) was clinically important, and it is possible that the study was underpowered to establish statistical significance.

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