JAMA Internal Medicine | Original Investigation

Autonomous Oxygen Titration for Maintaining Normoxemia in Acutely Ill Adults
The SAVE-O_2 AI Randomized Clinical Trial

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IMPORTANCE For acutely ill adults who are hospitalized with hypoxemia, supplemental oxygen is titrated to maintain normoxemia. In current practice, clinicians intermittently titrate oxygen, potentially exposing patients to hypoxemia and hyperoxemia between assessments. Autonomous oxygen titration may address these challenges by independently titrating supplemental oxygen flow to maintain peripheral oxygen saturation (Spo_2) within a predefined range.

OBJECTIVE To determine whether autonomous oxygen titration increases the proportion of time spent in a targeted normoxemia range compared with usual care in acutely ill adults.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, unblinded, parallel-group, randomized clinical trial was conducted at 4 US hospitals from May 6, 2024, to November 17, 2025, among adults hospitalized for acute respiratory illness, trauma, burn, or acute care surgery who were receiving supplemental oxygen.

INTERVENTION Patients were randomly assigned to receive oxygen titration via either autonomous oxygen titration or usual care (manual oxygen titration by clinicians) during the first 72 hours after randomization.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of time spent within the targeted normoxemia range (Spo_2 90%-96%). The key secondary outcome was the proportion of time spent in hypoxemia (Spo_2 <88%).

RESULTS Among 300 patients randomized and included in the trial population (median [IQR] age, 66 (55-75) years; 162 [54%] female), 152 were assigned to autonomous oxygen titration and 148 to usual care. Participants represented a range of skin pigmentation categories defined by the Monk Skin Tone Scale, including 67 (22%) categorized as light, 168 (56%) as medium, and 65 (22%) as dark. The mean (SE) proportion of time spent in normoxemia was greater in the autonomous oxygen titration group than in the usual care group (85% [1%] vs 63% [2%]; adjusted risk difference [RD], 21 percentage points [pp]; 95% CI, 18-25 pp; $P < .001$). The mean (SE) proportion of time spent in hypoxemia was lower in the autonomous oxygen titration group than in the usual care group (2.0% [0.2%] vs 3.6% [0.4%]; adjusted RD, −1.3 pp; 95% CI, −2.0 to −0.5 pp; $P = .002$). The mean (SE) proportion of time spent in hyperoxemia (Spo_2 >96%) was 9.2% (1.0%) in the autonomous oxygen titration group and 29.1% (1.7%) in the usual care group. The mean (SE) proportion of time spent in borderline hypoxemia (Spo_2 88%-89%) was 3.4% (0.3%) in the autonomous oxygen titration group and 4.0% (0.4%) in the usual care group. Results were consistent across prespecified subgroups.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial among adults hospitalized with an acute illness or injury and receiving supplemental oxygen, autonomous oxygen titration substantially increased the proportion of time spent in normoxemia and decreased time spent in hypoxemia compared with usual care.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT06374225

JAMA Intern Med. doi:10.1001/jamainternmed.2026.4023
Published online August 3, 2026.

Visual Abstract
Invited Commentary
Supplemental content

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Group Information: A complete list of the investigators and collaborators in the Strategy to Avoid Excessive Oxygen Using Autonomous Oxygen Titration Intervention (SAVE-O_2 AI) Network appears in Supplement 4.

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Supplemental oxygen is one of the most common medical treatments used in acutely ill adults to prevent and treat hypoxemia.[1-3] Hypoxemia among hospitalized patients is associated with an up to 50% in-hospital mortality when oxygen delivery is inadequate.[4] The widespread implementation of pulse oximetry and continuous peripheral oxygen saturation (Spo_2) monitoring only solved half of the problem.[5] Once hypoxemia is identified, it must be addressed. Currently, clinicians intermittently titrate oxygen, potentially exposing patients to hypoxemia between assessments. Autonomous oxygen titration may provide a better solution.

Closed-loop, autonomous oxygen titration systems automatically adjust the flow of oxygen to maintain oxygen saturation within a clinician-determined target range.[6-8] Autonomous oxygen titration during mechanical ventilation is reliable and cost-effective.[6,7,9] However, supplemental oxygen is most commonly administered through a nasal cannula or face mask.[10-13] Limited evidence exists on autonomous oxygen titration for acutely ill patients who do not undergo mechanical ventilation.[14,15]

We conducted the Strategy to Avoid Excessive Oxygen Using Autonomous Oxygen Titration Intervention (SAVE-O_2 AI) trial to determine whether autonomous oxygen titration in hospitalized adults receiving supplemental oxygen increases the time spent in normoxemia (Spo_2 90%-96%) and decreases the time spent in hypoxemia (Spo_2 <88%) and hyperoxemia (Spo_2 >96%). We hypothesized that autonomous oxygen titration would increase the proportion of time spent in normoxemia compared to usual care.

Key Points

Question Can autonomous oxygen titration increase the proportion of time acutely ill adults receiving supplemental oxygen spend in a targeted normoxemia range (peripheral oxygen saturation 90%-96%) and decrease time spent in hypoxemia (peripheral oxygen saturation <88%)?

Findings In this randomized clinical trial among 300 acutely ill adults in 4 US hospitals, autonomous oxygen titration increased the proportion of time spent in normoxemia and decreased the proportion of time spent in hypoxemia compared to usual care.

Meaning Autonomous oxygen titration safely increased the time that acutely ill adults spent in a targeted normoxemia range compared with oxygen delivery in current clinical care.

Methods

Trial Design and Oversight

SAVE-O_2 AI was a multicenter, parallel-group, patient-level randomized clinical trial conducted at 4 tertiary care hospitals from different geographic regions of the US. A list of participating sites has been previously published,[16] as have the full trial protocol and a prespecified statistical analysis plan, which are also included in Supplements 1 and 2, respectively. Additional information on study methods is also available in the eMethods in Supplement 3.

The trial was initiated by investigators and approved by the Colorado Multiple Institutional Review Board (23-0866) for all trial sites. Additional approval was obtained by the Defense Health Agency Office of Human Research Oversight (E01218.2). The trial was registered at ClinicalTrials.gov before initiation of enrollment (NCT06374225) and was conducted under a US Food and Drug Administration (FDA) investigational device exemption (G230325). Written informed consent was obtained from patients meeting eligibility criteria and/or their legally authorized representative before randomization. Complete information on informed consent procedures has been previously published.[16] The trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[17]

Trial Population and Randomization

From May 6, 2024, to November 17, 2025, we enrolled adults (≥18 years old) hospitalized with acute respiratory illness, trauma, burns, or acute care surgery receiving 1 to 10 L of supplemental oxygen, and who could be randomized within 36 hours of hospitalization. Acute respiratory illness was defined as a primary or secondary lung insult resulting in hypoxemia. Hypoxemia attributable primarily to altered mental status or sedation was not considered an acute respiratory illness. We excluded patients who were pregnant, incarcerated, anticipated to be discharged within 24 hours, or transitioning to room air imminently, or who had imminent plans to escalate to high-flow nasal oxygen, noninvasive ventilation, or invasive mechanical ventilation. We also excluded patients for whom the clinical team was unwilling or unable to follow the prescribed oxygen titration method and target range. Enrolled participants were randomly assigned in a 1:1 ratio to receive the intervention (autonomous oxygen titration) or usual care (manual oxygen titration by clinicians).

Autonomous Oxygen Titration System Information

The O2matic PRO100 is a closed-loop, trend-based, autonomous oxygen titration system approved for clinical use in multiple countries outside the US.[18] It was not FDA cleared for clinical use in the US during the conduct of this trial. Using pulse oximetry input, the system automatically titrates supplemental oxygen flow (0-15 L/min) to maintain Spo_2 within a specified target range using the lowest effective flow. All participants were mandated to wear 2 pulse oximeters, 1 for the device and 1 for the hospital monitor. The latter connected to central monitoring and alerted clinicians to changes in Spo_2 measurements. Additional system specifications have been previously reported.[16]

Study Interventions

We previously reported details of the trial interventions.[16] In brief, participants in both treatment groups received a target Spo_2 of 93% (acceptable range, 90%-96%).[19] Participants were connected to pulse oximeters from both the autonomous system and the hospital monitor for up to 72 hours after randomization or until hospital discharge, whichever occurred first.

All study pulse oximeters are FDA cleared for use in hospitalized patients. The 2 pulse oximeters were typically placed on opposite hands. All other aspects of clinical care were left to usual practice.

Both bedside nurses and respiratory therapists were responsible for oxygen titration. The standard frequency of Spo_2 and oxygen flow rate assessments was every 1 to 2 hours (intensive care unit), and every 4 to 8 hours (inpatient wards). Clinical assessments and vital sign monitoring were similar in both groups.

Participants in both groups were allowed to receive nocturnal noninvasive ventilation for sleep-disordered breathing. On discontinuation of noninvasive ventilation, oxygen titration was resumed according to the assigned treatment group.

Study interventions were discontinued if the participant escalated to higher-flow oxygen (>15 L/min) or required noninvasive or invasive mechanical ventilation, per usual clinical care. When participants achieved room air for at least 12 consecutive hours, oxygen delivery could be discontinued per the clinical team's discretion; however, participants remained connected to both pulse oximeters for the remainder of the intervention period.

Autonomous Oxygen Titration Group

In the autonomous oxygen titration group, supplemental oxygen was automatically titrated by the autonomous oxygen titration system for up to 72 hours. Routine clinical monitoring and documentation of vital signs continued per usual care.

Usual Care (Manual Titration) Group

In the usual care group, supplemental oxygen was titrated by clinical staff according to local hospital protocols at each site. Participants were connected to both pulse oximeters, and autonomous titration was disabled for the autonomous oxygen titration system. In this mode, the system was used solely for Spo_2 data collection and did not inform titration decisions. The recommended Spo_2 target (93%) and acceptable range (90%-96%) were reinforced regularly to the clinical team throughout the 72-hour intervention period.

Data Collection

Site research staff collected data on baseline characteristics and in-hospital outcomes. We extracted all recorded Spo_2 and oxygen flow rate measurements directly from the electronic health record and from the autonomous oxygen titration system for all participants.[19] Trial personnel collected prespecified data elements manually using standardized operating procedures, including home supplemental oxygen use. Adverse events were collected and reported if they were (1) serious or unexpected, and (2) were definitely, probably, or possibly related—or of an uncertain relationship—to trial procedures.[16]

Skin Pigmentation

We directly measured skin pigmentation for all enrolled participants, in accordance with FDA guidance.[20-22] We used 2 validated scales: Monk Skin Tone Scale[23] and Fitzpatrick skin scale.[24]

Outcome Measures

The primary outcome was the proportion of time spent within the targeted normoxemia range (Spo_2 90%-96%) as measured by 2 continuous noninvasive pulse oximeters during the first 72 hours after randomization. We calculated the average of the 2 measurements weighted by the total number of observed minutes per pulse oximeter. When data from one pulse oximeter were not available, the other contributed available Spo_2 measurements without imputation. Observation of the primary outcome ended at the earliest of the protocol-defined concluding events. Periods of time spent in the operating room, receiving noninvasive ventilation for sleep-disordered breathing, or under procedural sedation were excluded.

The key secondary outcome was the proportion of time spent in hypoxemia (Spo_2 <88%). Other secondary outcomes included proportion of time spent in hyperoxemia (Spo_2 >96%), proportion of time spent in borderline hypoxemia (Spo_2 88%-89%), the total volume of supplemental oxygen administered during the first 72 hours after randomization, and time to room air through day 28. Exploratory outcomes included hospital-free days through day 28 and in-hospital all-cause 28-day mortality.

We also completed prespecified subgroup and sensitivity analyses to evaluate the robustness of treatment effect. Prespecified subgroups included skin pigmentation, home oxygen use, oxygen flow rate at randomization, and indication for hospital admission. We evaluated sensitivity by the different pulse oximeters and duration of Spo_2 monitoring.

Statistical Analysis

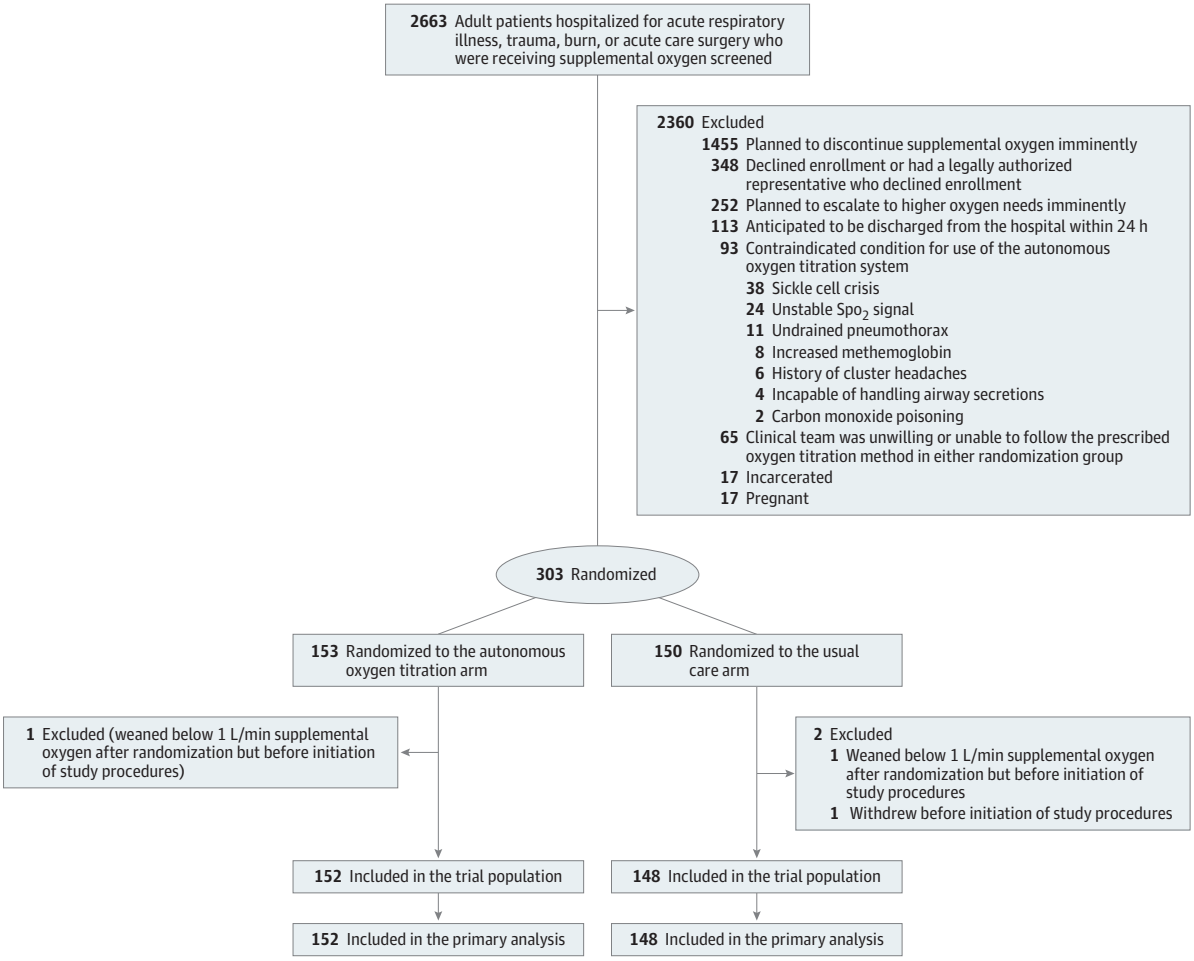
Based on prior trials,[19,25,26] we estimated that the mean proportion of time spent in normoxemia (primary outcome) in the usual care (control) group would be 60%. We calculated that enrolling 300 participants (150 per group) would allow us to detect a 10% difference in time spent in normoxemia between groups with more than 99% power (α = .05).

We analyzed the primary outcome following an intention-to-treat comparison using a quasi-binomial generalized linear model with an identity link to estimate the adjusted risk difference (RD) in mean proportions. We included fixed effects for study site and indication for hospitalization and used robust standard errors at the participant level to account for repeated measures.

Participant time spent in hyperoxemia was considered nonmodifiable if the participant was receiving room air but had Spo_2 higher than 96% (ie, in the hyperoxemia range) and was included in the normoxemia category. All participants with valid Spo_2 data (defined as any Spo_2 60%-100%) from at least 1 pulse oximeter were included in the primary analysis. The primary outcome was calculated separately using data from both pulse oximeters. The quasi-binomial model incorporated the total number of observed minutes per pulse oximeter in its estimation and implicitly weighted each measurement by total observed time.

We analyzed proportional secondary outcomes (eg, time spent in hypoxemia) using the same methods as the primary

Figure 1. Flow Diagram of Participants Through the Trial



Spo$_2$ indicates peripheral oxygen saturation.

analysis. We used a quasi-Poisson regression model for countlike continuous outcomes (eg, total amount of supplemental oxygen administered) and analyzed time-to-event outcomes using a competing risks framework (eg, all-cause mortality). We used a proportional odds model to analyze ordinal outcomes (eg, supplemental oxygen-free days). All analyses were performed in R, version 4.2.2 (R Foundation for Statistical Computing),[27] and Cox models used the survival package.[28] A 2-sided significance level of $P < .05$ was used for all statistical tests.

Results

Trial Population

A total of 300 adults hospitalized with an acute illness or injury who were receiving supplemental oxygen were randomized and included: 152 in the autonomous oxygen titration group and 148 in the usual care group (**Figure 1**). Among participants, the median (IQR) age was 66 (55-75) years, 162 (54%) were female, 208 (69%) were admitted for an acute respiratory illness, and 155 (52%) were receiving at least 3 L/min of oxygen at randomization. Participants represented a range of skin pigmentation categories (67 [22%] light, 168 [56%] medium, and 65 [22%] dark by Monk Skin Tone Scale; eFigure 1 in Supplement 3). A complete list of baseline characteristics is summarized in **Table 1** and eTable 1 in Supplement 3. The median (IQR) time receiving study interventions for participants was 42 (23-60) hours in the autonomous titration group and 41 (18-59) hours in the usual care group. The most common reasons for follow-up to end were completion of the 72-hour study period in 143 participants (48%) and tolerating room air for at least 12 consecutive hours in 71 (24%) (eTable 2 and eFigure 2 in Supplement 3). The median (IQR) number of oxygen titrations of at least 1 L/min per day on study was 1.0 (0.3-2.5) in the autonomous oxygen titration group and 1.3 (0.7-2.4) in the usual care group. There was a median of 7.3 flow rate changes recorded per day overall (median [IQR] of 7.7 [5.1-10.3] in the usual care group and 6.8 [4.3-10.0] in the autonomous oxygen titration group).

Table 1. Patient Demographics and Characteristics at Baseline

Characteristic	No. (%)	
	Autonomous oxygen titration group (n = 152)	Usual care group (n = 148)
Age, median (IQR), y	68 (59-77)	64 (53-72)
Sex		
Female	87 (57)	75 (51)
Male	65 (43)	73 (49)
Race and ethnicity[a]		
Black, non-Hispanic	26 (17)	28 (19)
Hispanic	9 (6)	10 (7)
White, non-Hispanic	113 (74)	105 (71)
Other	4 (3)	5 (3)
Monk Skin Tone Scale[b]		
Light	38 (25)	29 (20)
Medium	83 (55)	85 (57)
Dark	31 (20)	34 (23)
Primary reason for hospital admission		
Acute respiratory illness	106 (70)	102 (69)
Traumatic injury/burn/acute surgery	46 (30)	46 (31)
Admitted to an ICU at time of enrollment	38 (25)	35 (24)
Admitted to an ICU at any point during the study period	41 (27)	41 (28)
Oxygen flow rate at randomization, L/min		
1.0-2.9	77 (51)	68 (46)
3.0-4.9	57 (38)	53 (36)
5.0-10	18 (12)	27 (18)
Chronic pulmonary disease	65 (43)	63 (43)
Chronic obstructive pulmonary disease	39 (26)	39 (26)
Currently or formerly smoke	64 (42)	78 (53)
Oxygen use at baseline	14 (9)	17 (11)
BMI, median (IQR)	28 (24-34)	29 (25-35)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICU, intensive care unit.

[a] Race and ethnicity were self-reported by participants. The other race and ethnicity category includes participants reporting as American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, multiple races, other race or ethnicity, and unknown or not reported. These groups are reported together owing to small sample sizes.

[b] Monk Skin Tone Scale categories were grouped as light (Monk 1-3), medium (Monk 4-6), and dark (Monk 7-10).

Primary and Key Secondary Outcomes

The mean (SE) proportion of time spent in normoxemia (Spo_2 90%-96%) was greater in the autonomous oxygen titration group than in the usual care group (85% [1%] vs 63% [2%]; adjusted RD, 21 percentage points [pp]; 95% CI, 18-25 pp; $P < .001$) (**Table 2** and **Figure 2**). The mean (SE) proportion of time spent in hypoxemia (Spo_2 <88%), the key secondary outcome, was lower in the autonomous oxygen titration group than in the usual care group (2.0% [0.2%] vs 3.6% [0.4%]; adjusted RD, −1.3 pp; 95% CI, −2.0 to −0.5 pp; $P = .002$). When hypoxemia was defined as Spo_2 lower than 85% (ie, severe hypoxemia) in a post hoc analysis, the mean (SE) proportion of time spent was also lower in the autonomous oxygen titration group than in the usual care group (1.0% [0.1%] vs 1.9% [0.2%]; adjusted RD, −0.7 pp; 95% CI, −1.2 to −0.3 pp; eTable 3 in Supplement 3).

Secondary and Exploratory Outcomes

The mean (SE) proportion of time spent in hyperoxemia (Spo_2 >96%) was 9.2% (1.0%) in the autonomous oxygen titration group and 29.1% (1.7%) in the usual care group (adjusted RD, −18 pp; 95% CI, −22 to −14 pp; eFigure 3 in Supplement 3). The mean (SE) proportion of time spent in borderline hypoxemia (Spo_2 88%-89%) was 3.4% (0.3%) in the autonomous titration group and 4.0% (0.4%) in the usual care group (adjusted RD, −0.3 pp; 95% CI, −1.2 to 0.6 pp). The total volume of supplemental oxygen administered per participant per day was 2310 L in the autonomous oxygen titration group and 2992 L in the usual care group (incidence rate ratio, 0.83; 95% CI, 0.67-1.02). Most patients received less than 6 L/min supplemental oxygen during the first 72 hours after randomization, and participants in the autonomous oxygen titration group generally received lower flow rates than those in the usual care group (**Figure 3**). In a post hoc analysis, the total volume of supplemental oxygen administered was lower in the autonomous titration group during the first 24 hours after randomization (eTable 3 in Supplement 3). The median (IQR) time to achieve room air was 1.05 (0.45-2.91) days in the autonomous oxygen titration group and 1.15 (0.64-2.65) days in the usual care group (adjusted hazard ratio, 1.03; 95% CI, 0.79-1.34; eFigure 4 in Supplement 3).

In-hospital mortality to day 28 was uncommon and similar in the autonomous titration group and usual care group (4 deaths [2.6%] vs 5 deaths [3.4%]; adjusted hazard ratio, 1.03; 95% CI, 0.22-4.84; eFigure 5 in Supplement 3). The median supplemental oxygen-free days and hospital-free days were similar between groups, as were the remaining exploratory outcomes (eFigures 6 and 7 in Supplement 3). There were no reported serious adverse events in either treatment group.

Table 2. Primary, Secondary, and Exploratory Outcomes

Outcome	Autonomous oxygen titration group (n = 152)	Usual care group (n = 148)	Effect measure, difference (95% CI)[a]	*P* value
Primary outcome: proportion of time spent in targeted normoxemia (Spo_2 90%-96%), mean (SE), %	85 (1)	63 (2)	aRD, 21 pp (18 to 25 pp)	<.001
Secondary outcomes				
Key secondary outcome: proportion of time spent in hypoxemia (Spo_2 <88%), mean (SE), %	2.0 (0.2)	3.6 (0.4)	aRD, −1.3 pp (−2.0 to −0.5 pp)	.002
Proportion of time spent in hyperoxemia (Spo_2 >96%), mean (SE), %	9 (1)	29 (2)	aRD, −18 pp (−22 to −14 pp)	NA
Proportion of time spent in borderline hypoxemia (Spo_2 88%-89%), mean (SE), %	3.4 (0.3)	4.0 (0.4)	aRD, −0.3 pp (−1.2 to 0.6 pp)	NA
Total volume of supplemental oxygen administered per participant per d, median (IQR), thousands of L[b]	2.31 (1.05 to 3.57)	2.99 (2.30 to 4.27)	IRR, 0.83 (0.67 to 1.02)	NA
Time to room air, median (IQR), d	1.05 (0.45 to 2.91)	1.15 (0.64 to 2.65)	HR, 1.03 (0.79 to 1.34)	NA
Exploratory outcomes				
Supplemental oxygen-free days to day 28, median (IQR)	25 (21 to 26)	24 (21 to 26)	COR, 1.39 (0.92 to 2.04)	NA
In-hospital mortality to day 28, No. (%)	4 (3)	5 (3)	HR, 1.03 (0.22 to 4.84)	NA
Respiratory failure to day 28, No. (%)[c]	14 (9)	11 (7)	NA	NA
Time to respiratory failure, median (IQR), d[c]	3.2 (1.7 to 4.9)	2.7 (0.9 to 5.2)	HR, 1.42 (0.63 to 3.17)	NA
Hospital-free days to day 28, median (IQR), d	23 (20 to 25)	22 (19 to 24)	COR, 1.31 (0.88 to 1.95)	NA
Hospital length of stay, median (IQR), d[d]	5.2 (3.1 to 7.9)	5.8 (3.5 to 9.0)	NA	NA
ICU length of stay, median (IQR), d[e]	3.1 (1.7 to 4.4)	2.0 (1.3 to 5.1)	NA	NA
Proportion of time receiving no supplemental oxygen during observed study time, median (IQR), %	2 (0 to 28)	3 (0 to 24)	aRD, −1 pp (−5 to 3 pp)	NA

Abbreviations: aRD, adjusted risk difference; COR, cumulative odds ratio; HR, hazard ratio; ICU, intensive care unit; IRR, incidence rate ratio; NA, not applicable; pp, percentage point; Spo_2, peripheral oxygen saturation.

[a] All effect measures are adjusted for study site and reason for hospital admission (acute respiratory illness vs trauma/burn/surgical).

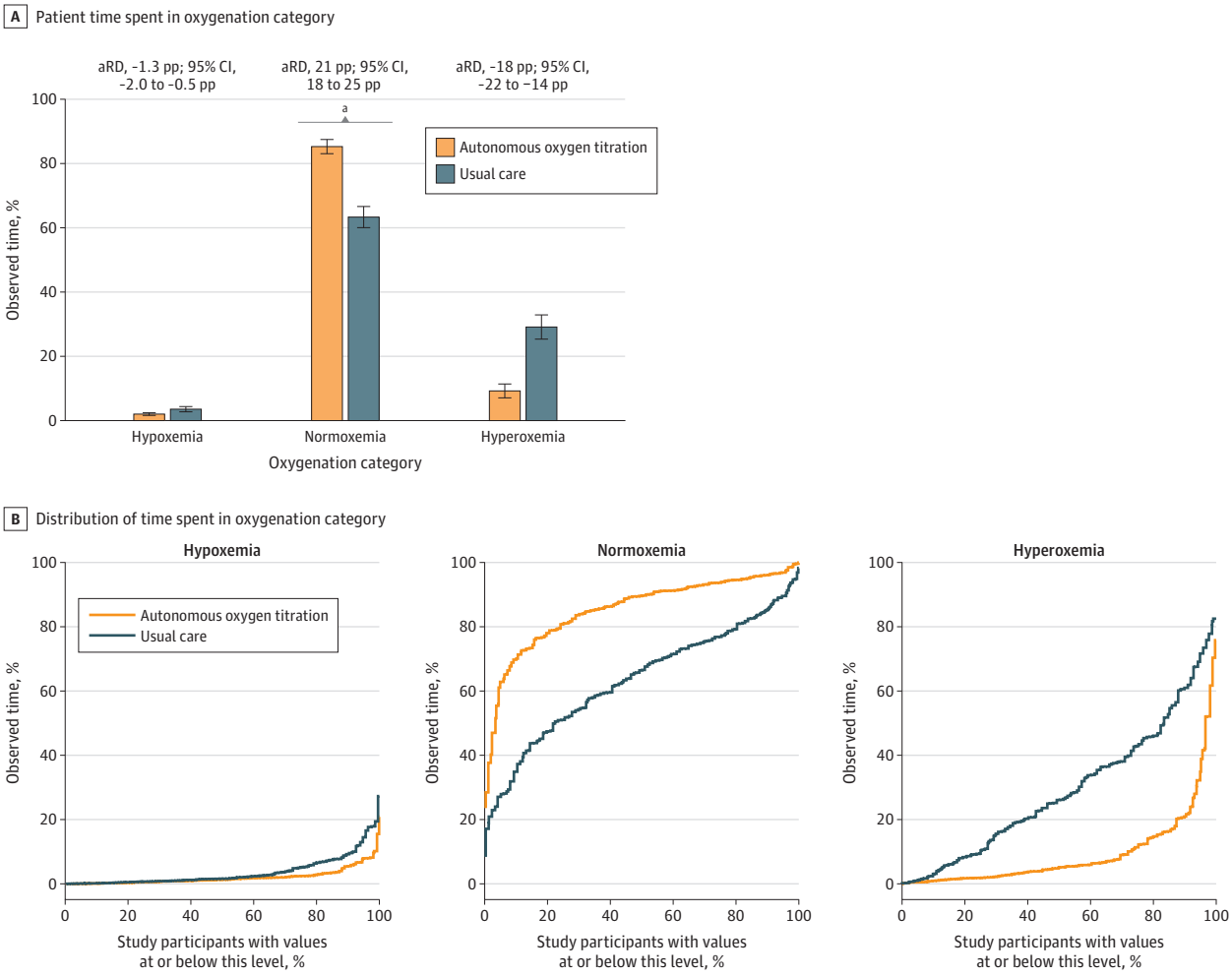
[b] Total volume of supplemental oxygen was calculated during the time when patients were following their assigned treatment group, up to the first 72 hours after enrollment.

[c] Respiratory failure was defined as progression to receipt of heated high-flow nasal cannula, noninvasive ventilation, or invasive mechanical ventilation, to day 28 or hospital discharge, whichever is first, excluding time in the operating room.

[d] Hospital length of stay was calculated only for the 291 patients who survived for 28 days after enrollment.

[e] ICU length of stay was calculated only for 92 patients who were admitted to an ICU at the time of enrollment.

Figure 2. Bar and Line Graphs of Proportion of Time Participants Spent in Hypoxemia, Normoxemia, and Hyperoxemia by Receipt of Autonomous Oxygen Titration vs Usual Care



A, Proportion of patient time spent in oxygenation categories by group. Bars represent group-specific estimates with error bars denoting 95% CIs. B, Distribution of participant time spent in each oxygenation category by group. Curves represent the cumulative proportion of participants as a function of the proportion of their observed time spent in the indicated oxygenation category. Participant time spent in hyperoxemia (peripheral oxygen saturation [Spo_2] >96%) that was nonmodifiable was included in the normoxemia (Spo_2 90%-96%) category. Time was considered nonmodifiable if the participant was receiving room air or 21% fraction of inspired oxygen but had an Spo_2 higher than 96% (ie, was in the hyperoxemia range). A total of 2% of observed time met the nonmodifiable criteria. Hypoxemia is defined as Spo_2 lower than 88%. aRD indicates adjusted risk difference; pp, percentage point.

[a] $P < .001$.

Reported adverse events included epistaxis in 2 participants and discomfort associated with the nasal cannula or face mask in 2 participants, all in the autonomous oxygen titration group (eTables 4 and 5 in Supplement 3). This was addressed by a protocol amendment requiring humidification of supplemental oxygen when flow rates exceeded 8 L/min.

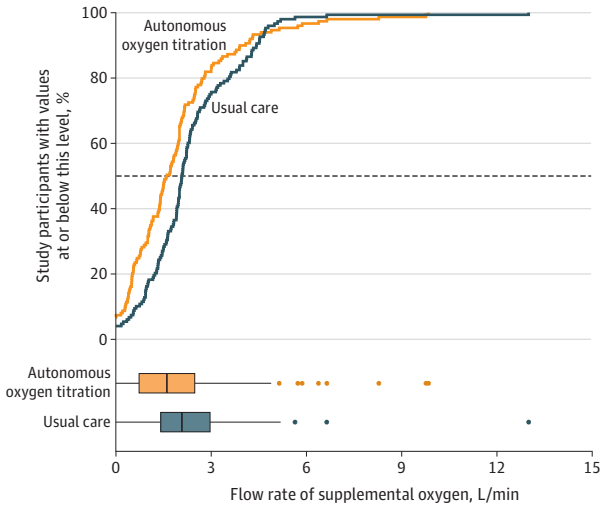
Subgroup Analyses

The results of the prespecified subgroup analyses are shown in eFigure 8 in Supplement 3. The treatment effect on the primary outcome considerably favored autonomous titration across all prespecified subgroups, including by skin pigmentation categories. The treatment effect on the key secondary outcome (time spent in hypoxemia) favored autonomous titration across all prespecified subgroups (eFigure 9 in Supplement 3) in a post hoc analysis. Therefore, none of the prespecified characteristics modified the effect of autonomous titration on the proportion of time spent in either normoxemia or hypoxemia.

Sensitivity Analyses

The difference in the mean proportion of time spent in normoxemia was greater when Spo_2 measurements from only the autonomous device pulse oximeter were used (adjusted RD, 28 pp; 95% CI, 25-32 pp) compared to Spo_2 measurements from only the hospital pulse oximeter (adjusted RD, 14 pp; 95% CI, 9-18 pp; eFigure 10 in Supplement 3). Results were similar in sensitivity analyses that progressively restricted the primary

Figure 3. Line Graph and Box Plots Showing Supplemental Oxygen Flow Rates by Receipt of Autonomous Oxygen Titration vs Usual Care



The line graph displays the empirical cumulative distribution function of oxygen flow rates. The y-axis represents the proportion of participants with an observed oxygen flow rate less than or equal to the value on the x-axis. Shaded bands indicate uncertainty around the empirical distributions. The horizontal dashed line indicates the median of the participant-level distribution. The box plots present the same data, with boxes indicating the IQR (25th to 75th percentiles) and the central line in the boxes denoting the median. Whiskers extend to the most extreme values within 1.5 times the IQR. Points represent individual observations beyond this range.

analysis to participants with greater amounts of valid Spo_2 data. A scatterplot of Spo_2 measurements comparing usual care and autonomous oxygen titration pulse oximeters is provided in eFigure 11 in Supplement 3.

Discussion

Among adults hospitalized with an acute illness or injury receiving supplemental oxygen, titrating oxygen using an autonomous system increased the proportion of time spent in normoxemia and decreased the proportion of time spent in hypoxemia and hyperoxemia compared with usual care using manual oxygen titration by clinicians. Together, these findings indicate that autonomous oxygen titration safely and effectively maintains oxygen saturation within a prespecified target range and reduces time spent in hypoxemia compared with usual care in hospitalized medical and surgical patients.

The ability of autonomous oxygen titration to correct hypoxemia once it has been detected—in a more quickly and sustained fashion than manual oxygen titration—may improve clinical outcomes when applied at a population level. Indeed, autonomous titration also decreased time spent in severe hypoxemia (Spo_2 <85%) in a post hoc analysis, which aligns with primary end points of hypoxemia trials.[29] Autonomous oxygen titration also decreased the proportion of time spent in hyperoxemia in the present trial. Excessive supplemental oxygen administration and resultant hyperoxemia may have adverse physiologic consequences.[30,31] Additionally, supplemental oxygen administration was lower in the autonomous oxygen titration group during the first 24 hours in this trial. Therefore, autonomous oxygen titration reduces exposure to potentially harmful hyperoxemia and may also decrease supplemental oxygen use. Conserving oxygen by safely reducing the use of supplemental oxygen may also improve logistics in austere settings where the oxygen supply is limited.[32]

Prior studies have demonstrated similar clinical benefits for autonomous oxygen titration devices in specific populations that did not undergo mechanical ventilation, such as patients with chronic obstructive pulmonary disease,[14] major abdominal or thoracic surgery,[25] and acute COVID-19 infection.[13] However, these prior studies were conducted outside of the US and included mostly patients with light skin pigmentation, limiting their applicability to US populations. This is particularly important given concerns about the accuracy and precision of pulse oximetry in patients with darker skin pigmentation.[33] The present trial included participants with a wide range of skin pigmentation, with 78% having medium or dark skin pigmentation. Autonomous titration appeared to benefit participants in all skin pigmentation groups (eFigure 8 in Supplement 3). Furthermore, we enrolled patients from 4 geographically and demographically distinct sites, with multiple indications for hospital admission, and across a broad range of oxygen flow rates at randomization. This clinical and demographic heterogeneity supports the generalizability and real-world relevance of the findings.

Participants in the usual care group spent a much higher proportion of time in normoxemia and a lower proportion in hypoxemia compared to previous studies. In prior trials, participants in the usual care (manual titration) groups spent approximately 40% to 50% of their time in normoxemia and 4% to 18% in hypoxemia.[25,34] In this trial, participants in the usual care group spent 63% of their time in the targeted normoxemia range and only 3.6% in hypoxemia. Therefore, the control group in this trial likely represented enhanced usual care. Even in this context, autonomous oxygen titration still meaningfully increased time spent in normoxemia and decreased time spent in hypoxemia. This finding suggests that autonomous oxygen titration provides benefit even when usual care performance is enhanced. In settings with lower staffing ratios or less frequent patient assessments, the benefits of autonomous oxygen titration may be even greater.

Strengths and Limitations

This trial has several strengths. We used the weighted average of 2 simultaneously collected Spo_2 measurements. The autonomous oxygen titration device was blind to the hospital Spo_2 measurements and titrated solely on input from its own pulse oximeter. Conversely, titration in the usual care group was based solely on Spo_2 measurements from the hospital pulse oximeter. Therefore, measurements from the device pulse oximeter would be expected to favor the autonomous titration group, and from the hospital pulse oximeter would be expected to favor the usual care group. In a sensitivity analysis, we found that the RD between treatment groups in proportion of time in normoxemia was greater when using only the device pulse oximeter (adjusted RD, 28 pp; 95% CI, 25- 32 pp)

and less when using only the hospital pulse oximeter (adjusted RD, 14 pp; 95% CI, 9-18 pp) (eFigure 10 in Supplement 3). However, results from both approaches were consistent with the primary analysis and favored autonomous oxygen titration.

This trial also has several limitations. Because the trial was not blinded, awareness of the trial group assignments could have influenced the participants' behavior or clinicians' treatment decisions. Such awareness, including education and just-in-time reminders from site research teams, may have influenced usual care during the trial. However, such influence would be expected to bias results toward the null by improving usual care performance. This trial assessed only the PRO100 device, so the results may not be generalizable to other autonomous oxygen titration systems. The limitations of currently available pulse oximeters are well established.[5] The FDA recently highlighted the need for improvements in pulse oximeter accuracy and precision, particularly to address biases present in current devices.[20,21] Importantly, an autonomous oxygen titration system titrates oxygen to a clinician-specified Spo_2 target based on the pulse oximeter's measured value. Therefore, the system does not correct for inaccuracy or imprecision in pulse oximetry measurements, but will reliably maintain oxygen saturation at the chosen target. Improvements in pulse oximetry technology would be expected to enhance the performance of autonomous oxygen titration systems by providing measurements that more accurately reflect true arterial oxygen saturation.

Conclusions

In this randomized clinical trial among adults hospitalized with an acute illness or injury and receiving 1 to 10 L/min of supplemental oxygen, autonomous oxygen titration substantially increased the proportion of time spent in normoxemia and decreased time spent in hypoxemia compared with manual oxygen titration.

ARTICLE INFORMATION

Accepted for Publication: June 15, 2026.

Published Online: August 3, 2026. doi:10.1001/jamainternmed.2026.4023

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Obtained funding: Rice, Anderson, Bebarta, Ginde.
Administrative, technical, or material support: Douin, Withers, Sullivan, Anderson, Cheng, Banasiewicz, Semler, Lloyd, Stettler, Wright, Wiktor, Bebarta, Ginde.
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Conflict of Interest Disclosures: Dr Douin reported grants from the National Heart, Lung, and Blood Institute outside the submitted work. Dr Xiao reported grants from the National Institutes of Health outside the submitted work. Dr Cheng reported grants from Advanced Technology International and the National Institutes of Health during the conduct of the study. Dr Semler reported institutional grants from the US Department of Defense during the conduct of the study, as well as personal fees from Reprieve Cardiovascular, DynaMedex, and Baxter International outside the submitted work. Dr Gibbs reported grants from the US Department of Defense during the conduct of the study, as well as grants from the National Institutes of Health and the Patient-Centered Outcomes Research Institute outside the submitted work. Dr Khan reported grants from Dompe Pharmaceuticals, Direct Biologics, and 4DMedical outside the submitted work. Dr Ginde reported grants from the US Department of Defense during the conduct of the study. No other disclosures were reported.

Funding/Support: This effort was sponsored by the US Department of War's Defense Health Agency Research and Engineering Directorate, Combat Casualty Care Portfolio via the Medical Technology Enterprise Consortium under Other Transaction Number W81XWH-15-9-0001. Additional support was provided by the National Center for Advancing Clinical and Translational Sciences under grant No. U24 TR004437. The investigational device exemption sponsor was IDTS Medical. PRO100 devices were rented from O2matic (Herlev, Denmark) for the trial.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: A complete list of the investigators and collaborators in the Strategy to Avoid Excessive Oxygen Using Autonomous Oxygen Titration Intervention (SAVE-O_2 AI) Network appears in Supplement 4.

Disclaimer: The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of the US government.

Meeting Presentation: This study was presented at the 2026 Military Health System Research Symposium; August 3, 2026; Kissimmee, Florida.

Data Sharing Statement: See Supplement 5.

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